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James, Michael, Frank, Mansel

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The Role of Magnesium Sulphate in the Control of Catecholamine Induced Cardiovascular Disturbances

Michael Frank Mansel James

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ABSTRACT

The purpose of this thesis was to investigate the value in clinical situations of the well known *in vitro* anti-adrenergic effects of magnesium. Research interest in magnesium has been growing rapidly over the last twenty years. However, most of this interest has focused on the clinical consequences of magnesium deficiency states and little attention has been given to magnesium as a therapeutic agent. Despite the wide use of infusions of magnesium sulphate in obstetric practice, there is a dearth of knowledge regarding the actions of magnesium on a cardiovascular system. In laboratory studies, magnesium was shown to inhibit the release of catecholamines from adrenergic nerve terminals, an action which might have great clinical implications.

The effects of increasing dosages of magnesium on the cardiovascular system of the intact baboon were investigated. It was found that magnesium produced a consistent vasodilator effect which correlated well with the serum magnesium levels but the hypotensive effects at serum levels below 5mmol/l were minimal due to a concomitant increase cardiac output which was primarily mediated through an increase stroke volume. There was no evidence of negative

inotropic effects. The actions of magnesium on adrenaline-induced cardiovascular disturbances were investigated. Magnesium sulphate infusions exerted vasodilator and anti-arrhythmic effects of a magnitude likely to be of clinical benefit without producing negative inotropic effects. To demonstrate the safety of magnesium infusions *in* the presence of alpha and beta blockade, the interactions of magnesium in the presence of adrenaline with phentolomine and propranolol were investigated. No deleterious interactions were noted and it appeared that magnesium/propranolol combinations did not potentiate the negative inotropic effects of beta blockade.

In the clinical studies, the ability of magnesium infusions to inhibit catecholamine release in response to the stress of endotracheal intubation was demonstrated. Conditions in which catecholamine excess consistently produces major difficulties include tetanus and phaeochromocytoma. These two conditions are relatively uncommon and this fact precluded controlled trials. Nevertheless, when suitable patients presented studies on the use of magnesium in these conditions were conducted. In tetanus magnesium infusions improved cardiovascular control and reduced catecholamine production. In phaeochromocytomas magnesium enhanced intra-operative control of cardiovascular disturbances and apart from periods of tumour handling reduced catecholamine production. It is concluded that magnesium infusions may be a valuable adjunct to the anaesthetic management of patients with high catecholamine output states.

I declare that this dissertation is my own, unaided work, except for the assistance acknowledged in the preface. It is being submitted for the degree of Doctor of Philosophy in Medicine, Johannesburg. It has not been submitted before for any degree or examination in any other University.

Michael Frank Mansel James

23rd August, 1988

To my family for all their support over the years.

Table of Contents

Preface ..... **xiii**

1. Introduction **1**

1.1 The Metabolic Significance of Magnesium 2
1.2 Assessment of Magnesium Status 3
1.3 Interactions with Calcium and Potassium 5
1.4 Magnesium in the Central Nervous System 6
1.5 Magnesium and the Peripheral Nervous System 8
1.6 Magnesium and the Cardiovascular System 9
1.7 Magnesium and the Respiratory System 13
1.8 Magnesium in Pregnancy 14
1.9 Magnesium and Other Organ Systems 15

2. Clinical Consequences of Hypermagnesaemia **18**

2.1 Central Nervous System 19
2.2 Peripheral Nervous System 20
2.3 Cardiovascular System 22
2.4 Genitourinary System 28
2.5 Endocrine Systems 30
2.6 Coagulation of Blood 31

3. Therapeutic Use of Magnesium 34

3.1 History of Magnesium Therapy.....35
3.2 Pre-eclampsia and Eclampsia.....37
3.3 Magnesium and Arrhythmias.....39
3.4 Magnesium and Ischaemia.....41

4. Aims and Scope of this Thesis.....46

4.1 Animal Studies.....47
4.2 Clinical Studies.....47

5. Cardiovascular Effects of Magnesium.....49

5.1 Methods.....50
5.2 Results.....53
5.3 Discussion.....65

6. Interactions With Adrenaline And Its Antagonists.....73

6.1 Methods.....74
6.2 Results.....76
6.3 Discussion.....85
6.4 Interactions with Alpha-adrenergic Blocking Drugs.....89
6.5 Methods.....90
6.6 Results.....91
6.7 Discussion.....98
6.8 Interactions with Beta-adrenergic Blocking Drugs.....100
6.9 Methods.....101
6.10 Results.....102
6.11 Discussion.....106
6.12 Conclusions.....107

7. Catecholamine Release at Endotracheal Intubation.....109

7.2 Methods.....111

7.3 Results.....112

7.4 Discussion.....117

8. Magnesium And The Management Of Severe Tetanus.....122

8.1 Methods.....124

8.2 Results.....127

8.3 Discussion.....135

8.4 Magnesium And Catecholamine Release In Tetanus.....141

8.5 Case Report.....141

8.6 Discussion.....147

9. Magnesium And Anaesthesia For Phaeochromocytoma.....150

9.1 Patients And Methods.....151

9.2 Results.....157

9.3 Discussion.....169

10. Conclusions.....175

10.1 Cardiovascular Effects.....175

10.2 Anti-adrenergic Effects.....176

10.3 Clinical Studies.....177

10.4 Unanswered Questions.....177

10.5 Further studies.....180

References.....183

Appendices.....234

List of Illustrations

Figure 5.1 Scattergram of changes in systolic blood pressure against serum magnesium levels..... 55

Figure 5.2 Scattergram of changes in diastolic blood pressure against serum magnesium levels..... 57

Figure 5.3 Systolic and Diastolic Blood Pressure and Heart Rate v. Serum Magnesium for grouped data 57

Figure 5.4 Scattergram of changes in heart rate against serum magnesium levels..... 58

Figure 5.5 Scattergram of systemic vascular resistance against serum magnesium levels..... 59

Figure 5.6 Scattergram of changes in cardiac output against serum magnesium levels..... 60

Figure 5.7 Cardiac Output v. Serum Magnesium for grouped data..... 61

Figure 5.8 Scattergram of changes in stroke volume against serum magnesium levels..... 62

Figure 5.9 Stroke Volume v. Serum Magnesium for grouped data..... 62

Figure 5.10 Scattergram of changes in stroke work against serum magnesium levels..... 63

Figure 5.11 Stroke Work v. Serum Magnesium for grouped data..... 63

Figure 5.12 Scattergram of changes in central venous pressure against serum magnesium levels 65

Figure 6.1. Changes in systolic arterial pressure with changes in serum magnesium 78

Figure 6.2. Changes in Heart Rate with changes in serum magnesium 79

Figure 6.3. Changes in Cardiac Output with changes in serum magnesium 80

Figure 6.4. Changes in Stroke Volume with changes in serum magnesium 81

Figure 6.5. Changes in systemic vascular resistance with changes in serum magnesium 82

Figure 6.6. Changes in central venous pressure with changes in serum magnesium 83

Figure 6.7. Changes in systolic arterial pressure during adrenaline infusion with phentolamine-magnesium or magnesium 92

Figure 6.8. Changes in heart rate during adrenaline infusion with phentolamine-magnesium or magnesium 93

Figure 6.9. Changes in cardiac output during adrenaline infusion with phentolamine-magnesium or magnesium 94

Figure 6.10. Changes in stroke volume during adrenaline infusion with phentolamine-magnesium or magnesium alone 95

Figure 6.11. Changes in systemic vascular resistance during adrenaline infusion with phentolamine-magnesium or magnesium 96

Figure 6.12 Changes in stroke volume during adrenaline infusion with phentolamine-propranolol-magnesium sequence 103

Figure 7.1 The effect of either $MgSO_4$ or saline on heart rate at the time of endotracheal intubation..... 113

Figure 7.2 The effect of either $MgSO_4$ or saline on systolic blood pressure at the time of endotracheal intubation..... 114

Figure 7.3 The effect of either $MgSO_4$ or saline on adrenaline levels at the time of endotracheal intubation..... 116

Figure 7.4 The effect of either $MgSO_4$ or saline on noradrenaline levels at the time of endotracheal intubation..... 116

Figure 8.1 Severe cardiovascular disturbances in a patient with tetanus at Day 7 prior to admission to the trial..... 130

Figure 8.2 The same patient as in figure 8.1 at Day 9, two days after the commencement of magnesium therapy..... 129

Figure 8.3 Cardiovascular disturbances on Day 12, the day of commencement of magnesium therapy..... 130

Figure 8.4 The same patient as in figure 8.3 at Day 13..... 130

Figure 8.5 Hourly heart rate and blood pressure chart on day 18..... 143

Figure 8.6 Hourly heart rate and blood pressure changes on day 19 during the introduction of magnesium..... 145

Figure 8.7 Hourly heart rate and blood pressure changes on day 20..... 145

Figure 8.8 Hourly heart rate and blood pressure changes on day 21..... 146

Figure 8.9 Hourly heart rate and blood pressure changes following the withdrawal of all sedation on day 22..... 146

Figure 9.1 Initial cardiovascular changes in response to infusion of $MgSO_4$ in phaeochromocytoma case 1 157

Figure 9.2 Blood pressure response to insertion of a CVP line, and its control by MgSO4 158

Figure 9.3 Cardiovascular responses and $MgSO_4$ administration during tumour handling 158

Figure 9.4 Systolic blood pressure in case 8 in whom control was designated as good 159

Figure 9.5 Systolic blood pressure in case 12 in whom control was designated as fair 160

Figure 9.6 SBP changes during caesarean section in case 4 161

Figure 9.7 SBP changes in case 4 during tumour removal 162

Figure 9.8 SBP changes during anaesthesia and surgery in case 16 163

Figure 9.9 SBP changes in case 15 where the diagnosis was made intraoperatively 164

Figure 9.10 Changes in adrenaline concentrations in 5 patients 167

Figure 9.11 Changes in noradrenaline concentrations in 5 patients 168

List of Tables

Table 1.1 Manifestations of magnesium deficiency..... 17

Table 2.1 Effects of Hypermagnesaemia..... 33

Table 5.1. Data groups determined by serum magnesium levels..... 54

Table 6.1. Significant cardiovascular changes following magnesium injection in adrenaline-treated baboons..... 84

Table 6.2. Principal cardiovascular changes following magnesium injection in adrenaline treated α- and β-blocked baboons..... 105

Table 8.1 Sequence and dosage in which sedative drugs were administered to adult patients with severe tetanus..... 124

Table 8.2 Pulse rates and blood pressures in tetanus patients before and after magnesium therapy..... 132

Table 8.3 Cardiovascular indices in six tetanus patients before and after magnesium therapy had been instituted..... 133

Table 8.4 Catecholamine levels in tetanus during the initiation of magnesium therapy..... 147

Table 9.1 Summary of phaeochromocytoma patient details..... 154

Table 9.2. Intra-operative control of cardiovascular events..... 165

PREFACE

My interest in magnesium as a therapeutic agent in the presence of catecholamine excess was originally aroused by the problems posed by patients suffering from tetanus in Zimbabwe. The neuromuscular effects of magnesium and their potential benefit in reducing the muscle spasms of tetanus was originally suggested to me as a possible therapeutic modality by Dr. E.D.M. Manson whose key role in arousing my interest in this substance I gratefully acknowledge. It was originally hoped that magnesium might provide a cheap and simple method of management of tetanus on a conservative base which would enable the treatment of this life-threatening condition to be conducted in areas where intensive care therapy was impracticable. However, it rapidly became apparent that in this condition magnesium produced profound neuromuscular blockade which required the use of positive pressure ventilation and this line of research was abandoned. However, it was noticed in passing that patients given magnesium appeared more cardiovascularly stable than those treated conventionally. This raised the possibility that magnesium might be exerting anti-adrenergic effects and a literature search revealed that such effects had been well established in laboratory conditions but had never been put to any clinical use. Consequently the animal work detailed in this thesis

was undertaken to investigate this possibility and the results of using the agent in the management of tetanus were encouraging. The investigations culminated in the first use of this agent in a patient severely cardiovascularly unstable due to a phaeochromocytoma. The remarkable results achieved in this case confirmed the theoretical concept that this drug ought to have a valuable place in anaesthetic management. The studies reported in this thesis were undertaken with the approval of the animal and human ethics committees of the University of Rhodesia (later Zimbabwe), with the exception of the study on endotracheal intubation which was approved by the human ethics committtee of the University of the Witwatersrand (clearance certificate No. 18/2/88).

As both tetanus and phaeochromocytomas are relatively uncommon conditions it has taken several years to compile the clinical material necessary for this thesis. It has also involved the co-operation of a number of my colleagues to whom I wish to express my thanks. Firstly, I would like to thank Dr. Randall C. Cork of Tucson, Arizona, whose statistical advice on the animal studies section of the thesis was invaluable. Secondly, I would like to thank my clinical colleagues whose co-operation enabled me to collect the clinical material reported. In particular I would like to thank Mr. R. Dent, Dr. K.R.L. Huddle, Dr. A. Manell and Dr. M. Plant, whose interest and enthusiasm helped me to gather large series of patients with phaeochromocytomas. Mr. J.F. White, Sr. J. Dennett, and Sr. G.M. Harlen of the Department of Anaesthesia, University of Zimbabwe, assisted with all of the animal studies, and much of the clinical work

and their help is gratefully acknowledged. I am also grateful to Professor G. Harrison and Professor C. Rosendorf for their advice and suggestions. Finally I would like to thank a number of people whose enthusiastic assistance enabled me to produce this document. In particular I would like to thank Mrs. Rita Mendelson who helped with much of the transcribing of original publications into the thesis. In addition I wish to record my gratitude to Mrs. S. King who assisted with the production of several of the computer generated illustrations and Mrs. S. Green whose secretarial assistance has proved invaluable. As a concluding note I would like to comment that this thesis has been produced using a desk-top publishing package and I would like to thank Mr. N. Dennett of the Department of Anaesthetics of the University of the Witwatersrand for his assistance in running the programme. The entire processing of this document was my own work.

Several published articles have arisen from this thesis. They are as follows:

1.James, MFM; Cork, RC; Dennett JE. Cardiovascular effects of magnesium sulphate in the baboon; Magnesium 1987 6: 314-324

2. James, MFM; Cork, RC; Harlen, GM; White JF. Interactions of adrenalin and magnesium on the cardiovascular system of the baboon. Magnesium 1988 7: 37-43

3. James, MFM; Manson EDM. The use of magnesium sulphate infusion in the management of very severe tetanus. Intensive Care Medicine 1985 11: 5-12

4.James, MFM. Magnesium sulphate in phaeochromocytoma. Anesthesiology 1985 62: 188-189

5. James MFM, Huddle KRL, Owen AD, van der Veen BW. Use of magnesium sulphate in the anaesthetic management of phaeochromocytoma in pregnancy. Canadian Journal of Anaesthesia 1988 35: 178-182.

6. James, MFM. Magnesium sulphate in the anaesthetic management of phaeochromocytoma - a report of 17 anaesthetics. British Journal of Anaesthesia 1989 62: 616-623.

7. James, MFM, Beer, RE. Inhibition of catecholamine release at intubation using magnesium sulphate. Anesthesia and Analgesia 1989 68: 772-776.

8. James, MFM. Magnesium in anaesthesia. In: Zorab JSM (Ed) Lectures in Anaesthesiology 1988/1, Blackwell Scientific Publications, London pp 63-78.

9. Lipman, J; James, MFM; Erskine, J; Plitt, ML; Eidelman, J; Esser, JD. Autonomic dysfunction in severe tetanus : magnesium sulphate as an adjunct in deep sedation. Critical Care Medicine 1987 15: 987-988.

1. Introduction

Magnesium has been an important substance in biologic evolution since the process first began. Present in large quantities in the primordial seas, the ion appears to have acquired a central role early in the evolutionary process since almost all reactions involved in fundamental cell processes such as protein biosynthesis and anaerobic energy production are magnesium dependent (Aikawa, 1981). The ion is also known to catalyze many crucial prebiotic condensation reactions. Despite the central importance of these processes, magnesium has an even more fundamental role than this in the genesis of life on this planet. Central to all forms of life is the mechanism whereby the energy of the sun is captured and converted into chemical energy in the process of photosynthesis. Some three billion years ago, the porphyrin ring, the basic structure of such vital substances such as haemoglobin and the cytochromes, had been synthesized. The incorporation of magnesium in the centre of this molecule, resulted in the green pigment chlorophyll. This structure, which produces carbohydrate by the reduction of carbon dioxide with the liberation of oxygen using solar energy, is responsible for the large quantities of oxygen that has made life in its present form possible on this planet. Whilst other metals can be incorporated into the porphyrin ring, magnesium appears to offer

the best combination of photochemical activity and molecular stability. In a study of the reasons why various metals play their highly selective roles in biochemical processes, Fuhrhop and Mauzerall (1969) concluded "if the aim of the biological system is minimum redox potential combined with maximal stability in a protonic solvent, then magnesium is a good mini-max solution to these requirements".

1.1 The Metabolic Significance of Magnesium

The emergence of compounds with high energy bonds from which energy could be readily released such as adenosine triphosphate completed the chain of energy utilization from the sun to the intracellular spaces of cells. The process of oxidative phosphorylation in which energy stored in carbon compounds is released and bound to ATP is the essential step which enables the aerobic cell to harness the energy of oxidation. Magnesium is the main catalyst involved in oxidative phosphorylation and is the essential cofactor without which ATP cannot function. *Wherever ATP exists, there is an obligatory need for magnesium* (Aikawa,1981). In fact, virtually all enzymatic reactions in which phosphate-containing compounds play a role, and thus all biological energy-producing processes, are dependent on magnesium for activation (Ebel & Gunther, 1980). Over 300 other enzyme systems are dependent on magnesium for activation including those involved in protein synthesis,

carbohydrate metabolism, DNA and RNA metabolism and regulation of intracellular electrolyte content (Wacker & Parisi, 1968; Ebel & Gunther, 1980; Olhaberry et al, 1983 a & b). So extensive is the involvement of magnesium in cellular physiology that it has been suggested that the ion be given serious consideration as a pervasive regulator of intracellular responses (Vidair & Rubin, 1981). In his extensive review of the biochemical role of magnesium Wacker (1980) concluded that "all cells require it for the completion of major metabolic functions, including, for example, photosynthesis, oxidative phosphorylation, nerve conduction, muscle contraction, membrane transport, and nucleic acid and protein synthesis".

1.2 Assessment of Magnesium Status

Despite this vital role in biochemical processes, magnesium has received scant attention, and it is only relatively recently that its importance in human biology has become apparent. Part of the explanation for this is that magnesium is difficult to measure accurately, and it is only since the development of atomic absorption spectrophotometry (Walsh, 1955; Wacker and Vallee 1964, Wacker, 1980) that simple and accurate methods of measurement of the ion have been available. Durlach has recently reviewed the application of this technique to the measurement of magnesium levels in various tissues (Durlach, 1988). There is considerable controversy as to the lower level at which hypomagnesaemia

can be said to exist, with quoted laboratory lower limits ranging from 0.65 to 0.9 mmol/l. The general consensus appears to centre around a value of 0.75 mmol/l, with an upper limit of 1.1 - 1.3 mmol/l, and a mean of 0.88 mmol/l although there is much debate as to whether serum levels are of any value in predicting total body magnesium states (See Durlach, 1988 for a review). It is generally felt that serum magnesium values are a relatively poor guide to the overall magnesium status in the body and that significant deficits can exist in company with a relatively normal serum value. However, there is no clear cut agreement as to which measurement can be said to be superior, with various claims being made for red cell magnesium, leukocyte magnesium and muscle biopsy as the best guides (Lim et al, 1969), with magnesium load testing being regarded as the only absolute method of detecting whole body magnesium deficits (Seelig, 1980). However, as magnesium penetrates cells with difficulty, it is generally accepted that serum magnesium levels are a satisfactory index of the therapeutic level, and thus these levels will be used throughout this study.

The homeostatic mechanisms which control total body magnesium are beyond the scope of this review, but the interested reader is referred to Wacker (1969), Seelig (1980), Ebel & Gunther (1980), Durlach & Durlach (1984) and Durlach (1988). It is, however, worth noting that a number of factors of relevance to anaesthetists may deplete body stores of magnesium. These include surgery (Heaton, 1964; Sawyer et al, 1970; Henzel et al, 1967), possibly on the basis of aldosterone release (Horton & Biglieri, 1962), catecholamine excess (Whyte et al, 1987; Joburn et al, 1985; Rayssiguer, 1977), diuretics (vide infra) and

emotional stress (Henrotte, 1986). Anaesthetists ought, therefore, to be aware of this problem, and the hazards which it may provoke (see Whang, 1984; Aldrete, 1987; Gambling et al, 1988; James, 1988 for reviews).

1.3 Interactions with Calcium and Potassium

Calcium exerts a nearly universal role in stimulus-response coupling (Gevers, 1981; Rasmussen, 1986 a & b), and particularly in the communication between excitable cells through the release of neurotransmitter substances (Carafoli & Penniston, 1985). It has been known since the beginning of this century that magnesium can antagonize many of the actions of calcium (Meltzer & Auer, 1908) and it does so by competing with calcium at various sites. Magnesium inhibits the release of calcium from endoplasmic reticular storage sites, notably the sarcoplasmic reticulum in skeletal and cardiac muscle (Dunnett & Naylor, 1978; Vierling et al, 1978; Meissner & Henderson, 1987). The ion also regulates cytosolic calcium levels by enhancing calcium uptake by the sarcoplasmic reticulum (Stephenson & Podolsky, 1977) and activating ATPase-dependent pumps which extrude calcium from the intracellular space. In addition, magnesium competes with calcium for binding sites on troponin C and calmodulin (Podolsky & Constantin,1964; Potter et al, 1976, 1981). Furthermore, and perhaps most importantly from the anaesthetic viewpoint, magnesium competes with calcium for membrane channels (Jenkinson,1957)

and consequently can regulate the ease of ingress of calcium to the intracellular space. As a result of this multiplicity of actions, magnesium has been described as the physiological calcium antagonist (Iseri & French, 1984; Levine & Coburn, 1984) which can, and does, modify many calcium-mediated responses. This ability of magnesium to regulate calcium dependent processes has important physiological and pharmacological consequences.

Magnesium is a vital regulator of intracellular potassium stores, inhibiting efflux and stimulating active transport of potassium into the cell (Bara & Guiet-Bara, 1984). Depletion of intracellular magnesium decreases the activity of Na^+/K^+-ATPase and increases potassium efflux from the intracellular space (Shine & Douglas, 1974; Dorderick et al, 1976; Shine, 1979; Whang & Welt, 1963). Low serum potassium levels accompanied by magnesium deficits can only be corrected with prior replacement of magnesium (Dyckner & Wester, 1984) and skeletal potassium is similarly magnesium dependent (Dyckner & Wester, 1978; Whang & Welt, 1963). Muscle potassium content correlates directly with muscle magnesium levels and intracellular magnesium/potassium deficiency results in down-regulation of the sodium-potassium pumps (Dørup et al, 1988).

1.4 Magnesium in the Central Nervous System

In the central nervous system (CNS), the magnesium level of the cerebrospinal fluid (CSF) is tightly controlled by an active transport mechanism which not only

maintains the CSF above normal plasma levels, but also appears to prevent significant rises in CSF magnesium in the face of hypermagnesaemia (Pritchard, 1955; Chutkow, 1981). Whilst the exact roles of calcium and magnesium in the exocytosis of potential CNS neurotransmitter substances have not been well worked out, there is some data to indicate that competition between calcium and magnesium regulates the release of certain putative neurotransmitters such as acetylcholine, glutamate, aspartate and gamma aminobutyrate (Blioch et al, 1968; Chutkow, 1981). Clark and Roman (1980) showed that magnesium can inhibit the sodium-mediated release of calcium from brain mitochondria, and this may provide a mechanism whereby magnesium may contribute to the control of neuronal function. A central role for magnesium in the regulation of adenosine receptors has also been suggested (Cooper et al, 1984), and magnesium may affect central opiate receptor binding (Sadee et al, 1982). In the face of sustained hypomagnesaemia the active transport mechanisms for magnesium fail, and a fall in CSF magnesium results. Magnesium deficiency is associated with a variety of CNS disorders including apathy, anorexia, nystagmus, vertigo and psychiatric abnormalities (Vallee et al, 1960; Fishman 1965; Hanna 1961; Hanna et al, 1960), and ultimately coma and convulsions (Paunier et al, 1968; Berkelhammer & Bear, 1985; Matthey et al, 1986; Ravindran & Correlli, 1987). Alcohol depletes the body of magnesium and hypomagnesaemia has been suggested as a factor which may contribute to the aetiology of delirium tremens (Milner & Johnson, 1965).

1.5 Magnesium and the Peripheral Nervous System

Peripherally, the role of magnesium in nervous system function is more clearly established. Magnesium is necessary for axonal stability, and can substitute for calcium in this role (Frankenhause & Meves, 1958). Hypomagnesaemia is associated with tetany even in the face of normal calcium levels and normal acid-base states (Wacker et al, 1962; Wilkinson et al, 1986; James & Wright, 1986). Whilst magnesium can produce direct suppression of axonal transmission, the levels of magnesium required to do this are so great as to have no clinical significance (Mordes & Wacker, 1978), and this action will not be further considered. It has been known since the end of the last century that calcium was essential for the contraction of skeletal muscle in response to afferent nerve stimulation and later investigators have shown that the role of calcium was to trigger the release of acetylcholine in response to pre-synaptic denervation (Llinas, 1982; Rubin, 1970; Landau, 1969; Boullin, 1967). The release of acetylcholine at the motor end-plate is not only calcium dependent but can be antagonized by magnesium, and there is a direct competition between extracellular calcium and magnesium for the facilitation or inhibition of acetylcholine release at both the motor end plate and in autonomic ganglia (Wacker, 1980; Del Castillo & Engbaek, 1954; Del Castillo & Katz, 1954; Hutter & Kostial, 1954; Hubbard et al, 1968; Livingston & Wacker, 1971 & 1976; Mordes & Wacker, 1978). Intracellular magnesium does not appear to exert this effect, presumably because the competition between calcium and magnesium is for transmembrane transfer (Kharash et al, 1981). Similarly, the release of

adrenaline and noradrenaline from the adrenal gland and at adrenergic nerve terminals is also calcium dependent (Rubin, 1970; Rasmussen, 1986 a & b; Knight & Baker, 1982). Low magnesium concentrations augment catecholamine release from adrenergic granules in response to direct stimulation (Baker & Rink, 1975; Douglas & Rubin, 1963) and hypermagnesaemia inhibits this function at levels readily obtained in clinical practice (Birmingham et al, 1960; Boullin, 1967; Kirpekar & Misu, 1967; Chutkow, 1981; Burn & Gibbons, 1964). Surprisingly, although this action of magnesium has been known for over 25 years, no clinical use has been made of this potentially valuable phenomenon.

1.6 Magnesium and the Cardiovascular System

The role of magnesium in regulating the cardiovascular system has been a major focus for study.

1.6.1 Myocardium: On the myocardium magnesium appears to play a calcium antagonistic role both at a membrane level and within the myocardial cell (Kerrick & Donaldson, 1975; Guillain, 1982). Myocardial cells have a high magnesium content which is tightly regulated into subcellular compartments resulting in a free cytosolic magnesium of approximately 1mmol/l (Ebel & Gunther, 1980; Polimeni & Page, 1973). Within the myocardium, magnesium plays a vital role in energy metabolism and in the regulation of calcium release from, and re-uptake by, sarcotubular stores (Hasselbach et al, 1981; Ford & Podolsky, 1972; Polimeni & Page, 1973). In the presence of magnesium depletion, ATP becomes

inactivated and oxidative phosphorylation is inhibited (Krasner, 1979). There is much current interest in the role of hypomagnesaemia and the susceptibility of the myocardium to ischaemic injury. Calcium has been suggested as an important component of the so-called reperfusion injury (McCord, 1985) and increases in free cytosolic myocardial calcium have been shown to occur following ischaemic damage (Bers, 1985; Nayler et al, 1979). There is an association between magnesium deficiency and an increased risk of sudden death due to coronary artery disease (Anderson et al, 1975; Johnson et al, 1979; Karppanen, 1981; Leary & Reyes, 1983 a & b; Chipperfield & Chipperfield, 1977; Leary, 1986). Myocardial losses of magnesium following ischaemic events have been widely reported (Boddy et al, 1978; Leary & Reyes, 1983 a & b; Page & Polimeni, 1972; Sheehan & Seelig, 1984; Abraham et al, 1977; Ebel & Gunther, 1983; Chipperfield & Chipperfield, 1973; Dyckner, 1980; Schroeder, 1960; Shen & Ennings, 1972; Johnson et al, 1979) and hypomagnesaemia is associated with an increased incidence of post-ischaemic arrhythmias, and a decreased tolerance of hypoxia (Chang et al, 1985; Borchgrevink et al, 1987; Solomon, 1984; Bloom, 1986). Magnesium appears to exert an important role in the genesis, severity and outcome of ischaemic heart disease (Seelig & Heggtveit, 1974). Hypomagnesaemia has also been described as a common causative factor in arrhythmias of many other types (Loeb et al, 1968; Krasner et al, 1981; Laban & Charbon, 1986; Eisenberg, 1986), particularly in association with the use of diuretics and digoxin (Iseri & French, 1984; Chadda et al, 1968 & 1972; Burch & Giles, 1977; Fisher & Abrams, 1977; Rude & Singer, 1981; Hollifield, 1984; DeCarli et al, 1986; Schipperheyn, 1984). These arrhythmias may prove refractory to any therapy other than replacement of magnesium. Magnesium is a crucial regulator of potassium exchange across the myocardial sarcolemma, opposing efflux (Hearse et al, 1978; Sheehan & Seelig, 1984; Dyckner &

Wester, 1982) and increasing uptake of potassium into the cytosol (Vincent 1982; Dyckner & Wester, 1978 & 1979). A possible basis for this association between magnesium, potassium and digitalis sensitivity has been provided recently by the demonstration that magnesium and potassium deficiency in skeletal muscle results in down-regulation of sodium-potassium pumps, thus preventing the muscle from retaining potassium adequately (Dørup et al, 1988).

Magnesium has also been described as being a major regulator of coronary artery tone and hypomagnesaemia may worsen myocardial ischaemia by provoking coronary artery spasm (Vide infra). Magnesium deficiency may also worsen myocardial ischaemia by allowing ATP depletion (Borchgrevink et al, 1987). Stress is a major factor provoking magnesium loss (Sheehan & Seelig, 1984), probably at least partly due to the actions of catecholamines on lipolysis (Rayssiguier, 1977), and this may worsen the outcome following myocardial infarction. Magnesium deficiency can, of its own, aggravate the cardiovascular damage associated with stress and dietary magnesium supplementation may protect against this (Iseri et al, 1975; Classen, 1986). Magnesium deficiency has also been implicated in the arrhythmias associated with mitral valve prolapse (Galland et al, 1986; Frances et al, 1986) and those of the torsades de pointes type (Ramee, 1985).

The role of magnesium in myocardial contractility is unclear. There is some evidence that reducing magnesium levels may produce a loss of myocardial ATP and consequently a reduction in myocardial contractility (Skou et al, 1971), and that this may add to the cardiac failure following ischaemic injury (Borchgrevink et al, 1987). Magnesium levels were noted to be low in association with cardiac failure (Wilkins & Cullen,

1933; Iseri et al, 1952). Histological damage associated with magnesium deficiency has been described by many authors. Hypomagnesaemia renders the myocardium more susceptible to catecholamine-induced injury (Vormann et al, 1983), and has been associated with the development of cardiomyopathy (Kurnik et al, 1988; Bloom, 1986; Altura & Altura, 1986; see Seelig, 1980 for a review). Magnesium is essential for the inotropic action of the catecholamines, and even high levels of extracellular magnesium do not block myocardial contractile responses to adrenaline (Paddle & Haugaard, 1971; Levin et al, 1976).

1.6.2 Blood Vessels: There is a wealth of evidence associating alterations in magnesium homeostasis with disordered vascular contractile states. It has been extensively shown that magnesium functions as a calcium antagonist on blood vessels and that magnesium directly alters baseline vascular tone (Haddy, 1960; Haddy et al, 1973; Haddy & Scott 1973; Frohlich et al, 1962; Altura & Altura, 1974; 1978 a & b; 1979; 1980; 1981 a, b & c; 1982 a, b, & c; 1984 a, b & c; 1985 a & b; Altura et al., 1983). Magnesium is also known to alter vascular responsiveness to a wide range of vasoconstrictor substances including noradrenaline, serotonin, vasopressin, angiotensin II,prostaglandins and potassium, hypermagnesaemia reducing and hypomagnesaemia increasing vascular responsiveness to these agents (Altura & Altura, 1976 a & b; 1978 b, 1981 b, 1982 a, 1984 a, b & c; Altura et al, 1976; Overbeck et al, 1969; Frohlich et al 1962; Viveros & Somjen, 1968; Carrier et al, 1976; Fujiwara et al, 1978; Turlapaty, 1981; Turlapaty & Altura, 1982 a & b; Nishio et al, 1985). In addition, magnesium appears to be essential for the vasodilatory action of a number of substances including beta-adrenergic agonists, sodium nitroprusside, calcium antagonists, prostaglandins and

adenosine, and elevations in extracellular magnesium levels potentiate the actions of these vasodilators (Altura & Altura, 1971, 1976 a & b, 1981 b, 1984 a & c, 1985 b; Altura, 1985; Askar & Mustafa, 1983; Foley, 1983; Turlapaty, 1981; Turlapaty & Altura, 1982 a & b; Arnold & Tackett, 1985; Thomas & Randall, 1985). Despite this clear-cut evidence of the importance of magnesium in regulating vascular tone, the relationship between magnesium and hypertension is less clear-cut than might be imagined. Hypomagnesaemia has been implicated as a causative factor in the genesis of atherosclerosis (Rayssiguier, 1984; Ryan & Brady, 1984) and in the development of hypertension (Resnick et al, 1983; Emerson et al, 1970) but the role of magnesium in the management of hypertension is uncertain. Lau & Oasa (1984) concluded that the role of disturbances in magnesium homeostasis, if any, has not been sufficiently defined in the pathogenesis and/or maintenance of hypertension to allow logical therapeutic decisions to be made. On the other hand Dyckner & Wester (1983) claimed that magnesium supplementation improved the response to antihypertensive medication, and Karppanen (1985) stated that increased dietary intakes of magnesium and potassium are safe and potentially beneficial in prevention and treatment of arterial hypertension. In an extensive dietary study, Joffres et al (1987) suggested that magnesium may have a role to play in hypertension, but his results were inconclusive.

1.7 Magnesium and the Respiratory System

The role of magnesium in respiratory function has not been extensively studied. At a peripheral level, magnesium is essential for oxidative phosphorylation (vide

supra) but little is known about the role of magnesium in lung mechanics. It has, however, been shown that pulmonary vessels demonstrate a similar response to magnesium to that shown by vessels in other parts of the body (Altura & Altura, 1981c). It has also been shown that bronchial smooth muscle reacts in a similar fashion to vascular smooth muscle to variations in magnesium levels (Haury, 1938). It was suggested by Haury (1940) that magnesium sulphate infusions may be beneficial in asthmatic patients and this effect has recently been confirmed (Okayama, 1987; Rolla et al, 1987). Magnesium deficiency decreases the stability of mast cells and increases histamine production, which may provide an explanation for this role in bronchial asthma (Bois, 1963). There is no evidence of a central ventilatory depressant action of magnesium and the only action of magnesium on ventilation appears to be as a result of its neuromuscular blocking properties.

1.8 Magnesium in Pregnancy

Magnesium plays a vital role in the physiology of normal pregnancy. Magnesium levels have been shown to decline during pregnancy reaching their lowest point at the end of the first trimester (De Jorge et al, 1965), and in her extensive review of magnesium deficiency, Seelig (1980) stated that magnesium intake during pregnancy was likely to be suboptimal. There is a growing body of evidence that magnesium deficiency is common in pregnancy and may

contribute towards placental insufficiency and to the development of pre-eclamptic toxaemia and to frank eclampsia (Flowers, 1965; McGanity, 1965; Seelig, 1980; Weaver, 1986). This apparent association between hypomagnesaemia and toxaemia of pregnancy has been strengthened by recent work which has suggested that the essential regulatory role of magnesium in prostaglandin synthesis may play a crucial role in the genesis of this syndrome when magnesium is deficient (Watson et al, 1986). It has also been shown that magnesium deficiency can produce umbilical artery spasm and that this may contribute to foetal growth retardation as well having a possible causative part to play in the development of pre-eclamptic toxaemia (Altura et al, 1983). A recent study has suggested that magnesium supplementation during pregnancy can reduce maternal morbidity and improve foetal outcome, but the study was too small and non-specific to indicate any effect on the development of pre-eclampsia (Spatling & Spatling, 1988).

1.9 Magnesium and Other Organ Systems

Magnesium appears to play an important role in the functioning of various other organ systems. Magnesium is an important regulator of gastrointestinal smooth muscle and hypomagnesaemia has been associated with dysphagia (Hamed & Lindeman, 1978; Flink, 1978).

Renal function is also critically dependent on magnesium and magnesium deficiency has been associated with nephrocalcinosis and tubular damage (Leder, 1980; see Seelig, 1980 for an extensive review). Diuretics which result in potassium loss also produce magnesium depletion (Duarte, 1968; Dyckner & Wester, 1979; Reyes & Leary, 1982, 1984 a & b; Reyes et al, 1984; Leary, 1987). Magnesium has also been shown to be essential for normal bone development and may contribute to osteosclerosis and abnormal vitamin D metabolism. Magnesium appears to be necessary for normal functioning of vitamin D (see Seelig, 1980 for a review). Magnesium is necessary for normal carbohydrate metabolism and is an important coherent controller of glycolysis and the Krebs cycle (Garfinkel & Garfinkel, 1985). Magnesium deficiency inhibits insulin secretion and results in an impaired glucose tolerance curve (Durlach & Collery, 1984; Legrand et al, 1987; Thomas, 1977). As diabetes itself may cause losses of magnesium, the ion may be of crucial importance in diabetic patients. Magnesium may also be of importance in regulating thyroid function and magnesium deficiency may accompany thyroid dysfunction (Rizek et al, 1965, 1966).

It can thus be seen that magnesium plays a vast and crucial role in most of the biochemical processes essential to life. Consequently, magnesium deficiency is associated with an array of well defined syndromes, (see table 1.1) which are currently being extensively studied, and their importance quantified. Only 30 years ago magnesium was regarded as merely a trace element. It is now being

realized that this ion is one of the most important regulators of biochemical activity.

Table 1.1

Alterations in potassium, calcium and phosphate balance	
	Hypokalemia
	Hypocalcemia
	Hypophosphatemia
Neuropsychiatric manifestations	
	Personality changes (including apathy, depression, agitation, confusion, delirium)
	Seizures
	Vertigo, nystagmus, ataxia, coma, movement disorders (rarely)
Neuromuscular manifestations	
	Chvostek's and Trousseau's signs
	Muscle twitching and tremor
	Spontaneous carpopedal spasms
	Muscle cramps
	Muscle (including respiratory) weakness
	Paresthesia
Cardiac manifestations	
	Predisposition to digoxin-mediated arrhythmias
	Electrocardiographic changes (including prolonged (QT interval)
	Cardiac arrhythmias (including ventricular premature beats, ventricular tachycardia, torsades de pointes, ventricular fibrillation)
Alterations in vascular tone and blood pressure	
	Increased vascular smooth muscle tone and reactivity, leading to spasm
	Increased blood pressure

Table 1.1 Manifestations of magnesium deficiency

2. Clinical Consequences of Hypermagnesaemia

Raised serum magnesium levels are rare in clinical medicine as the ion is relatively poorly absorbed from the gastrointestinal tract (Agus, 1982; Aikawa, 1980) and the renal elimination of any excess magnesium is extremely rapid (Barker et al, 1959; Chesley & Tepper, 1958; Pritchard, 1955, Aikawa et al, 1968; Quamme, 1986), excretion of a magnesium load by the kidney being complete within 4-8 hours (Smith et al, 1962). Hypermagnesaemia was first reported in association with renal failure by Salveson and Linder (1923), and it is now well recognized that impaired renal function is the most common prerequisite for the development of hypermagnesaemia (Wacker & Parisi, 1968). In order to produce a significant increase in serum magnesium levels for therapeutic purposes in the presence of normal renal function, it is necessary to administer the agent intravenously or intramuscularly. Magnesium has a moderately large volume of distribution which approximates to the volume of the extracellular space (Chesley, 1979) and this, coupled with the rapid renal elimination, means that large loading doses and continuous infusions or intramuscular injections are necessary to maintain serum magnesium levels in the generally accepted therapeutic range of 2-4 mmol/l. Despite the extensive therapeutic use to which

magnesium has been put, there is a surprising amount of controversy regarding its precise mechanisms of action.

Hypermagnesaemia affects almost every organ system in the body.

2.1 Central Nervous System

Until recently it was widely assumed that magnesium is a powerful central sedative and may even have anaesthetic properties (Meltzer & Auer, 1905 a & b, 1906a; Peck & Meltzer, 1916; Engbaek, 1952b; Aldrete et al, 1968, Fishman, 1965; Katzman, 1966; Crossland, 1971). Meltzer and Auer (1905 a & b, 1906a) described general anaesthesia, respiratory and cardiovascular depression, and reflex suppression which they ascribed to central effects of peripheral injections of magnesium salts, in particular depression of the medulla oblongata. When administered directly into the CSF by ventricular injection magnesium produces a sleep-like state (Feldberg, 1958; Feldberg & Sherwood, 1957). It is now known that magnesium penetrates the blood brain barrier extremely poorly and that its level in the CSF is tightly controlled, probably by an active transport mechanism (Chutkow, 1981). Even in cases where high levels of serum magnesium have been maintained for several days CSF magnesium has been found to be only marginally above normal (Pritchard,

1955). Therefore, since magnesium penetrates the brain with such difficulty, several authors have queried whether parenterally administered magnesium can produce significant sedative effects (Berns & Kollmeyer, 1976; Guthrie & Ryan, 1910; Rubin et al, 1943). Somjen et al (1966) demonstrated in three subjects that full consciousness was maintained at serum magnesium levels in excess of 14 mEq/l provided that ventilation was artificially supported. Mordes & Wacker (1978) concluded that "magnesium is not an anaesthetic nor even a major central nervous system depressant". More recently, however, Thurneau et al (1987) described a small but highly statistically significant increase in CSF magnesium concentrations following magnesium treatment in pre-eclamptic patients. They suggested that this small increase might be sufficient to explain some of the anticonvulsant actions of the agent. Thompson et al (1988) described a reduction in minimum alveolar concentration of halothane in magnesium treated rats which they ascribed to a central effect of the ion.

2.2 Peripheral Nervous System

Magnesium primarily affects the peripheral nerves by interfering with the release of neurotransmitter substances at all synaptic junctions.

2.2.1 Motor End Plate: It has been known since the middle of the 19th century that magnesium can exert a curare-like effect, and early this century it was shown that this action could be reversed by neostigmine (Joseph & Meltzer, 1910). It is now well documented that this effect is due to

pre-synaptic inhibition of acetylcholine release by competition with calcium for membrane channels on the pre-synaptic terminal (Engbaek, 1952 a & b; Del Castillo & Engbaek, 1954; Jenkinson & Engbaek, 1954; Hutter & Kostial, 1954; Jenkinson, 1957; Livingston & Wacker, 1971; Mordes & Wacker, 1978). As a result, magnesium will potentiate the action of the non-depolarising muscle relaxants (Ghonheim & Long, 1970; Giesecke et al., 1968; Morris & Giesecke, 1968; Sinatra et al, 1985). The interaction of magnesium with the depolarizing muscle relaxants is less clear-cut. Although it is generally assumed that magnesium prolongs the action of depolarizing relaxants as well as those of the non-depolarising group (Giesecke et al, 1968; Skaredoff et al, 1982), this is not invariable (Sinatra et al, 1985) and the interaction between magnesium and suxamethonium is much more complex than that with the competitive relaxants. Patients treated with magnesium sulphate do not demonstrate fasciculations (De Vore & Asrami, 1980). Whilst prolonged treatment with magnesium may prolong the duration of suxamethonium blockade, acute hypermagnesaemia does not (James et al, 1986). Baraka and Yazigi (1987) found no prolongation of the action of a single dose of suxamethonium in magnesium-treated pre-eclamptic mothers. It is possible that Ghonheim's in vitro study created an erroneous impression of prolongation of the action of suxamethonium due to washout of pseudocholinesterase from the preparation. Acute administration of magnesium sulphate prior to the use of suxamethonium appears to prevent the release of potassium provoked by the relaxant (Aldrete et al, 1970; James et al, 1986). To the present time, no clinical use has been made of these interactions, although the possibility exists that magnesium may reduce the incidence and severity of suxamethonium-induced muscle pains, and may make suxamethonium usable in those circumstance in which the risks of excessive potassium release currently make the relaxant contra-indicated.

2.2.2 Autonomic Nerve Terminals: Magnesium exerts a similar, although less well known, effect on autonomic ganglia (Hutter & Kostial, 1954; Stanbury, 1948) and on vagal nerve terminals (Kuriyama, 1964; Somjen & Baskerville, 1968) to that demonstrated at the motor end plate. Magnesium similarly inhibits the neurogenically mediated release of catecholamines from the adrenal gland and from adrenergic nerve terminals (Kirpekar & Misu, 1967; Bouillin, 1967; Douglas & Rubin, 1963; Burn & Gibbons, 1964; George & Leach, 1971).

2.3 Cardiovascular System

The complex interrelationships between magnesium and cardiac and vascular contractility have already been mentioned. Raised serum levels of magnesium ought to produce marked hypotension as a result of the negative inotropic action of the ion on the myocardium, the direct vasodilating properties of magnesium on blood vessels and the reduction in sympathetic drive which magnesium ought to produce. Clinically, however, evidence for magnesium induced hypotension is varied and conflicting. In early investigations, hypotension following the infusion of magnesium was noted in several studies using animal models (Meltzer & Auer, 1905b, 1906a; Hoff et al, 1939; Rubin et al, 1943; Lee et al, 1984). More recently, Maxwell et al (1965), Aldrete et al (1968) and McCubbin et al (1981) have also supported this observation in various intact animal models, whereas Dandavino et al (1977) using pregnant sheep, found only transient hypotension.

In humans, very conflicting results have been reported. Where hypermagnesaemia complicated renal failure, several authors have found that marked reductions in blood pressure occurred in association with raised serum magnesium levels (Blackfan & Hamilton, 1925; Randall et al, 1964; Alfrey et al, 1970), and there have been a number of other case reports of significant hypotension in association with hypermagnesaemia without renal failure (Boos, 1910; Moore & Wingo, 1942; Grantham et al, 1960; Mordes et al, 1975; Bourgeois et al, 1986; Prestley, 1912). Most investigators studying human volunteers have found some evidence of a reduction in blood pressure as a result of magnesium infusions but these changes have been generally minimal and of short duration (Kelly et al, 1960; Somjen et al, 1966; Winkler et al, 1942; Morl, 1978; Mroczek et al, 1977; Young & Weinstein, 1977). However, some authors have reported little, if any, cardiovascular effect even at high infusion rates of magnesium (Flowers et al, 1962; Kelly et al, 1960), although in both of these reports bolus doses appeared to produce a greater effect. Hypotension is not consistently produced by magnesium in the management of pregnancy-induced hypertension (Flowers et al, 1962; Pritchard et al, 1984; Pritchard & Pritchard, 1975), and consequently, magnesium has been described as a poor vasodilator (Scott et al, 1968; Morris & Assali, 1981).

2.3.1 Vascular Resistance: Clearly, magnesium can exert profound effects on vascular smooth muscle and has been shown to be an important regulator of blood vessel tone in a wide variety of tissues. The evidence for this was reviewed in the previous chapter. There is also extensive evidence of increased peripheral blood flow, regional vasodilatation and increased microcirculatory perfusion as a result of magnesium infusions

(Haury, 1939; Overbeck et al, 1969; Mroczek et al, 1977; Altura & Altura, 1985 a, b & c; Dandavino et al, 1977). In addition to its direct effects on the vessel wall, raised serum magnesium levels may also reduce peripheral vascular tone by a number of other mechanisms:

a) Central Nervous System. Although there is some evidence that direct administration of magnesium into the ventricular system may produce a reduction in the output of the vasomotor centre (Leusen, 1949), available data tend to argue against a major central role for the hypotensive effects of hypermagnesaemia (Lau & Oasa, 1984). The levels of CSF magnesium required to inhibit vasomotor centre function are very high (10 mmol/l) and it is extremely unlikely that peripheral administration of magnesium salts could increase CSF magnesium levels sufficiently to cause a significant alteration in vasomotor output. As has been discussed in the previous chapter, CSF magnesium is tightly controlled and little affected by alterations in magnesium levels of the blood.

b) Sympathetic Ganglia. Sympathetic blockade has been shown to occur in heart-lung preparations (Hutter & Kostial, 1954; Stanbury, 1948) with elevations in the magnesium content of the perfusate, and it is possible that this effect may play a role in hypermagnesaemic hypotension (Mordes & Wacker, 1978). Against this is the fact that animals with a totally ablated central nervous system still produced a hypotensive response to magnesium injections (Hoppe & Emmerson, 1974; Haury, 1939) indicating that other mechanisms than just sympathetic control must be involved.

c) Catecholamines. As has been reviewed above, there is no doubt that levels of hypermagnesaemia commonly used in clinical practice can inhibit the release of catecholamines from both the adrenal medulla and from peripheral nerve terminals. However, this effect had until now only

been demonstrated on isolated tissue and there is currently no evidence to suggest that this action of magnesium plays a significant role in hypermagnesaemic hypotension. Under normal circumstances, circulating catecholamines exert little regulatory effect on resting vascular tone (Cryer, 1980) and it seems unlikely that this mechanism plays a major role in the reduction of vascular tone caused by magnesium infusions under normal circumstances. However, as none of the studies on magnesium-induced hypotension has considered the possible effect that the magnesium infusion may have had on catecholamine levels in the experimental model, this remains speculative. Magnesium may also interfere with the peripheral action of catecholamines. Noradrenaline has been reported as being ineffective in severe human hypermagnesaemic shock (Mordes et al, 1975). Diminished responsiveness to vasoconstrictor catecholamines has been demonstrated on perfused rat mesentery (George & Leach, 1971; Suzuki et al, 1982), in the forelimb of dogs (Haddy, 1960) and on vessels in the ear of rabbits (Farmer & Campbell, 1967). In addition, several authors have shown the dependence of vasoconstrictor agents on normal serum magnesium levels (vide supra). All of these studies have looked at isolated tissue or limited areas, and there is no data available on the effect that magnesium may have on catecholamine-induced vascular responses in the intact subject. Magnesium ought to have useful anti-adrenergic properties, but this possibility awaits further study.

When all of these factors are considered, there can be little doubt that magnesium produces peripheral vasodilatation despite the fact that the hypotensive effect of parenteral administration is inconsistent.

2.3.1 Myocardium: Myocardial depression may or may not play a part in magnesium induced hypotension. Because magnesium is a calcium antagonist, increased levels of magnesium ought to produce a reduction in myocardial contractile force, and indeed, isolated skinned fibres of ventricular muscle do show a reduction in tension development in the presence of elevated magnesium levels (Donaldson & Kerrick, 1978; Fabiato & Fabiato, 1975). There is generally assumed to be little change in the cardiac action potential produced by high levels of magnesium in isolated heart perfusates (Hoffman & Suckling, 1956). Recent work has, however, questioned this assumption (Katholi et al, 1979; Kraft et al, 1980; Moe, 1984) and Altura (1985) believes that magnesium inhibits the calcium dependent inward current, which may help to explain its anti-arrhythmic effects particularly in the presence of ischaemia. Using an isolated heart/lung preparation, Stanbury and Farah (1950) found a decreased stroke volume and increased right and left atrial pressures proportionate to the extracellular magnesium level. On the isolated heart, increased concentrations of extracellular magnesium ion produces marked depression of contractile force (Paddle & Haugaard, 1971; Shine & Douglas, 1974 & 1975; Kovacs & O'Donnell, 1975; Levin et al, 1976). Wallis et al (1986) reported severe myocardial depression with combinations of magnesium and diltiazem, but not with magnesium alone. In all of the above studies, rather high levels of magnesium (10 - 40 mmol/l) were used, and this makes it very difficult to extrapolate the data to the clinical setting in which serum magnesium levels are unlikely to exceed 4-6mmol/l. In the intact animal, the evidence for cardiac depression by clinically useful levels of raised magnesium is less clear. Various studies in both animals and humans have shown some evidence of a negative inotropic action, principally a raised central venous pressure (Szekely, 1945; Aldrete et al, 1968; Bristow et al, 1977 a & b; Critelli et al, 1977; Mori, 1978; Charbon 1983). However, other studies

have failed to demonstrate any myocardial depression and several authors have found an increase in cardiac output associated with raised serum magnesium levels (Cotton et al, 1984; Dandavino et al, 1977; Maxwell et al, 1965; Mroczek et al, 1977). Mordes & Wacker (1978) concluded that some form of myocardial compromise was probably necessary for the maintenance of hypermagnesaemic hypotension and expressed the opinion that more research on the haemodynamic consequences of hypermagnesaemia was necessary. As it appears that clinically employed levels of serum magnesium do not produce significant myocardial depression, sustained, or even increased cardiac output may be the explanation for the minimal hypotensive effect of magnesium infusions despite significant vasodilatation.

The inherent electrical rhythmicity of the heart seems particularly resistant to the effects of magnesium, with cardiac arrest only occurring when the serum magnesium levels are extremely high - above 12.5 mmol/l - levels not normally attainable in the clinical situation. It is generally accepted that excess magnesium in the range of 2.5 - 5 mmol/l produces prolongation of the PR and QT intervals (Wacker & Parisi, 1968; Wacker, 1980) as a result of the reports of Miller and Van Dellen (1938 & 1941) and Smith et al (1939). However, other reports have failed to show significant conduction defects following magnesium administration, provided the calcium level is maintained (Young & Weinstein, 1977; Surawicz et al, 1961) or that there are no major changes in the serum potassium level (Watanabe & Dreyfus, 1972). DiCarlo et al (1986) studying human volunteers found an increase in the PR interval with rapid bolus injection of $MgSO_4$, but no change in the QT or QTc intervals. On the isolated heart, magnesium produces a bradycardia (Stanbury, 1948; Stanbury & Farah,1950; Haury, 1939), and there have been clinical reports of bradycardia in association with

hypermagnesaemia and renal failure. Berns and Kollmeyer (1976) described a patient in whom the use of magnesium containing antacids was associated with junctional bradycardias at relatively low levels of serum magnesium (2.25 - 2.4 mmol/l). On the other hand, Enselberg et al (1950) found an initial increase followed by a slight slowing of heart rate with rapid intravenous injection of magnesium sulphate, and DiCarlo et al (1986), Winkler et al (1942) and Szekley (1946) found no change in heart rate following magnesium infusion. Cardiorespiratory arrest has been described following magnesium infusion (Richards et al, 1985) but it is likely that respiratory arrest due to neuromuscular pararalysis was the precipitating event. In normal subjects, there may be an increase in heart rate with increased serum magnesium levels as a result of a reduction in vagal tone due to the inhibition of acetylcholine release which can result from increased magnesium (Somjen et al, 1966; Somjen & Baskerville, 1968, Toda & West, 1967). Magnesium infusions increase both atrial and ventricular refractory periods, and this may account for its general anti-arrhythmic action.

2.4 Genitourinary System

The effects of hypermagnesaemia on renal function are unclear. Several authors have described a reduction in glomerular filtration rate in association with hypermagnesaemia (de Alvarez & Richards, 1952; Hammarsten et al, 1957; Heller et al, 1953), whereas Kelly et al (1960) found an increase in renal plasma flow. Altura & Altura (1985b) have described renal vasodilating effects of magnesium and vasoconstriction resulting from hypomagnesaemia. A

magnesium load is rapidly filtered through the kidneys, and this might be expected to exert a diuretic effect. There appears to be a tubular maximum for magnesium which is close to the upper limit normal serum magnesium values, and therefore any excess magnesium filtered through the glomerulus is rapidly excreted, whereas, at normal serum magnesium values, 95-99% of the filtered load is reabsorbed (Aikawa, 1981). Duarte (1968) suggested the possibility of an active tubular excretory mechanism for magnesium but this has not been confirmed (Roy, 1985). Hypermagnesaemia reduces the tubular reabsorption of both water and sodium (DiBona & Sawin, 1971) which would also be likely to have a diuretic effect. As a result of the renal vasodilatation, the reduced reabsorption of sodium and water, and the rapid excretion of magnesium itself, magnesium infusions ought to produce a brisk diuresis, but there is very little data on the action of infused magnesium on renal output. Calcium excretion is also increased by increased urinary excretion of magnesium (Kelly et al, 1960), but is unclear whether or not this is due to intra-renal effects or to the negative feed-back loop which exists between parathyroid hormone release and serum magnesium levels (Dawson 1984; Massry et al, 1970; Zumkley & Lehnert, 1984). Certainly, prolonged elevations in serum magnesium may produce a reduction in serum calcium levels, but which mechanisms predominate is not well established.

The use of magnesium in the management of pre-eclamptic toxaemia will be discussed in more detail later, but there are several effects of

hypermagnesaemia on the female reproductive system which are pertinent to the present discussion. Although it generally assumed that magnesium infusions do not interfere with normal labour (Hutchinson et al, 1964), magnesium can reduce uterine tone (Miller et al, 1982; Reece et al, 1984). Magnesium also vasodilates the uterine blood vessels (Altura et al, 1983) and increases uterine blood flow without reducing systemic arterial pressure (Dandavino et al, 1977). Although magnesium does cross the placenta readily, the effects on the neonate are difficult to distinguish from those of pre-eclampsia. Stone & Pritchard (1970) noted no ill effects in a large series of infants born to toxaemic mothers who had been given magnesium, and Green et al (1983) were unable to demonstrate any relationship between serum magnesium levels in neonates and diminished neurobehavioural scores.

2.5 Endocrine Systems

Negative feed-back loops appear to exist between magnesium and catecholamines, parathyroid hormone, calcitonin and insulin (Durlach & Durlach, 1984). It is well known that sustained hypermagnesaemia can result in inhibition of parathyroid hormone release (Buckle et al, 1968; Gitelman et al, 1968; Massry et al, 1970; Sherwood et al, 1970) and possibly in reduced hormone receptor sensitivity (Slatopolsky et al, 1976), with consequent falls in serum calcium. In view of the evidence that magnesium deficiency worsens

diabetic control and reduces insulin sensitivity, it might be anticipated that hypermagnesaemia might increase insulin sensitivity and reduce blood sugar. There is, however, no information on this subject. Deliberate hypermagnesaemia has been used occasionally in the treatment of thyrotoxicosis, but it has been shown that magnesium infusions have no consistent influence on the peripheral actions of thyroid hormone (Wiswell, 1961).

2.6 Coagulation of Blood

An increase in the magnesium/calcium ratio will increase clotting times (Genville & Lehman, 1944) and reduce platelet adhesiveness (Davies et al, 1968; Hughes & Tonks, 1965; Rayssiguier, 1986). It has been suggested that magnesium may increase thromboresistance in vascular endothelium by increasing the production of PGI_2 (Watson et al, 1986), but there is little clinical evidence that hypermagnesaemia significantly alters coagulation. Such reports as there are relate to abnormalities of coagulation with hypermagnesaemia compounding renal failure where the action of magnesium is difficult to determine with any precision. It seems significant that coagulation abnormalities have not been reported in obstetric patients treated with magnesium infusions, despite, or perhaps because of, the fact that

disseminated intravascular coagulopathy is frequently associated with pre-eclampsia.

Hypermagnesaemia has a wide variety of actions, many of which have been imperfectly investigated (see table 2.1). Several aspects of the action of this agent are potentially of great clinical interest, particularly the unique capability of magnesium to inhibit the release of catecholamines, the anti-adrenergic effects of the agent, and its value as a vasodilator and anti-arrhythmic, in addition to its interaction with neuromuscular blocking drugs. If these actions could be confirmed in clinical circumstances, then magnesium would appear to offer a useful addition to the anaesthetic armamentarium.

Table 2.1

Central Nervous System
- Cerebral vasodilatation
- Minimal central sedation

Peripheral Nervous System
- Inhibition of transmitter release
  - Motor end plate - paralysis
  - Autonomic Nerve terminals

Cardiovascular System
- Possible myocardial depression
- Possible alterations in electrical conduction
- General and regional vasodilatation
- Moderate hypotension

Genitourinary System
- Relaxes pregnant uterus
- Vasodilates uterine blood vessels

Metabolism
- Inhibits parathyroid hormone and lowers serum calcium
- May improve diabetic control

Coagulation
- Mild anticoagulant effect

Table 2.1 Effects of Hypermagnesaemia

3. Therapeutic Use of Magnesium

Magnesium has been used as a therapeutic agent for centuries. The first medicinal use of this drug was described in Renaissance Italy when magnesium salts were employed for their aperient properties. The medicinal properties of the waters of the Epsom Spa were discovered in 1618 and accounted in large measure for the popularity of Epsom as a resort. According to the *Encyclopedia Brittanica* magnesium sulphate was isolated from Epsom water by Grew in 1695 and Sir Humphrey Davy first isolated the metal in 1808. In the early 19th Century oral administration of magnesium oxide was used to treat patients with urinary calculi and by the middle of that century it had been shown that intravenous magnesium sulphate given to animals mimicked curare (Wacker, 1980). With the possible exception of the treatment of urinary calculi, where the object is to increase the urinary content of magnesium, orally administered magnesium is more properly regarded as a dietary supplement rather than as a therapeutic agent. This is because it is impossible in normal circumstances to achieve any significant increase in serum magnesium levels by oral administration of the agent because of the rapid renal elimination. Therefore, although oral administration of magnesium salts has been widely advocated in a variety of conditions in which magnesium deficiency is likely to

occur, this review is confined to the parenteral administration of magnesium salts to achieve deliberate hypermagnesaemia.

3.1 History of Magnesium Therapy

At the beginning of this century, several attempts were made to use parenteral magnesium sulphate as a therapeutic agent. Blake (1906) described the effects of magnesium sulphate administered by the intrathecal route. His review noted that magnesium sulphate injections produced profound muscle relaxation in most patients with a variable sensory block. The unpredictable nature of the block led him to doubt that intrathecal magnesium injections should be advocated for anaesthesia but the prolonged duration of effect prompted him to use this technique in the management of tetanus. He administered intrathecal magnesium sulphate to two patients suffering from the end stages of tetanus. In both cases the injections produced relief of symptoms for a variable period of time from four to twelve hours and one patient made a complete recovery. Blake also noted that if enough magnesium sulphate was given, and particularly if the patient was placed in a head down position, profound loss of consciousness could be produced by this route of administration. According to Meltzer (1916), a surgeon - Thedor Kocher - made a favourable report on the action of magnesium sulphate in tetanus and Meltzer himself reported the use of magnesium sulphate by intravenous, intraspinal and

subcutaneous injections. He asserted that "no other remedy is capable of relieving the furious symptoms [of tetanus] to such a satisfactory degree as do the injections of magnesium sulphate" (Meltzer, 1916). He included in this paper a report of one patient who received a total of 131 gms of magnesium sulphate parenterally over a seventeen day period with complete recovery. Meltzer and Auer reported studies on animals and humans in which they claimed to produce anaesthesia by intravenous and subcutaneous injections of magnesium sulphate (Meltzer & Auer, 1905 a & b, 1906 a & b). Peck and Meltzer (1916) described the performance of surgery on several patients in whom intravenous magnesium sulphate was the sole anaesthetic agent used. Meltzer also described the use of magnesium sulphate as an anticonvulsant when given by intrathecal injection (Meltzer & Auer, 1906b). Subsequently, there have been several other reports of the use of magnesium as an anticonvulsant (Blackfan & McKhann, 1931; Moore and Wingo, 1942; Winkler et al, 1942). However, this use of magnesium has now largely disappeared except for the use of magnesium sulphate in the treatment of pre-eclamptic toxaemia, probably because of the very poor levels of CSF magnesium that can be achieved by intravenous administration (vide supra). It seems most likely that the majority of the effects observed by early workers were due to a combination of peripheral neuromuscular inhibition and cerebral hypoxia secondary to respiratory insufficiency. In their review of the effects of excess magnesium Mordes and Wacker (1978) commented that the central anticonvulsant activity following peripheral administration of magnesium is unproven.

3.2 Pre-eclampsia and Eclampsia

Probably the most widely accepted use of magnesium sulphate has been the parenteral administration of this agent in the management of pre-eclamptic toxaemia. This form of therapy which was first introduced in the 1920's was popularized by the extensive work of Pritchard and his colleagues (Pritchard, 1955; Pritchard & Pritchard, 1975, Pritchard et al, 1984). In the United States this form of therapy is now standard practice but its use is controversial. In Britain it is widely assumed that magnesium has no anticonvulsant effect and produces purely peripheral control of convulsions (Crawford 1982), and even in centres where the use of magnesium is accepted there is a fierce debate over its mechanism of action. Sibai and others (1984) were unable to show any alteration in pre-convulsant EEG patterns in pre-eclamptic patients given magnesium infusions, and questioned the effectiveness of magnesium as an anticonvulsant. Donaldson (1986) has recently reviewed the evidence against magnesium exerting significant anticonvulsant actions and has queried its value in pre-eclampsia. Much of the controversy surrounding the role of magnesium in the management of pre-eclamptic toxaemia is due to the incomplete information available as to the pathogenesis of eclamptic convulsions and the influence of magnesium on the disease process. The cerebral pathology has been attributed, at least in part, to severe cerebral vasoconstriction (Pritchard, 1980). This theory neatly explains the probable role of magnesium in reversing the convulsions as magnesium is known to be a powerful cerebral vasodilator (Seelig et al, 1983; Altura & Altura, 1984) and would thus antagonize the

regional vasoconstriction and improve cerebral oxygenation. On the other hand, Donaldson (1986) attributes the cerebral pathology to endothelial injury and vasodilatation leading to local cerebral oedema. The evidence for this arises from post-mortem studies and its exact relevance to the clinical condition prior to a convulsion is unclear. If however, this were the case, magnesium would be expected to worsen cerebral oedema. There is no evidence that this occurs. It is possible that the local vascular injury allows penetration of magnesium into the damaged brain tissue, thus explaining the anticonvulsant effect (Borges & Gücer, 1978) There is clear evidence of the failure of magnesium to reduce blood pressure significantly. The studies that are available tend to suggest that the failure of magnesium infusions to produce hypotension in pre-eclampsia is primarily due to a compensatory increase in cardiac output but this is by no means established. No dose response curves for magnesium infusions exist and there is considerable controversy over the precise actions of magnesium on the cardiovascular system (vide supra).

More recently other authors have suggested that magnesium may play a role in genesis and management of pre-eclampsia by altering the production and activity of vasoactive substances. It has been shown that hypermagnesaemia increases the production of the vasodilator prostaglandin PGE_2 which may not only improve tissue perfusion in this condition but may also antagonize the hypercoagulability which is associated with pre-eclampsia (Watson et al, 1986). Fuentes and Goldkrand (1987) reported a reduction in the levels of angiotensin

converting enzyme in pregnant women with pre-eclampsia following the use of magnesium sulphate. Surprisingly, there are no controlled trials comparing sedative/vasodilator regimes with the results of magnesium therapy. The role of magnesium in the management of this potentially life-threatening condition therefore remains controversial.

Magnesium possesses tocolytic properties which potentiate the uterine relaxant properties of the ß-adrenergic stimulants (Osa & Ogasawara, 1979), and this has recently prompted investigation of the agent in the management of premature labour. Initial results have been promising (Miller et al, 1982; Reece et al, 1984) particularly in view of the fact that the use of magnesium appears to enhance foetal well-being (Reece et al, 1984) possibly on the basis of uterine vasodilatation (Suresh & Nelson, 1987).

3.3 Magnesium and Arrhythmias

In the last few years, interest has revived in the therapeutic potential of magnesium infusions and has focused on its anti-arrhythmic properties and its role as a calcium antagonist. Magnesium has been used as an anti-arrhythmic agent since the 1930's. In paroxysmal atrial tachycardia with ventricular extrasystoles magnesium appeared to have considerable beneficial effects

(Boyd & Sherf, 1943; Szekely, 1945; Op't Hof et al, 1980). The role of magnesium in digitalis intoxication is well established and the use of magnesium infusions for the management of digitalis-associated arrhythmias is widely accepted (Enselberg et al, 1950; Rude & Singer, 1981; Seller, 1971; Seller et al, 1970; Szekely & Wynne, 1951; DeCarli et al, 1985; Neff et al, 1972). As many of these reports focused on patients who were magnesium deficient it was unclear whether or not the beneficial effects noted were due to magnesium and potassium replacement particularly in the intracellular space (Watanabe & Dreyfus, 1972; Whang, 1986; Wills, 1986; Sheehan & Seelig, 1984) or whether this was a pharmacological effect of magnesium itself. Podell (1985) regarded the case for magnesium in the pathogenesis and treatment of arrhythmias as interesting but unproven. Recently, deliberate hypermagnesaemia has been suggested as being anti-arrhythmic in its own right even in patients who have normal serum magnesium levels (Enselberg et al, 1950; Ghani & Rabah, 1977; Iseri et al, 1983 & 1985; Iseri, 1986; Hayward & Zwerling, 1986; Zwerling 1987), and the mechanisms of action of magnesium on myocardial electrophysiology have been reviewed (DiCarlo et al, 1986; Dyckner & Wester, 1982; Ghani & Rabah, 1977; Shattock et al, 1987). Recent studies have shown that intravenous magnesium sulphate is extremely effective in terminating arrhythmias of the torsades de pointes type (Topol & Lerman, 1983; Tzivoni et al, 1984; Iseri, 1986). The arrhythmias associated with mitral valve prolapse have also been shown to respond to magnesium therapy (Frances et al, 1986; Galland et al, 1986). It has also been suggested that magnesium infusions may reverse

ventricular fibrillation due to hypothermia, or increase the likelihood of successful defibrillation (Buky, 1970).

3.4 Magnesium and Ischaemia

There has been much recent interest in the role of magnesium as a protective agent during periods of myocardial ischaemia. Harris et al (1953) showed that magnesium either as the sulphate or the chloride could suppress ventricular arrhythmias following myocardial infarctions. In the mid 1970's it was shown that the use of magnesium in cardioplegia infusates had a protective effect during ischaemic cardiac arrest (Hearse & Humphrey, 1975; Hearse et al, 1975, 1978, 1981), and it is has been demonstrated that magnesium can inhibit calcium influx into the sarcoplasmic reticulum (Koomen et al, 1983; Bers 1985). It was shown that the addition of 15mmol/l to the cardioplegia solution prevented potassium and magnesium efflux from and calcium influx into ischaemic cells resulting in fewer post-ischaemic arrhythmias and improved tension development. Döring & co-workers (1976) showed that magnesium-aspartate-procaine combinations provided both metabolic and structural protection during ischaemic arrests. Since then, other workers have confirmed the protective effects of hypermagnesaemia in the hypoxic myocardium (Shapiro, 1980; Bersohn et al, 1982; Kyosolo et al, 1985; Yano et al, 1985; Bers, 1985; Woods & Chapman, 1985), although Engelman et al (1978) questioned the

value of low levels of magnesium in the cardioplegia infusate. Ferrari et al (1986) compared the beneficial effects of nifedipine with those of high magnesium/low calcium infusates and found that the latter offered significantly better protection to the arrested heart. Galloway et al (1986) reported a case in which infusion of magnesium reversed early ischaemic contracture in the myocardium following cardiopulmonary bypass. As a result of these reports, the addition of magnesium to cardioplegic solutions remains popular, and Manners & Nielson (1981) noted that the return of the perfusate to the patient was harmless, and might offer the advantages of avoiding hypomagnesaemia to the post-bypass patient.

Several further studies have shown that patients dying from acute myocardial ischaemic events had a lowered myocardial magnesium (Abraham et al, 1977; Chipperfield & Chipperfield, 1973; Dyckner, 1980; Johnson et al, 1979; Leary and Reyes, 1983b; Schroeder, 1960; Shen & Ennings, 1972). Magnesium has been shown to be an important regulator of coronary artery tone and magnesium deficiency shown to produce spasms of the coronary arteries (Turlapaty & Altura, 1980). Acute magnesium deficiency reduces myocardial tolerance to ischaemia (Borchgrevink et al, 1987) and magnesium deficiency extends the size of myocardial infarctions (Chang et al, 1985). Recently, there have been several studies suggesting that magnesium infusions resulting in deliberate hypermagnesaemia may produce an improved outcome in patients suffering from myocardial ischaemic events by reducing infarct size (Weinstein

et al, 1986; Morton et al, 1984; Hughes & Tonks, 1965; Rasmussen et al, 1986). Woodward and Zakaria (1983) reported that potassium and magnesium infusions protected rat hearts against reperfusion-induced arrhythmias following coronary artery ligation. Clinical studies have confirmed that magnesium can reduce the incidence of post-infarction arrhythmias (Abraham et al, 1987; Rasmussen et al, 1987; Harris et al, 1953), thus improving patient outcome. Beneficial effects of infusions of magnesium have also been claimed in patients with angina and with peripheral vascular disease (Browne, 1969, 1984). Magnesium thus appears to offer considerable myocardial protection to the ischaemic heart.

The direct vasodilator effect of magnesium on coronary vessels has been used in the termination and prevention of Prinzmetal's variant angina (Cohen & Kitzes, 1984, 1986). It has also been suggested that the vasodilator and anticoagulant effects of magnesium may have beneficial effects on flap survival in patients undergoing microvascular surgery (Acland, 1972).

Realization that calcium may be the final common pathway mediating hypoxic cellular injury (Schanne et al, 1979) has led to suggestions that magnesium may be potentially beneficial in the protection of various other tissues from ischaemic events. The successful use of magnesium in resuscitation of the ischaemic brain was reported by White et al (1983) and this report was followed

by further evidence of this action (Ames & Nesbett, 1983; Vacanti & Ames,1984). Keane et al (1988) have recently shown improved cerebral recovery from asphyxiation with enhanced cerebral blood flow in post-asphyxic newborn lambs. On the other hand, Ruiz et al (1986) were unable to demonstrate any benefit in cerebral resuscitation from the use of magnesium or any of several other agents. Magnesium, in various concentrations, has been employed in flush solutions for the preservation of human cadaveric kidneys, with a value of 5 mmol/l appearing to offer optimal benefit (Schweitzer & Sutphen, 1982; Collins et al, 1984).

Application of the concept of magnesium as a calcium antagonist to skeletal muscle has led some investigators to study the role of the ion in malignant hyperpyrexia. Sair et al (1970) reported improved preservation of porcine muscle creatine phosphate during hyperpyrexia when magnesium was administered, and some improvement in survival was reported in hyperpyrexia-susceptible swine following intravenous administration of magnesium sulphate (Flewellen & Nelson, 1980). Nevertheless, it seems unlikely that magnesium will have a major role to play in this intracellular disorder since it penetrates the intracellular space so poorly. Gordon (1976) noted that magnesium decreased the responsiveness of chronically denervated muscle to acetylcholine, and Clinton et al (1985) made use of this effect to treat painful muscle spasms in a paraplegic patient.

The fact that ATP exists only as a magnesium chelate has resulted in the investigation of the role of a combination of ATP-Mg in the management of low-perfusion states. Some success in ameliorating the effects of reperfusion on the kidney (Hirasawa et al, 1985) and the liver (Clemens et al, 1985) has been reported recently, and further work is needed in this field. The rationale for the use of this combination in ischaemia and shock has recently been reviewed (Chaudry et al, 1986).

Magnesium in company with alkali has been reported to be of benefit in the management of sickle-cell anaemia in children (Hugh-Jones et al, 1964), probably on a multifactorial basis involving the vasodilator, anticoagulant and calcium antagonist properties of magnesium.

Magnesium, thus, has a wide variety of applications and potential benefits, some of which remain to be fully explored. Despite the well-known ability of magnesium to inhibit the release of catecholamines no attempt has been made, up till the present time, to use this potentially valuable action in the clinical sphere.

4. Aims and Scope of this Thesis

Magnesium appears to offer many actions that may be of benefit in a variety of clinical situations which have not been previously studied. Of particular interest in anaesthesia and intensive care is the apparent ability of magnesium to antagonise adrenergically-mediated responses which may be harmful to the patient. It has been demonstrated in the laboratory that magnesium has alpha-adrenergic receptor blocking properties and in addition has the unique capacity to inhibit the release of catecholamines from the adrenal gland and from the peripheral adrenergic nerve endings. Although these properties of magnesium are well established they have never been investigated in a clinical situation. This thesis therefore aims to investigate the clinical potential of magnesium in patients in whom catecholamine excess is anticipated and in whom such excess may be deleterious.

4.1 Animal Studies

Before embarking on clinical studies of the use of magnesium, it appeared necessary to clarify and to extend the knowledge of the action of magnesium on the cardiovascular system and its interaction with catecholamines.

4.1.1 Cardiovascular Effects of Magnesium Infusions: To study the action of a wide range of serum concentrations of magnesium in a situation as closely resembling the clinical environment as possible, infusions of magnesium were studied in intact lightly anaesthetised and minimally instrumented baboons and a dose-response relationships established for a range of cardiovascular variables.

4.1.2 Interactions of Adrenaline and Magnesium: It seemed necessary to extend the knowledge regarding the interaction of magnesium with adrenergic agonists to studies in the intact animal. Using the same model, studies of the action of magnesium in baboons receiving high dose adrenaline infusions were conducted. The animal experimentation was completed by comparing the anti-adrenergic actions of magnesium with those of standard alpha- and beta-adrenergic receptor blocking agents and by investigating the interaction of magnesium with these agents.

4.2 Clinical Studies

Despite the wide range of clinical circumstances in which infusions of magnesium salts have been employed, there have been no *in vivo* studies of the

interaction of magnesium with catecholamines in patients with adrenergic excess.

4.2.1 Endotracheal Intubation: In the clinical setting the commonest situation in which surges of catecholamine release occur is during laryngoscopy and the insertion of an endotracheal tube. The potential harm to patients as a result of these adrenergic surges is considerable and the role of magnesium in preventing the release of catecholamines in response to this stress stimulus was investigated.

4.2.2 Tetanus: Catecholamine excess is a common problem in the management of very severe tetanus. The ability of magnesium to control the cardiovascular consequences of catecholamine excess during the management of 10 patients with very severe tetanus was investigated. A later case presented the opportunity for study of the effect of magnesium infusions on catecholamine levels in a patient with this condition.

4.2.3 Phaeochromocytoma: In the anaesthetic management of patients undergoing surgery for the removal of phaeochromocytomas, the prevention of the release of excess catecholamines and the control of cardiovascular disturbances that inevitably occur present one of the greatest challenges in modern anaesthesia. The final section of this thesis therefore included an investigation of the value of magnesium infusions in the inhibition of catecholamine release and the obtunding of the cardiovascular consequences of adrenergic excess where release of these agents was not preventable.

5. Cardiovascular Effects of Magnesium

Despite the wide range of clinical conditions in which magnesium has been used, the mechanism of action of the agent remains controversial largely because of discrepancies between laboratory data and observed clinical effects. Magnesium has well established vasodilator effects *in vitro* and *in vivo* (Altura & Altura, 1981a), but the hypotensive effects appear to be transitory (Kirpekar & Misu, 1967; Winkler et al, 1942), and myocardial depression may be required for the maintenance of magnesium-induced hypotension (Mordes & Wacker, 1978). Although magnesium has been shown to inhibit contractile force in isolated, perfused hearts and in cardiac muscle strips (Kovacs & O'Donnell, 1975; Levin et al, 1976; Paddle & Haugaard, 1971; Shine & Douglas, 1974), studies in intact animals and humans have been less conclusive, negative inotropic effects being demonstrated in some studies (Cotton et al, 1984; Dandavino et al, 1977; Maxwell et al, 1965; Mroczek et al, 1977), but not in others (Aldrete et al, 1968; Critelli et al, 1977; Mori, 1978; Szekely, 1946; Altura & Altura, 1985 a & b; Friedman et al, 1987).

There have been surprisingly few detailed studies of the effects of magnesium on cardiovascular function in intact animals, and dose-response relationships have not been well described. This study was undertaken in order to define more accurately the effects of a wide range of serum magnesium concentrations on the cardiovascular system. In order to approximate as closely as possible to the clinical situation, lightly anaesthetized, intact and minimally instrumented baboons were chosen as the experimental model.

5.1 METHODS

Seven adult male chacma baboons were studied with the approval of the animal experimentation ethics committee. The animals were initially sedated with ketamine 10 mg/kg i.m. and then transferred to a heated operating table. Anaesthesia was induced with thiopentone 4 mg/kg i.v., and the trachea intubated under muscle relaxation induced with suxamethonium 1 mg/kg. The lungs were ventilated with 25% oxygen in nitrous oxide. End-expired carbon dioxide was monitored using a Datex CD300 infra-red capnograph with nitrous oxide compensation, and minute ventilation adjusted to keep the CO_2 within a range of 32-36 mmHg. The capnograph was calibrated against a mixture of oxygen and carbon dioxide containing a known partial pressure of CO_2 (approximately 40mmHg), prior to each experiment. The use of a known partial pressure rather than percentage of CO_2 to calibrate the capnograph prevents

errors in measurement due to alterations in barometric pressure, and is the most accurate way to use this instrument at altitude (James & White, 1984). Blood gas analysis was not available for animal samples in Zimbabwe at this time, as facilities were limited and restricted to human specimens only. Urine was collected by bladder expression, and plasmalyte B infused to replace excreted volume so as to maintain fluid balance. Electrocardiographic leads were attached to each limb, and lead II monitored throughout the experiment. A 21-gauge cannula was inserted into the femoral artery, and an Edwards 7-french gauge triple-lumen thermodilution pulmonary artery catheter (Edwards 93A-131-7F) inserted via the femoral vein into the pulmonary artery. All lines were placed by percutaneous push-in in order to leave minimal residual pain from catheter insertion sites during the experimental period and following the experiment as these were survival experiments. Systemic arterial, pulmonary arterial, and central venous pressures pressures were monitored using Hewlett Packard strain gauge transducers (HP 1280C), pressure module (HP 8805D). A continuous written record was made of the transducer output and of the ECG on a Hewlett Packard 4-channel pen recorder (HP 7754A) at a chart speed of 25mm/sec. The transducers were electronically zeroed using the zero facility built into the equipment, and the calibration of the transducers was checked against a mercury column prior to and after each experiment. Core temperatures were monitored throughout using the thermistor probe on the pulmonary artery catheter. Pulmonary capillary wedge pressures were measured intermittently. Muscular relaxation was maintained with alcuronium 0.3 mg/kg. Stable conditions such that heart rate, arterial blood pressure and

cardiac output remained within a range of 10% on either side of preceding readings were maintained for 1h before any recordings were taken.

Baseline recordings of heart rate, pulmonary and systemic arterial pressures, central venous pressure, pulmonary capillary wedge pressure and cardiac output were then made. Cardiac output (CO) was estimated by thermodilution (see Appendix A) using 5 ml of cold 5% dextrose using a Hewlett Packard cardiac output computer (HP 78231C). Systemic and pulmonary vascular resistances, stroke volume and stroke work were calculated. Arterial blood samples for serum calcium and magnesium levels were taken, and the samples analysed by the methods detailed in appendix A. The first baboon was used to validate the methods used and to ensure that stable experimental conditions could be maintained and that appropriate cardiovascular measurements could be achieved. In the remaining six animals, a loading dose of 60 mg/kg magnesium sulphate ($MgSO_4$) as a 50% solution in water was administered over one minute and all the measurements repeated. A continuous infusion of 50% $MgSO_4$ was commenced at a rate of 12.5 mg/min and continued until cardiovascular stability, judged by variation in successive measurements of less than 10%, had been maintained for at least 5 min. All measurements were again repeated. The infusion rate was increased to 25 mg/min and then by 25 mg/min increments up to a maximum of 200 mg/min, with repetition of measurements at each infusion rate once cardiovascular stability had been achieved. Any ECG abnormalities were noted. At the end of each experiment, neuromuscular reversal was performed using neostigmine and atropine and

adequate reversal checked using a nerve stimulator before returning the animals to the animal house. Calcium was added if necessary. This latter precaution was necessary as two fatalities had occured in earlier experiments as a result of inadequate recovery from neuromuscular blockade following withdrawal of ventilatory support.

Data from all 6 baboons was pooled for each variable and rank ordered according to the serum magnesium. The data for each variable was then divided into groups as follows: group 1 included all data collected at a serum magnesium of 1 mmol/l or less. Subsequent groups represented data collected within a group width of 1 mmol/l above the previous group. The individual groups were then analyzed by analysis of variance for differences from baseline values and from other groups. Where analysis of variance indicated that significant differences existed between groups, the groups which were significantly different at the 5% level were determined using the Duncan multiple-range procedure.

Using ungrouped pooled data, cardiovascular parameters and serum magnesium levels were analyzed for association by regression analysis. Finally, data obtained with serum magnesium levels between 1 and 5 mmol/l were compared with baseline values and with data obtained at serum magnesium levels greater than 5 mmol/l using Student's t-test with the Bonferroni modification for multiple comparisons. Significance was defined as $p < 0.05$. Data analysis was performed using the Statistical Package for Social Sciences (SPSS) statistical package on a mainframe computer.

5.2 RESULTS

Satisfactory anaesthesia was established readily, and no additional doses of muscle relaxants were necessary after the one hour stabilization period. As no painful procedures were performed during the experimental period, the light levels of anaesthesia used appeared adequate at all times. Results are presented as means $\pm$ 1 Standard error of the mean (SEM).

5.2.1 Serum Magnesium: The mean baseline serum magnesium was 0.617 $\pm$ 0.015 mmol/l. Bolus injection always produced higher serum magnesium levels than subsequent infusions of less than 50 mg/min (3 g/h). The maximum serum magnesium level attained was 9.4 mmol/l and values greater than 8 mmol/l were achieved on only three occasions. Values of greater than 7 mmol/l were therefore grouped together giving eight groups covering a range of serum magnesium from <1 to 7+ mmol/l. The number of data points obtained in each group is shown in table 1.

Table 5.1

Group	SeMg	Number
1	<1	9
2	1-2	13
3	2-3	12
4	3-4	10
5	4-5	3
6	5-6	6
7	6-7	7
8	7+	6

Table 5.1. Data groups determined by serum magnesium levels.
SeMg - serum magnesium in mmol/l

5.2.2 *Serum Calcium:* Serum calcium was unchanged throughout.

5.2.3 *Arterial Blood Pressure:* A scattergram plot of systolic blood pressure changes against serum magnesium levels showed a moderate negative correlation ($r = -0.555$), and a significant slope to the line fitted to the data points ($p < 0.001$, Figure 5.1).

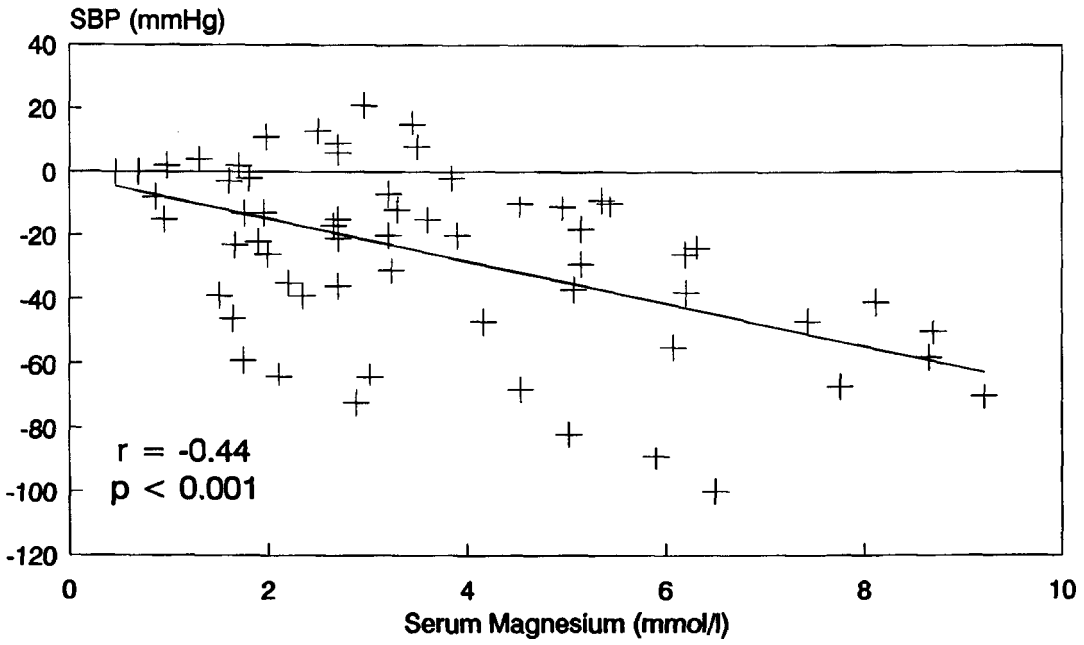


Figure 5.1 Scattergram of changes in systolic blood pressure against serum magnesium levels.

In the grouped data analysis, the only group of those with serum magnesium mmol/l to show a significant reduction in SBP was the 2-3 mmol/l group (-20.1 ± 7.3 mmHg, $p<0.05$). The mean reduction in SBP for all the groups with serum magnesium levels below 5 mmol/l was 15.6 ± 3.5 ($p<0.01$). At higher serum magnesium levels SBP fell to 47.8 ± 12.8 mmHg below baseline values in the 5-6 mmol/l group ($p<0.05$), and declined steadily to a mean value of 60.2 ± 14.5 mmHg below baseline in the 7+ mmol/l group ($p<0.05$). These changes are summarized in figure 5.3. There was a small but significant reduction in systolic pressure in the group with serum magnesium levels <5mmol/l of 15.67 mmHg ($p<0.01$). The mean reduction in SBP from baseline at serum magnesium levels of >5 mmol/l was 54.23 ± 7.46 mmHg which was significantly different from the reduction obtained in the <5mmol/l group ($p<0.001$).

Diastolic arterial pressure (DBP) correlated well with changes in serum magnesium levels ($r=-0.72$, $p<0.001$), but the changes were small (Figure 5.2), and in the grouped data only reached significance at levels of serum magnesium greater than 5 mmol/l (Figure 5.3). In the 5-6 mmol/l group, the mean decrease in DBP was 27.4 ± 5.4 mmHg and in the 7+ mmol/l group was 44.5 ± 11.5 mmHg ($p<0.05$). The mean reduction in diastolic blood pressure with serum magnesium levels <5mmol/l was 4.09 ± 3.58 mmHg which did not reach statistical significance. There was a highly significant reduction in diastolic pressure at serum magnesium levels >5mmol/l of 54.23 ± 7.46 mmHg ($p<0.001$) and this group was significantly different from the <5mmol/l group ($p<0.0001$).

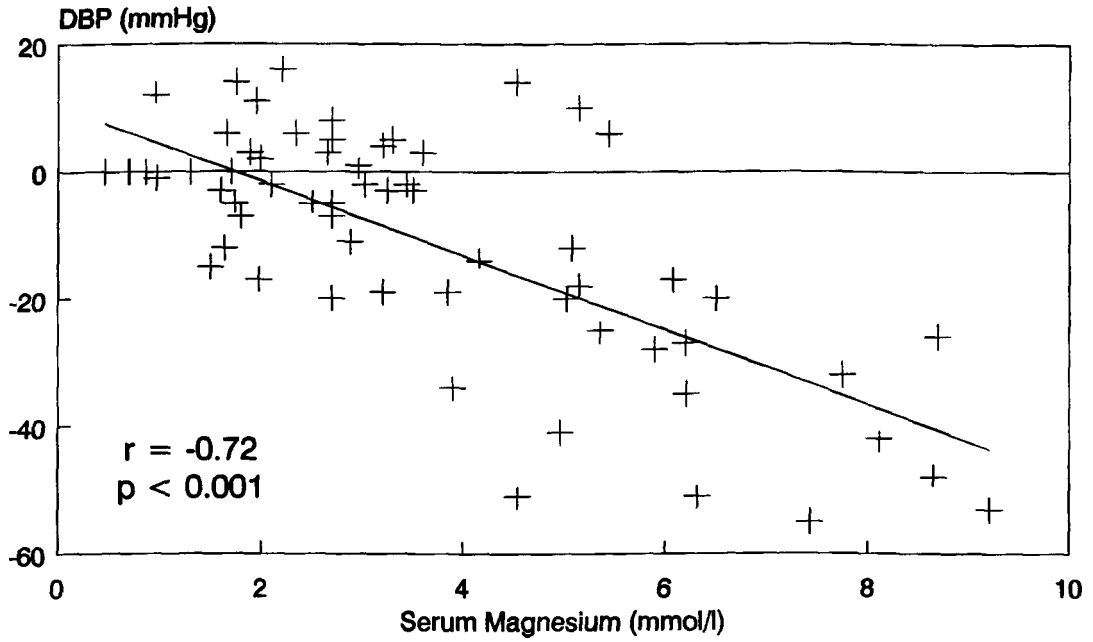


Figure 5.2 Scattergram of changes in diastolic blood pressure against serum magnesium

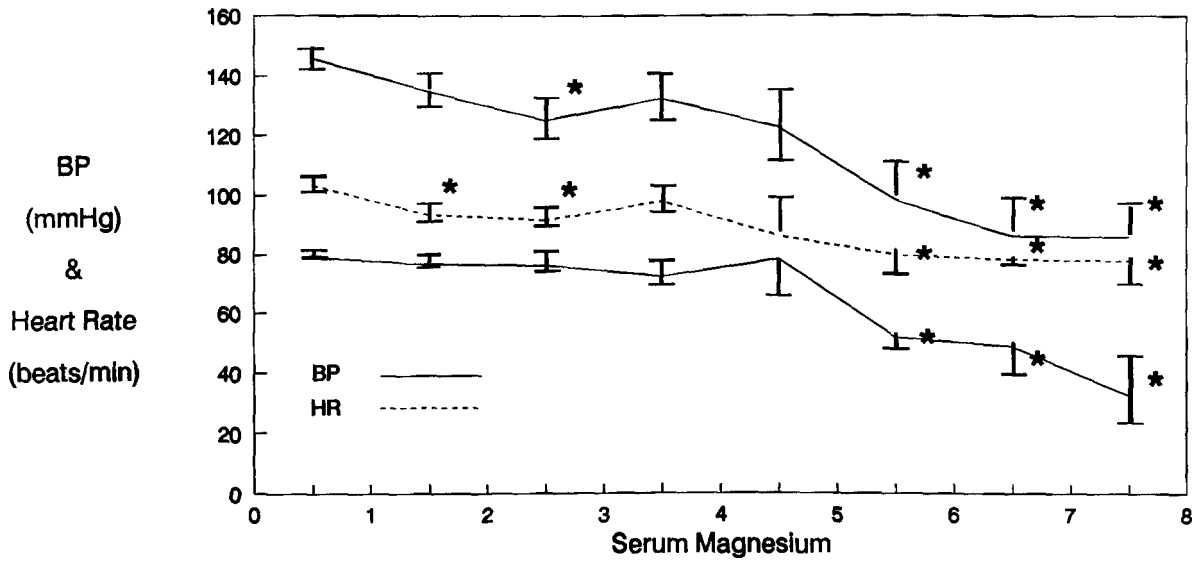


Figure 5.3 Systolic and Diastolic Blood Pressure and Heart Rate for grouped data
** - $p<0.05$*

5.2.4 Heart Rate: Changes in HR correlated poorly with magnesium levels on the scattergram plot ($r = -0.391$), although a line with a significant negative slope could be fitted to the data points ($p < 0.01$, Figure 5.4). In the grouped data (Figure 5.1), the only significant change at magnesium levels of mmol/l was a small decline in HR of 9.8 $\pm$ 2.7 bpm ($p < 0.05$) in the 1-2 mmol/l group (Figure 5.3). In the 5-6 mmol/l group, HR fell sharply to 23.5 $\pm$ 7.1 bpm below baseline ($p < 0.05$), and declined slightly thereafter. The overall change in HR for magnesium levels of <5mmol/l was -9.8 $\pm$ 1.9 bpm ($p < 0.01$), whereas for the higher group the mean was -24.5 $\pm$ 4.6 bpm ($p < 0.01$). The difference between these two groups was highly significant ($p < 0.001$).

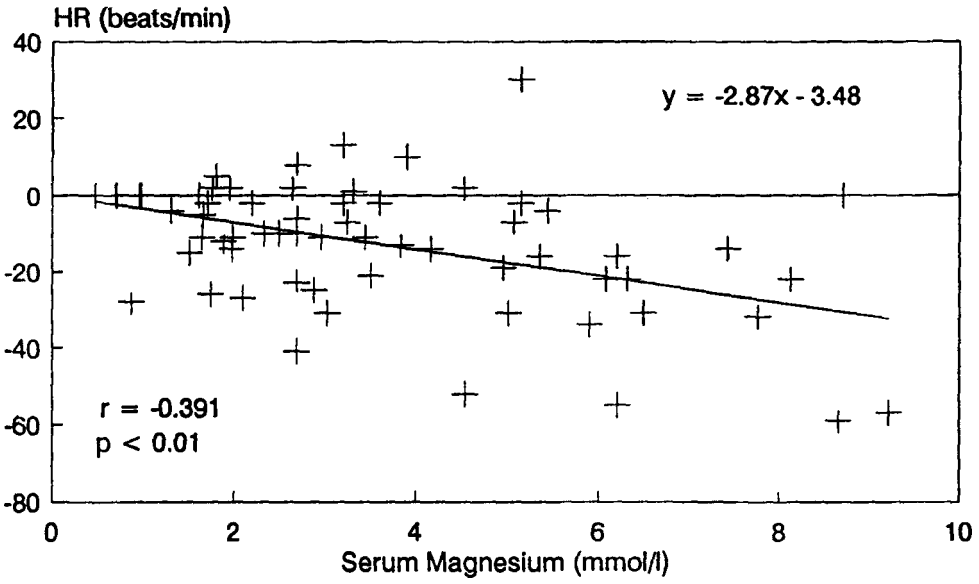


Figure 5.4 Scattergram of changes in heart rate against serum magnesium levels

5.2.5 Rhythm and Conduction: Arrhythmias were uncommon. At serum magnesium levels above 6.5 mmol/l, three animals showed brief

episodes of nodal rhythm, always of less than 30 seconds duration, which resolved spontaneously as the experiment proceeded, despite increasing serum magnesium levels. PR intervals were not significantly altered at any time except for the periods of nodal rhythm. QTc intervals and QRS complexes were not altered at any stage, and there was no evidence of intraventricular conduction defects.

5.2.6 *Systemic Vascular Resistance:* There was a steady decline in SVR which correlated well with serum magnesium levels ($r = -0.67$, $p < 0.001$) on the scattergram plot (Figure 5.5). The reduction in SVR was significant in all groups with magnesium levels above 1 mmol/l. In the overall group with a serum magnesium value <5mmol/l the mean reduction in SVR was 357 $\pm$ 49 dyne.sec.cm^{-5} ($p < 0.001$). The reduction in SVR in the >5mmol/l group was also highly statistically significant and the mean value in this group was 1008.51 $\pm$ 152.36 dyne.sec.cm^{-5} below baseline ($p < 0.001$). The difference between these groups was significant at the 0.001 level.

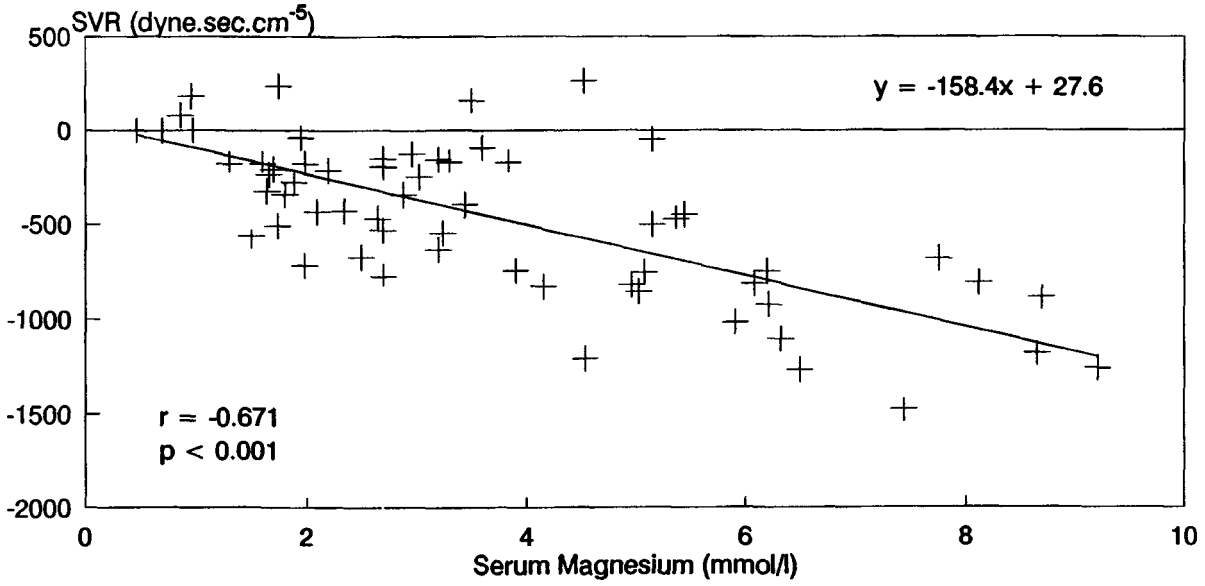


Figure 5.5 Scattergram of systemic vascular resistance against serum magnesium levels.

were not significantly altered at any time except for the periods of nodal rhythm. QTc intervals and QRS complexes were not altered at any stage, and there was no evidence of intraventricular conduction defects.

5.2.6 Systemic Vascular Resistance: There was a steady decline in SVR which correlated well with serum magnesium levels ($r = -0.67$, $p < 0.001$) on the scattergram plot (Figure 5.5). The reduction in SVR was significant in all groups with magnesium levels above 1 mmol/l. In the overall group with a serum magnesium value <5mmol/l the mean reduction in SVR was 357 $\pm$ 49 dyne.sec.cm^{-5} ($p < 0.001$). The reduction in SVR in the >5mmol/l group was also highly statistically significant and the mean value in this group was 1008.51 $\pm$ 152.36 dyne.sec.cm^{-5} below baseline ($p < 0.001$). The difference between these groups was significant at the 0.001 level.

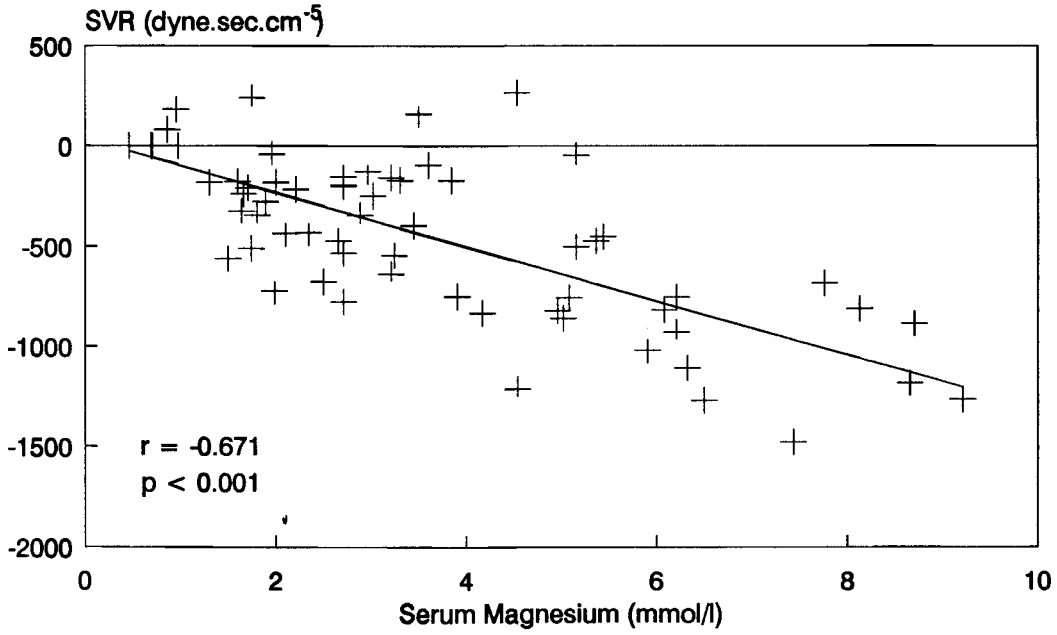


Figure 5.5 Scattergram of systemic vascular resistance against serum magnesium levels.

5.2.7 Cardiac Output: There was no correlation (r=-0.160, n.s.) between cardiac output and serum magnesium levels on the scattergram plot (Figure 5.6). When the grouped data was considered (Figure 5.7), the change in CO was seen to be biphasic with CO significantly increasing at all levels of serum magnesium between 1 mmol/l and 5 mmol/l, the mean increase for the group being 286.5 ± 60 ml/min ($p<0.001$). Above 5 mmol/l, CO returned towards the baseline, and the mean change in the 5mmol/l group was a decrease of 38 ± 149 ml/min which was not significantly different from baseline. The difference between the <5mmol/l and the 5mmol/l group was statistically significant ($p<0.05$).

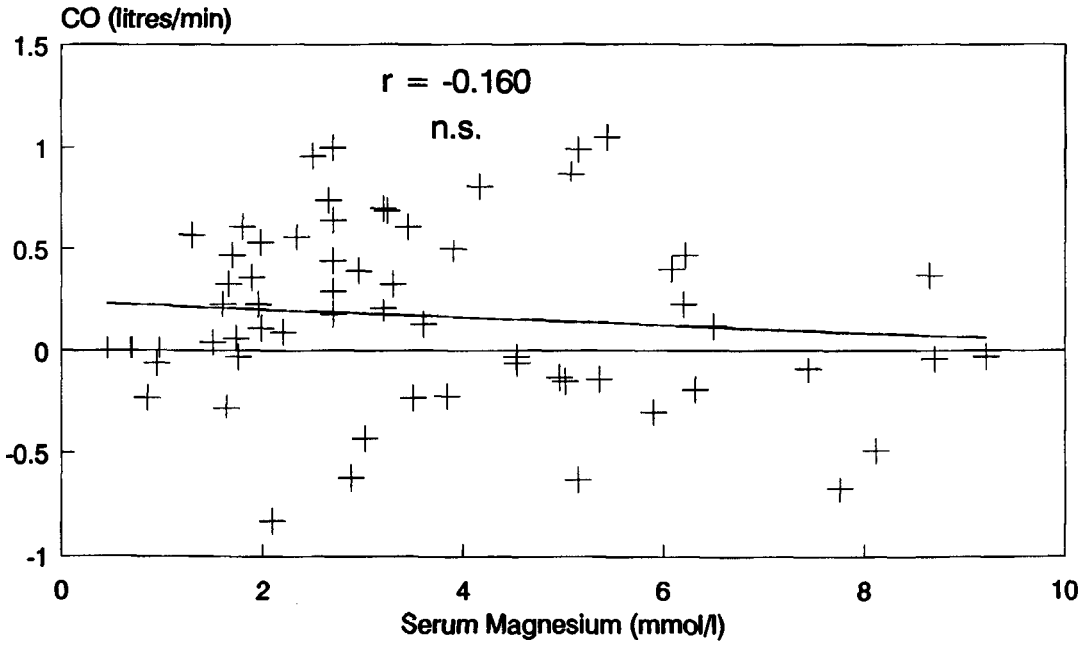


Figure 5.6 Scattergram of changes in cardiac output against serum magnesium levels.

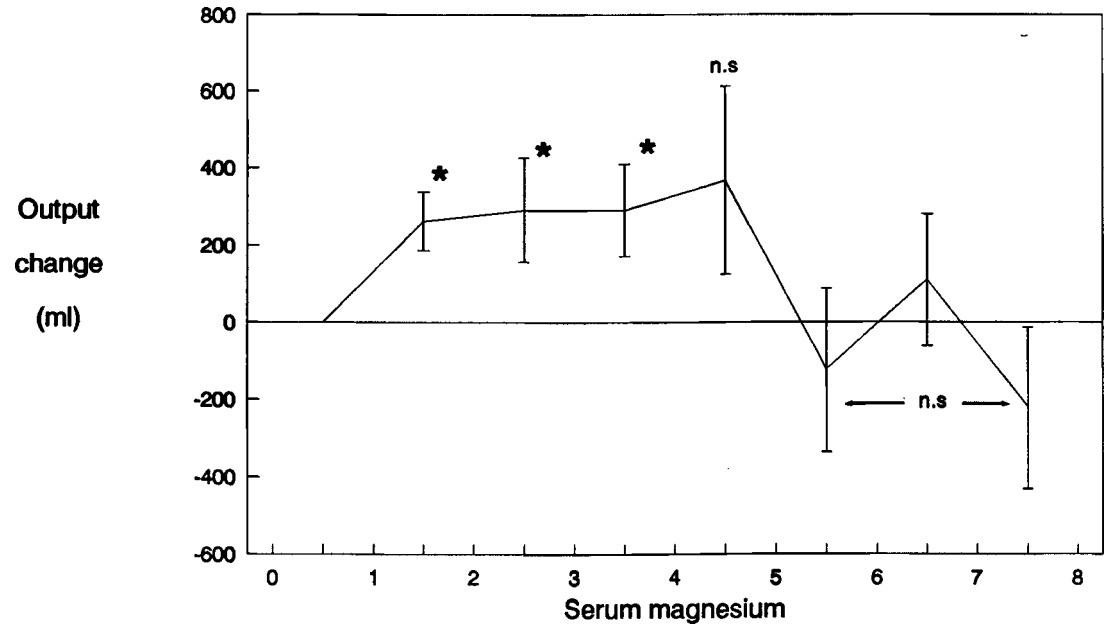


Figure 5.7 Cardiac Output v. Serum Magnesium for grouped data.
** - $p<0.05$*

5.2.8 Stroke Volume: Although there was a significant slope to the regression line for stroke volume against serum magnesium ($p<0.01$), the correlation was poor ($r=0.256$, Figure 5.8). Slightly better correlation could be demonstrated between SV and serum magnesium values below 5mmol/l ($r=0.367$, $p<0.01$). Changes in SV for the grouped data are shown in Figure 5.9. SV was elevated above baseline at all levels of increased magnesium. There was a 15% increase above baseline in the 1-2 mmol/l group (5.28 $\pm$ 1.13 ml/beat, $p<0.05$) which rose to a maximum of 34.6% above baseline (11.0 $\pm$ 2.6 ml/beat) in the 6-7 mmol/l group ($p<0.05$).

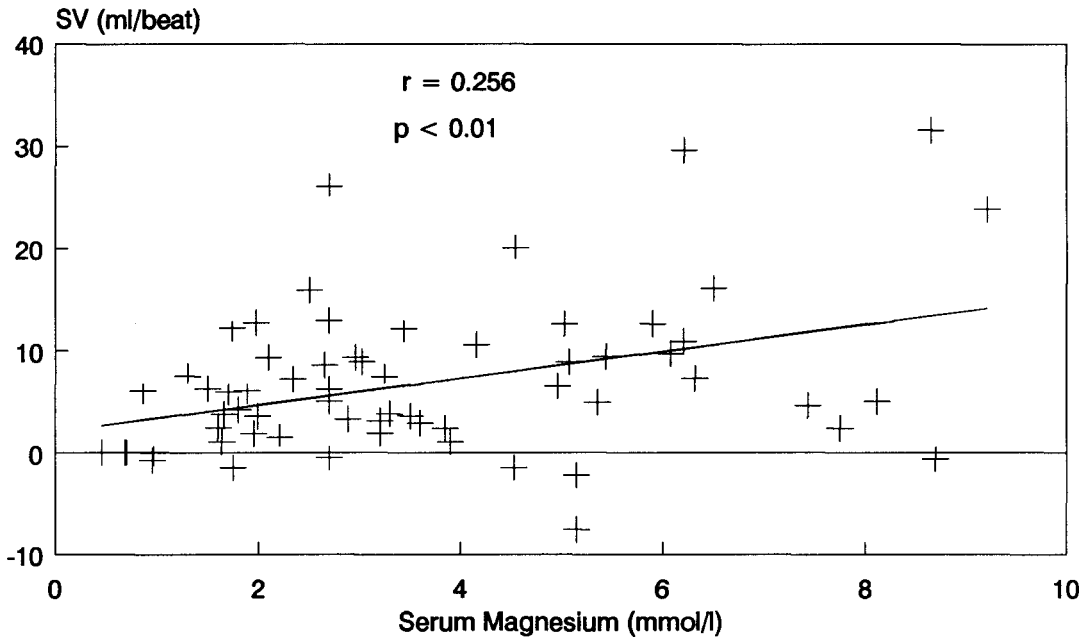


Figure 5.8 Scattergram of changes in stroke volume against serum magnesium levels.

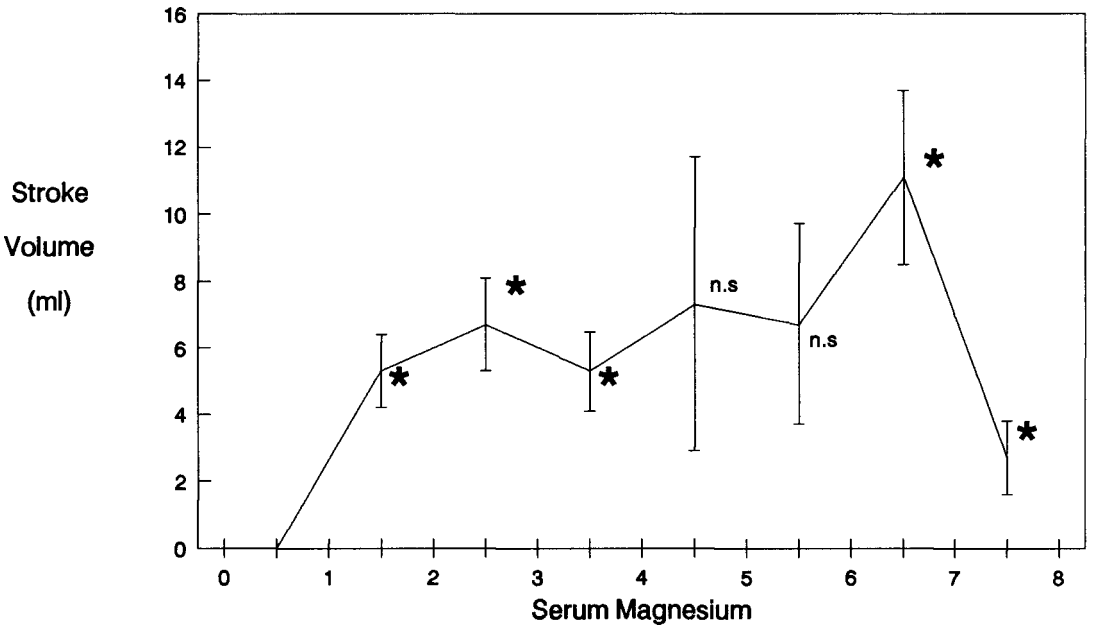


Figure 5.9 Stroke Volume v. Serum Magnesium for grouped data.
** - 0.05*

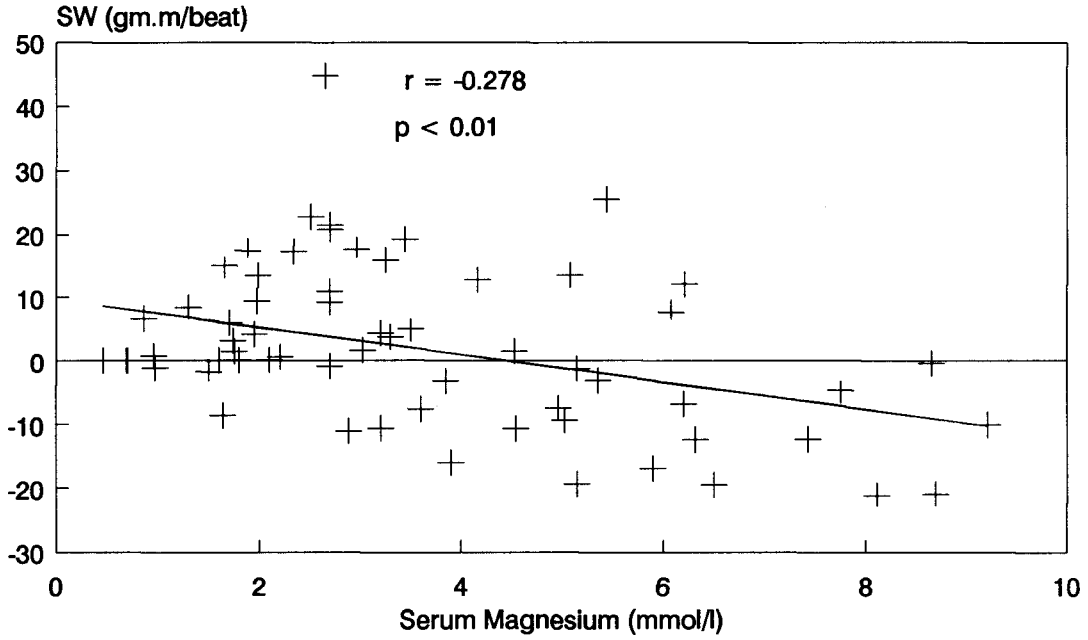


Figure 5.10 Scattergram of changes in stroke work against serum magnesium levels.

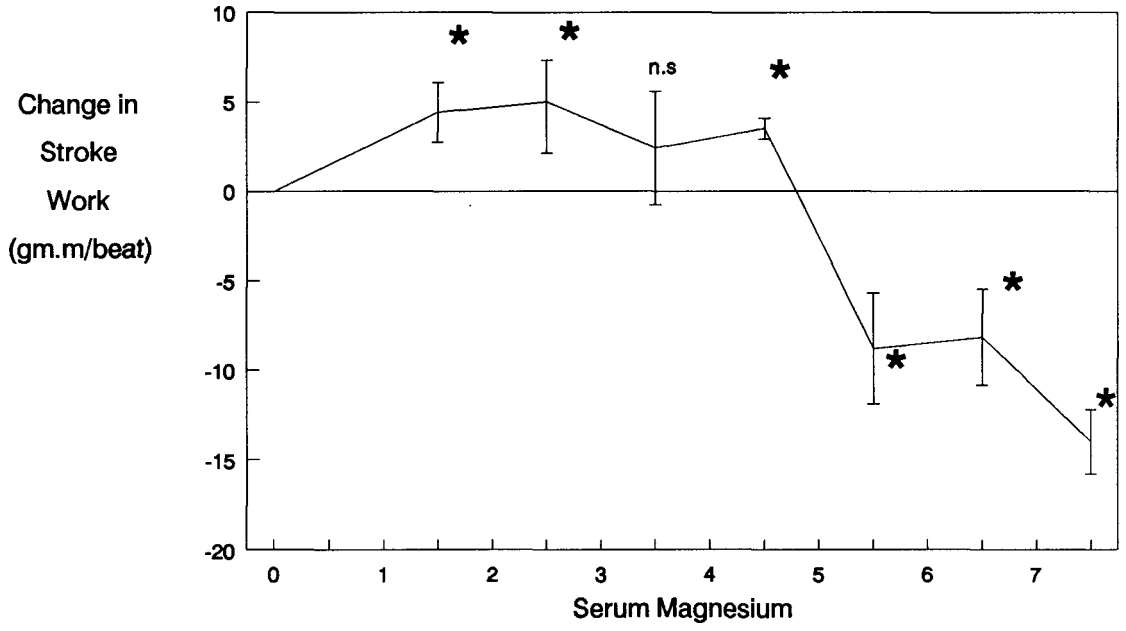


Figure 5.11 Stroke Work v. Serum Magnesium for grouped data.
** - p<0.05*

5.2.9 Stroke Work : Although there was a significant negative corrleation between serum magnesium concentrations and SW (Figure 5.10), the response was biphasic. SW increased in all groups with serum magnesium values of less than 5 mmol/l (Figure 5.11), giving a mean increase from baseline of 4.1 $\pm$ 1.2 gm.m/beat in the <5 mmol/l group ($p<0.001$). In all groups with magnesium levels above 5 mmol/l, SW fell significantly below baseline ($p<0.001$), the overall change in this group being -10.2 $\pm$ 1.9 gm.m/beat

5.2.10 Pulmonary Arterial Pressure: PAP was not significantly altered at any stage of the experiment and there was no correlation between PAP and serum magnesium levels.

5.2.11 Pulmonary Vascular Resistance: PVR did not change significantly during the experiment.

5.2.12 Pulmonary Capillary Wedge Pressure: There were no significant changes in PCWP demonstrable in the grouped data analysis, and on the scattergram there was no correlation between changes in PCWP and serum magnesium levels.

5.2.13 Central Venous Pressure: CVP also showed a biphasic response, but the changes were extremely small (Figure 5.12). There was a weak positive correlation between serum magnesium levels and CVP ($r=0.338$, $p<0.01$) but in the grouped data, no single data point was significantly different from baseline. The only detectable significant change was a small decrease in the <5 mmol/l group (-0.97 $\pm$ 0.287 mmHg), and a small increase in the >5 mmol/l group (1.23 $\pm$ 0.65 mmHg). The groups were significantly different from each other ($p<0.01$) but not from baseline.

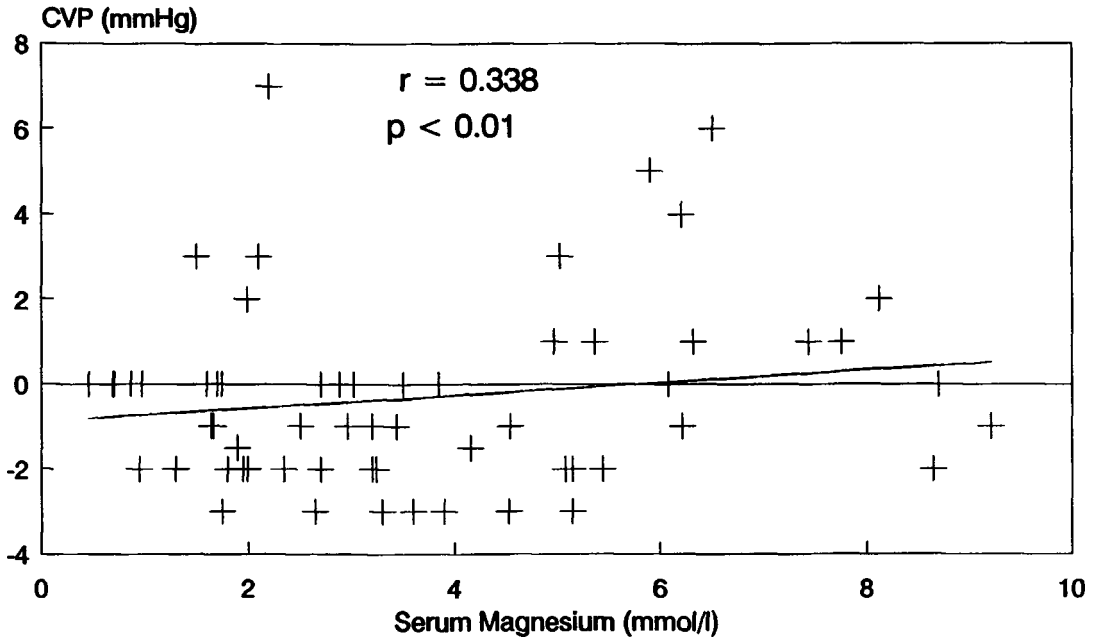


Figure 5.12 Scattergram of changes in central venous pressure against serum magnesium levels

5.2.14 Bolus Injection: Following bolus injection, two of the animals reached serum magnesium levels in the 1-2 mmol/l range, two in the 2-3 mmol/l range and two in the 3-4 mmol/l range. All of the results produced by bolus injection were within one standard deviation of the mean of the appropriate group.

5.3 DISCUSSION

The dose-related reduction in systemic vascular resistance shown in the present study confirms the vasodilator properties of magnesium previously demonstrated in a variety of tissues in various species (Altura & Altura, 1981 a, b & c; Altura & Altura, 1978 a & b; Turlapaty & Altura, 1978; Turlapaty et al,

1980), and also in intact animals and humans (Haddy, 1960; Haury, 1939; Overbeck et al, 1969). This effect is due to the direct action on vascular smooth muscle (Altura & Altura, 1981b; Altura & Altura, 1984c), to interference with the action of various vasoconstrictor agents (Altura & Altura, 1981 b & c; Altura & Altura, 1977; Levin et al, 1976; Turlapaty & Altura, 1980), and possibly blockade of sympathetic ganglia (Hutter & Kostial, 1954; Stanbury, 1948). The hypotensive effect of magnesium has been ascribed to a combination of all of these effects (Engbaek, 1952). The absence of effect on venous pressure suggests that the major role of magnesium in intact animals is on resistance rather than capacitance vessels, although some recent work on the microcirculation questions this notion (Altura & Altura, 1985b).

In the face of this clear-cut evidence of the vasodilator action of magnesium, the conflicting evidence regarding hypermagnesaemic hypotension requires explanation. Although a hypotensive response to acute hypermagnesaemia has been well described both in animals and humans (Alfrey et al, 1970; Altura & Altura, 1985a; Blackfan & Hamilton, 1925; Hoff et al, 1939; Matthews & Brooks, 1910; Meltzer & Auer, 1906b; Moore & Wingo, 1942; Mordes et al, 1975; Mroczek et al, 1977; Pritchard et al, 1984; Randall et al, 1959; Scott et al, 1968; Young & Weinstein, 1977), the effect appears to be inconsistent. In humans, some authors have reported little cardiovascular effect at high serum magnesium levels (Flowers et al, 1962; Kelly et al, 1960), whilst others have found marked but transient hypotension (Mroczek et al, 1977). In animals, both

transient (Dandavino et al, 1977) and sustained (McCubbin et al, 1981) hypotension has been reported. Hypotension is not consistently produced by magnesium in the management of pregnancy-induced hypertension (Flowers et al, 1962; Pritchard et al, 1984; Pritchard & Pritchard, 1975), and consequently, magnesium has been described as a poor vasodilator (Scott et al, 1968). Part of the explanation for this inconsistent hypotension may lie in the rapid clearance of magnesium from the plasma. This study illustrates the difficulties of maintaining high serum magnesium levels in the presence of normal renal function as even massive infusion rates produced a maximum serum magnesium level of only 9.4 mmol/l. In this study, as in others (Maxwell et al, 1965; Mroczek et al, 1977), the fall in blood pressure correlated moderately with changes in serum magnesium. As many of the papers describing the transitory hypotensive effect of magnesium did not include serum magnesium estimations, and inadequate serum magnesium levels are common in obstetric patients (Herbert et al, 1968; Sibai et al, 1981), probably due to underlying magnesium deficiency (Cadell et al, 1975), inadequate magnesium levels must be considered as part of the explanation of this phenomenon. The frequently repeated observation that a bolus of $MgSO_4$ produces a greater effect than does a continuous infusion may also reflect poorly maintained magnesium levels. There was no indication in the present study that the magnesium levels obtained following the loading dose produced a different effect to that of similar serum magnesium levels maintained by constant infusion.

However, poorly maintained magnesium levels cannot provide a complete answer to the problem of magnesium-induced hypotension, and the effects of magnesium on CO must also play a part. The present study has shown that although there was a significant reduction in systemic vascular resistance, relatively little hypotension was produced by levels of serum magnesium below 5 mmol/l, a finding in agreement with other studies (Cohen et al, 1984; Dandavino et al,1977; Mroczek et al, 1977). This can only be explained by a concomitant increase in CO which largely compensated for the fall in SVR. In the present study, significant falls in blood pressure only occurred once CO had returned to near-baseline values. Magnesium administration has been shown to increase CO and stroke volume (Mroczek et al, 1977; Stanbury & Farah, 1950), but an increase in SW has not been demonstrated before. In the present study, SW increased up to levels of serum magnesium of 5 mmol/l. This increased SW, along with an increased CO suggests improved myocardial contractility.

Magnesium is generally regarded as having a negative inotropic action. Magnesium inhibits the contractile force of isolated heart muscle (Langer, 1968; Shine & Douglas, 1974; Solaro & Shiner, 1975; Stanbury & Farah, 1950), although the effect is small as long as the calcium levels remain within normal limits (Kovacs & O'Donnell, 1975; Levin et al, 1976; Shine, 1979). A reduction in myocardial performance in humans has been claimed in some studies (Aldrete et al, 1968; Critelli et al, 1977; Mori, 1978), but the increased CO

demonstrated in others (Mroczek et al, 1977) argues against significant myocardial depression. In the present study, there was no clear evidence that even high levels of serum magnesium exerted a significant negative inotropic effect. Although CVP was significantly higher at levels of serum magnesium above 5 mmol/l when compared to the lower magnesium group, this difference was small (1.26 $\pm$ 0.65 mmHg) and PCWP was unaffected. The return of CO to baseline levels in the higher range of serum magnesium was the result of a reduction of HR alone as SV was always above baseline values. The reduction in SW at higher magnesium levels may be construed as indicating impaired contractility, but, since stroke volume was not reduced, this reduction is entirely accounted for by changes in mean arterial and wedge pressures (see equation in Appendix A). As arterial pressure is the product of peripheral resistance and cardiac output, and cardiac output was not significantly different from baseline at the higher magnesium levels, it must be concluded that the reduction in stroke work was mainly the result of the reduction in peripheral resistance and thus unlikely to be due to impaired contractility. In a non-steady state model such as that used in these experiments, in which all the factors that may alter contractility (preload, afterload and heart rate) are varying independently, direct measurements of contractility such as dp/dt_{max} themselves vary, and are no longer true reflections of contractility. It is therefore difficult to make absolute statements regarding the effects of magnesium on contractility but it is reasonable to conclude that myocardial performance was not depressed in this study, and the possibility that moderate elevations in serum magnesium improved function remains. A possible

explanation is that β-receptor agonist binding in the myocardium may have been enhanced. Magnesium does augment β-agonist receptor binding in certain tissues (Bird & Maguire, 1978; Morton & James, 1985; Vincent, 1982; Williams et al, 1978), although this effect has not been studied in myocardial tissue. Both the use of ketamine, and the very light level of anaesthesia used could have increased catecholamine levels, as could the adrenergic response to reductions in arterial pressure. Higher levels of magnesium may have inhibited the release of catecholamines (Douglas & Rubin, 1963; Kirpekar & Misu, 1967; Lishajko, 1970; Von Euler & Lishajko, 1973) thus reducing the circulating level and producing a decline in SW. Estimations of catecholamine levels were not available at the time of these experiments, and this possibility needs further study. The other anaesthetic agents used are unlikely to have influenced these results significantly as nitrous oxide has minimal cardiac effects, and suxamethonium should not affect contractility. Alcuronium may produce mild hypotension, but this was not seen at the start of the experiments, and as no alcuronium was given within 1 hour of starting measurements this effect should not have influenced the results. Acid-base disturbances are extremely unlikely to have influenced these results as the CO_2 levels were kept constant and perfusion was always good. Although arterial blood gas analysis was not available, end-expiratory CO_2 estimation represents a reasonable approximation in the absence of lung disease or gross reduction in cardiac output, and is particularly useful in detecting changes (Nunn, 1987). There is no evidence that $MgSO_4$ infusion of itself provokes an acidosis either in obstetrics (Pritchard, 1975) or in the later parts of this thesis when large

infusions of the salt were used in the management of patients with tetanus and phaeochromocytoma.

Magnesium is generally thought to produce prolongation of the PR and QT intervals (Miller & Van Dellen, 1941; Smith et al, 1939; Van Dellen & Miller, 1939; Von Euler & Lishajko, 1973), although other reports have not shown significant conduction defects provided the serum calcium and potassium levels are maintained (McCubbin et al, 1981; Surawicz et al, 1961; Watanabe & Dreyfus, 1972; Young & Weinstein, 1977). The ECG changes found in this study were minimal, but may this be the result of species variation. It is possible that the use of suxamethonium for intubation contributed to the slowing of heart rate in the initial groups, but highly unlikely that this effect would have persisted, and the change at magnesium levels above 5 mmol/l is most likely to be a pure magnesium effect. The levels of magnesium used in clinical practice seem unlikely to produce serious ECG abnormalities other than a possible prolongation of atrial conduction time.

The apparent absence of effect of magnesium on pulmonary vessels is surprising in view of other reports of pulmonary vasculature behaving in the same manner as the systemic vascular tree to magnesium loads (Altura & Altura, 1981c; Howell & Carrier, 1986). This experiment does not shed any light on the reason for this observation, but species peculiarity may account for it.

Magnesium competes with calcium at the cell membrane, and may be regarded in many circumstances as a physiological calcium antagonist (Altura & Altura, 1981 a & b; Altura & Altura, 1985 a, b & c; Iseri & French, 1984). The present study lends support to this concept. It has been shown that magnesium exerts a consistent, dose-related vasodilator effect, and the relatively weak hypotensive action of this substance is probably the result of compensatory increases in CO. The absence of a major negative inotropic effect has been demonstrated, and even relatively large elevations of serum magnesium did not produce serious arrhythmias or conduction defects.

From this study, it may be concluded that magnesium increases peripheral perfusion, but is unlikely to depress myocardial contractility or produce serious hypotensive consequences. It is thus likely to prove a safe agent in clinical circumstances where a reduction in afterload or an increase in peripheral perfusion is required. The potential benefit of these observations in conditions of catecholamine excess are investigated in later sections of this thesis.

6. INTERACTIONS WITH ADRENALINE AND ITS ANTAGONISTS

As a result of the investigations described in the previous chapter, it may be concluded that magnesium can exert significant vasodilator effects which may, in part, be due to interactions between magnesium and adrenergic agonists. It has been shown *in vitro* that magnesium interferes with the peripheral action of catecholamines, and that it may regulate the release of catecholamines from both the adrenal gland and peripheral nerve terminals (Altura & Altura, 1977; Hutter & Kostial, 1954; Levin et al., 1976; Stanbury, 1948; Turlapaty & Altura, 1982). However, these effects have not been demonstrated in the intact animal, and no attempt has been made to quantify the extent of the interaction between magnesium and catecholamines *in vivo*. Before clinical consideration could be given to the use of magnesium in conditions of catecholamine excess, it would be necessary to establish a number of facts. Firstly, it would need to be established whether or not the degree of magnesium inhibition of adrenergic receptors was sufficient to be of clinical use. Secondly, it would be important to know whether or not the interaction was potentially hazardous in terms of massive vasodilatation or severe disturbances of heart rhythm. Finally, it is known that some other alpha-adrenergic antagonists, such as phentolamine,

have anti-arrhythmic properties, and it would be interesting to find out whether or not the well-known anti-arrhythmic properties of magnesium extended to situations of catecholamine overactivity. This study was designed to investigate the interaction between magnesium and adrenaline on the cardiovascular system of the intact baboon. Adrenaline was chosen as the adrenergic agonist since the combined alpha- and beta-adrenergic stimulant effect of high doses of this agent would most closely approximate to the clinical situation. Furthermore, if, as seemed likely prior to the study, magnesium exerted primarily α-antagonist properties, the use of adrenaline would allow the unmasking of potentially dangerous interactions between β-agonists and magnesium such as severe tachyarrhythmias.

6.1 METHODS

Twelve adult male Chacma baboons were studied with the approval of the animal experimentation ethics committee, and the experimental procedure was essentially similar to that used in the previous study. The animals were initially sedated with ketamine 10 mg/kg i.m. and then transferred to the operating room and placed on a heated operating table. Anaesthesia was induced with thiopentone 4 mg/kg i.v. and the trachea intubated under muscle relaxation induced with suxamethonium 1 mg/kg. The lungs were ventilated with 25% oxygen in nitrous oxide and minute ventilation adjusted to keep the end-expired

carbon dioxide level within the normal range. Electrocardiographic leads were attached to each limb and lead II monitored throughout the experiment. An arterial cannula was inserted into the left femoral artery and an Edwards 7FG triple lumen thermodilution pulmonary artery catheter inserted via the right femoral vein, and a written record of the transduced pressures and the ECG made as in the previous experiment. Muscular relaxation was maintained with intermittent doses of suxamethonium as required to prevent movement. This relaxant was chosen as the previous study had shown that sustained muscle relaxation seemed unnecessary once all lines had been established. This technique also removed any risk of problems pertaining to reversal of non-depolarising relaxants. Stable conditions as previously defined were maintained for one hour before any readings were made. Baseline recordings of heart rate, pulmonary and systemic systolic, diastolic and mean arterial pressures, central venous pressure, pulmonary artery wedge pressure and cardiac output were made at this time. Cardiac output was estimated by thermodilution using 5 ml of 5% dextrose held between 0-5^{o} Centigrade as the injectate. The mean of three consistent readings was taken on each occasion. From these values systemic and pulmonary vascular resistances, stroke volume and stroke work were calculated. Arterial blood samples for calcium and magnesium levels were taken.

An infusion of adrenaline 1 μg/kg/min. was then commenced and continued throughout the experiment. Once stable conditions had been present for at least 5 minutes of adrenaline administration, all measurements were repeated.

Stable conditions were defined on this occasion as a difference of less than 10% between successive measurements 5 minutes apart. Where arrhythmias occurred, all measurements were recorded during periods of sinus rhythm. At this point, animals were allocated at random to a control group, or to an experimental group. Animals in the experimental group then received a bolus of magnesium 60 mg/kg by intravenous injection, and cardiovascular parameters again measured, along with serum calcium and serum magnesium levels. Once the values had been recorded, a further bolus of magnesium was injected and all measurements again repeated. Bolus injection, rather than an infusion, of magnesium was used in order to achieve a rapid increase in serum magnesium levels, the previous experiment having shown infusions to produce slow and unpredictable changes in serum magnesium. Control animals were given two identical volume injections of saline instead of the magnesium.

The results within the treatment groups were analyzed by analysis of variance and significantly different results identified using Duncan's multiple range test. Between group comparisons were made using Student's t-test. Statistical tests were performed using the SPSS package. Significance was defined as $p < 0.05$.

6.2 RESULTS

As in the previous study, anaesthesia was maintained without difficulty throughout the experiment.

Results are presented as means ± 1 S.E.M., and the principal features are illustrated in table 1. Cardiovascular measurements in treatment and control groups were not significantly different either at baseline or after the infusion of adrenaline, and therefore measurements in the treatment group only are reported in the text for the sake of clarity. Saline injections produced no significant alterations in the adrenaline-induced changes and control group data is therefore presented only where there were significant differences from the treatment group.

6.2.1 Serum Magnesium: Baseline serum magnesium values were similar in all animals (0.617 ± 0.01 mmol/l). Initial bolus injection produced serum magnesium levels of 3.4 ± 0.31 mmol/l, and the second injection resulted in similar levels of 3.33 ± 0.29 mmol/l. Serum magnesium was unaltered from baseline in control animals.

6.2.2 Serum Calcium: Serum calcium levels were not significantly changed at any stage of the experiments.

6.2.3 Arterial Blood Pressure : Adrenaline produced a significant increase in systolic blood pressure (SBP) in both groups ($p < 0.05$). Within 60 seconds of the first injection of magnesium SBP decreased to a mean value 167.5 ± 20.1 mmHg, and after the second injection, the mean value was 166.8 ± 9.0 mmHg. The post-adrenaline SBP was significantly greater than baseline and this elevation persisted in the control animals. Both post-magnesium blood pressures were significantly lower than in saline-treated controls ($p < 0.05$). Post-magnesium values were not significantly different from baseline. These changes are summarized in figure 6.1.

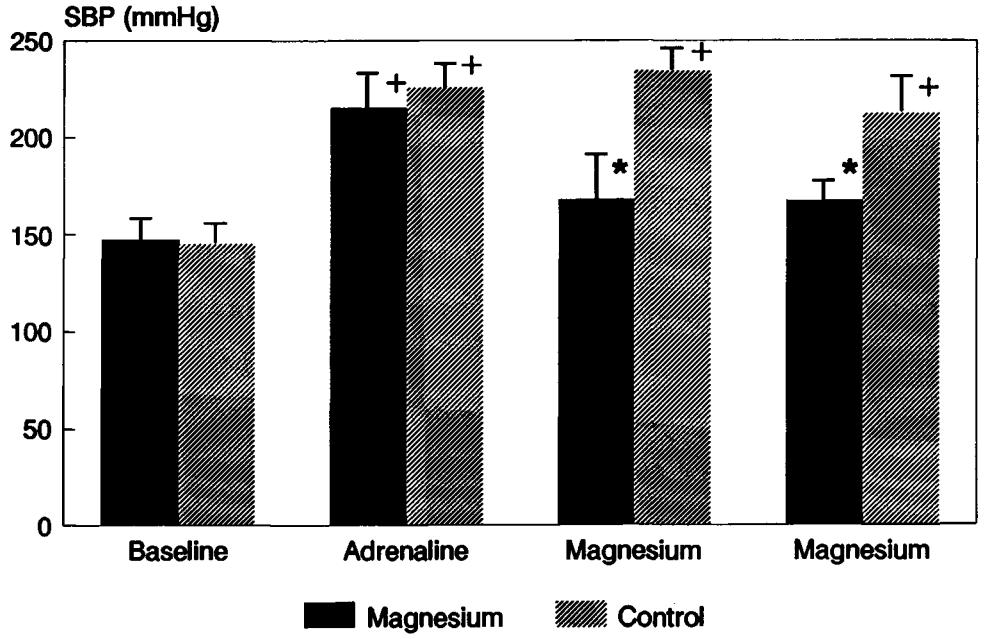


Figure 6.1. Changes in systolic arterial pressure.
** - $p<0.05$ for differences between $MgSO_4$ and saline*
+ - $p<0.05$ for differences from baseline.

Diastolic pressures were similarly affected, increasing significantly from a baseline value of 94.0 ± 6.5 mmHg to 125.2 ± 13.6 mmHg with the adrenaline infusion ($p<0.05$), and decreasing to 96.7 ± 8.2 mmHg and 84.2 ± 4.2 mmHg with the two doses of magnesium. Controls remained significantly above the treatment group ($p<0.05$).

6.2.4 Heart Rate: HR initially increased as the adrenaline infusion commenced, but rapidly slowed, presumably from vagal reflexes as a result of the raised arterial pressure, and multifocal ventricular and supra-ventricular arrhythmias were seen in all animals. At steady-state conditions during the adrenaline infusion, the mean HR was 89.8 ± 13.4 beats/min. which was not significantly different from the baseline value of 101.0 ± 3.2

beats/min. The first bolus injection of magnesium immediately abolished the arrhythmias and increased the HR to a mean of 130.33 ± 9.3 beats/min. with the second dose producing a further increase to 145.8 ± 4.9 beats/min., both of these post-magnesium values being significantly above baseline and post-adrenaline values ($p < 0.05$). The HR after each magnesium dose was significantly greater than saline-treated controls ($p < 0.05$), and saline had no effect on either the heart rate or the arrhythmias induced by the adrenaline infusion. The difference between the two $MgSO_4$ doses was not significant. These changes are summarized in figure 6.2.

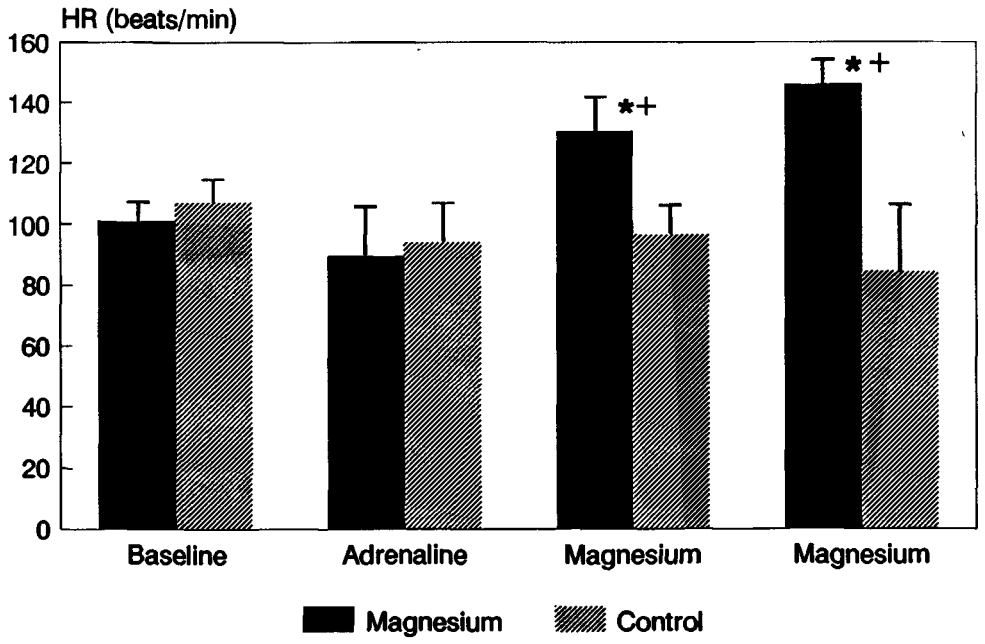


Figure 6.2. Changes in Heart Rate.
** - $p < 0.05$ for differences between $MgSO_4$ and saline*
\+ - $p < 0.05$ for differences from baseline

6.2.5 *Cardiac Output:* The adrenaline infusion caused a slight, but not significant reduction in CO in both groups. The first bolus of magnesium caused an increase in CO to 5.59 ± 0.83 l/min. and the second bolus

caused a further increase to 6.18 ± 0.72 l/min. The treatment group was significantly different from controls and from baseline after each bolus ($p < 0.005$ for both magnesium doses). The within-group difference in CO after each of the two doses of magnesium was not significant (figure 6.3).

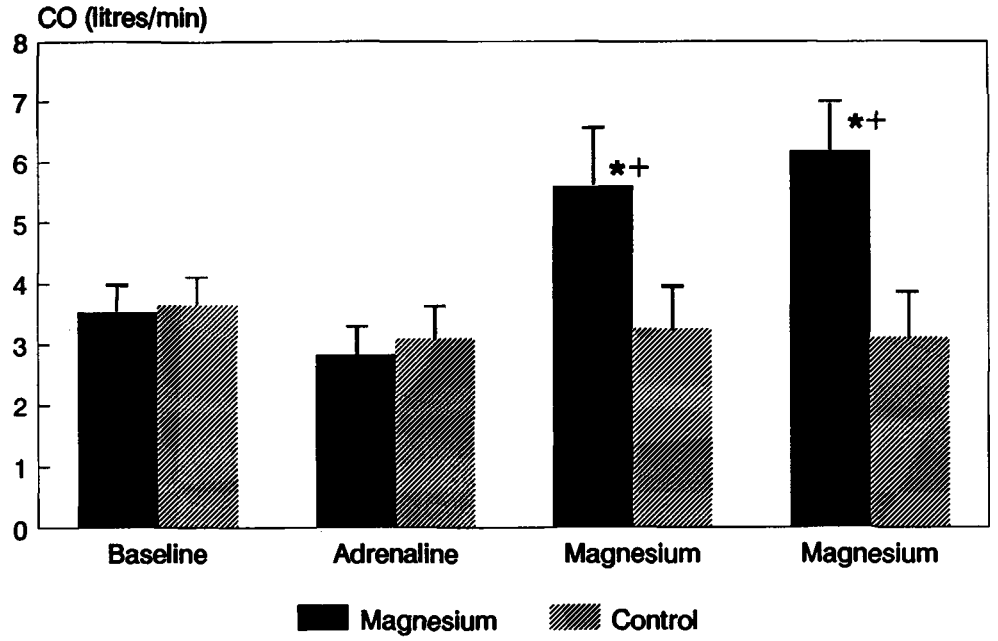


Figure 6.3. Changes in Cardiac Output.
** - $p < 0.005$ for differences between $MgSO_4$ and saline*
\+ - $p < 0.05$ for differences from baseline

6.2.6 Stroke Volume: Baseline mean SV was 34.73 ± 2.60 ml/beat. Adrenaline infusion reduced SV slightly in both groups but this change was not significant. Following the injections of magnesium, SV increased significantly from post-adrenaline levels to 42.26 ± 4.38 ml/beat and 42.38 ± 4.29 ml/beat ($p < 0.05$). The two post-magnesium levels of SV were significantly higher than those in the saline-treated controls ($p < 0.05$). These results are illustrated in figure 6.4.

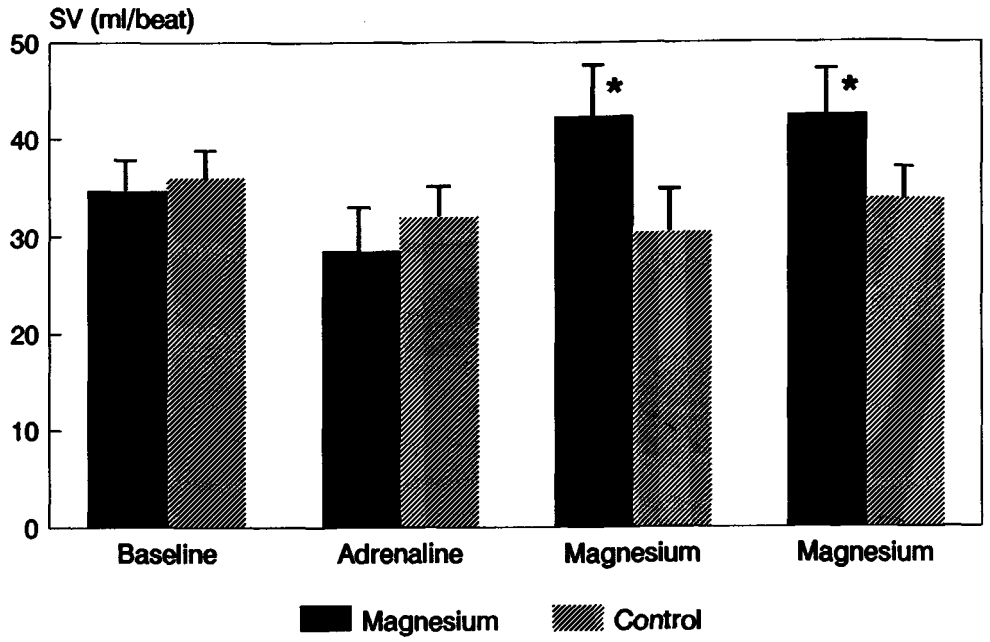


Figure 6.4. Changes in Stroke Volume.
** - $p < 0.05$ for differences between $MgSO_4$ and saline*

6.2.7 *Systemic Vascular Resistance:* In the treatment group, the adrenaline infusion increased SVR from a baseline mean of 2506 $\pm$ 207 dyne.sec.cm^{-5} to a mean of 4378 $\pm$ 497 dyne.sec.cm^{-5} ($p < 0.05$), with a similar significant increase occurring in the control group. The first magnesium injection reduced SVR to 1809 $\pm$ 303 dyne.sec.cm^{-5} and the second produced a further reduction in SVR to 1451 $\pm$ 135 dyne. sec.cm^{-5}. This second value was significantly below baseline SVR ($p < 0.05$). SVR in control animals remained unchanged from the post-adrenaline levels, and the difference between the controls and magnesium-treated animals was significant at the 0.005 level for each of the post-magnesium values (figure 6.5).

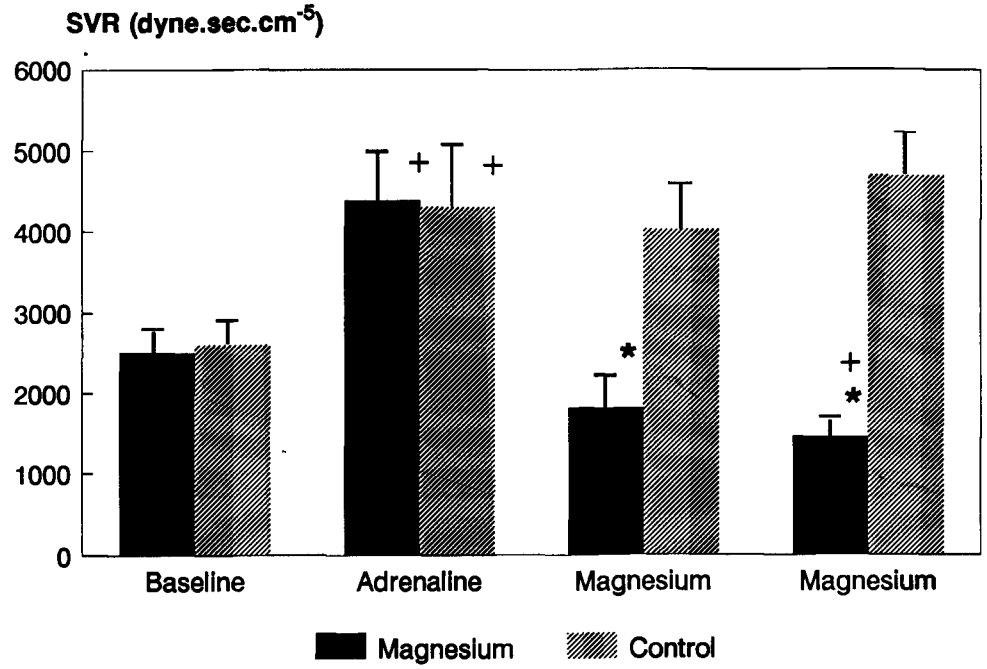


Figure 6.5. Changes in systemic vascular resistance.
** - $p < 0.05$ for differences from baseline*
\+ - $p < 0.005$ for differences between $MgSO_4$ and saline

6.2.8 *Pulmonary Artery Pressure:* Following adrenaline, pulmonary systolic pressure increased from a mean baseline value of 18.7 $\pm$ 3.8 mmHg to 36.33 $\pm$ 15.4 mmHg ($p < 0.05$). The injections of magnesium produced a small but non-significant reduction in pressure to means of 32.3 $\pm$ 4.3 mmHg and 30.7 $\pm$ 4.7 mmHg respectively.

Pulmonary diastolic pressures showed a similar pattern, but none of the changes reached statistical significance.

6.2.9 *Pulmonary Vascular Resistance:* PVR was increased by adrenaline from 109.8 $\pm$ 14.7 to 182 $\pm$ 47.4. Magnesium reduced PVR to 108.7 $\pm$ 24.5 and 114 $\pm$ 19.2 but neither of these changes reached statistical significance due to the large variability in the samples.

6.2.10 Central Venous Pressure: CVP increased significantly from a baseline value of 4.67 ± 0.76 mmHg to 9.33 ± 1.31 mmHg following adrenaline. Following the first magnesium injection, CVP fell to 6.50 ±1.54 mmHg and after the second injection to 5.33 ± 1.36 mmHg. Neither of the post-magnesium values was significantly different from baseline. The difference between saline-treated controls and the magnesium group was not significant after the first dose of magnesium, but CVP was significantly lower in the magnesium group after the second dose ($p < 0.02$). When the change in CVP from baseline was considered, the post adrenaline increase of 4.67 ± 1.02 mmHg was significantly different from baseline and from both post-magnesium values.

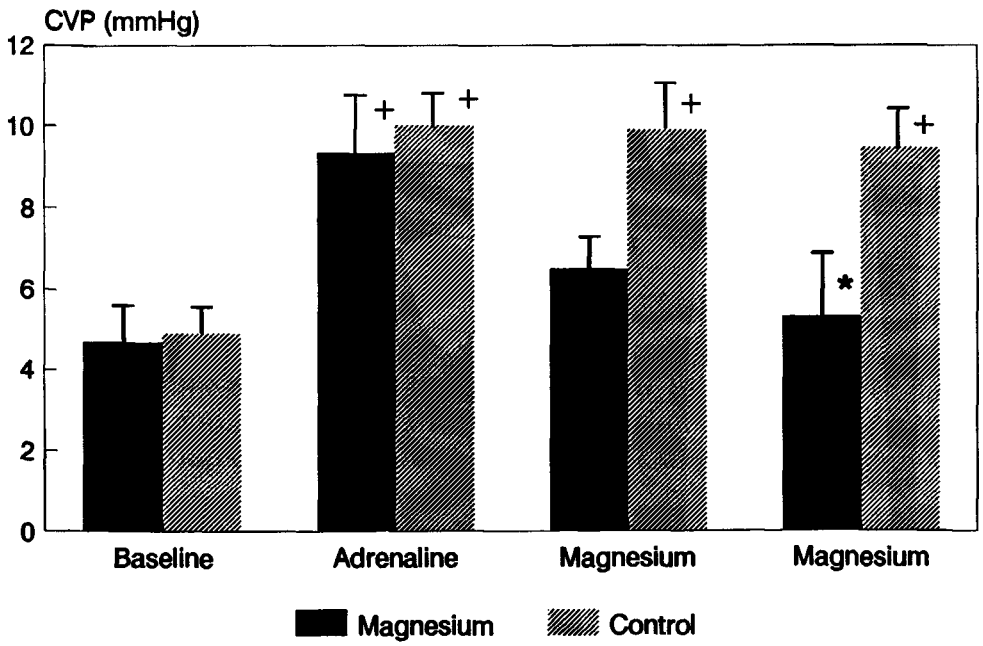


Figure 6.6. Changes in central venous pressure
** - $p < 0.05$ for differences between $MgSO_4$ and saline*
\+ - $p < 0.05$ for differences from baseline

6.2.11 Pulmonary Capillary Wedge Pressure: Adrenaline significantly raised PCWP from baseline by a mean of 10.8 ± 3.4 mmHg ($p < 0.05$). Following the first magnesium injection, PCWP was 6.0 ± 2.7 mmHg above baseline, and after the second injection PCWP was 2.83 ± 2.91 mmHg above baseline. The changes in PCWP following magnesium injections were not significantly different from either baseline values, or post-adrenaline levels. There was no significant difference between treatment and control groups.

TABLE 6.1

EVENT	BASELINE	ADRENALINE	MAGNESIUM1	MAGNESIUM2	SALINE
SBP	147.3±8.2	214.7±16.5*	167.5±20.1+	166.8±9.0+	207.5±14.3'
DBP	94.0±6.5	125.2±13.6*	96.7±8.2+	84.2±4.2+	121.2±11.7'
HR	101.0±3.2	89.8±13.4	130.3±9.3*+	145.8±4.9*+	94.9±10.4
CO	3.54±0.35	2.83±0.36	5.59±0.83*+	6.19±0.72*+	2.79±0.42
SV	34.7±2.6	28.5±3.8	42.3±4.4*+	42.4±4.3*+	30.4±4.8
SVR	2505±207	4378±497*	1809±303+	1451±135*+	4298±387*

Table 6.1. Significant changes in cardiovascular parameters with infusion of adrenaline and subsequent injections of magnesium or saline. As the values after each injection of saline were virtually identical, a single value for controls is shown.

SBP - systolic blood pressure in mmHg

DBP - diastolic blood pressure in mmHg

HR - heart rate in beats per minute

CO - cardiac output in litres per minute

SV - stroke volume in ml per beat

SVR - systemic vascular resistance in dyne.sec.cm^{-5}

* - significant difference from baseline values $p < 0.05$

\+ - significant difference from control values $p < 0.05$

6.3 DISCUSSION

Magnesium is necessary for normal smooth muscle physiology (Altura & Altura, 1981b) and variations in serum magnesium can profoundly affect vascular tone. Hypermagnesaemia reduces vascular tone by a number of mechanisms including direct action on vascular smooth muscle (Altura & Altura, 1981c; Altura & Altura, 1984 a & b), interference with the action of various vasoconstrictor agents (Altura & Altura, 1977; Levin et al., 1976; Turlapaty & Altura, 1980), and possibly blockade of sympathetic ganglia (Hutter & Kostial, 1954; Stanbury, 1948). The hypotensive effect of magnesium has been ascribed to a combination of all of these effects (Engbaek, 1952). The reduction in vascular resistance demonstrated in this study could be explained by any of these mechanisms. However, in this study SVR was reduced to one third of the pre-magnesium level which is far in excess of the reduction demonstrated in the same baboons without adrenaline in whom similar levels of serum magnesium reduced the SVR by 20% (vide supra). As both ganglionic blockade and direct vasodilatation should have been operative to the same extent in this and the previous study, it seems reasonable to conclude that the large reduction in peripheral resistance shown in the present study was primarily due to alpha-adrenergic blockade as a result of the increased serum magnesium. Alpha-adrenergic blockade produced by hypermagnesaemia has been well described in isolated vessels in various organs from different species (Altura & Altura, 1981; Burn & Gibbons, 1964; Farmer & Campbell, 1967; Turlapaty & Altura, 1982) but has not previously been shown to have a clinically useful

action in an intact animal. Since blood pressure was restored to baseline by the infusion of magnesium it is highly likely that this effect will be of clinical value.

Magnesium is well known as an anti-arrhythmic agent in various circumstances, notably in the presence of digitalis (Boyd & Sherf, 1943; Chadda et al., 1968; Enselberg et al., 1950; Iseri et al., 1975; Szekely, 1946). However, anti-arrhythmic properties of magnesium in the face of high levels of adrenaline have not been previously shown, and this adds to the usefulness of magnesium in patients who may have raised circulating catecholamine levels. Interestingly, part of the ability of magnesium to counteract cardiac glycoside-induced arrhythmias has recently been ascribed to a reduction in sympathetic tone produced by magnesium (Tackett, 1986). The failure of adrenaline to increase heart rate in this experiment was almost certainly due to two factors. The first of these would have been reflex vagal inhibition of the heart in response to baroreceptor stimulation by the elevated blood pressure; the fact that a brief tachycardia was seen initially prior to the rise on blood pressure supports this hypothesis. The multifocal arrhythmias which occurred frequently resulted in compensatory pauses which would also have contributed to the overall decrease in rate. The increase in heart rate seen after the injection of $MgSO_4$ was probably due to the unopposed β-adrenergic effect of adrenaline in the absence of arrhythmias. However, alterations in vagal tone probably also played a part. The reduction in arterial blood pressure alone would have reduced the level of vagal inhibition, but in addition, magnesium has been

shown to inhibit the release of acetylcholine from vagal nerve terminals (Somjen & Baskerville, 1968; Toda & West, 1967). The relative importance of this action is difficult to assess in view of the direct inhibitory action of magnesium on the SA node.

The marked increase in cardiac output and stroke volume seen in this experiment following the administration of $MgSO_4$ was probably due to a combination of the reduction in afterload produced by the fall in SVR, and the unopposed β-adrenergic action of adrenaline. It is unlikely that magnesium produced any increase in contractility in its own right. However, an increase in β-agonist binding in the presence of elevated magnesium levels has been shown in some tissues (Bird & Maguire, 1978; Morton & James, 1985; Vincent, 1982; Williams et al, 1978), although this effect has not been studied in myocardial tissue. If this increase in agonist binding occurs in the myocardium, the increase in cardiac output and stroke volume could, in part, have been due to increased adrenergic stimulation. Whether or not magnesium enhances β-agonist binding, its use in situations of catecholamine excess may be of value to the myocardium on other grounds. It has been shown that magnesium does not interfere with the inotropic effect of adrenergic stimulation of the myocardium, but that high levels of magnesium reduce lactate production by the myocardium, thus presumably protecting the myocardium against some of the adverse metabolic consequences of adrenaline (Paddle & Haugaard, 1971). It is clear from this study that the relatively normal blood pressure obtained after the magnesium injections was due in large part to the increased cardiac

output, as peripheral resistance was significantly lower than baseline at this time.

It is interesting to note that despite the use of large doses of $MgSO_4$, serum magnesium levels were similar after each bolus dose. The explanation for this is likely to lie in very rapid clearance of the substance from the blood, but this result does seem remarkable in view of the rather longer half-life of magnesium shown in other studies. It is probable that at least part of the explanation for this remarkably rapid removal of magnesium lies in the enhancement of magnesium clearance by catecholamine stimulation. An increased disappearance of magnesium from the blood stream during catecholamine stimulation has been shown although whether this indicates increased renal losses of magnesium or increased intracellular uptake of the ion is at present unclear. Whilst Whyte et al (1987) believe that catecholamine stimulation causes magnesium to move into the intracellular space, other evidence suggests that catecholamines cause intracellular losses of magnesium resulting in initially raised serum magnesium concentrations, but ultimately magnesium deficiency (see Durlach, 1988 for a review). One thing is clear, however, and that is that if effective serum levels of magnesium are to be achieved in patients with catecholamine excess, quite large doses of $MgSO_4$ of at least the upper dosage range recommended in obstetrics (Sibai et al, 1981; Pritchard et al, 1984) will have to be administered. An appropriate initial dosage schedule might therefore be to start with a loading dose of 60mg/kg $MgSO_4$ followed by an infusion of 30mg/kg/hour.

In conclusion, this study has shown that magnesium may be a useful, rapid acting α-adrenergic blocker, as well as a useful anti-arrhythmic in the presence of high levels of circulating catecholamines. In addition, it is possible that magnesium may inhibit the release of catecholamines from the adrenal gland. There is thus a sound basis for the use of magnesium infusions in the management of conditions of catecholamine excess.

6.4 Interactions with Alpha-Adrenergic Blocking Drugs

The above described study demonstrated that magnesium has useful adrenergic antagonist properties, which may be of use in certain clinical circumstances. However, patients with conditions of catecholamine excess are likely to be treated with other adrenergic blocking drugs, particularly α-blockers. Therefore, before the hypothesis that magnesium may be useful in such conditions could be tested in humans, the extent of its interaction with other adrenergic blockers had to be investigated. In particular, it was essential to determine whether or not a combination of magnesium and α-blockade was likely to produce catastrophic hypotension. The purpose of this study was to compare the cardiovascular effects of magnesium in the presence of adrenaline with those of a standard α-adrenergic antagonist, phentolamine.

6.5 METHODS

In order to derive maximum information from this study, the same six animals who had served as the magnesium group in the previous experiment were used for this study, and the results obtained compared with those from the previous investigation. The anaesthetic protocol was identical to that already described in previous experiments, and identical instrumentation was used. As before, stable conditions were maintained for one hour before any readings were taken. Baseline recordings of heart rate, pulmonary and systemic systolic, diastolic and mean arterial pressures, central venous pressure, pulmonary artery wedge pressure and cardiac output were then made.

An infusion of adrenaline 1 μg/kg/min was then commenced and continued throughout the experiment. Once stable conditions had been present for at least 5 minutes, all measurements were repeated. Where arrhythmias occurred, measurements were recorded during periods of sinus rhythm. All six animals then received 0.2mg/kg phentolamine intravenously, followed by a bolus of $MgSO_4$ 60mg/kg iv. After each drug, all cardiovascular parameters were again measured, along with serum calcium and serum magnesium levels.

The results within the treatment groups were analyzed by analysis of variance and significantly different results identified using Duncan's multiple range test.

Between group comparisons with the results obtained from the use of magnesium alone were made using Student's t-test. Significance was defined as $p < 0.05$.

6.6 RESULTS

Results are presented as means $\pm$ 1 S.E.M.

6.6.1 Serum magnesium: Baseline serum magnesium values were similar in all animals with a mean of 0.617 $\pm$ 0.01 mMol/l. The $MgSO_4$ bolus increased serum magnesium levels to 3.15 $\pm$ 0.31 mmol/l. This compared well with the previous study in which the initial bolus injection produced serum magnesium levels of 3.4 $\pm$ 0.31 mMol/l, and the second injection resulted in similar levels of 3.33 $\pm$ 0.29 mMol/l.

6.6.2 Serum Calcium: Serum calcium levels were not significantly changed at any stage of the experiments.

6.6.3 Arterial Blood Pressure : Adrenaline produced a significant increase in systolic blood pressure (SBP) from a mean of 154.8 $\pm$ 7.9 mmHg ($p < 0.05$) to a mean of 227.3 $\pm$ 11.3 mmHg. Phentolamine significantly reduced SBP to 110.0 $\pm$ 9.5 mmHg ($p < 0.05$) and following the injection of $MgSO_4$ SBP was 130.8 $\pm$ 16.4 mmHg, which was not significantly different from the post-phentolamine level. This was a significantly greater reduction than that produced by the first injection of magnesium alone ($p < 0.05$), but after the second magnesium injection, values were not significantly different. In both studies, the SBP following either

phentolamine or magnesium was not significantly different from baseline (figure 6.7).

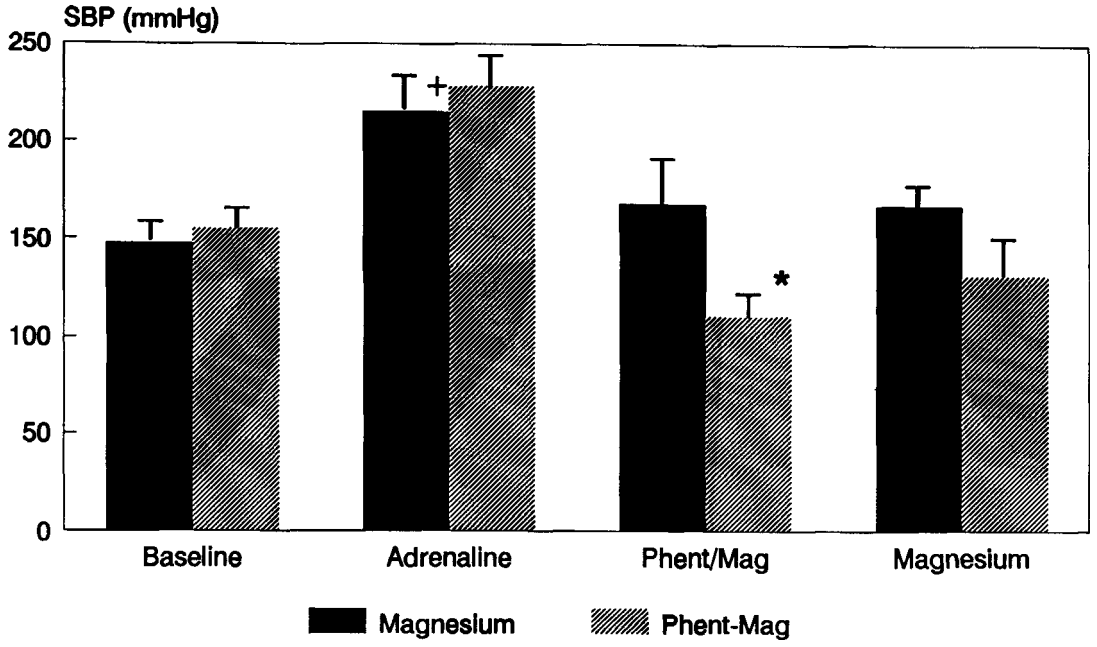


Figure 6.7. Changes in systolic arterial pressure during adrenaline infusion with either phentolamine-magnesium sequence or magnesium alone.
+ - Significant changes from baseline
** - Significant differences between groups*
Phent-Mag - phentolamine-magnesium sequence
Phent/Mag - administration of either phentolamine or $MgSO_4$

Diastolic pressures were similarly affected, increasing significantly from a baseline value of 92.5 $\pm$ 6.4 to 128.2 $\pm$ 6.1 mmHg ($p<0.05$). Phentolamine significantly reduced DBP to 49.8 $\pm$ 6.9 ($p<0.05$), and following $MgSO_4$ the DBP was 65.8 $\pm$ 9.2 mmHg. Again, the reduction in DBP was significantly greater after phentolamine than after the first dose of magnesium alone ($p<0.01$), although after the second dose of $MgSO_4$ there were no significant differences.

6.6.4 Heart Rate: As in the previous experiment, HR initially increased as the adrenaline infusion commenced, but rapidly fell and became very irregular, with multifocal ventricular and supra-ventricular arrhythmias seen in all animals. At steady-state conditions during the adrenaline infusion, the mean HR was 95.7 ± 7.5 beats/min which was not significantly different from the baseline value of 116.2 ± 3.4 beats/min. Phentolamine immediately abolished the arrhythmias and significantly increased HR to a mean of 188.3 ± 5.8 beats/min. Phentolamine produced a significantly greater increase in HR than that seen after magnesium alone ($p < 0.01$). Injection of $MgSO_4$ after phentolamine produced a slight drop in heart rate to 174.0 ± 5.2 beats/min (figure 6.8).

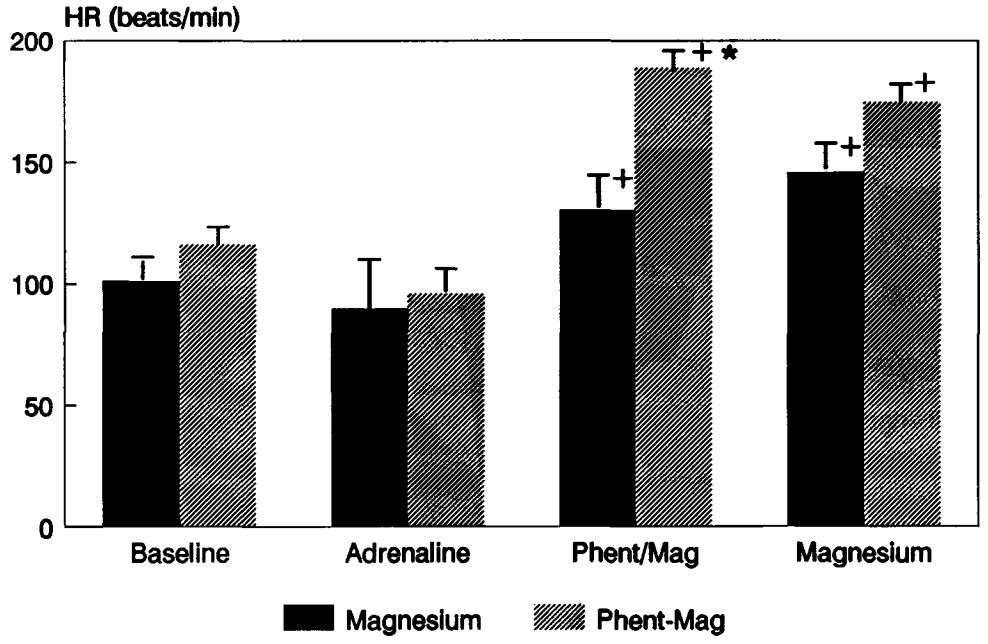


Figure 6.8. Changes in heart rate during adrenaline infusion with either phentolamine-magnesium sequence or magnesium alone.

+ - Significant changes from baseline

** - Significant differences between groups*

Phent-Mag - phentolamine-magnesium sequence

Phent/Mag - administration of either phentolamine or $MgSO_4$

6.6.5 *Cardiac Output:* **The adrenaline infusion caused a slight, but not significant reduction in CO from a mean of 3.51 ± 0.27l/min to a mean of 3.17 ± 3.0 l/min. Phentolamine caused a marked increase in CO to 5.98 ± 0.36 l.min and after magnesium the CO was 6.7 ± 0.49 l/min; both of these values were significantly different from both baseline and post adrenaline values, but not from each other, or from the values obtained using magnesium alone (figure 6.9).**

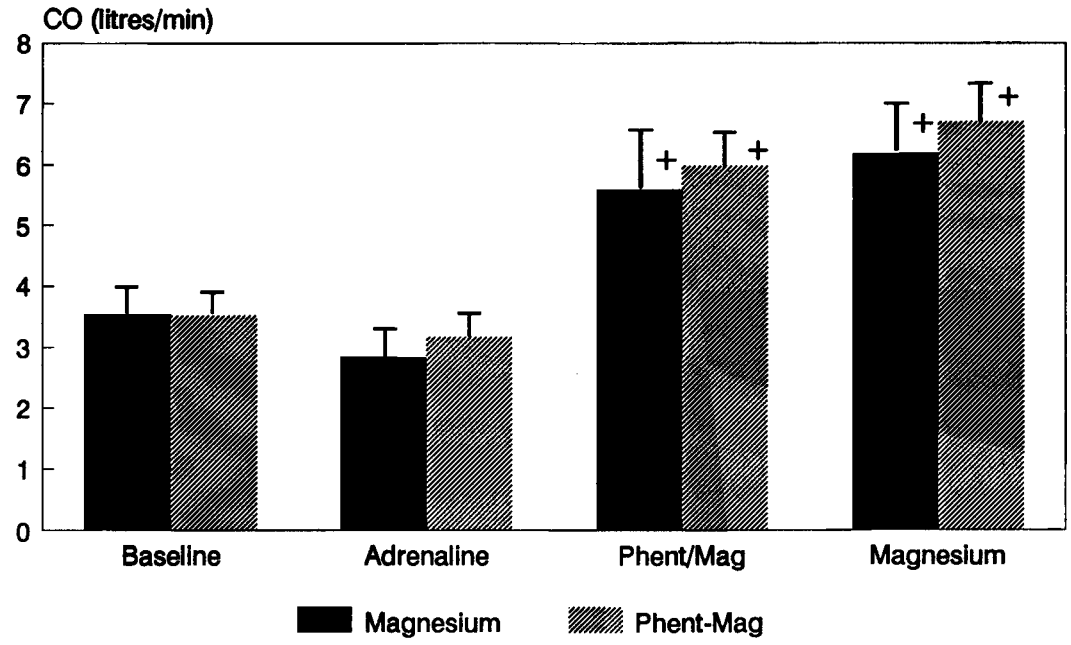


Figure 6.9. Changes in cardiac output during adrenaline infusion with either phentolamine-magnesium sequence or magnesium alone.
+ - Significant differences from baseline
Phent-Mag - phentolamine-magnesium sequence
Phent/Mag - administration of either phentolamine or $MgSO_4$

6.6.6 Stroke Volume: Baseline mean SV was 30.11 ± 1.97 ml/beat. After the adrenaline infusion SV was 33.02 ± 1.4 ml/beat but this difference was not significant. After phentolamine SV was 34.75 ± 3.35 ml/beat, and after the addition of magnesium the SV was 38.91 ± 2.53 ml/beat, the SV after magnesium being significantly higher than baseline ($p<0.05$), but not significantly different from other values (figure 6.10).

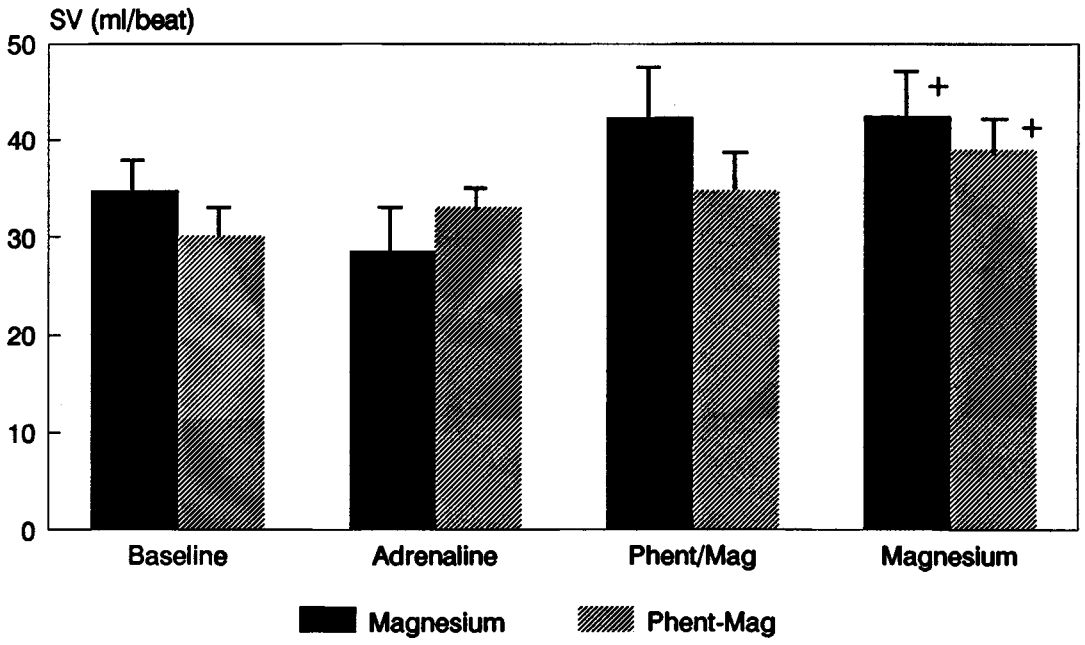


Figure 6.10. Changes in stroke volume with either phentolamine-magnesium sequence or magnesium alone.
+ - Significant differences from baseline
Phent-Mag - phentolamine-magnesium sequence
Phent/Mag - administration of either phentolamine or $MgSO_4$

6.6.7 Systemic Vascular Resistance: The adrenaline infusion increased SVR from a baseline mean of 2502 ± 91 dyne.sec.cm^{-5} to a mean of 3938 ± 240 dyne.sec.cm^{-5} ($p<0.05$). Phentolamine significantly reduced SVR to

801 ± 54 dyne.sec.cm^{-5} ($p < 0.05$) and after magnesium the value was 904 ± 88 dyne.sec.cm^{-5}.

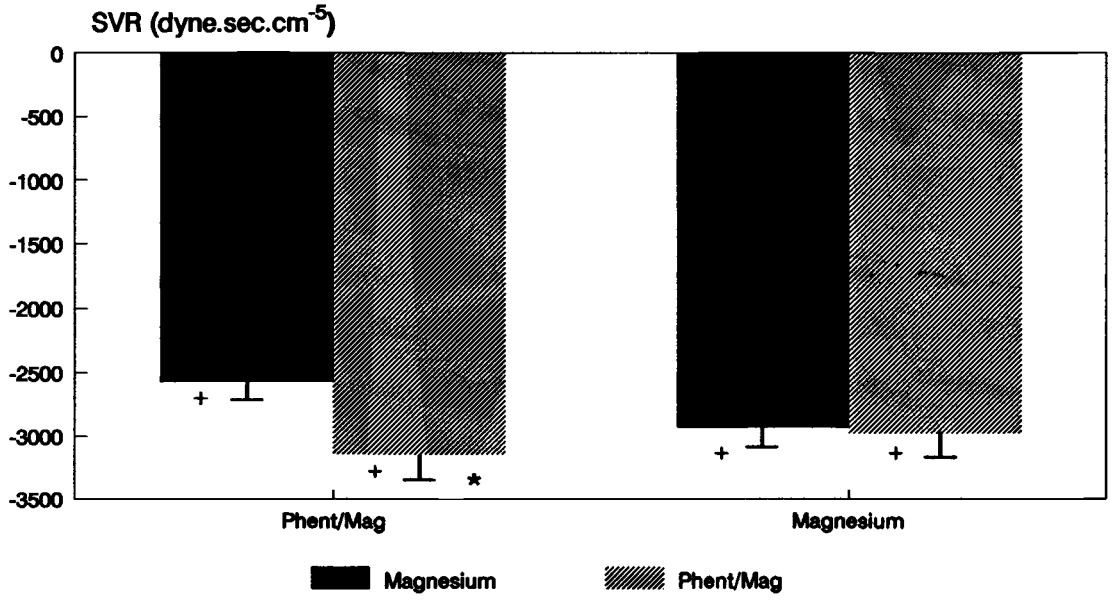


Figure 6.11. Changes in systemic vascular resistance, after the administration of adrenaline, with either phentolamine-magnesium sequence or magnesium alone.
+ - Significant changes from post-adrenaline values
** - Significant diferences between groups*
Phent-Mag - phentolamine-magnesium sequence
Phent/Mag - administration of either phentolamine or $MgSO_4$

The reduction in SVR produced by phentolamine was significantly greater than that produced by the first dose of $MgSO_4$ in the initial study, but there was no significant difference between the groups after the final magnesium dose. When the post-adrenaline value for SVR was taken as the base point for between group comparisons, there was a significant, but small, difference between the reduction in SVR produced by phentolamine after adrenaline and that produced

by the first magnesium dose, but the reduction in SVR after the final magnesium dose was virtually identical in the two study groups (figure 6.11).

6.6.8 Pulmonary Artery Pressure: Following adrenaline, pulmonary systolic pressure increased from a mean baseline value of 21.5 $\pm$ 1.6 mmHg to 36.0 $\pm$ 4.0 mmHg ($p<0.05$) which compared well with similar changes found in the previous study. Neither phentolamine nor $MgSO_4$ produced a significant reduction in PAP, and there were no differences between the results in the two studies. Diastolic pressures showed a similar pattern, but none of the changes reached statistical significance.

6.6.9 Central Venous Pressure: Adrenaline produced an significant increase in CVP of 4.7 $\pm$ 1.0 mmHg from baseline in both groups ($p<0.05$). In both groups, the CVP returned to baseline after the administration of the vasodilator drugs.

6.6.10 Pulmonary Capillary Wedge Pressure: Adrenaline significantly raised PCWP from baseline by a mean of 12.2 mmHg ($p<0.05$). Phentolamine returned PCWP to baseline, and the levels of PCWP after phentolamine were significantly lower than those after adrenaline ($p<0.05$). This result compared well with that obtained in the previous study in which there was a similar trend, but the changes did not reach statistical significance. There were no significant differences between the groups.

6.7 DISCUSSION

At the level of serum magnesium attained in these experiments, magnesium appeared to exert similar cardiovascular effects to those produced by phentolamine. Phentolamine produced a significantly greater increase in heart rate than that produced by magnesium alone, but this was probably simply due to a reflex response to the greater hypotensive effect of phentolamine compared to that produced by magnesium alone. It could be argued that the tendency of magnesium to reduce heart rate might have contributed to the lesser increase in heart rate, particularly in view of the tendency for heart rate to decrease in the phentolamine group following the administration of magnesium. The results of these experiments, however, do not permit the drawing of that conclusion, and that must remain a purely speculative possibility. Cardiac output changes in the two groups were similar, although magnesium produced an increase in stroke volume, whereas stroke volume following phentolamine was unchanged. This is probably because the slower heart rate after magnesium allowed more time for ventricular filling, although it should be noted that in the magnesium group the increased stroke volume was achieved against a significantly higher vascular resistance than that pertaining following phentolamine.

Phentolamine produced a greater reduction in SVR than that produced by magnesium, but the difference was small. The addition of magnesium to

phentolamine produced no significant changes in any of the cardiovascular variables measured, and it seems likely, therefore, that the two drugs were acting through similar mechanisms, and that this large dose of phentolamine produced near-maximal α-adrenergic blockade. Although magnesium is well known to be a direct vasodilator, in the presence of adrenaline, its α – blocking properties appear to predominate.

Although it is difficult to draw any concrete conclusions regarding contractility from a study of this nature in which preload and afterload are continuously varying, there were no obvious signs of negative inotropic effects of magnesium in this study. On the contrary, following the infusion of magnesium, stroke volume was significantly increased above baseline despite the fact that preload and afterload were at similar level as those prior to adrenaline infusion. The only significant increase in stroke volume in the phentolamine group occurred after the addition of magnesium. This might be taken to imply that magnesium might have exerted a positive inotropic effect in the presence of adrenaline as no such increase in stroke volume was seen in the phentolamine group despite a lower afterload. There is no evidence that magnesium exerts a positive inotropic effect in its own right, and the only likely explanation for this is that magnesium could have enhanced β-agonist binding to the myocardium. Magnesium does augment β-agonist receptor binding in certain tissues (vide supra), although this effect has not been studied in myocardial tissue.

This study has confirmed that magnesium has useful α-adrenergic blocking properties, similar to those possessed by phentolamine although of lesser magnitude at the dosages used. It seems unlikely to produce dangerous additional effects in patients already treated with other α-adrenergic blocking drugs. In addition it has been shown that magnesium can exert useful anti-arrhythmic effects in the presence of catecholamines and it is unlikely to produce any myocardial depression under the circumstances of raised adrenaline levels. There is a possibility that magnesium may have a protective effect on the adrenergically-stimulated heart.

6.8 Interactions with Beta-Adrenergic Blocking Drugs

The final piece of information required to indicate that magnesium sulphate would be safe to use in conditions of catecholamine excess was the extent of possible interaction with β-blocking agents. In the management of these patients, α-adrenergic blockade is almost invariably the first-line choice. Administration of a β-adrenergic blocker to a patient with catecholamine excess is likely to be extremely hazardous as the unopposed alpha effects could produce severe hypertension and cardiac failure (Hull, 1987; Edmondson & Flowers, 1979; Buchanan et al., 1978). The only circumstances in which β-adrenergic blockers should be used to treat adrenergic overload should be

in conjunction with the use of α-blockade. Therefore, in order to investigate the potential for interaction between magnesium and β-blockers it was decided to use the same experimental model as that employed in the previous experiments described in this chapter, but in addition to administer β-blockade subsequent to the α-blockade in order to restore near-normal cardiovascular status to the animal despite the continuing adrenaline infusion. Subsequent administration of magnesium should thus unmask any potentially dangerous interaction, in particular the danger of myocardial depression, as is known to occur with other calcium antagonist drugs in the presence of β-blockade.

6.9 METHODS

Six chacma baboons were studied using the same experimental design as has been previously described, with the same monitoring devices, and the same anaesthetic technique. As in the previous experiments, an infusion of adrenaline was administered at a rate of 1μg/kg/min. and continued throughout the experiment. Phentolamine was then administered intravenously, with repetition of all measurements, followed by the administration of 1mg propranolol intravenously, at which point all measurements were again repeated. $MgSO_4$ at a dose of 60mg/kg was then administered and a final set of measurements made.

6.10 RESULTS

Results are presented as means ± 1 S.E.M. The main points from the results are summarized in table 6.2.

6.10.1 Serum Magnesium: Serum magnesium levels were increased from a baseline value of 0.68 ± 0.045 mmol/l to 3.26 ± 0.12 mmol/l by the magnesium infusion.

6.10.2 Heart Rate: As in the previous experiment, adrenaline produced an initial tachycardia followed by a return of heart rate to baseline values accompanied by multifocal arrhythmias. Phentolamine again abolished the arrhythmias and produced a rapid increase in heart rate to a mean of 187.17 ± 6.76 beats per min. Propranolol reduced the heart rate to a mean of 122.67 ± 8.27 which was not significantly different from the baseline value of 116.83 ± 7.87 beats per min. The administration of $MgSO_4$ was accompanied by a further slight, not significant decline in heart rate to 109.83 ± 2.55 beats per min.

6.10.3 Systemic Blood Pressure: As in the previous experiment, the infusion of adrenaline increased blood pressure significantly to 235.17 ± 19.4 mmHg and the use of phentolamine reduced the blood pressure to 100.80 ± 11.04 mmHg, which was not significantly different from the baseline value of 123.17 ± 8.27 mmHg. Neither propranolol nor magnesium caused any further significant change in blood pressure.

Diastolic blood pressure was similarly affected with adrenaline causing a significant increase above and phentolamine causing a significant reduction below baseline. Propranolol restored DBP to baseline levels and magnesium produced no further significant change.

6.10.4 Cardiac Output: As in the previous experiments, at steady state conditions during the adrenaline infusion CO was not significantly different from baseline. Phentolamine produced a significant increase in heart rate and this was restored to baseline levels by the administration of the beta-blocker. Magnesium produced a small increase in cardiac output, but this did not reach statistical significance.

6.10.5 Stroke Volume: There were no significant differences for the values of stroke volume at the various stages of the experiment. However, when the changes in stroke volume from baseline were considered, magnesium produced a significant increase in stroke volume (figure 6.12).

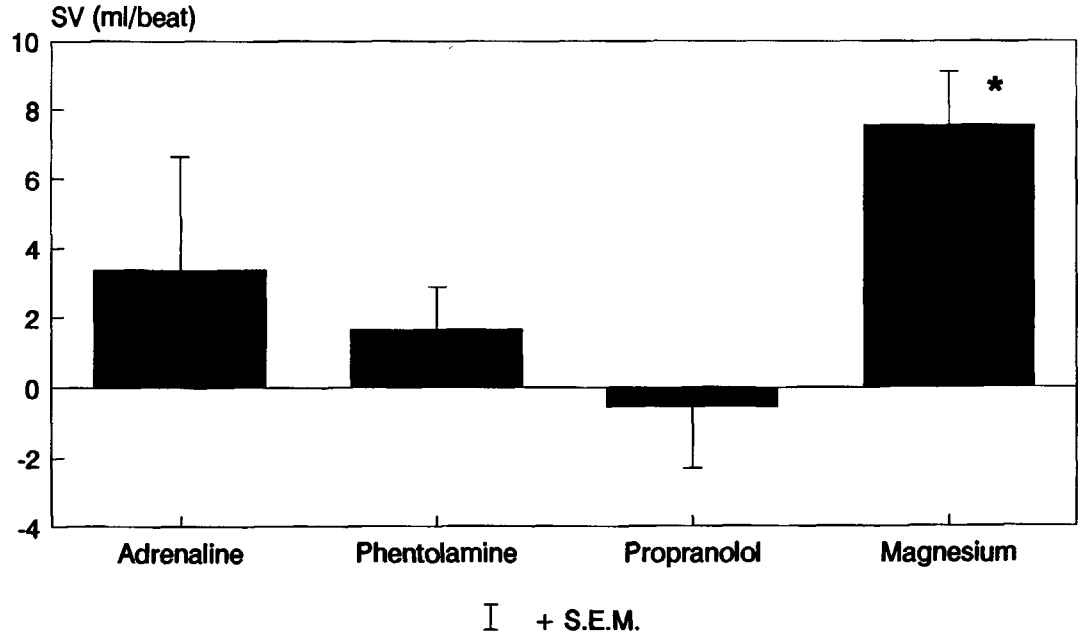


Figure 6.12 Changes in stroke volume from baseline at each stage of the experiment.
** - $p < 0.05$ for differences from baseline.*

6.10.6 Pulmonary Arterial Pressure: As in the previous studies adrenaline caused a significant increase in both systolic and diastolic pressures and phentolamine restored these values to their baseline levels. Neither propranolol nor magnesium produced any further significant changes.

6.10.7 Central Venous Pressure: CVP was significantly increased by the adrenaline infusion and this was restored to baseline by phentolamine. Neither propranolol nor magnesium caused any further significant changes in CVP.

6.10.8 Pulmonary Capillary Wedge Pressure: The changes in PCWP were identical to those in CVP with adrenaline producing a significant increase in wedge pressure, but no other result being significantly different from baseline

Table 6.2/ over

TABLE 6.2

	Base	Adren	Phent	Prop	Magnesium
HR	116.83	107.00	187.17*	122.67	109.83
b.p.m.	(7.87)	(14.01)	(6.76)	(3.56)	(2.55)
SBP	123.17	235.17*	100.80	114.67	116.63
mmHg	(8.27)	(19.40)	(11.04)	(8.41)	(6.95)
DBP	76.17	128.17*	38.33*	71.83	65.67
mmHg	(7.14)	(10.63)	(2.24)	(5.84)	(4.07)
CO	3.63	3.41	6.27*	3.81	4.33
l/min	(0.27)	(0.21)	(0.42)	(0.41)	(0.38)
SV	32.18	35.56	33.84	31.63	39.72
ml/beat	(3.21)	(5.15)	(2.76)	(4.04)	(3.92)

Table 6.2. Principle cardiovascular changes found with magnesium injection in adrenaline treated α- and β-blocked baboons. Figures in parentheses indicate one standard error of the mean.

Base - baseline values
Adren - results following adrenaline infusion
Phent - results following phentolamine administration
Prop - results following propranolol administration
HR - heart rate
SBP - systolic arterial blood pressure
DBP - diastolic arterial blood pressure
CO - cardiac output
SV - stroke volume
* - $p < 0.05$ for differences from baseline.

6.11 DISCUSSION

As in the previous experiment, phentolamine reversed the hypertensive, vasoconstrictor and arrhythmic effects of adrenaline, allowing the unopposed beta effects to produce significant increases in cardiac output and heart rate, but not stroke volume. The marked decrease in systemic vascular resistance was probably in part due to β-mediated vasodilatation as well as to α-blockade. The administration of propranolol reversed these β-adrenergically mediated changes and restored all of the measured cardiovascular variables to baseline values. It is reasonable to assume, therefore, that α- and β-adrenergic blockade, at the doses used, had totally reversed the effects of adrenaline in these animals. The further addition of magnesium to the preparation produced very little further change in cardiovascular parameters, the only significant change being the increase in stroke volume from baseline values.

On the basis of these results it would seem reasonable to conclude that magnesium is not likely to exhibit additive effects with those of the β-blockers in patients with catecholamine excess. In particular, there was no evidence at all that magnesium was likely to produce potentially hazardous negative inotropic actions in combination with β-antagonists in such patients. On the contrary, the increase in stroke volume might be interpreted as an increased β-agonist effect, although this interpretation must be regarded with caution as the complex interrelationships between preload and afterload in this model

make hard conclusions about contractility very difficult to draw. By far the most reasonable conclusion is that magnesium is unlikely to be dangerous in the presence of β-blockade in patients with adrenergic excess.

6.12 CONCLUSIONS

These experiments have demonstrated for the first time in the intact animal a number of interesting, and potentially valuable, interactions between magnesium and adrenergically active agents. In the first experiment it was shown that magnesium can exert anti-adrenergic effects of a magnitude that would be likely to be useful in the clinical situation. The second experiment showed that these actions of magnesium were qualitatively similar to those of phentolamine, and that there were no obvious potentially hazardous interactions between magnesium and this alpha-adrenergic blocker. Finally, it was shown that magnesium did not appear to have any apparently hazardous interactions with beta-blockers. In particular, the theoretically possible potentiation of the negative inotropic effects of beta-adrenergic blockade did not appear to occur. Combinations of alpha- and beta-blockade with magnesium seem, therefore, unlikely to be dangerous in a patient with catecholamine excess.

Magnesium does, therefore, appear to have a considerable number of potential applications in conditions of catecholamine overload. The useful alpha-adrenergic antagonistic effects of this agent combined with its capacity for inhibiting the release of catecholamines could make magnesium uniquely beneficial in such clinical situations. There is also the interesting possibility that magnesium may protect the myocardium from the adverse metabolic consequences of catecholamine drive. Demonstration of the fact that the theoretical possibility that magnesium can inhibit the release of catecholamines is, in fact, borne out in the clinical situation is the theme of the final chapters of this thesis.

7. Catecholamine Release at Endotracheal Intubation

It has been shown in preceding chapters that magnesium has anti-adrenergic properties which may be clinically useful in conditions of adrenergic excess. The unique additional ability of this agent to inhibit the release of catecholamines from adrenergic nerve terminals and from the adrenal gland in vitro (Douglas & Rubin, 1963; Lishajko, 1970), may have many clinical applications, but this action has never been investigated in intact animals or humans.

The commonest situation in which an anaesthetist faces a predictable stress response in his patients is at the time of endotracheal intubation. It is well known that laryngoscopy and intubation produce marked increases in heart rate and blood pressure (Siedlecki, 1975), which carries with it a risk of myocardial strain. The problem has been extensively reviewed by Ng (1985). This response is associated with the release of catecholamines in large amounts (Russell et al., 1981; Derbyshire et al., 1983). There are various techniques by which this intubation-related stress response can be attenuated, all of which

depend on reduction in input stimuli by local anaesthetics or centrally-acting analgesics, or the peripheral blockade of adrenergic responses. These methods include the use of lignocaine both topically and by intravenous injection (Stoelting, 1978); the administration of beta-blocking drugs (Sledlecki, 1975); the use of direct-acting vasodilators (Stoelting, 1979); and the use of large doses of opiates, notably fentanyl and alfentanil (Stanley et al., 1980, Crawford & Fell, 1987). All of these techniques have disadvantages related to either cardiovascular or respiratory depression, and none of them directly inhibits the release of catecholamines.

As has been demonstrated in previous chapters, magnesium seems to have relatively minor cardiovascular side effects at moderate blood levels, despite its apparently useful anti-adrenergic properties. Such cardiovascular effects as do occur are likely to be beneficial to a stressed myocardium - reduction in afterload and a decrease in heart rate. The only respiratory depressant effect of this agent is related to its well-known ability to potentiate the action of the non-depolarising neuromuscular blocking drugs (Ghonheim & Long, 1970). The stress of endotracheal intubation therefore seemed an appropriate model in which to investigate the ability of magnesium to control cardiovascular disturbances and to inhibit the release of catecholamines under repeatable and controlled situations.

7.2 METHODS

The study was approved by the Ethics Committee of Hillbrow Hospital and the University of Witwatersrand and all patients gave informed consent.

7.2.1 Patient selection: Participants in the trial were male ASA I-II patients booked for elective maxillo-facial surgery in which the anaesthetic technique would require endotracheal intubation. Patients were randomly allocated to one of two Groups, Group A or Group B, using tables of random numbers. There were 15 patients in each group.

7.2.2 Anaesthetic Technique. All patients were premedicated with diazepam 10 mg p.o. 1 hour preoperatively. Under local anaesthesia, an intravenous cannula was inserted into one forearm for infusion of drugs, and a central venous line was placed via an antecubital vein for blood sampling. Anaesthesia was induced with a sleep dose of thiopentone, and Group A patients then received an infusion of $MgSO_4$ 60mg/kg i.v. over 1 minute. Group B subjects received an equivalent volume of saline also over 1 minute. During these infusions, 50% nitrous oxide in oxygen was inhaled. Subjects in both groups then received suxamethonium 1mg/kg intravenously. Tracheal intubation was performed 60 sec. after the administration of suxamethonium. Based on the rapidity of onset of the anti-adrenergic effect of magnesium (see chapter 6), this timing ought to have allowed for the magnesium to exert its full effect. The person performing the intubation and the laboratory staff performing catecholamine estimations were blind as to the group to which the patient belonged.

7.2.3 Catecholamine Estimations. Blood samples for estimation of catecholamines were taken by an assistant at the following times: immediately

prior to induction, immediately prior to intubation, immediately following intubation and at 2 and 5 minutes after intubation. Tubes with blood samples for plasma catecholamine measurement were immediately placed on ice. Samples were centrifuged at 3 000 revolutions per minute for 10 min at 4° C. Aliquots of the serum were stored at -70°C for not longer than 1 week. Fractionated serum catecholamine concentrations were determined using reversed-phase high-performance liquid chromatography with electrochemical detection and an internal standard (Krstulovic, 1982; Causen & Carruthers, 1982). The lower limit of sensitivity of this method is 10 pg/ml (see Appendix A).

Standard ECG leads were monitored throughout the procedure and blood pressure was monitored non-invasively using an automatic oscillotonometric device which recorded the blood pressure every 60 sec. Heart rate was also recorded every 60 sec. Statistical analysis was performed using Student's t-test to detect differences if any between the groups. Significance was defined as ($p < 0.05$).

7.3 RESULTS

Results are reported as means $\pm$ 1 S.E.M.

The mean thiopentone dose used in Group A was 304.6 $\pm$ 15.2 mg and 322 $\pm$ 18.4 mg in Group B. There was no significant difference between the groups.

7.3.1 Serum Magnesium: Baseline serum magnesium concentrations were 0.85 ± 0.24 mmol/l in Group A and 0.81 ± 0.31 mmol/l in Group B. In Group A serum magnesium levels increased to 2.95 ± 0.56 mmol/l following intubation and remained unchanged in Group B.

7.3.2 Cardiovascular System: Induction of anaesthesia produced minimal non-significant changes in heart rate and blood pressure in both groups. In the magnesium group the injection of magnesium produced a rise in heart rate of 13 ± 3.9 beats per minute from a pre-induction mean of 92.2 ± 2.9 b.p.m.; in the control group there was no significant change in heart rate from the baseline level of 90.4 ± 2.5 b.p.m. Following intubation heart rate increased to a maximum mean value of 120.9 ± 5.8 beats per minute at 2 minutes post-intubation in the control group and in the magnesium group heart rate remained virtually unchanged from post-magnesium values at 107.3 ± 3.9 beats per minute. The difference between groups at 2 min. post-intubation was significant at the 0.05 level (figure 7.1)

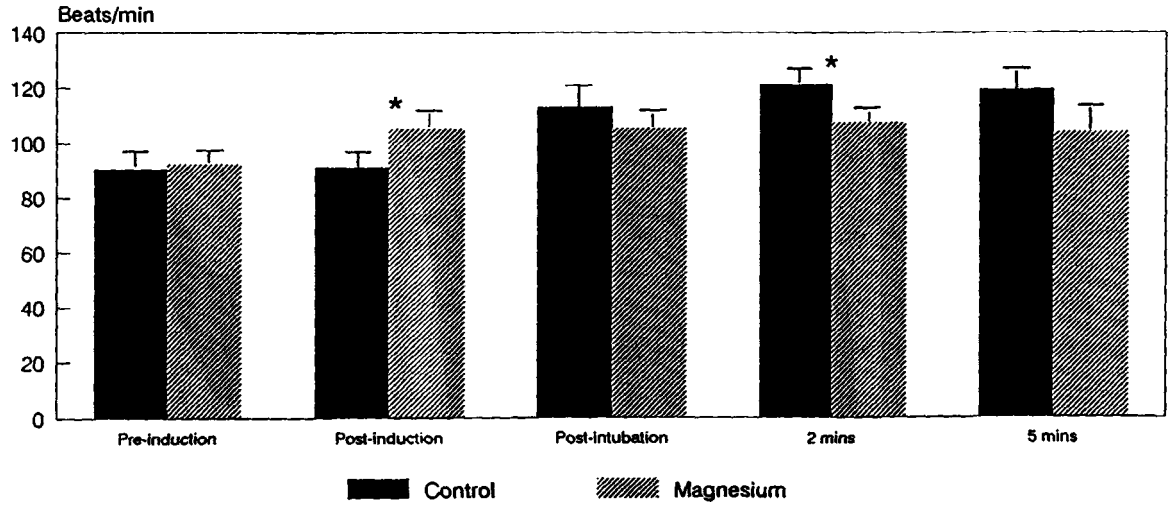


Figure 7.1 The effect of either $MgSO_4$ or saline on heart rate at the time of endotracheal intubation.
** - $p<0.05$*

Neither magnesium nor saline produced significant changes in systolic or diastolic arterial blood pressures. Systolic blood pressure prior to intubation was 108.4 ± 3.2 mmHg in the magnesium group and 105.5 ± 3.3 mmHg in the control group. At 2 minutes after intubation systolic blood pressure had increased to 128.1 ± 5.3 mmHg in the magnesium group and to 143.9 ± 4.8 mmHg in the control group ($p<0.05$, figure 7.2).

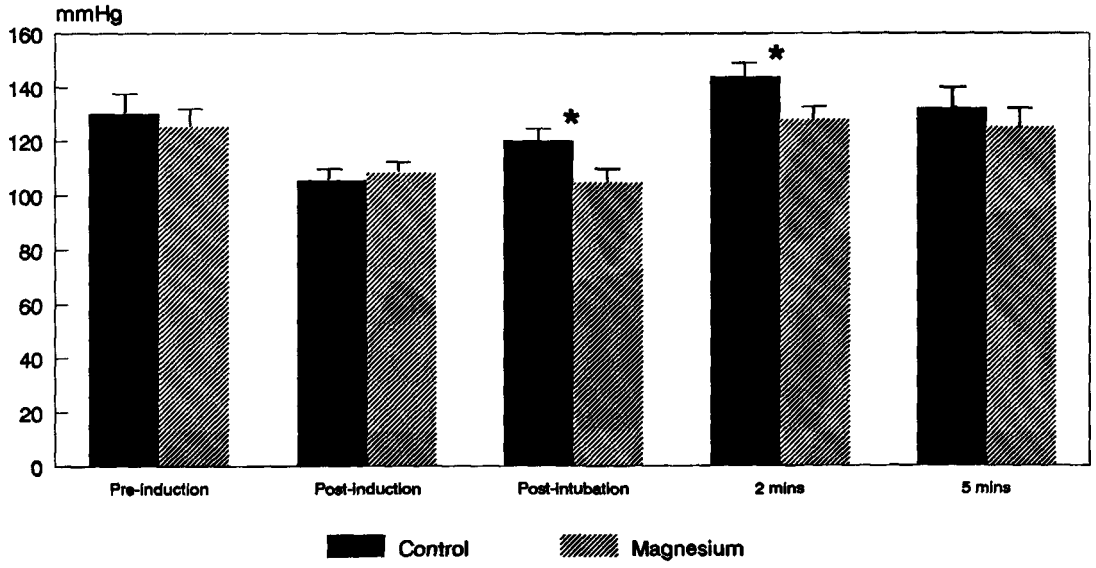


Figure 7.2 The effect of either $MgSO_4$ or saline on systolic blood pressure at the time of endotracheal intubation.
** - $p<0.05$*

Diastolic blood pressure increased in the magnesium group from a pre-intubation value of 69.9 ± 13.0 mmHg to a post-intubation value of 82.5 ± 15.0 mmHg. In the control group diastolic blood pressure increased from 68.8 ± 10.5 mmHg to 96.4 ± 14.4 mmHg following intubation. The difference between the groups was significant at the 0.02 level.

7.3.2 Catecholamines: Noradrenaline concentrations prior to induction were similar in the two groups: Group A 297.3 ± 27.9 pg/ml and Group B 271.4 ± 35.5 pg/ml and were not significantly changed by induction of anaesthesia. Following intubation, noradrenaline concentrations increased to 626.1 ± 59.4 pg/ml in Group B and to 469.4 ± 31.1 pg/ml in Group A ($p<0.05$). Two minutes after intubation noradrenaline concentrations in Group B increased to 944.6 ± 68.7 pg/ml whilst in Group A the noradrenaline value was 532.5 ± 30.1 pg/ml ($p<0.01$). Five minutes after intubation noradrenaline concentrations were 790.7 ± 68.7 pg/ml in Group B and 462.7 ± 40.0 pg/ml in Group A ($p<0.01$, figure 7.3).

Initial adrenaline levels were mildly elevated in both groups, probably as a result of the stress of impending surgery, despite the fact that the patients were apparently adequately premedicated. This effect has been described before (Derbyshire et al, 1983). Adrenaline values fell in both groups following induction of anaesthesia from 94.5 ± 16.9 pg/ml to 68.3 ± 11.2 in Group A and from 113.9 ± 19.5 pg/ml to 74.9 ± 14.2 pg/ml in Group B. In group A adrenaline concentrations remained at baseline levels throughout the study. In Group B, adrenaline concentrations increased following intubation to 158.9 ± 19.7 pg/ml ($p<0.01$) and to 279.6 ± 92.3 pg/ml ($p<0.05$) two minutes after intubation. At five minutes after intubation adrenaline concentrations had returned to post-induction values and were not significantly different from Group A (Figure 7.4).

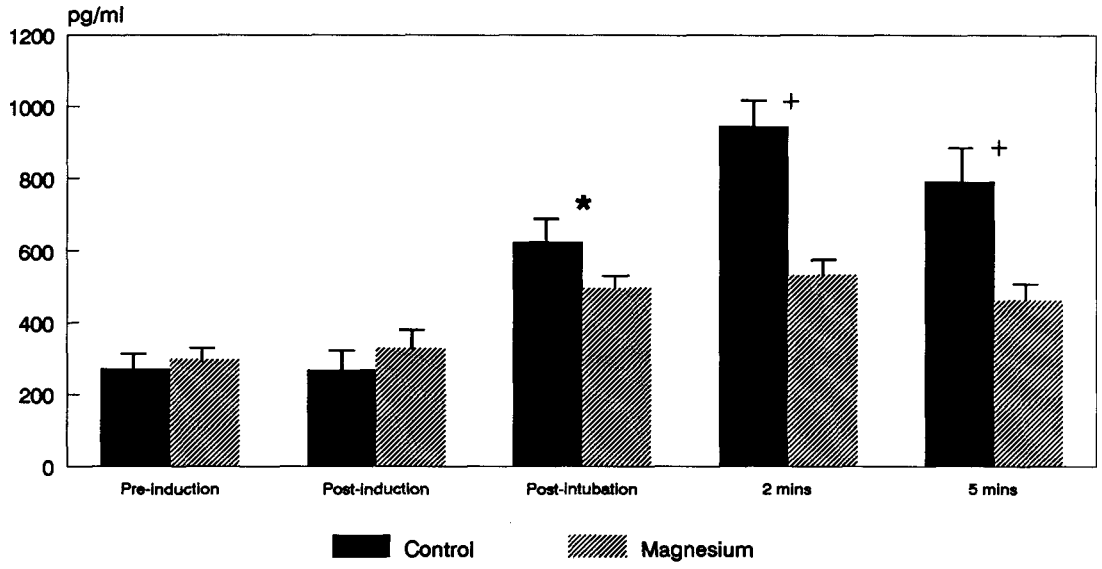


Figure 7.3 The effect of either $MgSO_4$ or saline on noradrenaline levels at the time of endotracheal intubation.
** - $p<0.05$ + - $p<0.01$*

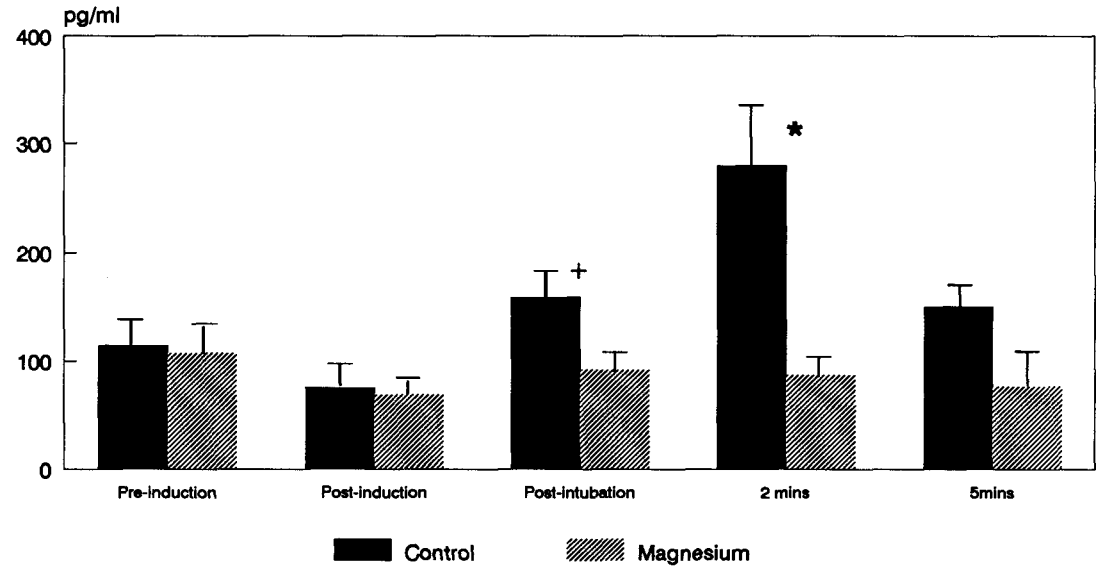


Figure 7.4 The effect of either $MgSO_4$ or saline on adrenaline levels at the time of endotracheal intubation.
** - $p<0.05$ + - $p<0.01$*

7.4 DISCUSSION

The ability of magnesium ions to inhibit the release of catecholamines from both the adrenal gland and from peripheral adrenergic nerve terminals has been known for over twenty-five years (Douglas & Rubin, 1963), and is now well established in laboratory experiments (Lishajko, 1970; Dandavino et al., 1977; Kirpekar & Misu, 1967; George & Leach, 1971), but the action of increased serum magnesium concentrations on the output of catecholamines in vivo has been poorly investigated. Although Lenz et al (1987) showed a small increase in noradrenaline values after magnesium infusion, they attributed this rise to reflex activation of the sympathetic nervous system by reduced arterial pressure; noradrenaline levels in this study remained within normal limits. The present study has shown that magnesium can significantly attenuate the output of catecholamines at the time of endotracheal intubation and thus reduce the severity of cardiovascular disturbances.

The cardiovascular effects observed in this study were particularly interesting. It might be expected that magnesium would produce a slowing of the atrial rate by inhibiting the calcium mediated depolarizing current in pacemaker tissue, and this effect has been demonstrated in isolated animal hearts (Turlapaty & Carrier, 1973). However, in the intact animal the ability of magnesium to inhibit the release of acetylcholine from the vagus nerve may predominate (Somjen & Baskerville, 1968) and this could explain the mild increase in heart

rate seen in this experiment. Although this result is slightly at variance with the earlier studies described in chapter 5, this discrepancy is small, and species differences may account for it. Despite this initial, small increase in heart rate, there was no further increase in heart rate following intubation in the magnesium group. Although heart rate in the control group was significantly lower than that in the magnesium group prior to intubation, the post-intubation heart rate in the control group was significantly higher than that in the magnesium group. This was presumably due to the fact that adrenaline concentrations in the magnesium group did not increase above baseline values whereas in the control group there was a significant increase in adrenaline concentrations.

The vasodilator effects of magnesium have been well described (Ghonheim & Long, 1970; Turlapaty & Carrier, 1973; Somjen & Baskerville, 1968; Altura & Altura, 1978a; Kelly et al, 1960; Farmer & Campbell, 1967), and are characterized by a mild and transient fall in blood pressure which is associated with peripheral vasodilatation and a consistent increase in cardiac index (Mroczek et al, 1977; Chapter 5, vide supra). Magnesium has also been shown to reduce the responsiveness of vascular smooth muscle to noradrenaline stimulation (Farmer & Campbell, 1967). In the present study, increases in both systolic and diastolic blood pressure were less in the magnesium group than those seen in the control group. In neither group was the release of noradrenaline totally prevented but the noradrenaline levels in the magnesium

group were significantly lower than those seen in the control group. The improved control of blood pressure in the magnesium group was probably therefore due to a combination of the vasodilatory effects of the ion and the inhibition of catecholamine release.

This study thus provides the first evidence that elevated serum magnesium concentrations can inhibit the release of catecholamines during periods of stress. This response is almost certainly due to direct calcium antagonism at adrenergic nerve terminals and in the adrenal gland. It might be argued that magnesium is producing its effect by a central sedative mechanism but this is unlikely as magnesium crosses the blood-brain barrier with difficulty, and has little or no central sedative effect even at much higher serum levels than those used in the present study (Somjen et al, 1966).

These actions of magnesium in protecting against the harmful effects of endotracheal intubation are probably not superior to the effects of the potent short-acting opiate agents, fentanyl and alfentanil. Alfentanil in particular shows considerable promise in this regard (Crawford & Fell, 1987). However, the use of opiates has been associated with muscle rigidity, bradycardias, hypotension, and respiratory depression and in those circumstances in which these complications may be undesirable magnesium could be a useful alternative. In the case of patients with pregnancy-associated hypertension, although the use of intravenous opiates has been advocated to attenuate the

potentially life-threatening hypertensive response to intubation at the time of caesarean section, the use of such drugs carries obvious hazards in terms of foetal depression. A serum magnesium level of 2-4 mmol/l at the time of endotracheal intubation may be particularly valuable in the hypertensive pregnant patient. In a brief study, this possible protective effect of magnesium in patients with pregnancy-associated hypertension was confirmed (Cork et al, 1984), with no apparent detrimental effects on the foetus. Even where magnesium has been used to control the convulsive risk in these patients, it would seem sensible to confirm the serum concentration of magnesium prior to the induction of anaesthesia, as standard doses of $MgSO_4$ frequently fail to produced this desirable therapeutic level. A further intriguing possibility is that combinations of short-acting opiates and magnesium may offer good cardiovascular control at lower doses of both agents and therefore with fewer side effects. This possibility remains to be evaluated.

Magnesium has also been shown to reduce fasciculations (De Vore & Asrami, 1980) and potassium release (Aldrete et al, 1970; James et al, 1986) following suxamethonium and these actions combined with the cardiovascular control that can be achieved by the use of magnesium may be of value. Firstly, the reduction in fasciculations should reduce the post-operative muscle discomfort which commonly accompanies the use of depolarizing relaxants. Secondly, by reducing the incidence and severity of the fasciculations, magnesium might protect against the increase in intraocular pressure which frequently

accompanies the onset of suxamethonium paralysis and this would obviate the need for the potentially dangerous use of a pretreatment dose of a non-depolarizing relaxant in patients with open eye injuries. Thirdly, by preventing the release of potassium at the time of depolarization, magnesium should offer protection in patients with electrolyte disturbances. None of these possibilities have been studied at the present time.

This study has, therefore, confirmed the *in vitro* work which demonstrated that excess magnesium can inhibit the release of catecholamines, probably by calcium antagonism at adrenergic nerve terminals and the adrenal gland. It has also shown that this effect occurs at clinically adequate and safe serum concentrations of magnesium, similar to those advocated for the management of pre-eclamptic toxaemia, and it has demonstrated that this effect is of sufficient magnitude as to be of use in clinical situations. This inhibition of catecholamine release coupled with the anti-adrenergic effects already demonstrated make magnesium a potentially very valuable agent in conditions of catecholamine excess, but its role in such conditions remains to be evaluated.

8. MAGNESIUM AND THE MANAGEMENT OF SEVERE TETANUS

Very severe tetanus is characterized by cardiovascular instability and other signs of autonomic nervous system disturbances. These disturbances have been shown to be due mainly to over activity of the sympathetic nervous system and are associated with elevated circulating catecholamine levels (Kerr et al, 1968; Keilty et al, 1968). Prys-Roberts and others (Prys-Roberts et al, 1969) used propranolol to control the characteristic tachycardias and hypertension, and this approach has become standard practice (Kerr, 1978). Addition of vasodilator drugs including phentolamine (Alfrey & Rauscher, 1979; Goldman et al, 1979), bethanidine (Kanarek et al, 1973) and phenoxybenzamine (Furste, 1980) has been recommended. More recently, labetalol has been used for its added α-blocking properties (Dundee & Morrow, 1979; Omar et al, 1979; Connor et al, 1979). Very heavy sedation has been claimed to reduce the incidence of autonomic dysfunction (Cole & Youngman, 1969; Edmondson & Flowers, 1979) but cardiovascular instability and elevated catecholamine levels may persist in severely intoxicated patients (Kerr et al., 1968; Buchanan et al, 1979) and the use of adrenergic blocking drugs to control the peaks of pulse rate and blood pressure is recommended in addition to sedation (Kanarek et al,

1973; Edmondson, 1980). It is now widely accepted practice to utilize deep sedation, coupled with muscle relaxants and positive pressure ventilation as the mainstay of treatment in an attempt to minimize input stimuli which may result in excessive autonomic activity. In some patients, however, these disturbances persist, despite very heavy sedation to the point of virtual anaesthesia. In this group of patients the mortality has been quoted as being in excess of 50%, even with the addition of adrenergic blocking drugs (Wesley et al, 1983) and it has been suggested that β-adrenergic blockade may have contributed to the fatal outcome in some of these patients. The use of β-adrenergic blocking drugs is not without hazard, as the heart may depend on β-adrenergic activity to maintain adequate tissue perfusion (Kerr, 1979). The commonest cause of death in these circumstances is sudden, unexpected cardiac arrest (Kanarek et al, 1973; Kerr, 1979; Trujillo et al, 1980) and this has been associated with the use of β-blockers (Edmondson & Flowers, 1979; Buchanan et al, 1978). Where adrenergic blockers are used, it is not uncommon to be faced with the problem of a relative overdose of these agents when the spasm of adrenergic discharge abruptly terminates. If it were possible to prevent the release of catecholamines, this would be an attractive alternative to trying to block their actions. The anti-adrenergic activity of magnesium which has been demonstrated in previous chapters as being potentially useful in clinical situations suggests that this agent may have a role in the management of the cardiovascular disturbances associated with severe tetanus. If, in addition, magnesium also inhibited the release of adrenaline and noradrenaline from the adrenal gland and from peripheral adrenergic nerve terminals, this would add

significantly to the ease with which the cardiovascular disturbances could be managed and should decrease both morbidity and mortality. Furthermore, the well-known neuromuscular blocking properties of this agent (Engbaek, 1952; Del Castillo & Engbaek, 1952; Jenkinson & Engbaek, 1954; Jenkinson, 1957) could be of value in controlling spasms. It therefore seemed worthy of investigation as a potential therapeutic agent in very severe tetanus.

8.1 METHODS

All patients admitted to the intensive care unit with a diagnosis of severe tetanus were treated by standard methods based on neuromuscular blockade and deep sedation, but omitting the use of β-blockers. Sedation was gradually increased as indicated by the patient's condition up to a pre-set maximum. The drugs and dosage schedules used are illustrated in table 8.1.

Table 8.1

Drug	Initial Dosage	Maximum Dosage
Diazepam	10mg every 2 h	20mg every hour
Morphine	5mg every 2 h	10mg every hour
Chlorpromazine	50mg every 12 h	100mg every 6 h
Phenobarbitone	50mg every 12 h	100mg every 6 h

Table 8.1 Sequence and dosage in which sedative drugs were administered to adult patients with severe tetanus. Dosages were appropriately scaled down for children.

Muscle relaxation was maintained with 10 mg of alcuronium i.v. as necessary to control persistent spasms. This form of therapy was followed for at least 7 days.

At the end of seven days, the patient's response to therapy was assessed. Criteria for judging current therapy as unsatisfactory were arbitrarily defined as follows: fluctuations of systolic arterial blood pressure of more than 40 mmHg per day, fluctuations of pulse rate of more than 40 beats per minute in a 24 hour period and frequency of spasms of more than one per hour. If all these criteria were met, the patient was then admitted to the trial.

At the time of admission to the trial, all patients had an arterial line placed, usually in the radial artery, using a 22G teflon cannula. This was to facilitate blood pressure monitoring, and to provide easy access for the frequent blood samples that the study required. Where possible, a flow-directed thermodilution pulmonary artery catheter (Edwards 93A-131-7F) was inserted at the same time.

Magnesium sulphate infusions have achieved an accepted place in the management of pre-eclamptic toxaemia (Pritchard & Pritchard, 1975; Cavenagh & Knuppel, 1981) and it was decided to use therapeutic regimes borrowed from standard obstetric practice as the basis for the use of magnesium in tetanus. Accordingly, each patient was given a loading dose of 70mg/Kg of magnesium sulphate as an infusion over 5 minutes. This was followed by an infusion at whatever rate was required to maintain a steady state blood level of between

2.5 and 4 mmol/litre. Serum magnesium levels were monitored every 4 hours, using atomic absorption spectrophotometry, and serum calcium levels monitored on a daily basis along with all the routine daily investigations. Cardiac output was estimated by thermodilution using 10 ml of iced 5% dextrose as an indicator and a Hewlett Packard cardiac output computer (HP 78231C). Measurements were made prior to the start of magnesium therapy, and then twice daily for the next two days. Measurements were made at the same time of day, and at least two hours after any disturbing procedure such as tracheal suction or physiotherapy, in order to ensure that measurements were relatively comparable. Readings of central venous and pulmonary artery wedge pressures were also made, and a value for peripheral vascular resistance calculated. In all patients, blood pressure recordings were made on an hourly basis, but peaks of pulse rate and blood pressure occurring between these intervals were also noted throughout the course of the illness. To minimize the risks of catheter-related sepsis, the pulmonary artery catheter was removed after two days, but the arterial pressure monitoring maintained continuously over the next two weeks using multiple sites. Following the institution of magnesium therapy, other forms of sedation were gradually decreased as the patient's condition allowed, commencing with the phenothiazines and benzodiazepines. If the patient failed to respond to magnesium therapy, provision was made in the protocol for additional doses of sedatives as well as allowance being made for the addition of α-adrenergic blockers in extreme cases. The magnesium infusion was gradually reduced after two weeks, or earlier if the patient's

condition permitted, but if cardiovascular instability recurred, the infusion was increased again.

8.2 RESULTS

Out of a total of twenty-one patients with tetanus admitted to the intensive care unit of the Paryrenyatwa Hospital, Harare, Zimbabwe, over a two year period from 1981 to 1983, ten patients qualified for admission to the trial. There were two children in the group, both under six years of age. Neonates were not considered for admission to the trial. Of the ten patients, eight survived. The cause of death in one patient was overwhelming sepsis and in the other severe pulmonary infection which predated her admission to the unit. Of the non-trial group, three patients died, two of whom had sympathetic overload, but died before the seven day point. One of these patients, a 70 year-old male, died suddenly, following a sudden fall in blood pressure, and a myocardial infarction was suspected. The other two both had aspiration pneumonia on admission, and this was the probable cause of death in these cases. In the pretrial period, therefore, there was a total of 12 patients with sympathetic overload, four of whom died, two without receiving magnesium. The mortality in the pretrial group was 3 out of 11, whilst in the post-trial group, 2 patients died out of 10. Of the 5 deaths over this period, four of these were due to infections with organisms resistant to the limited range of antibiotics available in Zimbabwe at

the time. One of the deaths in the pretrial group was probably the result of sympathetic overactivity. The surviving 8 patients in the non-study group were all easily controlled at relatively low levels of sedation and were not studied further.

The magnesium infusion was maintained for a mean of 22 days with a range of 9 to 31 days. In every surviving case, it was possible to stop all sedation except for morphine for the last few days, and to contain stiffness and spasms with magnesium alone. This allowed for a comfortable, awake and co-operative patient.

In all but one case, satisfactory control of cardiovascular function was achieved. The one case in whom control of the cardiovascular system could not be established was the one who died of severe sepsis. Since this patient's problems were related to sepsis, additional cardiovascular agents were not used in this case, although deep sedation was maintained. No other case required modification of the protocol. Typical records are illustrated in figures 8.1, 8.2, 8.3 and 8.4.

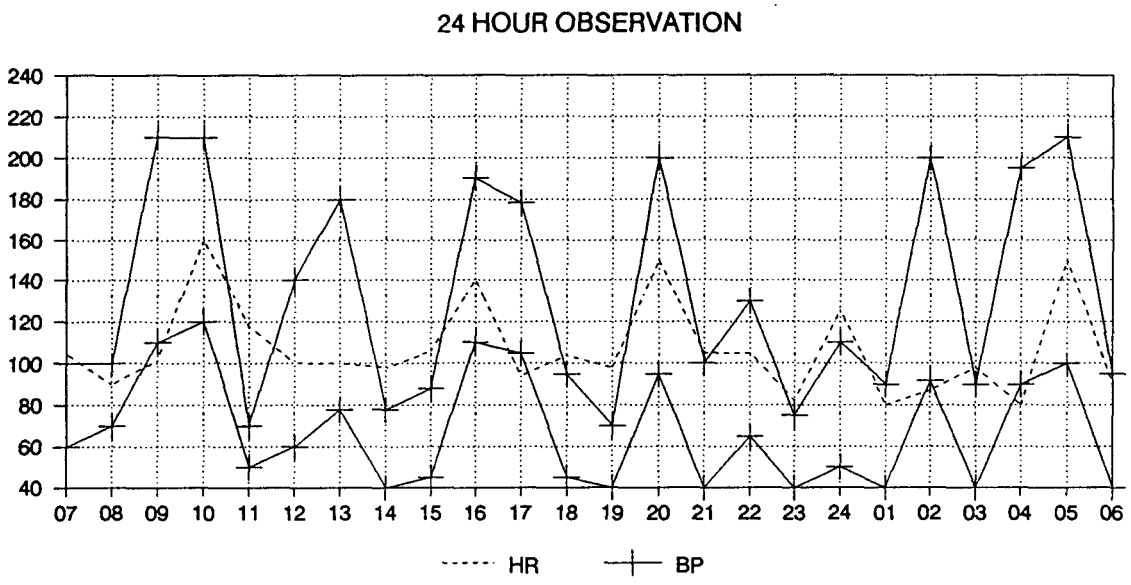


Figure 8.1 Hourly heart rate and blood pressure recordings in a patient with severe cardiovascular disturbances at Day 7 prior to admission to the trial

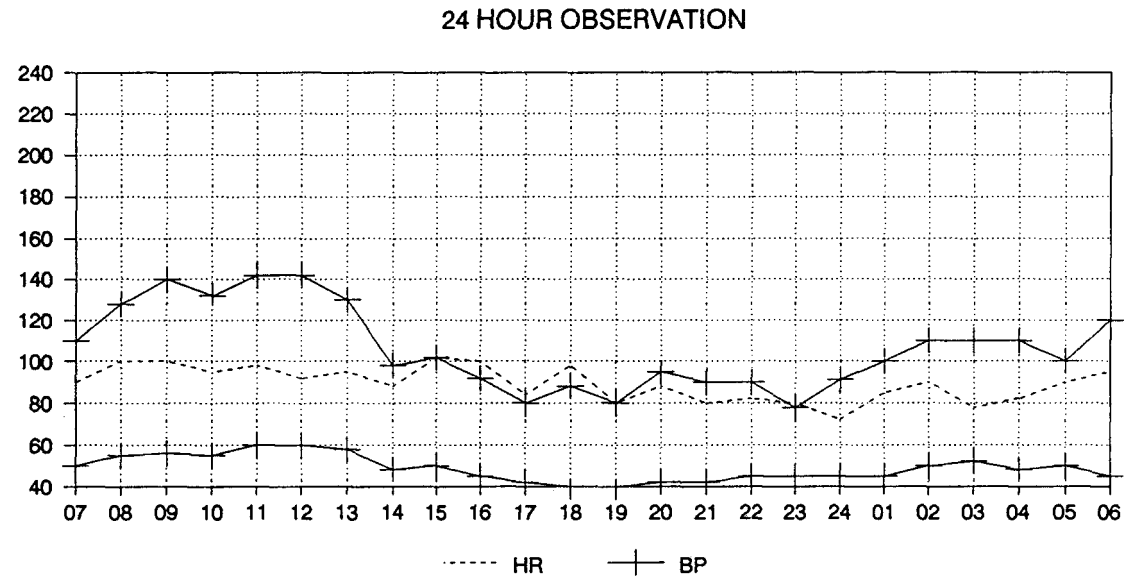


Figure 8.2 The same patient as in figure 8.1 at Day 9, two days after the commencement of magnesium therapy.

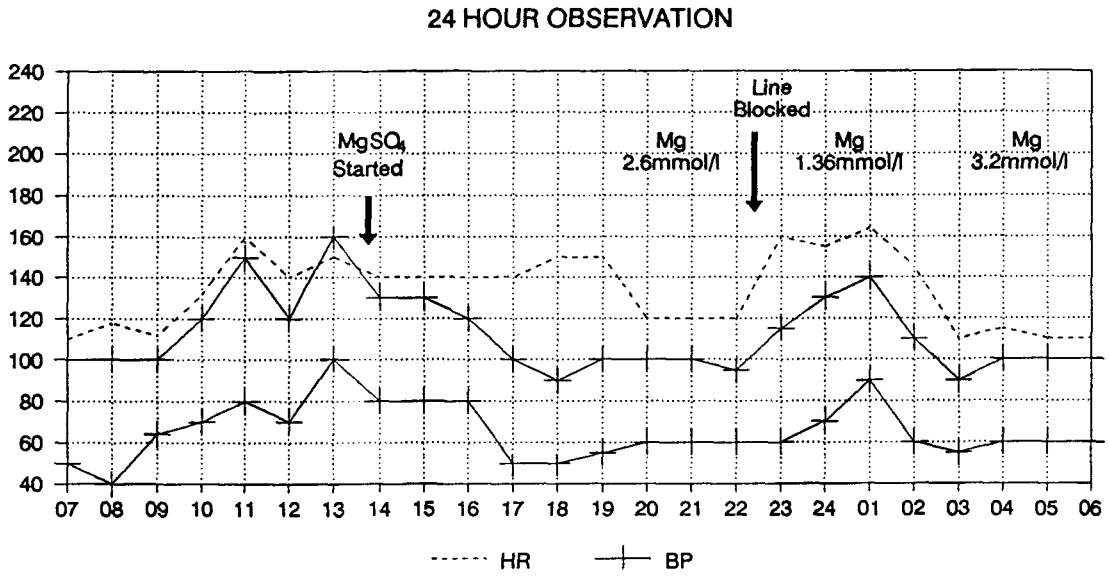


Figure 8.3 Cardiovascular disturbances in another patient on Day 12, the day of commencement of magnesium therapy. Between 23:00 and 24:00 the infusion was interrupted due to a blocked line. Note the re-appearance of instability at this time, and the drop in serum magnesium to below therapeutic levels.

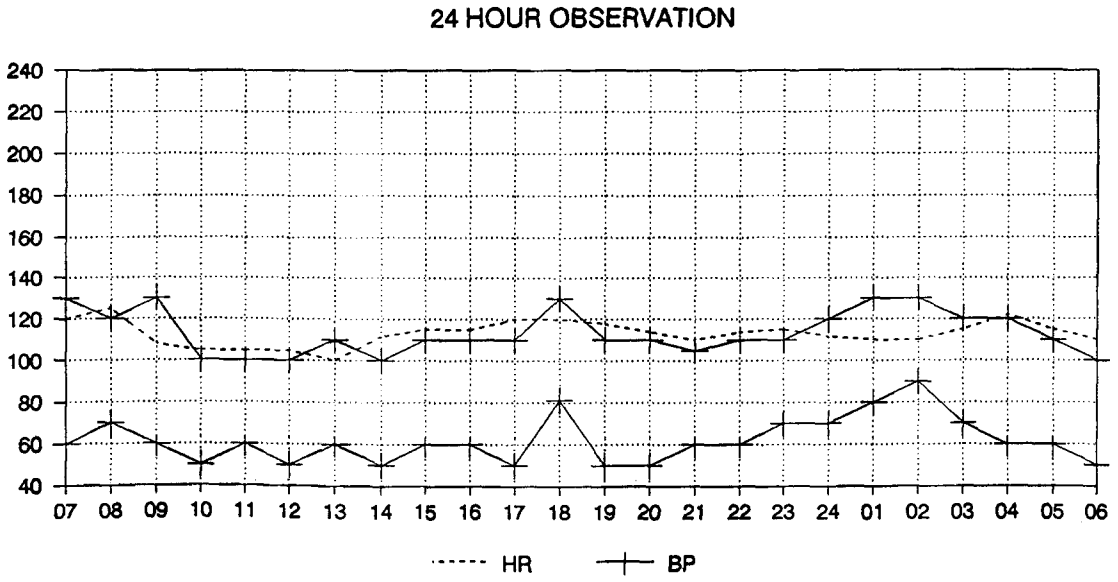


Figure 8.4 The same patient as in figure 8.3 at Day 13.

The range of blood pressure and pulse rate encountered before and during magnesium therapy is illustrated in table 8.2. The maximum pulse rate was reduced in all but the one case, and the difference in maximum heart rate before and during the magnesium infusion was highly significant. There was no significant change in the minimum rate. The maximum systolic blood pressure was also reduced in 9 cases, the difference again being significant.

Table 8.2

Pre-magnesium

SBP/DBP	SBP/DBP	Heart Rate	
Max	Min	Max	Min
160/110	60/40	165	60
240/110	90/40	160	68
160/70	110/60	130	82
150/100	90/60	160	110
160/90	80/40	150	104
170/120	130/100	164	80
176/130	60/20	140	64
142/102	80/45	152	94
150/70	90/50	150	80
130/60	60/30	146	74
Means 163.8±28	85±21	151.7±10	82±16

Post-magnesium

SBP/DBP	SBP/DBP	Heart Rate	
Max	Min	Max	Min
98/58	86/47	118	110
120/50	90/40	100	60
150/90	80/50	170	100
130/70	100/40	128	102
120/70	90/50	118	100
110/70	100/60	108	84
130/80	110/70	120	90
124/90	100/72	144	92
140/60	80/50	104	72
100/60	84/40	104	72
Means 122±16*	91.4±15	121±20*	92.9±9

Table 8.2 Pulse rates and blood pressures before and after magnesium therapy. Pre-magnesium values represent the greatest fluctuation in a 24 hour period for the 2 days prior to treatment. The post-magnesium values represent the greatest fluctuations during the first week after starting treatment.
* - $p < 0.05$

Pulmonary artery catheterisation was achieved in six cases. It was decided not to attempt it in the case of overwhelming sepsis, due to the risks of bacterial endocarditis, nor was it attempted in the two children. In one other case, catheterisation was impossible for technical reasons. The values for cardiac indices obtained are illustrated in table 8.3.

Table 8.3

	Pre-Magnesium				Post-Magnesium			
	HR	CI	SVI	SVR	HR	CI	SVI	SVR
	130	4.12	31.4	970	116	2.79	37.9	860
	106	4.46	47.4	1129	90	2.79	52.1	732
	120	4.72	40.3	869	80	4.00	50.0	695
	124	5.51	44.9	1067	76	5.23	68.9	636
	110	5.34	48.5	1109	60	7.08	68.0	745
	168	7.00	41.7	1008	72	4.29	49.9	868
Means	126	5.19	42.4	1025.3	82.3*	4.68	54.5*	757.3+
SEM	9.1	0.4	2.5	44.7	7.8	0.6	4.9	37.5

Table 8.3 Cardiovascular indices in six patients prior to the start of magnesium therapy, and two days after magnesium therapy had been instituted.

HR - heart rate in beats per minute
CI - cardiac index in l/min/m^2 body surface area
SVI - stroke volume index in ml/beat/m^2 body surface area
SVR - systemic vascular resistance in dyne.s.cm^{-5}
* - $p<0.05$
\+ - $p<0.01$

Not surprisingly, all patients exhibited an elevated cardiac index which was not markedly reduced by the magnesium infusion. In these patients pulse rate at the time of doing the readings was reduced in every case and the difference in mean pulse rate between the pre-magnesium and post-magnesium values was

statistically significant ($p < 0.05$). There was a parallel increase in stroke volume in all patients ($p < 0.05$ for the difference in means between pre- and post-magnesium groups) probably due to a reduction in afterload. The systemic vascular resistance was relatively low prior to the use of magnesium, presumably as a result of the chlorpromazine and barbiturate included in the sedative regime. Further significant reductions followed the use of magnesium ($p < 0.01$). Pulmonary capillary wedge pressure was within the normal range (5-12 mmHg) in all cases both before and after the commencement of the magnesium infusion, and appeared to be unaffected by it. Central venous pressure was similarly unchanged by magnesium in all cases.

In order to maintain a steady level of serum magnesium of between 2.5 and 4 mmol/L, an infusion rate of between 1 and 3 gm per hour was required. However, there was wide individual variation and also considerable day-to-day variation within each individual. No firm guide-lines could be determined for the infusion rate, and frequent estimation of the serum magnesium was the only safe way to keep control of the magnesium level. In two cases the serum magnesium rose to over 6 mmol/l on one occasion in each patient. These patients both exhibited prolongation of the PR interval with runs of nodal rhythm. The arrhythmias responded promptly to the infusion of calcium gluconate and reduction in the infusion rate of the magnesium sulphate, and did not recur. No other serious cardiac disturbances were noted in the series.

The commonest biochemical complication was a fall in serum calcium. This is not surprising, as magnesium inhibits the release of parathyroid hormone (Ebel

& Gunther, 1980). Calcium supplements were needed frequently in order to maintain the serum calcium level within the normal range. In no patient was the serum calcium level allowed to fall below 1.7mmol/l.

Four patients showed signs of high output renal failure prior to the commencement of magnesium sulphate therapy, with elevations of serum creatinine and urea, and a fall in creatinine clearance, despite adequate urine output in three of the four cases. One patient in this group died, this being the patient with severe sepsis, this patient ultimately developing oliguric renal failure as part of his septicaemic state.

The levels of serum magnesium used in this study (2.5-4 mmol/l) produced profound neuromuscular block in all patients. As a result, the amount of alcuronium required was drastically reduced from a general range of 250 - 300mg per day (approximately one dose every 45 to 60 min.) to around 100mg per day (approximately 2 to 3 hours between doses).

8.4 DISCUSSION

This is not the first time that a role for magnesium in the management of tetanus has been suggested. Blake (1906) described two cases of severe tetanus treated with intrathecal magnesium sulphate. One patient with a very heavy bacteraemia died twelve hours after the injection, but the other received 5

intrathecal injections of 12.5% magnesium sulphate over a ten day period and made a full recovery. In the same year, Meltzer described the use of magnesium by intravenous, intraspinal and subcutaneous routes and concluded that no other agent then available was as as effective in control of symptoms as was magnesium (Meltzer, 1906b). More recently, Natu and his colleagues described hypomagnesaemia in a series of 36 patients and correlated the level of serum magnesium with the severity of the disease (Natu et al, 1980). They suggested a role for magnesium infusions in the management of the condition, at least in those patients in whom the serum magnesium was low. The finding of hypomagnesaemia was not, however, confirmed in the present study.

Although it is impossible to make any firm statement about mortality in a small series like this one, the fact that no patients died from causes attributable to their tetanus was pleasing, particularly in view of the fact that four patients had episodes of high output renal failure, and only one of these died. Seedat et al. (1981) found that their patients with this complication of tetanus had a 65% mortality. The two deaths were both related to infections (one pulmonary, the other septicaemia of unknown source) with organism that were resistant to the available antibiotics. It is possible that, with a wider spectrum of antibiotics to call upon, these patients could also have been saved.

The control of the cardiovascular effects of severe tetanus demonstrated in this study are most encouraging. At the time of performing this study, facilities for the direct measurement of catecholamine levels were not available, and therefore the mode of action of magnesium in these cases remains conjectural.

The reduction in peripheral resistance that occurred could be mediated by a direct effect on the blood vessels (Kelly et al, 1960; Farmer & Campbell, 1967; Overbeck et al, 1969; George & Leach, 1971; Altura & Altura, 1981 a, b & c, chap 5). However, in vivo, the hypotension produced by raised serum magnesium is generally found to be evanescent (Pritchard & Pritchard, 1975; Maxwell et al, 1965; Dandavino et al, 1977; Mroczek et al, 1977). One of the features of this study was the consistent reduction in systolic blood pressure, and the control obtained over the paroxysmal episodes of hypertension. Although the daily range of blood pressure fluctuation still exceeded the admission criteria for the trial, the range of blood pressure was reduced in 8 of the 10 subjects and unchanged in one. The only case in which the range in blood pressure deteriorated was in the patient with severe progressive septicaemia. It is unlikely, therefore, that the control of blood pressure achieved was due solely to the direct vasodilator effects of magnesium. The reduction in heart rate that occurred is also unlikely to be due to a direct action of magnesium. The action of magnesium is to produce a mild slowing of heart rate in the isolated heart (Somjen & Baskerville, 1968), and this has also been shown to occur in the intact animal (see chapter 5). However, it has also been described that inhibition of acetylcholine release at the vagal terminals may predominate resulting in a mild increase in heart rate in humans (Garb, 1951; see chapter 7). The observed reduction in heart rate was very much greater than that seen in the animal experiments at similar magnesium levels, and opposite to the change seen in healthy human subjects where magnesium was used prior to endotracheal intubation (chapter 7). Thus, it seems probable that this

reduction in heart rate was, at least in part, due to a lessening of sympathetic tone. The range of heart rate fluctuation was also reduced in every case except the patient with septicaemia. It is most likely, therefore that the improvement in cardiovascular function in these subjects was due in some degree to a reduction in the level of circulating catecholamines. However, although it has been shown that magnesium infusion can inhibit the release of catecholamines, this study does not allow the assumption that the beneficial effects seen were entirely due to this action of magnesium. Whilst there is a strong circumstantial case to be made for this possibility, further evidence is required before this claim can be made with confidence.

Contrary to the popular view (see chapter 2), magnesium is not an anaesthetic nor even a major central nervous system depressant, unless applied directly to the nervous tissue via the cerebrospinal fluid (Mordes & Wacker, 1978). Somjen et al (1966) showed that, provided ventilation was maintained, serum magnesium levels of up to 8 mmol/L had no sedative effect in humans. Aldrete et al (1968) found that similar levels of magnesium produced a sleep-like state in dogs, but not anaesthesia. They attributed the decline in conscious level to impaired cardiovascular function. The failure of intravenously administered magnesium to produce anaesthesia is largely due to the fact that the blood-brain barrier is relatively impervious to magnesium and even in long-standing deliberate hypermagnesaemia, only small increases in CSF magnesium levels were found (Pritchard, 1955). Central actions of magnesium, therefore, probably did not contribute significantly to the observed results of this study.

The calcium antagonistic effects of magnesium might be expected to produce a reduction in myocardial contractility, and a fall in cardiac output. However, it has been shown that, provided hypocalcaemia is avoided, the negative inotropic effects of magnesium are minimal (Garb, 1951; Kovacs & O'Donnell, 1975). The preservation of cardiac output at elevated levels is also not surprising, as magnesium increases the cardiac output in baboons (chapter 5), particularly in the presence of catecholamines (chapter 6). It has also been shown that magnesium can increase the cardiac output in normal human subjects (Mroczek et al, 1977). Although magnesium diminishes the output of catecholamines, it is unlikely that total inhibition of catecholamine release can be achieved in the clinical situation. The hazards of β-blockade in the face of α-adrenergic discharge have already been described, and magnesium may offer a safer means of controlling the tachycardias. Not only does magnesium not depress myocardial contractility, but the ability of the heart to respond to adrenergic stimulation is preserved (Paddle & Haugaard, 1971; Levin et al, 1976). Indeed, it has been shown that magnesium is essential for the inotropic action of adrenaline (Vincent, 1982). It has been suggested that the toxic myocarditis occasionally described in tetanus may be merely a manifestation of catecholamine excess (Kerr et al, 1968), since the histological changes are similar to those described in myocardial damage associated with prolonged adrenergic stimulation (Raab, 1963). The failure of magnesium to block the increases in cardiac output caused by adrenergic stimulation might be considered a disadvantage. However, it has been shown that, although the contractile response is preserved by magnesium, the harmful biochemical

effects of adrenergic drive, such as glycogenolysis, lactate production, and ATP degradation are inhibited (Paddle & Haugaard, 1971; Levin et al, 1976). It is tempting to speculate, therefore, that magnesium may not only protect the cardiovascular system by limiting the fluctuations in catecholamine levels, but also may protect the myocardium from the adverse biochemical effects of excess adrenergic drive when it occurs.

In view of the fact that magnesium has been given intramuscularly to obstetric patients in whom only limited monitoring was used, it might be considered that it could be used in the conservative management of tetanus. However, in this study, magnesium sulphate infusions exerted a far more profound effect on neuromuscular transmission than would have been expected from experience gained with similar serum levels in obstetrics. Serum magnesium levels of less than 5 mmol/l are generally regarded as having no more than mild neuromuscular blocking properties, but in patients in this series marked neuromuscular block occurred at levels between 2.5 - 4 mmol/l. This could, perhaps have been anticipated as tetanus toxin is known to exhibit a botulinus-like action at the motor end plate (Kaeser & Saner, 1970; Mellanby & Green, 1981), producing a similar type of neuromuscular block to that produced by magnesium alone, and therefore leading to an additive effect. Whatever the mechanism of this enhanced neuromuscular block produced by magnesium, the marked neuromuscular blockade that was found in patients in this study precludes recommending the agent for use outside the intensive care unit at the present time.

In conclusion, magnesium sulphate infusions have been shown to be of potential benefit in assisting the control of cardiovascular disturbances associated with severe tetanus. Further studies into the use of this agent are, therefore justified in order to answer some of the remaining questions, particularly those pertaining to the use of magnesium in less severely intoxicated patients than those studied in this trial. It is also necessary to demonstrate that catecholamine concentrations can, indeed, be reduced by infusions of magnesium.

8.5 MAGNESIUM AND CATECHOLAMINE RELEASE IN TETANUS

A recent case of very severe tetanus presented the opportunity for studying the hypothesis that magnesium sulphate infusions could reduce circulating catecholamine levels and thus improve cardiovascular function.

8.6 CASE REPORT

The patient was a 29 year old black male, previously in good health, who was transferred from another hospital with a diagnosis of severe tetanus. The focus for his *clostridium tetanii* infection was a septic compound fracture of the right radius which he had sustained during an assault one week previously. There

was no record of his ever being vaccinated against tetanus and the phase of onset of the disease was only 48 hours . At the time of his transfer, he was having frank tetanic spasms, with opisthotonos, risus sardonicus and abdominal rigidity for which he had received 20mg of diazepam and 11 ampoules of human anti-tetanus globulin (10 ampoules IMI, and 1 ampoule intrathecally). Appropriate antibiotic therapy in the form of penicillin G 2 million units 2 hourly IVI had been instituted.

Physical examination findings were normal and his pulse was 130/min, blood pressure 150/100 and his perfusion good. However, the most minor stimulation provoked generalised muscular spasms. The patient was sedated with diazepam, paralysed with alcuronium, intubated and ventilated. Tetanus toxoid was administered, and a thorough debridement of the arm wound performed. A tracheostomy was subsequently performed on day 3. Initially, the patient was controlled on intravenous infusions of alcuronium (10mg/hr), and diazepam (5mg/hr). As his illness progressed these doses became totally inadequate as muscle spasms, tachycardia and severe hypertensive episodes associated with profuse sweating and oro-nasal secretions continued unabated. His muscle spasms were eventually controlled on alcuronium, at a dose of 17,5mg/hr but his blood pressure remained extremely labile.

Various combinations of diazepam, morphine and chlorpromazine, both as continuous infusions and hourly boluses, were tried. At his most unstable, he was receiving a diazepam infusion of 80mg/hr and boluses of 40mg/hr, morphine boluses of 30mg approximately every 4 hr., and chlorpromazine

20mg/hr. On one occasion, day 15, he was given 175mg of diazepam, plus 10mg of morphine in one hour; 195mg of diazepam in the next hour and 115mg of diazepam with 25 mg of chlorpromazine in the 3rd hour; the average hourly sedation for this day was 120 mg diazepam, 5 mg morphine and 10 mg chlorpromazine. The instability of the patient's blood pressure on day 18 can be seen in figure 8.5, although greater fluctuations in cardiovascular status actually occurred than can be shown on this periodic chart.

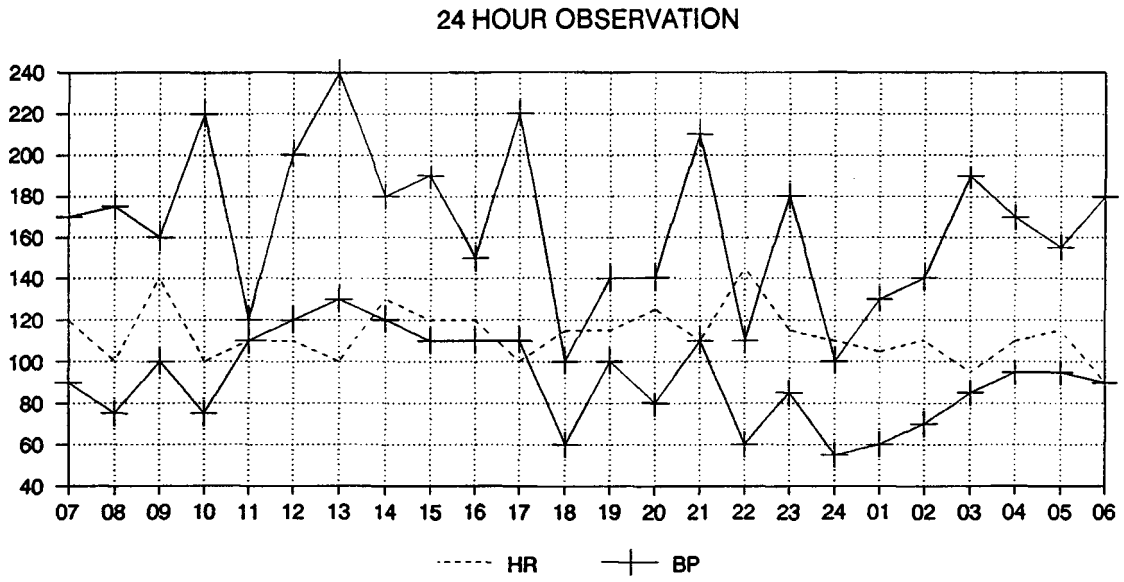


Figure 8.5 Hourly heart rate and blood pressure chart on day 18. The patient was receiving an average of 120mg diazepam and 7.5mg morphine each hour plus chlorpromazine 60 mg 6 hourly

On day 19, it was decided to try to stabilize the patient using large doses of magnesium sulphate given as a continuous infusion. The patient was being paralysed with alcuronium 17,5 mg per hour and the sedatives that were being used at that time are shown in figure 8.6.

A loading dose of 4g magnesium sulphate IVI over 20 minutes was administered, followed by a continuous infusion of 1g/hr (see figure 8.6). Serum calcium and magnesium levels were measured every 4 hrs, calcium supplemented as required, and the rate of magnesium infusion adjusted to keep the serum magnesium level between 2 and 4 mmol/l (see figures 8.5, 8.6, 8.7). This required high infusion rates and as a result adequate magnesium levels were not achieved until 18.00 hrs on day 20.

Following the institution of magnesium therapy, a distinct downward trend in systolic and diastolic pressures, mean blood pressure and pulse rate were noted; and smaller doses of sedatives were required. Once the rate of $MgSO_4$ was increased to above 2gm/hour, no systolic blood pressure of greater than 170 mmHg was recorded despite the fact that catecholamine levels were still elevated at this time. Fluctuations in blood pressure were also less marked. This is in contrast to the state prior to the advent of magnesium therapy when systolic pressures of over 200 mmHg were common with a range of systolic pressure of 140 mmHg. Catecholamine levels were recorded before and during the administration of magnesium (see Appendix B). These levels are recorded in table 8.4. Once magnesium levels above 2 mmol/l were established (18.00 hr. day 20) catecholamine levels returned to normal, with the exception of dopamine which remained marginally elevated.

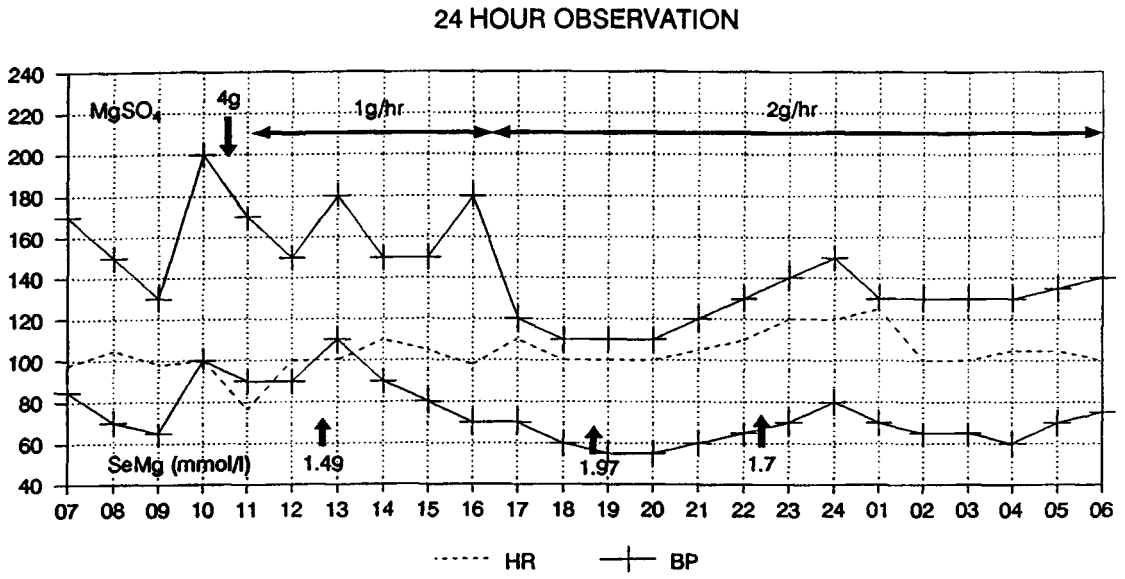


Figure 8.6 Hourly heart rate and blood pressure changes on day 19 during the introduction of magnesium. Diazepam dosage averaged 100mg/hr until 18.00hr. and 80mg/hr thereafter. Morphine dosage averaged 2.5mg/hr. No chlorpromazine was used.

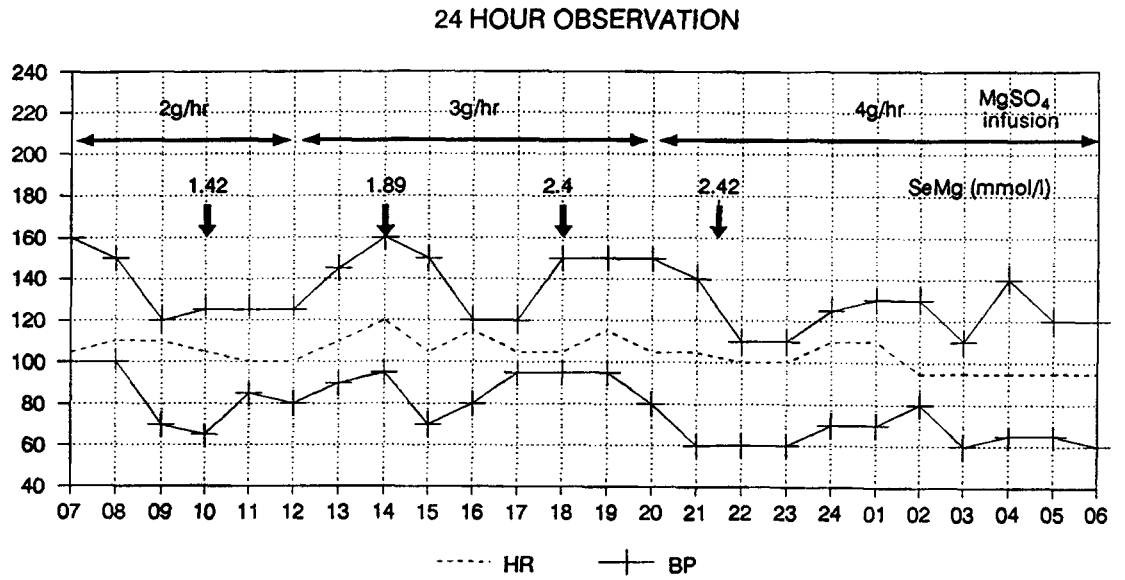


Figure 8.7 Hourly heart rate and blood pressure changes on day 20. Diazepam dosage averaged 80mg/hr and morphine dosage averaged 5mg every 4 hours. No chlorpromazine was used

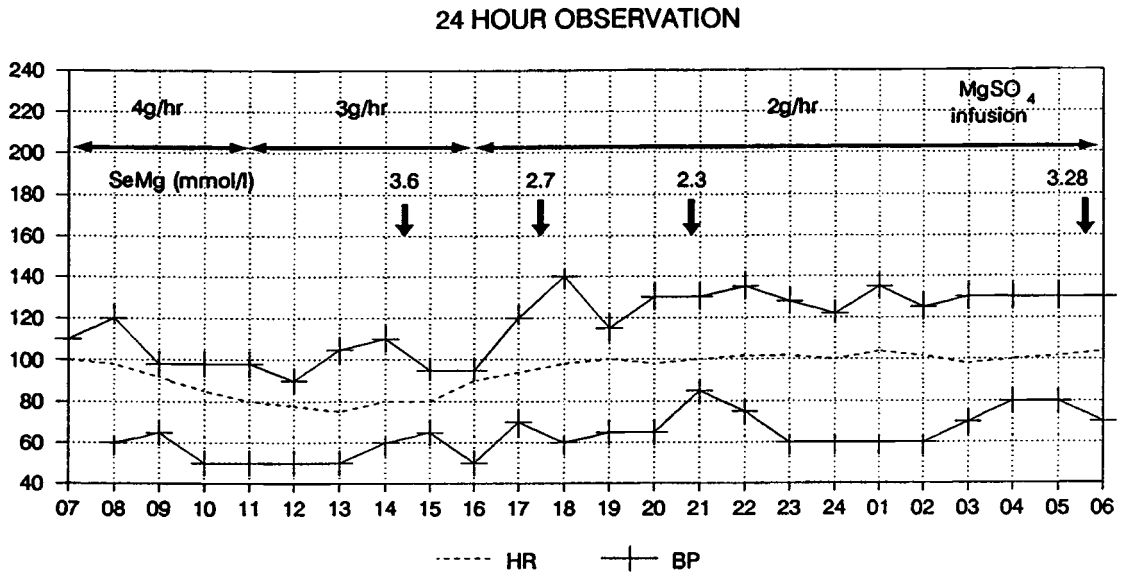


Figure 8.8 Hourly heart rate and blood pressure changes on day 21. No morphine or chlorpromazine was needed., and the diazepam infusion rate was 80mg/hr

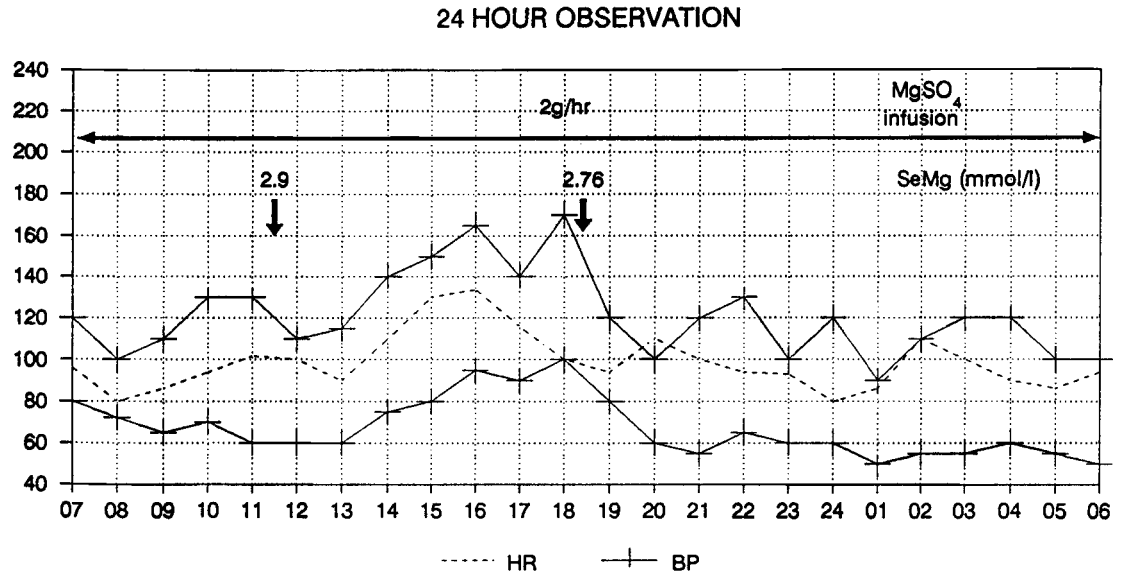


Figure 8.9 Hourly heart rate and blood pressure changes following the withdrawal of all sedation on day 22. Sedation was re-introduced at a rate of 80mg diazepam per hour at 18:00 hours

TABLE 8.4

DATE	TIME	NORADRENALINE	ADRENALINE	DOPAMINE
06/03/86	09h00	918,59	54,70	47,71
(Day 18)	13h40	747,68	78,71	22,81
	16h50	820,92	57,13	40,98
07/03/86	08h30	734,53	59,85	15,78
(Day 19)	09h45	1160,72	118,90	50,34
	15h30	1602,64	115,24	98,13
	16h15	1916,56	109,62	164,39
	17h30	983,95	58,10	38,30
08/03/86	10h15	429,4	62,48	18,98
(Day 20)				
09/03/86	12h00	178,98	21,66	22,80
(Day 21)				

Table 8.4 Catecholamine levels during the initiation of magnesium therapy. Mg started at 12h00 on 07/03/86.
All above values in picograms per ml. Normal (picograms per ml) : Noradrenaline 250 - 400; Adrenaline 10 - 50; Dopamine 0 - 20.

On the morning of day 22, the patient seemed very stable, and the diazepam infusion was stopped. This however precipitated a recurrence of haemodynamic instability, although this was less marked than prior to the institution of magnesium therapy (figure 8.9). Catecholamine levels could not be obtained at this time. The patient became increasingly unstable on $MgSO_4$ alone, and diazepam boluses were re-introduced after 11 hours, which re-established good control. The total sedation now received by the patient was 80 mg/hour in addition to a magnesium infusion of 2 gm/hour. No morphine or chlorpromazine was needed. This partial recurrence of instability strongly argues against the possibility that the changes seen above were due to spontaneous remission of the disease.

The patient was continued on magnesium and diazepam, and the subsequent course of the patient over the following 2 weeks was that of progressive improvement enabling gradual weaning of all sedatives.

8.7 DISCUSSION

It is apparent from this case report that even massive doses of sedative drugs may be unable to prevent the release of catecholamines in large amounts. Magnesium has been shown *in vitro* to inhibit the release of adrenaline and noradrenaline from both the adrenal gland and from peripheral nerve terminals, as well as reducing the sensitivity of the α-adrenergic receptors to these neurotransmitters (Douglas & Rubin, 1963; Kirpekar & Misu, 1967; Lishajko, 1970; George & Leach, 1971; Von Euler & Lishajko, 1973). It was shown in chapter 7 that this action of magnesium could be confirmed in normal human subjects submitted to the stress of endotracheal intubation. This case, however represents the first demonstration of the ability of magnesium to reduce the level of circulating adrenaline and noradrenaline in the presence of elevated circulating catecholamine concentrations. It is of interest that magnesium sulphate alone was unable to control the autonomic disturbances in this patient once the other sedatives were stopped. Unfortunately, catecholamine levels were not obtainable at this time, but it seems likely that magnesium would have continued to inhibit catecholamine release from the adrenal gland. The most

likely explanation for the recurrence of cardiovascular instability at this time is that magnesium is a poor central sedative (Somjen et al, 1966), and that the lightening level of consciousness of the patient led to an increase in sympathetic tone. It has already been shown (chapter 7) that magnesium appears to be more effective in blocking the release of adrenaline than noradrenaline. Possibly, sympathetic nerve terminals, which operate at much lower levels of noradrenaline than those needed to exert systemic effects (Cryer, 1980), are less susceptible to the effects of increased serum magnesium levels than are the cells of the adrenal medulla. Whatever the explanation, it is clear that, whilst magnesium may be a very useful adjunct in the management of the cardiovascular disturbances of tetanus, it is inadequate as a sole agent and should be used in addition to adequate sedation.

These two studies have demonstrated that magnesium can improve the cardiovascular stability in patients with very severe tetanus. It seems likely that the mechanism by which it achieves this action is a dual one involving both the anti-adrenergic actions of magnesium, and in addition, blocking the release of catecholamines from the adrenal medulla. Less sedation is required when magnesium is concomitantly infused. Magnesium is therefore a useful adjunct to sedation in the management of the cardiovascular disturbances of tetanus.

9. Magnesium and Anaesthesia for Phaeochromocytoma

The anaesthetic management of a phaeochromocytoma provides a considerable challenge to the anaesthetist and involves careful control of every phase of the procedure. Although there are no controlled trials on the subject, it is generally accepted that adequate preoperative adrenergic blockade, particularly of α-receptors, has enhanced patient safety and improved outcome. Preoperative preparation, therefore, usually entails the the use of α-adrenergic blockers such as phenoxybenzamine, with the addition of ß-adrenergic blockers, if necessary, to control tachycardias (Hull, 1986). Intraoperatively, the problem is approached on two fronts. Deep anaesthesia, usually with the generous use of opiate agonists, is employed to minimize input stimuli which may trigger neurogenically mediated catecholamine release. Control of the effects of excess catecholamine release is usually maintained by the use of adrenergic blocking drugs such as phentolamine and propranolol and/or vasodilators such as sodium nitroprusside; following tumour devascularization, vasoconstrictors may prove necessary (Hull, 1986; Roizen, 1986). Despite all of these therapeutic manoeuvers, the total elimination of cardiovascular disturbances is seldom achieved and some fluctuation in arterial pressure often

occurs, and arrhythmias are common (Roizen, 1986), due to surges of catecholamine release in response to minimal stimuli. None of the agents in common use has the ability to prevent or reduce the release of catecholamines other than by reducing noxious stimuli which may cause hormone release through stimulation of the autonomic nervous system. Magnesium, as has been shown in the previous chapters, can inhibit the release of catecholamines from both the adrenal medulla and peripheral adrenergic nerve terminals, as well as blocking catecholamine receptors directly. In addition, magnesium has, as has been discussed in previous chapters, a direct dilator effect on vessel walls. It therefore appeared worthy of a trial in phaeochromocytoma as an adjunct to conventional therapy.

9.1 PATIENTS AND METHODS

Over a period of 5 years, magnesium sulphate has been used as an adjunct to the anaesthetic management of 16 patients on 17 occasions. In the first of these cases, $MgSO_4$ was used, based on the rationale presented in previous chapters, in response to a situation in which conventional therapy appeared to be inadequate to meet the problems presented by the patient. The success achieved in the management of this case prompted the study of the remainder of the cases presented in this series. Relevant individual patients details are presented in the appendix, but the overall findings of this series, the general

approach to preoperative preparation, and the basic anaesthetic approach adopted, with relevant illustrations from selected cases is outlined below.

9.1.1 Patients: The age range of the patients was from 14 years to 55 years. There were 5 males and 11 females in the series. Two of the patients were pregnant at the time of presentation. One of these was delivered by Caesarean section and had her tumour resected on a separate occasion (case 4). The other had a malignant phaeochromocytoma for which she had had three previous excisions (case 7). In this case, an elective caesarean section was performed, and she was subsequently managed with radioactive meta-iodobenzylguanethidine (MIBG). Of the remainder, two had tumours that were locally invasive, one involving the right diaphragm and the other invading the left renal vein and inferior vena cava. The first of these patients had pre-existing chronic renal dysfunction (preoperative creatinine clearance 42 ml/hr). Two other patients had evidence of target organ damage in the form of a strain pattern on the ECG with inverted T-waves and depressed ST segments in one case, and left ventricular hypertrophy in the other. The remaining 10 patients all had uncomplicated tumours. Tumour size varied between 3cm and 12 cm.

9.1.2 Preoperative preparation: This consisted primarily of α-adrenergic blockade with either phenoxybenzamine (8 cases) or prazosin (8 cases) in increasing dosage until adequate control of symptomatology had been achieved. Beta-blockade was added as indicated by the occurrence of tachycardias and fluid replacement performed as indicated by cardiovascular measurements. In one case in which the author was

involved in an advisory capacity on the morning of surgery, the patient had been prepared primarily with ß-blockade (atenolol 100mg b.d.) and a small dose (40mg/day) of phenoxybenzamine (case 9). Fitness for surgery was judged in accordance with criteria laid down by Roizen (1986), but in case 9 these criteria were not met and surgery probably should have been postponed. One case was not prepared preoperatively as the diagnosis was made at laparotomy.

Premedication was generally achieved with a combination of diazepam 10mg and promethazine 25mg administered orally the night before surgery and again on the morning of operation. Despite this aggressive and apparently adequate preoperative preparation, several of the patients arrived in the operating room with elevated arterial pressures but minimal other clinical evidence of catecholamine excess such as sweating and anxiety. This was regarded as a manifestation of the stress of impending surgery, and not taken as a contra-indication to the procedure. A summary of patient data and preoperative presentation is presented in table 9.1.

Table 9.1

Case	Age	Sex	Preparation	Diagnosis	Comments
1	14	F	Phen, prop	Large RA	Hypertensive in Theatre
2	45	F	Phen, prop	Small RA	Hypertensive in Theatre
3	54	M	Phen, prop	V.large RA	Renal disease, Diaphragm
4	26	F	Praz, aten	Small RA	Pregnant, poor control
4	26	F	Praz, aten	Small RA	
5	48	M	Phen	Large LA	Renal vein, IVC involved
6	22	F	Praz, aten	Small RA	
7	24	F	Phen, aten	Multiple	Malignant, pregnant
8	26	F	Phen, aten	Small RA	
9	42	M	Aten, phen	Small LA	Inadequately prepared
10	34	F	Phen	Small LA	
11	32	F	Praz, aten	Small RA	
12	51	F	Praz, aten	Large LA	Hypertensive in Theatre
13	39	F	Praz, aten	Large RA	Hypertensive in Theatre
14	28	F	Praz, aten	Small LA	
15	55	F	Nil	PA	Diagnosed intra-op.
16	14	M	Praz, aten	Large PA	

Table 9.1 Summary of patient details

Phen - Phenoxybenzamine
Praz - Prazosin
Aten - atenolol
RA/LA - Right/left adrenal tumour
Diaphragm - diaphragm involved
IVC - inferior vena cava involved
PA - Para-aortic tumour

9.1.3 Anaesthetic technique: In most cases, patients were given a moderate dose of 3-5 μg/kg of fentanyl prior to induction of anaesthesia, followed by an intravenous infusion of magnesium sulphate ($MgSO_4$) 40mg/kg if the arrival systolic blood pressure (SBP) was within 20mm/Hg of the preoperative baseline, or 60 mg/kg if the arrival SBP was above this range. The two pregnant patients received magnesium but no opiate. In two other cases who arrived in theatre well controlled, magnesium sulphate was withheld until after induction of anaesthesia in order to allow an investigation of the separate effects of anaesthesia and $MgSO_4$ on catecholamine levels. In all patients, arterial and central venous pressure monitoring lines were inserted under local anaesthetic prior to induction of anaesthesia. Anaesthesia was induced with thiopentone and muscle relaxation achieved with alcuronium except in the pregnant patients in whom suxamethonium was used. Whilst individual variations occurred, the scheme by which $MgSO_4$ was administered was as follows. If the arterial pressure remained elevated after induction of anaesthesia, a further bolus of 40 mg/kg $MgSO_4$ was administered followed by endotracheal intubation. Anaesthesia was maintained throughout with nitrous oxide, oxygen and enflurane in all but the first case in which halothane was used as it was the only agent available at the time. A continuous infusion of $MgSO_4$ at between 1-2 gm/hr was started and maintained throughout the procedure. The rate of this infusion was adjusted according to the patients response. Cardiovascular control was aimed at keeping the systolic blood pressure within a range 30mmHg either side of the preoperative baseline. Peaks of arterial pressure were managed initially with up to three further boluses injections of $MgSO_4$, 20 mg/Kg on each occasion, but if this proved insufficient to restore SBP to within the stated limits, sodium nitroprusside was added. If SBP was controlled within the stated range by magnesium alone control was designated as good; if adequate control could be established by the

addition of either nitroprusside or phentolamine or both, control was designated as fair, and if adequate control could not be achieved by any combination, control was designated as poor. Once the tumour had been devascularized, magnesium was discontinued, and at the end of surgery neuromuscular blockade was reversed in the normal manner. Adequate reversal of neuromuscular blockade was demonstrated by the use of a peripheral nerve stimulator prior to extubation. Blood samples for serum magnesium were taken after the initial loading doses, and at regular intervals throughout the procedure. Serum magnesium concentrations were measured by atomic absorption spectrophotometry. Blood gases were sampled using heparinised 2ml syringes at regular intervals throughout all procedures and analysed without temperature correction on an ABL4 automatic blood gas analyzer.

9.1.4 Catecholamines: Catecholamine concentrations were measured using a radio-immune assay technique, as described in chapter 7, in five of the last six cases. In case 11, catecholamine concentrations were measured prior to induction, following tracheal intubation, and during periods of tumour handling. In cases 12 and 14, catecholamines were estimated preoperatively following the initial dose of $MgSO_4$, after induction of anaesthesia and after tracheal intubation, as well as during tumour handling. $MgSO_4$ was withheld until after induction of anaesthesia and administered just prior to intubation in cases 13 and 16. In these patients, catecholamine concentrations were measured prior to induction, following induction, after $MgSO_4$, after tracheal intubation, and during tumour handling.

9.2 RESULTS

In the first case of this series, magnesium provided remarkable control of cardiovascular function prior to induction of anaesthesia when conventional methods had failed (figure 9.1). Excellent control was maintained during induction of anaesthesia and intubation (figure 9.2). The surprising feature of this case, was the remarkably good control of cardiovascular function which was maintained throughout surgery, even during periods of tumour handling (figure 9.3), and it was this result which encouraged the continuation of the study.

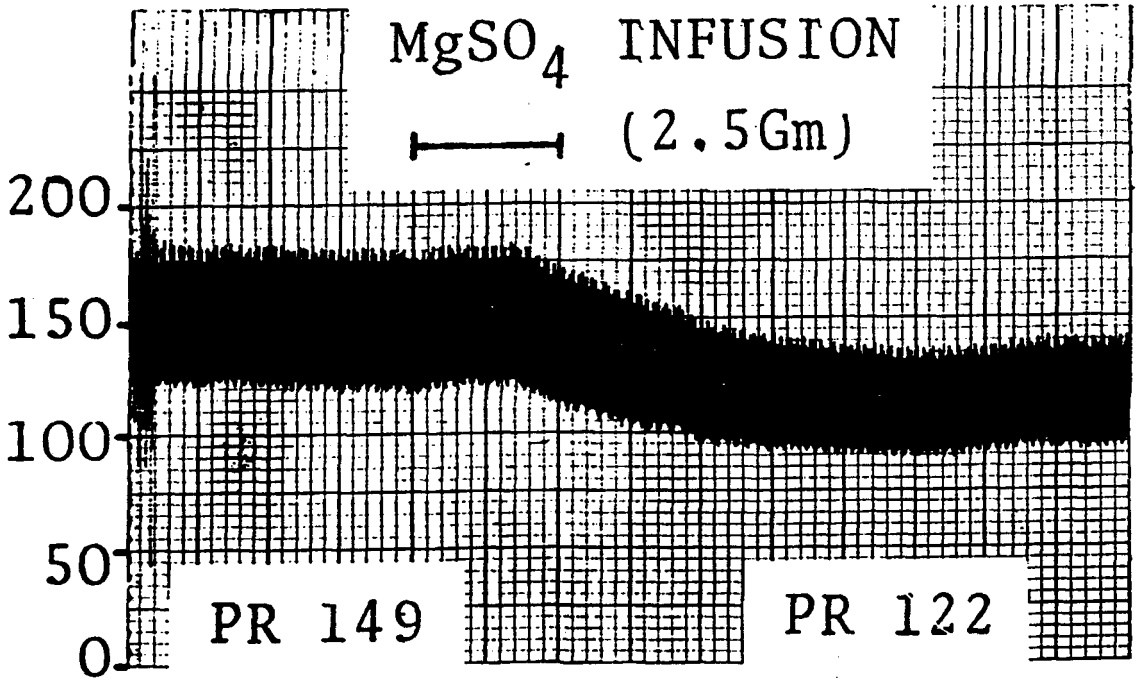


Figure 9.1 Initial cardiovascular changes in response to infusion of $MgSO_4$ in case 1 as recorded during the initial infusion of $MgSO_4$. Chart speed is 0.1mm/sec and one large square represents 50 seconds. The figures on the y-axis are in mmHg.

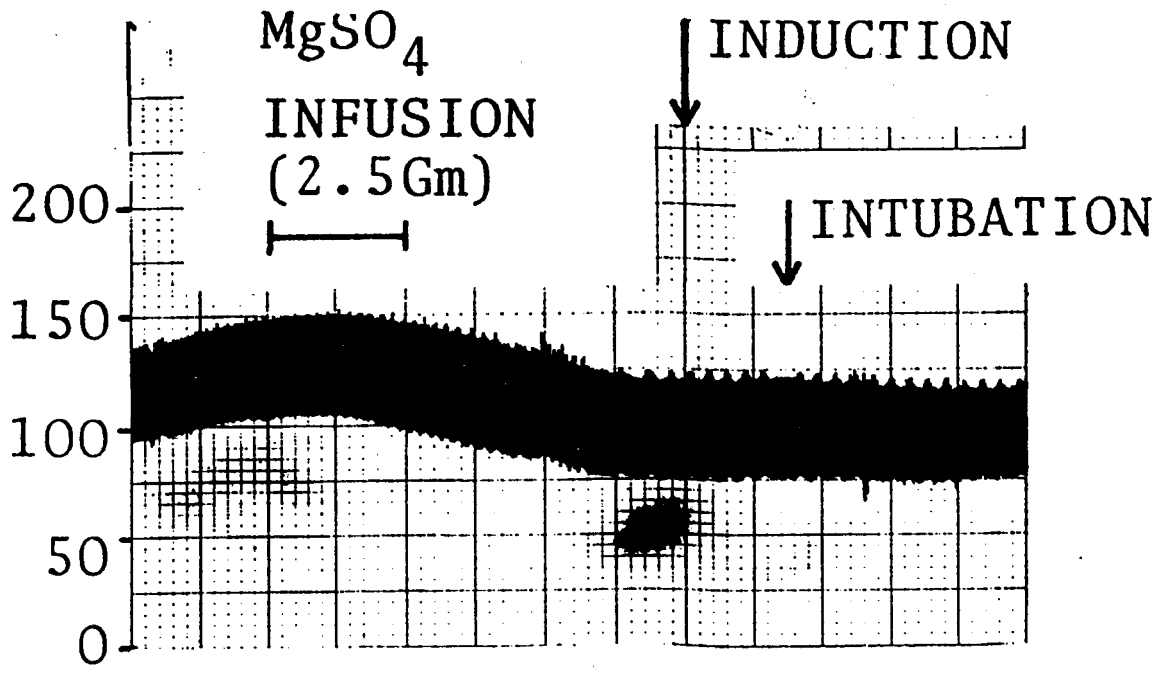


Figure 9.2 Blood pressure response to insertion of a CVP line, and its control by $MgSO_4$. Subsequent blood pressure response to induction and intubation is also shown. Chart speed is 0.1mm/sec and one large square represents 50 seconds. The figures on the y-axis are in mmHg.

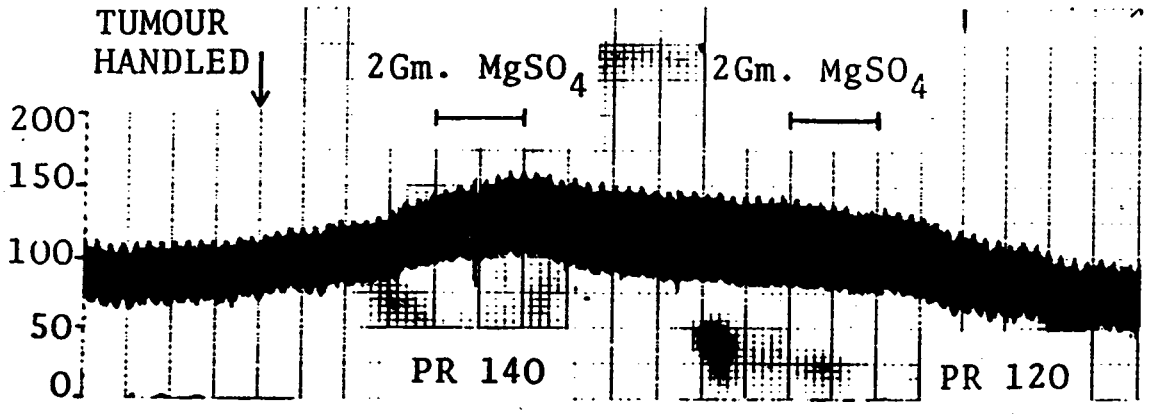


Figure 9.3 Cardiovascular responses and $MgSO_4$ administration during tumour handling. Chart speed is 0.1mm/sec and one large square represents 50 seconds. The figures on the y-axis are in mmHg.

In all but one of the remaining cases, magnesium provided satisfactory control of arterial blood pressure and heart rate up to the time of tumour handling. Where patients arrived in the operating room with elevated arterial pressures, the combination of magnesium and fentanyl satisfactorily controlled the arterial pressure in all but one patient. The only failure was the first of the pregnant patients (case 4, first anaesthetic). Only one other patient exhibited an increase in arterial pressure at intubation, and this was the second patient undergoing Caesarean section (case 7) in whom opiates were not administered prior to intubation. This increase was small (20 mmHg). In 11 of the 17 anaesthetics, $MgSO_4$ alone provided good cardiovascular control throughout the procedure. The case record of the worst controlled patient in this group is shown in figure 9.4.

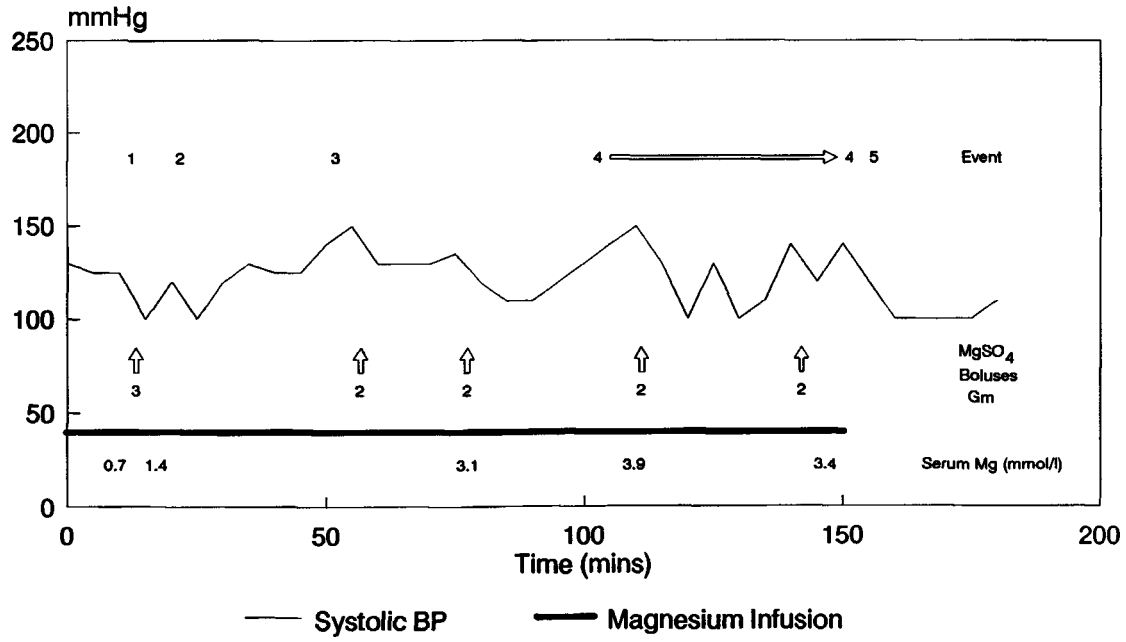


Figure 9.4 Systolic blood pressure in case 8 in whom control was designated as good. Events: 1 - induction; 2 - intubation; 3 - incision; 4 - tumour handling; 5 - tumour removal.

In four of the remaining six patients, two with locally invasive tumours, and two others with very large tumours, infusions of nitroprusside were required in addition to the $MgSO_4$ in order to control increases in arterial pressure at the time of tumour handling. The case record of the worst controlled patient in this group is shown in figure 9.5. In two of these cases (Cases 12 & 13), catecholamine levels were measured during tumour handling and found to be very high, although higher values than these have been reported in other series.

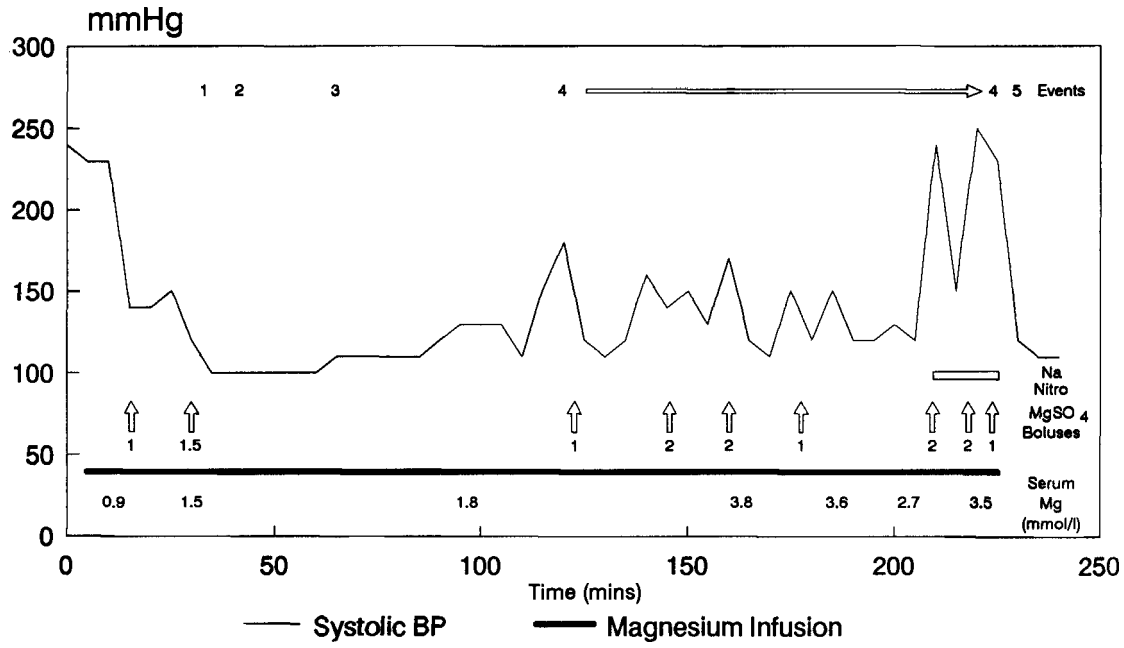


Figure 9.5 Systolic blood pressure in case 12 in whom control was designated as fair. Events: 1 - induction; 2 - intubation; 3 - incision; 4 - tumour handling; 5 - tumour removal.

In the first of the pregnant patients, $MgSO_4$ was without apparent benefit at any stage, but it was subsequently found that she had been grossly magnesium depleted, and therapeutic levels of magnesium were not approached. The highest serum magnesium level attained in this patient was 1.3 mmol/l (figure 9.6). In her subsequent anaesthetic for removal of her tumour she was well stabilised pre-operatively, therapeutic levels of magnesium were established and excellent control was maintained (figure 9.7). The fact that she was no longer pregnant would also have contributed to her greater ease of management.

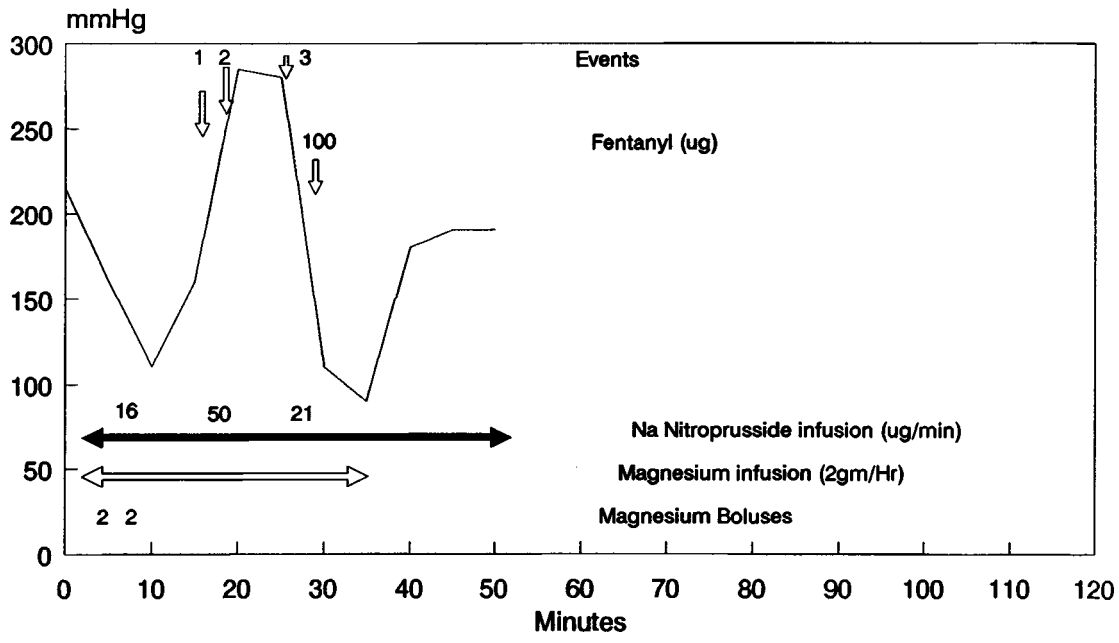


Figure 9.6 SBP changes during caesarean section in case 4.
Events: 1 - induction; 2 - incision; 3 - delivery.

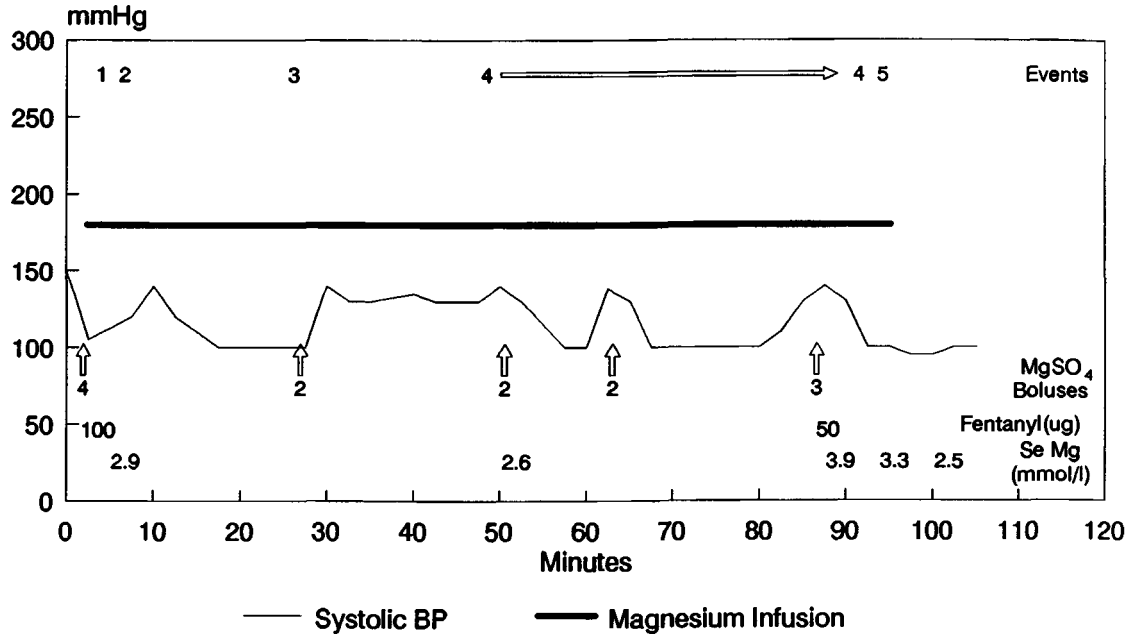


Figure 9.7 SBP changes in case 4 during tumour removal.
Events: 1 - induction; 2 - incision; 3 - incision; 4 - tumour handling; 5 - tumour removal.

In the other pregnant patient, no resection of the tumour was contemplated as the tumour was a malignant one with secondaries. In this case, after pre-operative control had been established in the usual manner, a routine Caesarean section anaesthetic was performed, with the sole addition of magnesium prior to induction and continuously throughout the procedure. Good cardiovascular control was maintained throughout the surgery. Withdrawal of magnesium after the procedure had ben completed resulted in a rapid and severe increase in blood pressure to 250/140 mmHg for which intravenous phenoxybenzamine had to be administered.

In the remainder, serum magnesium levels in the presumed therapeutic range of between 2-4 mmol/l were achieved and maintained. During tumour handling, all patients required supplemental doses of $MgSO_4$ to control increases in arterial pressure, and the total dose administered was in the range of 8-16 gm with a surgical duration ranging between 60 and 150 min. before tumour devascularization. No arrhythmias occurred in any of the patients studied. These results are summarized in Table 9.2. In case 16, the cardiovascular stability which was maintained during tumour handling was such that it led to the erroneous assumption that the tumour had been devascularized. Magnesium was therefore withdrawn prior to tumour removal, and this was followed by an immediate, steep increase in SBP which responded promptly to two further bolus injections of $MgSO_4$ (figure 9.8).

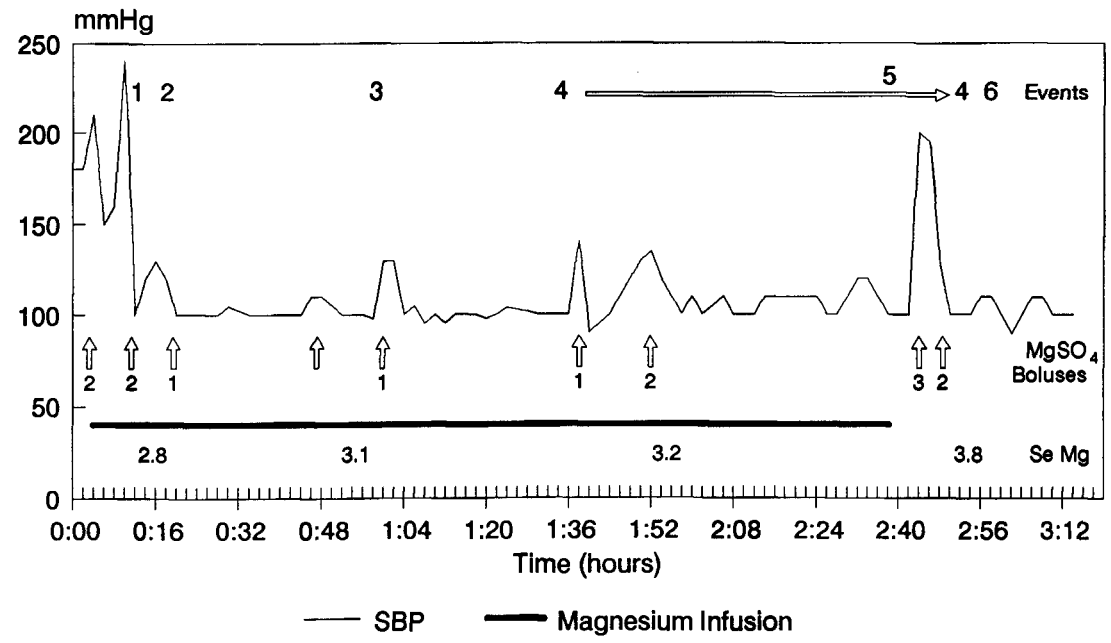


Figure 9.8 SBP changes during anaesthesia and surgery in case 16. Events: 1 - induction; 2 - intubation; 3 - incision; 4 - tumour handling; 5 - $MgSO_4$ withdrawn; 6 - tumour removal.

In case 15, the diagnosis was made as a result of severe hypertension and multifocal arrhythmias exhibited during exploration of a para-aortic abdominal mass. On this occasion, the administration of a 4gm bolus of $MgSO_4$ resulted in immediate, but short lived, reduction of blood pressure and control of arrhythmias. Two further 4gm boluses and one of 2gm were required to establish good cardiovascular control, and tumour removal then proceeded uneventfully (figure 9.9).

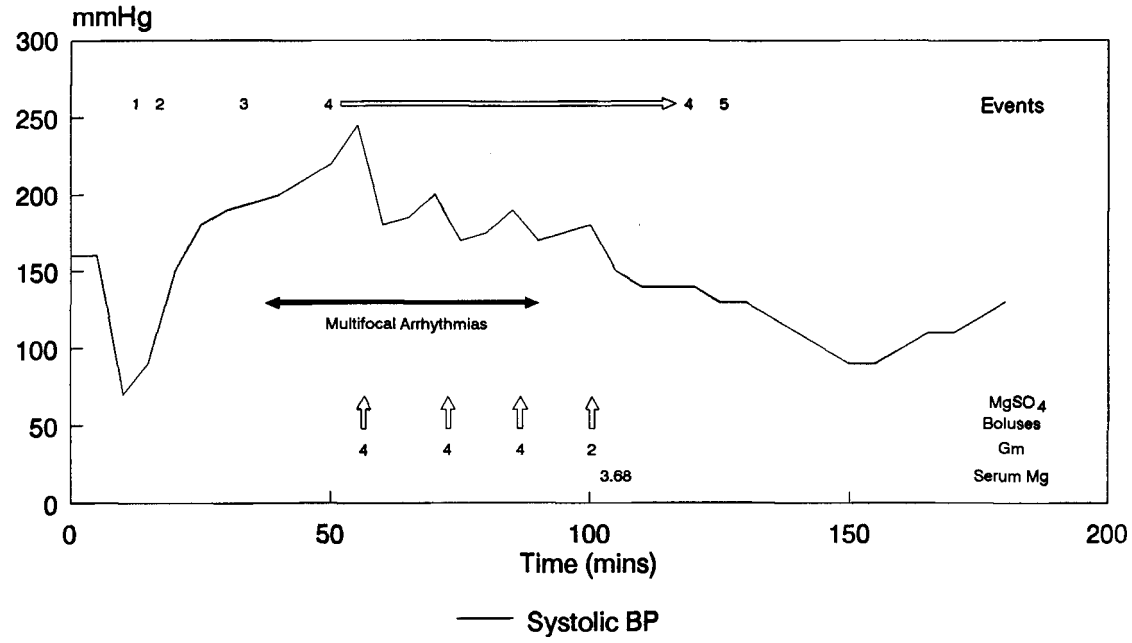


Figure 9.9 SBP changes in case 15 where the diagnosis was made intraoperatively. Events: 1 - induction; 2 - intubation; 3 - incision; 4 - tumour handling; 5 - tumour removal

Table 9.2

Case	SBP1	SBP2	IO Range	Stability	Other Agents
1	195	135	120-140	Good	Nil
2	220	115	110-140	Good	Nil
3	215	145	95-180	Fair	SNP
4a	220	150	85-220	Poor	SNP, PH
4b	130	110	100-140	Good	Nil
5	195	115	110-190	Fair	SNP
6	130	100	100-150	Good	Nil
7	170	150	120-150	Good	Nil
8	186	130	105-150	Good	Nil
9	205	100	100-140	Good	Nil
10	140	95	95-135	Good	Nil
11	150	100	95-140	Good	Nil
12	240	120	100-250	Fair	SNP
13	120	105	100-185	Fair	SNP
14	130	100	90-145	Good	Nil
15	150	175	70-260		Nil
16	130	95	90-200	Good	Nil

Table 9.2. Intra-operative control of cardiovascular events.
SNP - sodium nitroprusside used in addition to $MgSO_4$
PH - phentolamine used.
IO Range - intraoperative systolic blood pressure range.
SBP1 - Systolic blood pressure on arrival in the operating theatre.
SBP2 - Systolic pressure after $MgSO_4$ and induction of anaesthesia.

Note that case 16 is designated "Good" despite one episode of very high blood pressure as this was associated with inappropriate withdrawal of magnesium (see text and figure 9.8).

Two patients in this series required post-operative ventilation. The first was a 54 yr. old male with a tumour invading the diaphragm, and pre-existing renal dysfunction. In view of his renal disease, persistence of high levels of serum magnesium was anticipated, but the nature of the surgery made elective post-operative ventilation the method of choice. Neuromuscular transmission remained depressed for 12 hours postoperatively. In the other, adequate neuromuscular function was restored at the end of the procedure, but in view of her obesity, and the fact that a sub-costal incision had been performed, it was decided to institute elective post-operative ventilation for the first 12 hours postoperatively. In all of the other patients, neuromuscular blockade was reversed without difficulty, despite a mean serum magnesium level at the time of reversal of 1.9 mmol/l. In the first 3 cases, 1gm calcium gluconate was routinely administered prior to reversal of neuromuscular blockade, but this appeared unnecessary and was discontinued in the later cases. Good blood gases were maintained in all cases, with no acid-base disturbances seen.

Greatly increased adrenaline and noradrenaline concentrations were found on arrival in the operating theatre in the 5 patients in whom they were measured. Noradrenaline levels ranged from 1900 - 6650 pg/ml (normal range 100-600 pg/ml) and adrenaline levels from 120-390 pg/ml (normal range 10-80 pg/ml). Dopamine levels were normal. Noradrenaline and adrenaline levels were reduced following magnesium in all 5 cases, although the effect was greater on adrenaline than on noradrenaline. Adrenaline levels were reduced by

magnesium to within the normal range in all 5 cases, but noradrenaline levels, although reduced, remained markedly elevated. In the two patients in whom anaesthesia was induced prior to the administration of magnesium, noradrenaline and adrenaline levels increased following induction, and returned to pre-induction values following magnesium. No increase in catecholamine levels occurred following intubation. During tumour handling $MgSO_4$ appeared to be ineffective in blocking the release of catecholamines. In two cases, noradrenaline levels were very high and sodium nitroprusside was required in addition to magnesium to control arterial pressure during tumour handling. In the other three magnesium alone provided adequate control, despite the fact that adrenaline levels were similar in all 5 cases. The changes in catecholamine levels are illustrated in figures 9.10 and 9.11.

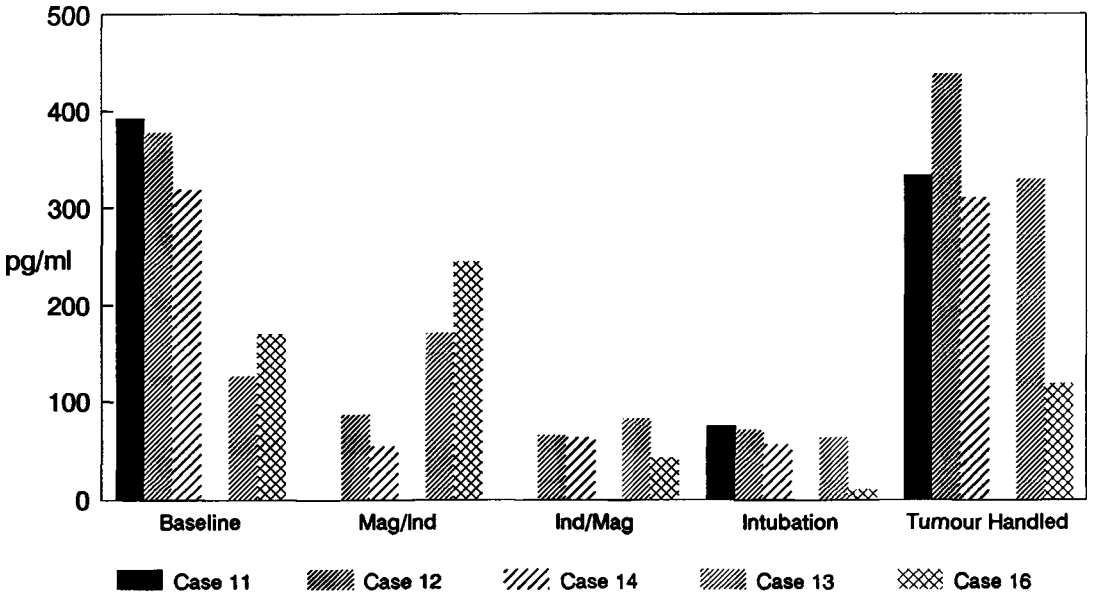


Figure 9.10 Changes in adrenaline concentrations in 5 patients. Mg/ind - induction of anaesthesia in cases 13 & 16; administration of $MgSO_4$ in the other 3 cases. Ind/mag - administration of $MgSO_4$ in cases 13 & 16; induction of anaesthesia in the other 3 cases.

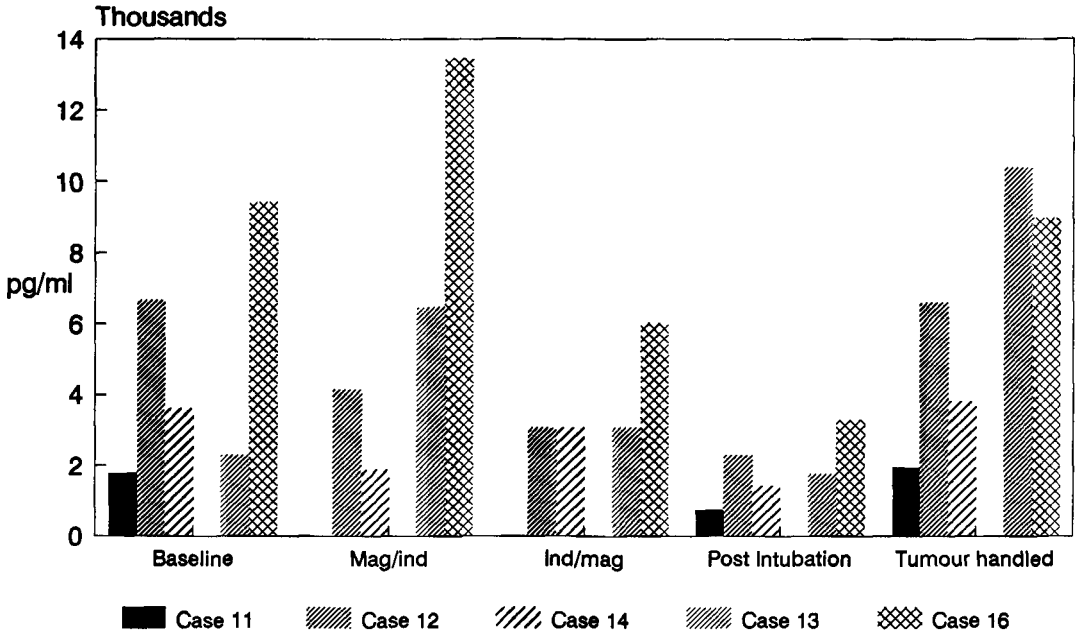


Figure 9.11 Changes in noradrenaline concentrations in 5 patients. Mg/ind - induction of anaesthesia in cases 13 & 16; administration of $MgSO_4$ in the other 3 cases. Ind/mag - administration of $MgSO_4$ in cases 13 & 16; induction of anaesthesia in the other 3 cases.

Complications: One patient developed severe hypotension following tumour removal and in association with massive blood loss. Blood transfusion and vasoconstrictors failed to improve the arterial pressure, and myocardial depression appeared to be contributing to the poor arterial pressure. An adrenaline infusion was required to maintain satisfactory arterial pressures during the remainder of the surgery and for 24 hours postoperatively. This patient (case 9) had been inadequately prepared for surgery, and his problem appeared to be principally due to an excess of ß-blockade persisting after tumour excision. As he continued to require adrenaline long after his serum magnesium levels had returned to normal, it seems most unlikely that his cardiovascular problem was due to the magnesium, although this possibility

cannot be ruled out completely. The only other complication was the well known unpleasant burning sensation produced by magnesium infusion. The only patient to complain of this was the second of the Caesarean section patients in whom $MgSO_4$ was given without the prior administration of any analgesic or sedative drugs. The other pregnant patient did not complain of this, but as she was in labour at the time this may account for her absence of symptoms. The concomitant use of fentanyl appeared to prevent complaint of this problem in the other patients.

9.3 DISCUSSION

The rationale for the use of $MgSO_4$ infusions in the anaesthetic management of phaeochromocytoma is based on the ability of magnesium to inhibit the release of catecholamines from the adrenal medulla as well as its vasodilator and anti-adrenergic properties which have been discussed in preceding chapters. The ability of magnesium infusions to control catecholamine-induced crises associated with severe tetanus, and reduction of catecholamine concentrations following infusions of magnesium in a patient with this condition have been described in the previous chapter. The safety of $MgSO_4$ at the serum concentrations used in this series is well established by the use of similar serum magnesium concentrations in the management of pregnancy-induced hypertension (Pritchard & Pritchard, 1975; Pritchard et al, 1984).

In the five patients in whom catecholamine concentrations were studied, magnesium reduced adrenaline concentrations to within the normal range and also reduced noradrenaline concentrations, although not to levels approaching normal values. The greater effect on adrenaline could simply be due to its shorter half-life, and therefore a more rapid clearance following the inhibition of release from the tumour. Although the stress of intubation is known to release catecholamines (Russell et al, 1981; Derbyshire et al, 1983), there was no increase in catecholamine concentrations following intubation. No comment can be made on the effect of magnesium on catecholamine release during tumour handling, as no comparisons were made with patients treated without magnesium. It is possible that magnesium may have had some inhibitory effect on catecholamine release at this time, but this possibility requires further study. The mechanism by which magnesium blocks catecholamine release is by competition with calcium for membrane channels as has been outlined previously, and it seems unlikely that this action would be important during physical stimulation of the tumour.

In addition to its action in blocking catecholamine release, magnesium exerts considerable cardiovascular effects of its own (chapter 5), all of which could be expected to be of benefit during anaesthesia in patients with phaeochromocytomas. The direct vasodilating properties of the agent are well established and as has been shown in chapter 6, magnesium infusions can

antagonize the adverse effects of high concentrations of circulating adrenaline in intact animals.

The results of this present study are in apparent conflict with the well established role of magnesium in obstetric practice in which magnesium appears to produce only mild hypotension, although profound hypotension following magnesium therapy in association with a blood volume deficit has been described (Bourgeois et al, 1986). There are several possible explanations for this discrepancy. Firstly, the dosages of magnesium generally used in obstetric practice frequently fail to produce the desired serum concentrations of magnesium (Sibai et al, 1981). In the present study, very large doses of magnesium sulphate were needed to maintain the serum magnesium concentrations within the required range. Secondly, the mild degree of hypotension produced by magnesium in obstetrics is generally regarded as indicating little cardiovascular effect. However, magnesium has been shown to produce marked vasodilatation in both experimental animals and humans accompanied by an increase in cardiac output (Mroczek et al, 1977; Lee et al, 1984; see chapter 5), which largely offsets the hypotensive effect of the vasodilatation. In the presence of excess catecholamines, the reduction in peripheral resistance produced by magnesium appears to be greater than that produced by magnesium under conditions in which catecholamine concentrations are not elevated (chapter 6), probably because of the α-blocking properties of magnesium. Further, the reduction of catecholamine

concentrations in patients with phaeochromocytoma will not only enhance the vasodilator effect but will prevent the usual increase in cardiac output, as was seen in the study on patients with severe tetanus (chapter 8). It is not surprising therefore that the cardiovascular effects of $MgSO_4$ infusion should be far more profound in phaeochromocytoma patients than in obstetric patients.

Magnesium is a potent anti-arrhythmic agent (Enselberg et al, 1950; Ghani & Rabah, 1977; Iseri et al, 1983) particularly in the presence of high concentrations of catecholamines (chapter 6) and no patient in this series developed intra-operative arrhythmias, even when there was massive catecholamine release. This was impressive, as almost all other agents used are associated with a high rate of transient intra-operative dysrhythmias (Roizen, 1986). Where arrhythmias occurred prior to the use of magnesium these were reversed, as in the unprepared patient, whose arrhythmias were completely controlled by the magnesium injections.

The rarity of phaeochromocytomas makes controlled trials in this condition extremely difficult. Consequently, reports of the management of this condition tend to be collections of case reports, and the present series is no exception. As this series of patients was collected over a considerable period of time and the patients were referred by many different practitioners, using different methods of initial patient preparation, a controlled trial of magnesium was not

feasible. Nevertheless, the ease of management of these cases, particularly during the induction and early surgical phases of the procedure, was in marked contrast to the author's personal experience of 10 previous phaeochromocytomas handled by conventional means. The author's experience with the use of magnesium in the cases presented here was so successful that it was felt that a personal controlled trial would be difficult to justify on ethical grounds. Whilst other anti-adrenergic and vasodilatory agents are more potent than magnesium, the unique capacity of magnesium to inhibit the release of catecholamines prior to tumour handling is probably the principal reason for the good cardiovascular control obtained in this series.

The anaesthetic management of pregnant patients with phaeochromocytomas presents a major anaesthetic problem and various techniques have been suggested. As in other cases, α-adrenergic blockade has been the mainstay of perioperative blood pressure control (Burgess, 1978), but is often inadequate on its own during the stresses of surgery (Fox et al, 1969;Griffith et al, 1974) and may be accompanied by severe hypotension at the time of delivery (Galletly et al, 1983; Burgess et al, 1978). The use of sodium nitroprusside in pregnant patients is controversial (Willoughby, 1984) as acidosis and cyanide accumulation occurs to a greater degree in foetal lambs than in the mother; the foetus may also have immature mechanism for cyanide metabolism (Naulty et al, 1977). In addition the drug may reduce uterine blood flow (Lieb et al, 1981). Regional blockade has been said to be contra-indicated (Schenker & Granat,

1982), although there have been reports of successful management with epidural anaesthesia (Davies & Navaratnarajah, 1984; Stoneham & Wakefield, 1983). It is worth noting that in the first of the two pregnant patients in this series epidural analgesia was totally ineffective in ameliorating cardiovascular disturbances. In view of these conflicts and difficulties in managing these rare but highly challenging cases, an agent with an already established place in obstetric practice such as magnesium sulphate may offer the anaesthetist a unique additional tool for the safe management of the patient. It is also worth noting that both of the pregnant patients in this series showed magnesium deficiency. This is not surprising in view of the fact that pregnancy itself is often associated with magnesium deficiency (Seelig, 1980), and catecholamine stimulation may prevent the influx of magnesium to the intracellular space (Maguire & Erdos, 1980; Erdos & Maguire, 1983). Such deficiency should always be looked for and corrected.

Magnesium appears to be a useful addition to the armamentarium available for the anaesthetic management of patients with phaeochromocytomas. It appears to be of particular value in controlling cardiovascular disturbances and catecholamine release at the times of induction and intubation, but can also be of use, in conjunction with other agents, in controlling arrhythmias and blood pressure disturbances during tumour handling.

10. Conclusions

The review of the biochemistry, physiology and pharmacology of magnesium invited speculation that magnesium infusions may have considerable benefits to offer in various circumstances pertaining to anaesthesia. On reviewing the literature it appeared that there were considerable deficiencies in the knowledge pertaining to the cardiovascular actions of this ion.

10.1 Cardiovascular Effects

Investigations of the cardiovascular effects of infusions of magnesium sulphate in intact baboons generally confirmed existing information available regarding the effects of the ion on blood pressure. In addition, it confirmed some of the human studies which have suggested that the relatively mild hypotensive effects that resulted from infusions of magnesium were the consequence of a combination of vasodilatation with an increased cardiac output rather than evidence of weak cardiovascular effects. This study also demonstrated, for the first time, that the effective range of serum magnesium concentrations

appeared to be between 2 and 5mmols per litre and that only at levels greater than 5mmols per litre were significant falls in blood pressure and heart rate likely to occur. Even at very high levels of serum magnesium the absence of significant myocardial depression was one of the most important findings of this study.

10.2 Anti-adrenergic Effects

It was also confirmed that the *in vitro* findings that magnesium could block adrenergic activity at the alpha receptor could be demonstrated in intact animals receiving an adrenaline infusion. The magnitude of this effect appeared to be such as to be of clinical value. It was also demonstrated, for the first time, that magnesium exerts important anti-arrhythmic effects in the presence of high levels of catecholamines. Finally it was demonstrated that magnesium did not appear to exert potentially hazardous interactions with either alpha or beta adrenergic blockade in animals treated with high levels of adrenaline.

The conclusions drawn from the animal experimentation section of this thesis were that magnesium exerted significant and potentially useful vasodilator effects while at the same time maintaining at least normal myocardial contractility, and, in addition, that magnesium exerted clinically useful and apparently safe anti-adrenergic effects in animals treated with high doses of adrenaline. These animal studies therefore justified trials of this agent in

clinical conditions in which catecholamine excess presented a therapeutic problem.

10.3 Clinical Studies

In the clinical studies section of this thesis it was shown that magnesium not only usefully antagonised excess adrenergic activity but also appeared to inhibit the release of catecholamines from adrenergic nerve terminals. This confirmed the findings of *in vitro* experiments in which this action of excess magnesium ions had been demonstrated. It can be concluded, therefore, that in conditions of catecholamine excess, infusions of magnesium sulphate, and probably of other salts of magnesium, may well provide clinicians with an additional tool to enable them to manage difficult clinical situations with a greater degree of patient safety.

10.4 Unanswered Questions

There are, however, a number of questions which remain unanswered.

10.4.1 Magnesium and Inotropy. One of the intriguing observations that emerged from both the animal work and from the clinical studies in tetanus, was the increase in cardiac stroke volume that was consistently

described. This increased stroke volume is, at least superficially, difficult to explain in view of the fact that magnesium is theoretically a calcium antagonist and, therefore, should have negative inotropic effects and that such effects have been described in isolated tissue experiments. There are a number of important considerations to be borne in mind when considering this rather surprising finding. Central to these arguments is the concept that magnesium is essential for energy metabolism and is probably essential for the action of beta adrenergic stimulants on the contractile state of the myocardium. In all of the experiments in which an increased stroke volume was found, increased adrenergic activity was likely to be present. Increased β-agonist binding has been described as one of the actions of magnesium and it is therefore possible that this is an explanation for the actions of magnesium in these situations. It is also possible, although less likely, that the experimental animals and the human subjects were marginally magnesium deficient at the start of the experiments. If this were the case, then the finding of an increased stroke volume would be less surprising because catecholamines require magnesium to exert their inotropic effects. It is also possible that these results were merely chance findings as there is some evidence, although none of it in essentially intact animal models such as those used for the present experiments, that magnesium may have negative inotropic effects in the intact animal. In general, these results were found in extensively instrumented animals in which rather deep anaesthesia would have been required, and the influence of this is unclear. It seems a safe conclusion to draw that magnesium is not a negative inotrope at the clinical concentrations used but it is difficult at this stage to be sure about what other effects it may have on contractility.

10.4.2 Catecholamines and tumour handling. It has not been investigated whether magnesium infusions had any effect at all on the output of catecholamines during tumour handling in patients undergoing surgery for the removal of a phaechromocytoma. One of the surprising features of the phaechromocytoma studies was that, in the majority of patients, cardiovascular disturbance could be well controlled even during the periods of tumour handling. Only a comparative study between magnesium and other forms of cardiovascular control could indicate whether or not magnesium was, in fact, inhibiting catecholamine release at this time. Unfortunately this author found the cardiovascular control so impressive as to make magnesium the drug of choice. Ethically, therefore, it would require someone else, less convinced of the benefits to do such a controlled study. This does, however, remain an intriguing possibility and worthy of further research. Whether or not this is the case the evidence presented here does suggest that magnesium may provide an extremely useful addition to the armamentarium of drugs available to the anaesthetist for the management of this problem.

10.4.3 Pre-eclamptic toxaemia. The role of magnesium in the management of pre-eclamptic toxaemia remains a controversial subject. Clinical experience would appear to indicate that magnesium both prevents and controls convulsions in this potentially life-threatening condition. The mechanism by which it does so are, however, obscure in view of the apparent inability of magnesium infusions to produce significant CNS depression. It seems most likely that magnesium is exerting its anti-convulsant effects secondarily to its action on the cardiovascular system and the most likely mechanism of action is cerebral vasodilatation and improved cerebral oxygenation. This possibility,

however, remains entirely speculative and the subject for much further research. An alternative possibility is that pre-eclampsia produces local areas of brain injury which act as epileptic foci. As such foci would be likely to have disrupted blood brain barriers it is possible that magnesium could penetrate such areas locally and exert anti-convulsant effects without altering CSF magnesium to any great extent.

10.5 Further studies

A further potentially fruitful area for magnesium research is the role of magnesium infusions in the protection of the stressed myocardium particularly during periods of actual or potential coronary ischaemia. The possibility exists that magnesium infusions may offer particular benefit in anaesthesia in cases where coronary perfusion may be at risk.

In a totally different direction, it appears that the interaction of magnesium with muscle relaxants has been inadequately evaluated. There are potentially exciting possibilities in the observation that magnesium appears to reduce the incidence in severity of suxamethonium-induced fasciculations and that it appears to inhibit the release of potassium, at least in normal subjects, following the use of this relaxant. If these observations are confirmed, it may imply a role for magnesium in reducing some of the hazards associated with the

use of depolarising muscle relaxants. It may protect against increases in intra-ocular pressure and thus make emergency anaesthesia in the patient with an open eye injury considerably safer. Inhibition of potassium release may also enable the use of depolarising relaxants in situations such as burns where the rapid, complete, and short duration paralysis produced is of benefit but currently prevented by the hazards of potassium induced arrhythmias.

An even more intriguing possibility lies in the recent confirmation of old observations that magnesium may reduce bronchial tone. Given the apparently beneficial interactions between magnesium and adrenaline which were demonstrated in this thesis, particularly the α-blockade and anti-arrhythmic properties of magnesium, the possibility exists that combinations of magnesium and adrenaline or indeed, other β-stimulants may not only improve the efficiency of bronchodilatation but may also increase the safety of β-agonists by suppressing the arrhythmic response. Furthermore, the possibility which has been suggested that magnesium may protect against the adverse metabolic effects of catecholamine stimulation on the myocardium further increases the potential benefit that could be gained from this interaction. One further interesting possibility is that if the enhancement of β-agonist binding by magnesium can be demonstrated in bronchial muscle it is likely that magnesium would have a synergistic action in asthma with the β-agonist stimulants.

It is also possible that combinations of magnesium and adrenaline may exert other beneficial effects. There is currently a resurgence of interest in the use of adrenaline in a wide variety of clinical conditions limited predominantly by the arrhythmic risk posed by infusions of this agent. Combinations of adrenaline and magnesium may well allow further manipulations of the cardiovascular system without the arrhythmic risk. In addition, magnesium is known to dilate renal blood vessels and may have a diuretic action. It is possible that magnesium may antagonise the adverse effects of adrenaline on renal blood flow and urine output. The studies reported in this thesis have shown that magnesium may have beneficial effects in conditions of catecholamine excess. The possibility exists that these studies are only the beginning of a wide range of future investigations into the clinical significance of magnesium as a therapeutic agent.

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Appendix A

Cardiac Output Estimation by Thermodilution

The thermodilution technique for determining cardiac output utilizes the Stewart-Hamilton indicator dilution equation as modified for thermal indicator. The following equation is the result:

$$C.O. = \frac{1.08\,(60)\,C_T\,V_I\,(T_B - T_I)}{1.22\int_0^{\tau} \Delta T_B\,(t)\,dt}$$

Where:

C.O. = Cardiac output in litres/minute

$$1.08 = \frac{\rho\ C_p\ (5\ \text{percent dextrose})}{\rho\ C_p\ (\text{Blood})}$$

The ratio of the density times the specific heat of 5 percent dextrose to the density times the specific heat of blood.

C_T = Correction factor for the injectate temperature rise through the catheter.

60 = Seconds/minute

V_I = Volume of injectate in litres

T_B = Initial blood temperature in °C

T_I = Initial injectate temperature in °

$1.22\int_0^{\tau} \Delta T_B\,(t)\,dt$ = Area under the time-temperature thermodilution curve in °C - sec

τ = Time to 30% of curve peak amplitude from START

1.22 = Compensation for area lost due to 30% termination

Basis for Modified Equation

One aspect of heat theory relates the change of heat in a substance to its mass and specific heat for a given change in temperature. In a static situation, if two substances at different temperatures are mixed, the resulting temperature of the mixture will fall between the original temperatures. If one of the masses is unknown, it can be determined by equating, at equilibrium, the change in heat of the two substances and calculating the unknown mass from the resulting equation. When applied to a system of continuous flow, as in the heart and vasculature, a small amount of cold indicator can be introduced into and mixed with the flowing substance (blood) to determine a time-temperature curve downstream. The area under this curve represents the sum of the instantaneous mixture temperature at the sensing point. When applied to the Stewart-Hamilton equation, the unknown flow of mass per unit time can be determined much as mass alone is determined in the static case.

The first four terms of the modified equation [(1.08) C_T (60) V_I] are pre-determined by the volume and physical properties of the injectate and the characteristics of the catheter. They can, therefore, be grouped and entered into the computer as a preset constant called the "Computation Constant". The components of the fifth term (TB - TI) are continuously measured by the thermistor probe on the catheter, and the injectate temperature sensor from the computer. The computer electronically determines the difference between TB and TI and multiplies the difference by the computation constant. The resulting value is internally held for later processing. The temperature of the

indicator-blood mixture is sensed by a thermistor in the catheter. The resulting time-temperature curve is amplified and integrated in the computer. Integration is automatically terminated when the curve returns to 30 percent of its peak. The ratio of the final value shown in the previous paragraph to this integrated value is the measured cardiac output. The area lost by cutting off the curve on the downslope at 30 percent of its peak amplitude amounts to approximately 22 percent of the remaining area. Compensation for this lost area is accomplished by amplifying the dilution signal presented to the integrator by 22 percent. The value of 30 percent is chosen as the cut-off point because of documented clinical studies which relate this point to minimal variability.(Ref: Edwards Laboratories Cardiac Output Computer Manual, 1980)

Thermodilution techniques have the advantage over other methods that the technique is nontoxic and readily repeatable. The values obtained by this method correlate well with those obtained by other techniques such as the Fick method or the use of indicator dilution curves (Keefer & Barash, 1985). Potential sources of error include injectate temperature changes prior to injection and along the catheter; incomplete mixing in low cardiac output states, and variations in pulmonary artery temperature with changes in the ventilatory cycle (Sykes et al, 1981). In this thesis, all cardiac output measurements were made using cold dextrose. The injectate, tubing and syringes were kept in a water bath for at least an hour prior to use, and until the moment of injection. The injectate temperature probe from the computer was placed in the water bath which wa frequently stirred to ensure an even

temperature distribution throughout the container. Syringe handling was kept to a minimum by the use of insulated syringes. All injections were made by the author to minimise variation induced by different injection styles. All readings were on animals or patients on controlled ventilation, and during readings ventilation was discontinued to minimise errors due to fluctuations in airway temperature.

Cardiovascular Measurements

In the cardiovascular investigations reported in chapters 5, 6 & 8 of this thesis, the following direct measurements were made:

Systolic, diastolic and mean systemic arterial blood pressure from the radial artery
Central venous pressure from the proximal port of the PA catheter
Systolic, diastolic and mean pulmonary arterial pressure from the distal port of the PA catheter
Pulmonary capillary wedge pressure from the distal port with the balloon inflated
Heart Rate from the rate counter of the ECG
Cardiac output

Mean systemic (MAP) and pulmonary (PAP) arterial pressures were determined by the monitoring apparatus by integration of the area under the curve of the arterial pressure wave. Central venous and pulmonary capillary wedge

pressures were read from the recorded trace at end of expiration.

From these measurements the following values were derived:

$$\text{Stroke volume} = \frac{\text{Cardiac Output}}{\text{Heart Rate}} \text{ ml/beat}$$

$$\text{Systemic Vascular Resistance} = \frac{(\text{MAP} - \text{CVP}) \times 80}{\text{Cardiac Output}} \text{ dyne.sec.cm}^{-5}$$

$$\text{Pulmonary Vascular Resistance} = \frac{(\text{PAP} - \text{CVP}) \times 80}{\text{Cardiac Output}} \text{ dyne.sec.cm}^{-5}$$

$$\text{Left Ventricular Stroke Work} = \text{SV} \times (\text{MAP} - \text{PCWP}) \times 0.0136 \text{ gm.m/beat}$$

$$\text{Right Ventricular Stroke Work} = \text{SV} \times (\text{PAP} - \text{CVP}) \times 0.0136 \text{ gm.m/beat}$$

In the tetanus study, body surface area (BSA) was determined for each patient using a nomogram relating height and weight to BSA and then cardiac index, stroke volume index and stroke work index derived by dividing the appropriate values by the body surface area. In the baboon studies this technique was not used since the animals were of reasonably consistent size and weight, and reliable BSA tables for baboons were not available.

Biochemical assays for magnesium and calcium

The various methods which can be used for the estimation of the magnesium content of body fluids have been reviewed extensively by Wacker (1980) and Aikawa (1981). Earlier techniques involved the use of colorimetric methods

including Titan-yellow and eriochrome black, but although both of these methods are simple, they are generally not regarded as sufficiently accurate or reproducible for research purposes. In 1955, Walsh developed a hollow cathode discharge lamp, using magnesium metal as the hollow cathode. When excited by an electric current, such a lamp emits a stable, high-intensity light at the wavelength specific for the metal. This light beam is focused through a flame which contains the unknown concentration of magnesium atoms at ground state. Absorption of the light beam occurs in the flame in proportion to the concentration of magnesium in the solution. Since the mid-1960s atomic absorption spectrophotometry has been available in commercial devices and has become the standard method for magnesium analysis as this technique considerably improves the precision and accuracy of the determination. In all of the studies contained in this series atomic absorption spectrophotometry was the method adopted. The principal problem with this technique is interference from phosphate, although this is a relatively minor problem with blood samples and only becomes a significant factor when CSF magnesium is estimated. In order to minimise this interference, the serum specimens studied were diluted 1:50 in 0.75% ethylenediaminetetra-acetic acid (EDTA). The EDTA has a high affinity for calcium and magnesium and all of the calcium and magnesium in the specimen is complexed, preventing the loss of magnesium phosphate from the estimation. The solution is then assayed for calcium and magnesium content using atomic absorption using lanthanum as an internal standard. As calcium and magnesium have very different absorption characteristics, the two substances are readily distinguished. Quality control

was maintained using standard commercially available stock solution diluted to yield standard magnesium concentrations from 0.25 to 1.75 mmol/l in 0.25 mmol/l increments and from 5 to 20 mmol/l concentrations in 5 mmol/l increments. Similar standards were prepared using calcium standards with concentration of 1 to 4 mmol/l with increments of 0.5 mmol/l. The accuracy of this method is to within 0.01 mmol/l, and the between run precision of the method is $\pm$ 5%.

Catecholamine Assays

Catecholamine assays reported in this thesis were performed by Dr. Jan Esser of the department of Nuclear Medicine, University of the Witwatersrand.

Tubes with blood samples for serum catecholamine measurement were immediately placed on ice. Samples were centrifuged at 3 000 revolutions per minute for 10 min at 4°C. Aliquots of the serum were stored at -70°C for not longer than one week. Catecholamine extraction was performed using a commercially available kit (Cat-A-Kit, Upjohn Pharmaceuticals) and fractionated serum catecholamine concentrations were determined using reversed-phase high-performance liquid chromatography with electrochemical detection using a Waters ECD machine. The lower limit of sensitivity of the detector is 0.5 nanoamps, and the lowest accurate readings are 10 pg/ml. An

internal standard DHBA was used for every estimation and the catecholamine concentration calculated is related to the recovery of DHBA.

The interassay variation is as follows:

Noradrenaline	1%
Adrenaline	2%
DHBA	4.7%
Dopamine	< 1%

The mean peak height and standard deviation of each estimate calculated by the integrator in mm for each substance are as follows:

Noradrenaline	36.921 $\pm$ 0.126
Adrenaline	17.501 $\pm$ 0.358
DHBA	39.690 $\pm$ 0.909
Dopamine	12.083 $\pm$ 0.052

APPENDIX B

CASE REPORTS.

Case 1. A 16 year old girl presented with peripheral gangrene and labile hypertension. A diagnosis of phaeochromocytoma was confirmed by angiography and by finding elevated urinary vanilmandelic acid levels. An initial dose of phenoxybenzamine 50mg i.v. was infused over 2 hours followed by 20mg orally 8 hourly for five days days with careful i.v. fluid replacement monitored by central venous pressure monitoring. The first doses of phenoxybenzamine produced hypotension with tachycardia which responded well to i.v. fluid therapy. Over the next few days good cardiovascular stability was achieved without the need for β-adrenergic blockers. During this time, the supine arterial blood pressure remained within the range 110/60 - 130/80 mmHg and on standing this decreased to between 100/60 and 90/40 mmHg. There were no hypertensive episodes. The heart rate remained below 100 b.p.m. at all times, and there were no arrhythmias detected or ECG abnormalities noted.

After a further three days the patient was then judged ready for surgery in accordance with the criteria laid down by Roizen (1987).

She was premedicated with chlorpromazine 50mg, papaveretum 15mg and scopolamine 0.4mg as well as being given 10mg phenoxybenzamine orally. On arrival in the anaesthetic room, her arterial blood pressure was 190/120 mmHg and her heart rate was 170 b.p.m. She was further sedated with 100μg fentanyl and 10mg droperidol i.v. without benefit to her cardiovascular status. Ventilation was gently assisted and 50% nitrous oxide in oxygen inhaled. The patient was now well sedated, but the severe tachycardia and hypertension persisted, although the patient was peripherally warm and vasodilated. As the tachycardia appeared to be the major problem, and in view of the fact that several α-adrenergic blockers had already been given, propranolol was administered in 2mg increments with continuous ECG monitoring, and blood pressure recording using an automatic doppler device. After 10 mg of propranolol, little improvement had been achieved and her arterial blood pressure was 180/120mmHg and her heart rate 149 b.p.m. At this point, abandonment of the procedure was contemplated, but in view of her excellent preoperative status, it was felt that this was an acute response to the stress of coming to the operating theatre. It was, therefore, decided to make one further attempt to control the cardiovascular disturbances at this time and a trial of magnesium therapy was initiated.

The patient was transferred to the operating theatre, an arterial line inserted into the left radial artery under local anaesthesia, and a magnesium sulphate infusion commenced at a rate of 2 gm per minute. After 1.5 min the arterial blood pressure had reduced to 130/90 mmHg, and the heart rate had decreased to 122 b.p.m. (Figure 9.1). As the central venous line had become displaced prior to the patient coming to theatre, a right subclavian catheter was inserted under local anaesthesia prior to induction of anaesthesia. This produced a mild increase in arterial blood pressure which responded well to infusion of an additional 2.5 gm magnesium sulphate. As eye lash and pharyngeal reflexes were still present, anaesthesia was then induced with 150 mg thiopentone i.v., paralysis with 15 mg alcuronium i.v., and the trachea then intubated. There was no cardiovascular response to endotracheal intubation and no change in heart rate (figure 9.2).

Surgery proceeded uneventfully under halothane, nitrous oxide and oxygen with controlled ventilation until mobilization of the tumour was attempted. The tumour was tightly adherent to the inferior vena cava, and ligation of the venous drainage proved to be impossible. As it was obvious that extensive tumour handling would be necessary to remove the mass, severe disturbances of cardiovascular function were anticipated. As expected, arterial blood pressure and heart rate began to increase, and before resorting to phentolamine and sodium nitroprusside as had been planned, a further infusion of magnesium sulphate was administered. A 2 gm infusion terminated the upward trend, and a further 2 gm restored the arterial pressure and heart rate to normal levels,

despite the fact that tumour handling was continuing throughout. Despite further manipulation of the mass, there were no further cardiovascular disturbances (Figure 9.3). Following tumour removal, mild hypotension and bradycardia occurred (arterial blood pressure 80/60mmHg and heart rate 64 b.p.m.) but this responded adequately to i.v. fluid therapy alone, and inotropic support was not required, although 1 gm calcium gluconate was given to counteract any remaining magnesium effects. This produced no significant change in cardiovascular status. Neuromuscular blockade was reversed with 2.5 mg neostigmine and 1.2mg atropine, following which good muscle tone was readily restored and satisfactory spontaneous ventilation established. The post operative course was uneventful.

Case 2. A 45 year old black female presented initially with long-standing hypertension and was diagnosed as having a phaeochromocytoma situated in the right adrenal gland. Preoperative preparation consisted of increasing doses of phenoxybenzamine up to a maximum dosage of 180mg per day and propranolol 40mg per day. She was judged as fit for anaesthesia according to the criteria laid down by Roizen. Premedication consisted of 10mg of diazepam and 25mg of phenergan both administered orally, 90 minutes preoperatively.

On arrival in the operating theatre the patient was mildly hypertensive but during placement of central venous and arterial monitoring lines under local anaesthesia she became severely hypertensive with a systolic blood pressure of 220mmHg. Fentanyl 200μg was administered i.v. followed by an infusion of 4gm $MgSO_4$. The blood pressure rapidly fell to 120mmHg and then anaesthesia was induced with thiopentone 300mg and muscle relaxation obtained with 15mg alcuronium. Endotracheal intubation was performed 3 min. after induction and produced no increase in blood pressure or heart rate. During the procedure a continuous infusion of $MgSO_4$ was administered at a rate of 2gm per hour and anaesthesia maintained with 50% nitrous oxide in oxygen and 1-3% enflurane. Excellent cardiovascular control was established and maintained throughout the procedure with 3 further boluses of $MgSO_4$ each of 2gm being administered during tumour handling. At the end of the procedure 1gm of calcium gluconate was given intravenously followed by reversal of the neuromuscular block with 2.5mg neostigmine and 1.2mg atropine. Good neuromuscular transmission was rapidly established and the patient made an uneventful recovery.

Case 3. This patient was a 54 year old adult male who had until recently been an underground mineworker. He had mild restrictive lung disease as a result of old tuberculosis and had been diagnosed as having a large phaeochromocytoma arising from the right adrenal gland as a result of recent onset hypertension. The patient also had reduced renal function with a creatinine clearance of 42ml/hr. Preoperative preparation consisted of

increasing doses of phenoxybenzamine to a maximum of 100mg per day and propranolol 60mg per day. Following routine oral premedication with diazepam and phenergan the patient arrived in the operating theatre with a systolic blood pressure of 215mmHg and a heart rate of 100 beats per minute. After the administration of 200μg fentanyl arterial and central venous pressure monitoring lines were placed and an infusion of 4gm $MgSO_4$ administered. Systolic blood pressure reduced to 145mmHg and heart rate fell to 80 beats per minute. Induction of anaesthesia with thiopentone and muscle relaxation with alcuronium 20mg did not alter the patient's haemodynamic status and there was no increase in blood pressure or heart rate following intubation. At laparotomy the tumour was found to be extremely large and attached to the right diaphragm. Extensive tumour handling and opening of the diaphragm were necessary. During this time an infusion of sodium nitroprusside was necessary to control systolic blood pressure in addition to a continuous infusion of $MgSO_4$ at a rate of 2gm per hour and four 2gm boluses. Inhalational anaesthesia consisted of 50% nitrous oxide in oxygen with 1-3% enflurane. At the end of the procedure the patient was transferred to a high care ward and electively ventilated for the next 24 hours. Serum magnesium levels of 3.7mmol/l were achieved intraoperatively and serum levels of greater than 2mmol/l persisted for six hours postoperatively, with evidenced of depressed neuromuscular transmission persisting for the next six hours. Thereafter the patient made an uneventful recovery.

Case 4. This patient was a 26-year old pregnant black woman who was investigated for secondary hypertension at a peripheral hospital. An elevated urinary vanillyl mandelic acid (VMA) level was found and she was transferred to a central hospital. She had had two previous uncomplicated pregnancies, the last in 1982.

Prominent symptoms on presentation included sweating, palpitations, headache, dizziness and backache, which had occurred intermittently during the preceding 15 months. Examination of the patient revealed a pregnancy of 38 weeks duration in association with a labile blood pressure (BP). No hypertensive target organ damage was noted. An elevated urinary VMA excretion was confirmed at 121 μmol/24 hours (normal <60 μmol/24 hours). The plasma adrenaline level was 2 pg/ml but the noradrenaline level was markedly elevated at 1164 pg/ml. Other biochemical measurements were within normal limits.

She was treated with prazosin 4 mg twice daily and atenolol 50 mg daily. After an initial hypotensive reaction, which responded to bed rest and intravenous fluid administration, her blood pressure stabilized at 150/100 mmHg from an admission level of 180/120 mmHg over the next five days, and her symptoms related to her catecholamine excess subsided. Foetal maturity was confirmed with ultrasound examination and it was decided to proceed with delivery.

Vaginal delivery under epidural anaesthesia was chosen as the mode of delivery. The establishment of arterial, central venous and peripheral lines under local anaesthesia produced a marked hypertensive response (BP 220/110 mmHg), and an infusion of phentolamine at a rate of 3 mg/hour was instituted with some improvement in the blood pressure. An epidural catheter was inserted and 10 ml 0.5% bupivicaine injected following a test dose, with no improvement in cardiovascular control. Membranes were ruptured to induce labour. These manoeuvres also produced a marked hypertensive response, which necessitated an increase in the rate of the phentolamine infusion to 10 mg/hour. Shortly after labour had begun, foetal bradycardia occurred which made immediate operative delivery imperative.

Prior to induction of anaesthesia, a 4 gm bolus of $MgSO_4$ was administered intravenously over 15 minutes, followed by a continuous infusion of 1.5gm/hour. This produced little improvement in the control of blood pressure. A sodium nitroprusside infusion was commenced at 0.27 μg/Kg/min which almost immediately reduced the BP to 102/60 mmHg. This infusion was maintained throughout the induction sequence. Following pre-oxygenation, lignocaine 60 mg was infused intravenously prior to induction. A standard rapid sequence induction and intubation was then performed using thiopentone sodium 4 mg/Kg and suxamethonium 1 mg/kg while cricoid pressure was applied, followed by a further 2 mg/Kg thiopentone just prior to intubation. Intubation produced a dramatic rise in BP to 265/165 mmHg which persisted for about 4 minutes, requiring an increase in nitroprusside infusion rate to 0.8 ug/Kg/min.

A healthy 2730 gm baby was delivered rapidly. Immediately after delivery, there was a precipitous fall in BP to 90 mmHg systolic which lasted for approximately 5 minutes. This responded to temporary discontinuation of the nitroprusside and intravenous fluids. Thereafter she maintained a SBP in the range 180-230 mmHg for the rest of the procedure (Figure 9.6).

Postoperatively, the patient required continuation of sodium nitroprusside infusion for the control of her persistent hypertension, until oral prazosin therapy could be re-established. It was subsequently found that her serum Mg level prior to the induction of anaesthesia was 0.5 mmol/l and despite the fairly large doses of $MgSO_4$ the maximum serum Mg level achieved was 1.4 mmol/l.

Prazosin and atenolol were recommenced postoperatively in the same dosages as before delivery, and she was maintained on these drugs for 5 weeks while tumour localizing procedures were being performed. She remained asymptomatic and her BP was well controlled at 130/90 mmHg. A right adrenal tumour was found on CT scan which had a positive uptake of ^{131}I meta-iodobenzylguanidine (MIBG), and the patient agreed to surgery for removal of the tumour.

The night prior to surgery, the patient was sedated with diazepam 7.5 mg orally, and on the morning of surgery she received 5 mg prazosin orally, 100 mg atenolol orally, and 15 mg papaveretum i.m. In the operating theatre she was reasonably well sedated but placement of central venous and radial arterial

lines under local anaesthetic produced a moderate pressor response with the BP rising to 160/100 mmHg.

Anaesthesia was induced with 150 μg fentanyl followed by 250 mg thiopentone and a bolus of 4 gm $MgSO_4$ given over 5 minutes. This produced a reduction in blood pressure to 110/70 mmHg. Muscular relaxation was achieved with 20 mg alcuronium and lignocaine 80 mg was given prior to intubation. Following induction, BP fell to 100 mmHg systolic, and returned to 120/80 mmHg following intubation. A continuous infusion of 1 gm/hour $MgSO_4$ was started. Incision produced an increase in blood pressure to 140 mmHg systolic which responded well to a further bolus of 2 gm $MgSO_4$. During tumour handling, three similar mild increases in BP occurred, and on each occasion these responded well to $MgSO_4$ boluses. Throughout the procedure, anaesthesia was maintained with 50% nitrous oxide in oxygen and 1-1.5% enflurane. No other anti-hypertensive medication was required. Following tumour excision, the $MgSO_4$ was discontinued and at the end of the procedure, muscular relaxation was easily reversed with 5 mg neostigmine preceded by 0.4 mg glycopyrrolate (Figure 9.7). There were no post-operative complications. A total of 16 gm of $MgSO_4$ had been administered over a 2-hour period, and the patient's intraoperative serum Mg levels were found to have been in the range of 2.6-3.9 mmol/l, with the maximum level just prior to tumour devascularization. At the time of reversal, one hour later, the serum Mg level was 2.5 mmol/l.

Case 5. A 24 year old white woman was transferred from a peripheral hospital because of uncontrollable blood pressure during pregnancy. She gave a history of having had an abdominal phaeochromocytoma removed in 1979 and three operations for recurrences in her neck in 1980, 1981 and 1983. She had had a normal vaginal delivery in 1982, and a miscarriage at 4 weeks in 1984. She had been well controlled medically until her pregnancy. She now complained of headache, visual disturbances and feeling flushed. On admission her arterial blood pressure was 170/110 mmHg and her heart rate 116 beats per minute. Foetal maturity was estimated at 32 weeks and confirmed on ultrasound examination. Significant laboratory findings included a VMA excretion of 205 μmol/24 hours and metadrenaline 42.5 μmol/24 hours (normal $<5.5\mu$mol/24 hours).

She was controlled on phenoxybenzamine 20mg 8 hourly and tenormin 50 mg daily. After an initial hypotensive episode this regime provided excellent control. Her progress was uneventful for the next 4 weeks, but it is of interest that her serum Mg level which was initially 0.83 mmol/l fell to 0.57 mmol/l during this period. On oral supplementation it improved but remained below normal at 0.71 mmol/l.

After 4 weeks of medical management, very poor foetal growth prompted concern. Adequate fetal maturity was established and it was decided to proceed with delivery by elective caesarean section under general anaesthesia. Preoperatively, she was well controlled with an arterial blood pressure in the range 150/90 - 140/80 mmHg and no postural hypotension.

Diazepam 10mg orally was administered the night prior to surgery, and repeated 30 minutes preoperatively, together with 10 mg metoclopramide and 30 ml sodium citrate. Phenoxybenzamine and tenormin were given on the morning of surgery. On arrival in the operating room, her arterial blood pressure pressure was 170/100 mmHg, and this increased during the insertion of arterial and central venous lines under local anesthesia to 200/120 mmHg. A bolus of 4 g of $MgSO_4$ was administered by slow intravenous injection, and this reduced the arterial blood pressure to 150/90 mmHg but produced an unpleasant burning sensation. Following 3 minutes of pre-oxygenation, anaesthesia was induced with thiopentone 4mg/Kg, and the trachea intubated under 100mg succinylcholine while cricoid pressure was applied. Intubation produced a mild increase in arterial blood pressure to 180/100 mmHg which responded well to a further bolus of 2 gm $MgSO_4$ and a continuous infusion of $MgSO_4$ was maintained at 2 gm/hour throughout the procedure. Anaesthesia was maintained with 50% oxygen in nitrous oxide with 0.75% enflurane, and relaxation with intermittent suxamethonium. Two further boluses of $MgSO_4$ were given intraoperatively to control small increases in arterial blood pressure but at no time did the blood pressure exceed 170/90 mmHg after the initial response to intubation. A healthy female infant weighing 1540 gm was delivered. Following surgery, spontaneous ventilation was resumed readily; when fully conscious she was extubated and the $MgSO_4$ infusion was discontinued. One hour later she required a continuous infusion of phenoxybenzamine in order to control her arterial blood pressure which had increased to 230/120 mmHg. The following day, she was restarted on oral

therapy, and made a satisfactory recovery. Intraoperative Mg level was found to have been in the range 2.4 - 3.3 mmol/l.

Case 6. A 48 year old male was diagnosed as having a large phaeochromocytoma arising from the left adrenal gland. Good preoperative cardiovascular control was established with a daily dosage of 160mg phenoxybenzamine. On arrival in the operating theatre his blood pressure was 195mmHg which settled following 200μg of fentanyl to 115 mmHg and remained stable at this level for the induction, intubation and initial surgery. At laparotomy the tumour was found to be locally invasive and extending along the renal vein and into the inferior vena cava. It was not therefore possible to gain control of the venous drainage from the tumour and during tumour manipulation $MgSO_4$ alone proved inadequate to control blood pressure. An infusion of sodium nitroprusside was required in addition to magnesium boluses and infusions to control hypertensive episodes. Once the tumour had been removed the patient's condition stabilized and he made an uneventful recovery.

Case 7. This patient was a 22 year old white female who presented with unstable hypertension and was diagnosed as having a phaeochromocytoma arising from the right adrenal gland. Good preoperative control was established with prazosin 4mg b.d. and atenolol 100mg daily. She arrived in theatre well controlled and anaesthesia was induced with fentanyl 100μg,

thiopentone 200mg and alcuronium 20mg following pretreatment with 3gm $MgSO_4$. During surgery a continuous infusion of 2gm per hour $MgSO_4$ was used with two additional 2gm boluses during tumour manipulation. Good cardiovascular control was maintained throughout and the patient made an uneventful recovery.

Case 8. A 26 year old white female presented with long-standing hypertension which was found to be attributable to a small right adrenal tumour. Preoperative ECG's showed a left ventricular strain pattern with inverted T-waves and depressed ST segments. Good preoperative control was established with phenoxybenzamine 240mg per day and atenolol 50mg daily, and over the two week preoperative period the ECG changes resolved. The patient arrived in the operating theatre mildly hypertensive with a systolic blood pressure of 186mmHg but no tachycardia. An infusion of 4gm $MgSO_4$ resulted in stabilization of the blood pressure at 130mmHg systolic. Induction of anaesthesia was performed using fentanyl 150μg, thiopentone 300mg and alcuronium 15mg. A continuous infusion of $MgSO_4$ was used throughout the procedure at the rate of 2gm per hour and four additional 2gm boluses were administered during tumour handling. Good cardiovascular control was maintained throughout the procedure and neuromuscular blockade was readily reversed at the end of surgery (Figure 9.4).

Case 9. This patient was a 42 year old male with long-standing hypertension who had been diagnosed as having a left adrenal gland tumour. Preoperative preparation consisted of tenormin 100mg b.d. and a small dose (40mg daily) of phenoxybenzamine. This patient did not meet the criteria for fitness for surgery at the time of operation. The decision to proceed with surgery had already been taken by the surgical team, but it was nevertheless decided to use $MgSO_4$ in this case in order to assist the cardiovascular control. On arrival in the operating theatre his systolic blood pressure was 205mmHg but this responded well to fentanyl 200μg and a 4gm infusion of $MgSO_4$. Intraoperative blood pressure control with a continuous infusion of 2gm per hour $MgSO_4$ and three boluses of 2gm each was satisfactory but at the time of tumour removal there was a sudden haemorrhage of approximately 2 litres from a torn spleen. This was accompanied by severe hypotension and bradycardia which was unresponsive to transfusion and vasopressor drugs. The patient required an adrenaline infusion for 24 hours postoperatively to sustain adequate cardiovascular function. At the time of tumour excision the serum magnesium level was 2.8mmol/l and this had dropped to 1.2mmol/l 6 hours postoperatively. After 24 hours the adrenaline infusion was gradually weaned and the patient made a good recovery.

Case 10. This patient was a 34 year old black female with a small phaeochromocytoma arising from the left adrenal gland. Good preoperative control was established on phenoxybenzamine alone and her intraoperative course was uneventful. She received a total of 11gm magnesium

intraoperatively and was well controlled throughout the procedure. There were no postoperative complications.

Case 11. A 32 year old black female presented with a small right adrenal tumour and was well controlled on prazosin 4mg b.d. and atenolol 50mg daily. Good intraoperative control was maintained with magnesium infusions alone and she made an uneventful recovery. Catecholamine levels were measured in this patient prior to induction and following intubation and again during tumour handling. Following the initial catecholamine measurement, 4gm $MgSO_4$ were given followed by a thiopentone-fentanyl-alcuronium induction sequence. Both adrenaline and noradrenaline concentrations were markedly elevated prior to induction and following intubation the levels of both hormones had been reduced although it is impossible to say that this reduction was due to magnesium as the other drugs used in the induction sequence may have contributed. During tumour handling both adrenaline and noradrenaline concentrations increased to preinduction levels but good cardiovascular control was maintained despite this.

Case 12. This patient was a 51 year old female with a large phaeochromocytoma arising from the left adrenal gland. Preoperative control was established with 4mg prazosin b.d. and 50mg atenolol daily. On arrival in the operating theatre this patient was markedly hypertensive (systolic blood

pressure 240mmHg) but this responded well to the administration of 200μg fentanyl and 4gm $MgSO_4$. Noradrenaline and adrenaline levels were markedly elevated at the time of arrival in the operating theatre. Following the administration of magnesium adrenaline levels fell to within the normal range and noradrenaline levels were reduced by 45%. Anaesthesia was induced with 350mg thiopentone and muscle relaxation achieved with 20mg alcuronium. Further catecholamine estimations were performed at this point which showed a slight further reduction in both adrenaline and noradrenaline concentrations. Intubation of the trachea produced no cardiovascular disturbance and no increase in catecholamine levels. Extensive tumour handling was unavoidable in this case and this produced increases of both adrenaline and noradrenaline to above baseline values. An infusion of sodium nitroprusside was necessary in addition to a total dose of 16gm $MgSO_4$ in order to maintain adequate blood pressure control. Once the tumour had been removed the remaining procedure was uneventful and the patient made a good recovery (Figure 9.5).

Case 13. This patient, a 39 year old female, was diagnosed as having a large right-sided adrenal tumour. Good cardiovascular was attained with prazosin 4mg b.d. and atenolol 100mg daily. On arrival in the operating theatre the patient's blood pressure was well controlled and anaesthesia was induced with 150μg fentanyl, 300mg thiopentone and 15 mg alcuronium. catecholamine levels were estimated prior to induction and were found to be moderately elevated with a marked increase in concentration of both adrenaline and

noradrenaline following induction of anaesthesia. Four gm $MgSO_4$ were then administered and catecholamine levels again estimated. Both adrenaline and noradrenaline concentrations were decreased following the administration of magnesium and endotracheal intubation was accompanied by a continuing decline in the concentration of both catecholamines. Intraoperatively both noradrenaline and adrenaline levels were markedly elevated during periods of tumour handling and an infusion of nitroprusside was required to provide adequate cardiovascular control. Postoperative course was uneventful.

Case 14. This patient was a 28 year old female who had a small right-sided adrenal tumour. Symptoms were well controlled on prazosin and atenolol and she arrived in the operating theatre well controlled. Following a bolus of 4gm $MgSO_4$ preceded by 100μg fentanyl, anaesthesia was induced with thiopentone 250mg and alcuronium 15mg. Catecholamine levels were moderately elevated prior to the administration of any drugs and were reduced by the magnesium/fentanyl treatment. Neither induction of anaesthesia nor endotracheal intubation produced any increase in catecholamine concentrations and although both hormones increased in concentration during tumour handling good cardiovascular control was maintained throughout the procedure using a total of 14gm of $MgSO_4$. The patient made an uneventful recovery.

Case 15. A 55 year old female presented for a diagnostic laparotomy to investigate an abdominal mass. The mass had been noted previously at hysterectomy 2 months previously, but although manipulation of the mass had produced severe intraoperative hypertension and cardiac dysrhythmias, the diagnosis of a phaeochromocytoma had not been made. Preoperative investigation had included a CT-scan of the abdomen which had shown a right-sided para-aortic mass. Induction of anaesthesia was performed using 100μg fentanyl, 350mg thiopentone and 6mg pancuronium. Endotracheal intubation produced a mild increase in blood pressure followed by a drop in pressure after the introduction of halothane to 70mmHg systolic. Commencement of surgery was accompanied by multifocal supraventricular and ventricular ectopic heart beats and a rapid rise in arterial blood pressure to 260/140mmHg when the tumour was touched. A diagnosis of phaeochromocytoma was entertained and 4gm $MgSO_4$ administered intravenously. This produced a transient reduction in blood pressure and temporary control of the arrhythmias. Two further 4gm boluses of $MgSO_4$ and one of 2gm established cardiovascular control, at which time the serum magnesium level was 3.68mmol/l (Figure 9.9). The tumour was then removed and subsequently proven to be a phaeochromocytoma on histology. The patient made a good recovery.

Case 16. This patient was a 14 year old black male who was diagnosed as having a large left-sided para-aortic phaeochromocytoma. Good preoperative control was established with 4mg prazosin b.d. and 50mg atenolol daily. On arrival in the operating theatre the patient was stable and after placement of monitoring lines anaesthesia was induced with 150μg fentanyl, 300mg thiopentone and 15mg alcuronium. Catecholamine levels, particularly noradrenaline, were markedly elevated prior to induction of anaesthesia and increased further following the induction sequence, accompanied by an increase in systolic blood pressure to 170 mmHg. An infusion of 4gm $MgSO_4$ immediately reduced the arterial blood pressure to 100/60mmHg and produced a marked drop in noradrenaline concentrations with the adrenaline concentration being reduced to within normal values. Following intubation there was no increase in blood pressure and the levels of both catecholamines continued to decline. A continuous infusion of 2gm/hr $MgSO_4$ was maintained during the procedure and six 2gm boluses of $MgSO_4$ were administered during the course of the procedure. The tumour was adherent to the inferior vena cava and to bowel but despite considerable tumour handling very little cardiovascular disturbance occurred. This prompted the erroneous assumption that the tumour had been devascularized prior to its removal and magnesium was withdrawn. Within a few minutes the blood pressure rapidly rose to 200/110mmHg but the administration of bolus doses of 3gm and 2gm $MgSO_4$ regained control within a few minutes. At the time of tumour excision serum magnesium levels were 3.8mmol/l. Neuromuscular blockade was readily reversed and the patient made an uneventful recovery (Figure 9.8).

Appendix C

Glossary of Abbreviations

ABP	Arterial blood pressure
AP	Arterial pressure
ASA I-II	American Society of Anesthesiologists patient fitness criteria. Indicates minimal intercurrent disease.
ATP	Adenosine triphosphate
BP	Blood pressure
CI	Cardiac index
CNS	Central nervous system
CO	Cardiac output
CO_2	Carbon dioxide
CSF	Cerebrospinal fluid
CT	Computerised tomography
CVP	Central venous pressure
DBP	Diastolic blood pressure
DNA	Deoxyribose nucleic acid
ECG	Electrocardiograph
Mg	Magnesium
$MgSO_4$	Magnesium sulphate

MIBG	Meta-iodobenzylguanethidine
PA	Pulmonary artery
PCWP	Pulmonary capillary wedge pressure
PGE_2	Prostaglandin E_2
PGI_2	Prostaglandin I_2
PVR	Pulmonary vascular resistance
RNA	Ribose nucleic acid
QT_c	QT interval corrected for heart rate
SA node	Sino-atrial node
SBP	Systolic blood pressure
SEM	Standard error of the mean
SeMg	Serum magnesium
SPSS	Statistical package for the Social Sciences
SV	Stroke volume
SVI	Stroke volume index
SVR	Systemic vascular resistance
SW	Stroke work