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# RAPID INHALATIONAL INDUCTION OF ANAESTHESIA- WITH SPECIAL REFERENCE TO THE USE OF ISOFLURANE

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A research report submitted to the Faculty of Medicine, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine (in the branch of Anaesthesia).

Johannesburg, 1991.

# DECLARATION

I declare that this dissertation is my own, unaided work. It is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. This study represents original work by the author and has not been submitted in any form to another University. Where use was made of the work of other authors it has been duly acknowledged in the text.

The experimental work described in this dissertation was carried out at the Dental Hospital and the Department of Anaesthesia of the Johannesburg Hospital and University of the Witwatersrand, Johannesburg under the supervision of Professor DF Morrell, and was carried out from January to March 1990.

.....

PETER VERNON VAN HEERDEN

29/7/91....

DATE

This research was approved by the Committee for Research on Human Subjects, University of the Witwatersrand (Protocol No 89/1/27).

For my wife, Fiona .....

and my little boys Daniel and Adam.

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## SUMMARY

Recognising that halothane is declining as the volatile anaesthetic agent of choice for inhalational induction and that isoflurane is replacing it, particularly in North America and Europe, this study was designed to determine whether isoflurane is comparable to halothane with respect to speed of induction and complication rate when used for rapid inhalational induction (RII) of anaesthesia.

Isoflurane, administered in oxygen or in nitrous oxide and oxygen, was compared to halothane, administered in oxygen, for RII in healthy, unpremedicated patients. Isoflurane, in both carrier gas mixtures, produced a faster RII than halothane. Complication rates and patient acceptance was similar for all three groups. Haemodynamic stability in patients subjected to RII with halothane and isoflurane was remarkable.

The candidate concludes that isoflurane is a useful agent for RII and is a viable alternative to halothane when contraindications exist to its use.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ANOVA | Analysis of variance |
| ASA | American Society of Anesthesiologists |
| B/G | Blood:gas |
| BP | Blood pressure |
| °C | Degrees Celsius |
| CII | Conventional inhalational induction |
| CVS | Cardiovascular System |
| EEG | Electroencephalograph |
| GA | General anaesthesia |
| HR | Heart rate |
| IV | Intravenous |
| LOC | Loss of consciousness |
| MAP | Mean arterial pressure |
| $N_2O$ | Nitrous oxide |
| $O_2$ | Oxygen |
| PE $CO_2$ | expired carbon dioxide |
| RII | Rapid inhalational induction |
| SD | Standard deviation |
| $SpO_2$ | Arterial oxygen saturation |
| VA | Alveolar ventilation |
| VCB | Vital capacity breath |

# CHAPTER 1

# INTRODUCTION

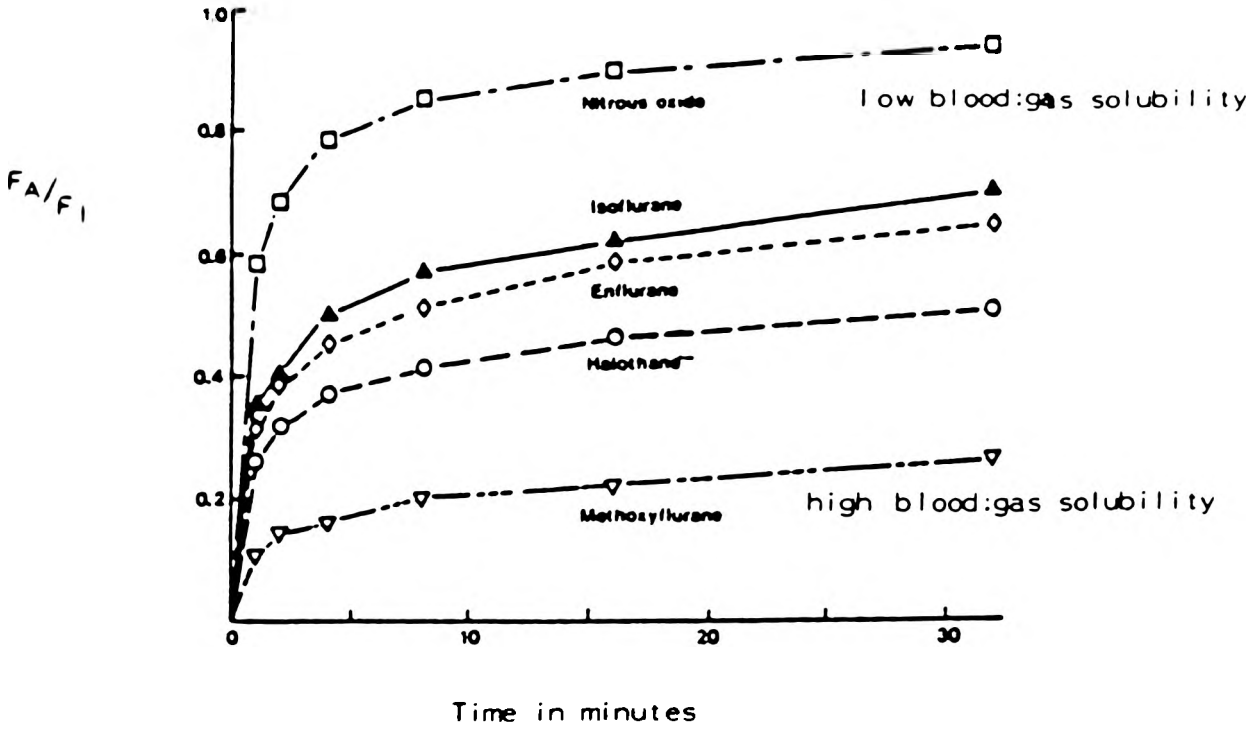
## 1.1 THE DEVELOPMENT OF INHALATIONAL ANAESTHESIA

The inhalational route of administration of anaesthesic agents has been used since the first demonstration of general anaesthesia (GA) using ether, at the Massachusetts General Hospital by William Morton on October 16th, 1846 [1]. This followed the failed attempt to demonstrate the effect of nitrous oxide ($N_2O$) by Horace Wells in 1845 at the same hospital [2].

Inhalational induction of anaesthesia as a technique is therefore as old as general anaesthesia itself. As newer agents have been developed for GA, many have been administered by this route. The inhalational route was, until comparatively recently, used for both the induction as well as the maintenance of anaesthesia, and the volatile agent used for this purpose, was often used as the sole anaesthetic agent. Ether is still used in this manner in many developing countries. Surgical anaesthesia, Stage 3 of anaesthesia as defined in Table 1 on page 5, is induced using an inhalational technique. Once an adequate level of anaesthesia has been achieved, the concentration of the volatile agent, such as ether, is decreased and the same agent is used for maintenance of anaesthesia. This provides a simple and safe anaesthetic technique that is essentially the same as that first demonstrated in 1846.

Despite the safety of the above technique, it has the disadvantage that induction of anaesthesia is very slow. This is especially true for the agents with high blood:gas solubility coefficients (for a definition of solubility coefficient, see Figure 1, page 4), such as ether and methoxyflurane. Ether has blood:gas solubility properties similar to methoxyflurane (B/G 12,1 vs. 13) and consequently a graph tracing like that shown for methoxyflurane in Figure 1, page 4. The speed of induction of anaesthesia with the inhaled volatile agents depends on the speed at which an adequate concentration of the agent is reached in the brain. This in turn is dependent on the concentration gradient of the agent between the circulation and the brain. The concentration of the agent in the circulation is determined by the rate of rise of concentration of the volatile agent in the alveoli and passive diffusion of the agent from the alveoli to the circulation. Agents such as those mentioned above, which have high blood gas solubility coefficients have a slow rate of rise of alveolar concentration. This is depicted in Figure 1 by classical "wash-in" curves.

The stages of anaesthesia related to the use of ether were defined by Plumley in January 1847. These stages were codified by Guedel during World War I and in 1943 Gillespie added reflex responses to the signs related to the stages of anaesthesia as defined by Guedel [5]. The stages of anaesthesia as defined by Gillespie are shown in Table 1 [6].




$F_A$ - alveolar concentration.

$F_I$ - inspired concentration.

FIGURE 1. The Rate of Rise of Alveolar Concentration of Anaesthetic Agents [3]

Definitions of Solubility Coefficients [4]:

The Bunsen solubility coefficient is the volume of gas, corrected to standard temperature and pressure, which dissolves in one unit volume of the liquid at the temperature concerned, where the partial pressure of the gas above the liquid is one standard atmosphere pressure.

The Ostwald solubility coefficient is the volume of gas which dissolves in one unit volume of the liquid at the temperature and pressure concerned.

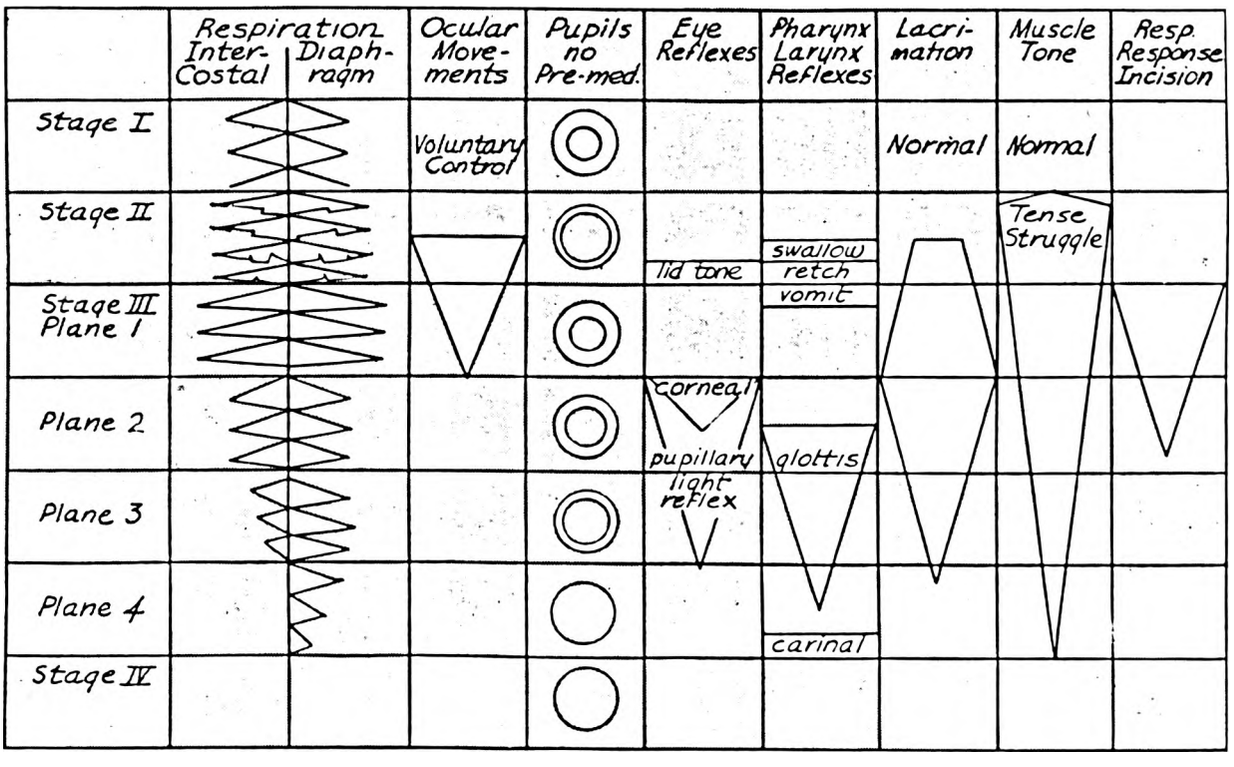



TABLE 1 The Stages of Anaesthesia as Defined by Gillespie [6]

From Table 1, it is evident that stage 2 of anaesthesia can be stressful for both the patient and the anaesthetist. Attempts were therefore made to ameliorate the effects of this stage. Premedication with a sedative or opioid drug and an anti-sialogogue, such as atropine, went some way towards decreasing the excitatory and upper airway responses of stage 2 anaesthesia. However, heavy premedication and the slow recovery inherent in the use of an agent such as ether, prolonged the recovery phase of general anaesthesia. Intravenous induction of anaesthesia was then developed to overcome the slow induction provided by the inhalational agents.

## 1.2 THE INTRODUCTION OF INTRAVENOUS INDUCTION OF ANAESTHESIA

As described above, intravenous induction agents were developed to meet specific requirements in anaesthetic practice. One of these was to provide a rapid induction of anaesthesia, which was both pleasant and safe for the patient.

As with most advances in anaesthesia, the development of a viable intravenous (IV) anaesthetic induction agent was a slow process. It began with the discovery of the first barbiturate, malonyl urea or barbituric acid, in 1864 by Adolf von Baeyer [7]. This was followed by the first use of methyl-propyl-carbinol-urethane (Hedonal) to produce sleep by Krawkow in St. Petersburg in 1905 [8]. All the barbiturates

available at this time had the disadvantages of slow onset and prolonged duration of action. The disadvantage of slow onset was overcome by the development of hexobarbitone and the thiobarbiturates in the 1930's [8]. Thiopentone, one of the thiobarbiturates, remains one of the most popular IV induction agents today.

Since the introduction of the thiobarbiturates, various other IV agents have been developed, such as ketamine (1965), etomidate (1973) and propofol (1977). All these agents have been developed with the same objectives as the original IV agents - to provide a safe rapid induction of anaesthesia. In this regard they have largely succeeded, following the inevitable mishaps which occur during the initial introduction of new drugs.

Therefore, by the 1930's the trend for modern anaesthetic practice had been set. This provided for a rapid IV induction followed by maintenance of anaesthesia with a volatile agent. This technique also has the advantage that it carries the approval of most patients when compared to the original inhalational technique described in Section 1.1 above. Since the days of ether, however, there have been marked advances in the field of volatile anaesthetic agents.

## 1.3 THE NEWER VOLATILE ANAESTHETIC AGENTS - HALOTHANE, ENFLURANE, ISOFLURANE, SEVOFLURANE AND DESFLURANE

The development of volatile agents in the light of improved understanding of structure-activity relationships began only in

the 1930's [9]. As fluorine chemistry advanced it became possible to exploit the properties which fluorination of molecules imparted to the volatile agents, namely non-combustibility, low toxicity and stability [9]. From the vast number of agents tested we now have three fluorinated volatile agents for use in clinical practice; halothane, enflurane and isoflurane. Two further agents are now undergoing clinical trials: sevoflurane and desflurane.

In addition to the improved stability and increased potency of these agents compared to older inhalational agents such as ether and chloroform, they also provide for a much more rapid induction of anaesthesia. This is related to their physical properties, and especially their blood:gas solubility coefficients (see Figure 1). Other physical properties of importance when considering the newer volatile agents are -

- **lipid solubility of the agent**, which is often defined as the oil: gas solubility coefficient. This relates to the potency of the agent. The more lipid soluble an agent is, the more potent it is [10], and

- **boiling point.** This gives an indication of the volatility of an agent.

The physical properties of ether, chloroform and the newer volatile agents are shown in Table 2 [9,11].

TABLE 2 PHYSICAL CHARACTERISTICS OF SOME OF THE INHALATION ANAESTHETIC AGENTS [9,11]

| | Chloroform | Ether | Desflurane | Sevoflurane | Isoflurane | Enflurane | Halothane |
|---|---|---|---|---|---|---|---|
| Molecular weight (Da) | 119.0 | 74.0 | 168.036 | 200.053 | 184.491 | 184.491 | 197.381 |
| Boiling point (°C) | - | - | 23.5 | 58.5 | 48.5 | 56.5 | 50.2 |
| Vapour pressure at 22°C (kPa) | 23.0 | 59.0 | 88.53 | 21.33 | 31.86 | 22.93 | 32.53 |
| Partition coefficients | | | | | | | |
| Blood: gas | 8.4 | 12.1 | 0.4 | 0.6 | 1.4 | 1.9 | 2.3 |
| Oil: gas | 265.0 | 65.0 | 19.0 | 53.0 | 91.0 | 96.0 | 224.0 |
| Preservative | None | None | None | None | None | None | Thymol |
| Stability in moist soda-lime | Stable | Stable | Stable | Unstable | Stable | Stable | Stable |
| MAC in oxygen | 0.7 | 1.92 | ~6.0% | ~2.0% | 1.2% | 1.6% | 0.7% |

MAC - See Appendix, page 81.

It is evident from the above that the newer agents offer a number of advantages over the original volatile anaesthetic agents such as ether. They are capable of rapidly inducing anaesthesia, as they all have relatively low blood:gas (B/G) solubility coefficients. For the same reason, it is possible to rapidly vary the depth of anaesthesia by adjusting the inhaled concentration of the volatile agent. At the end of an anaesthetic, these insoluble agents are quickly exhaled and eliminated from the body as the gradient used for induction of anaesthesia (from inspired gas —> the alveoli —> the circulation —> the brain) is reversed. Therefore, a rapid anaesthetic induction, followed by anaesthetic maintenance, which is easily variable in depth, and then a rapid recovery are possible with a single agent.

As all the IV agents produce some post-operative sedation (variable in intensity and duration), it would seem ideal to be able to avoid these agents if it were possible to do so, by use of only a volatile agent in the anaesthetic technique. Venous puncture may be avoided if intravenous agents are not used in the anaesthetic technique. This is a factor in children and patients with a needle phobia. If a rapid recovery were desired and if the speed of induction using the volatile agent matched that of the IV agent then an inhalational technique may be used to replace IV induction. These, essentially, are also the indications for inhalational induction of anaesthesia.

## 1.4 INDICATIONS FOR INHALATIONAL INDUCTION OF ANAESTHESIA

The indications for inhalational induction of anaesthesia are the same as those for the avoidance of intravenous induction. These indications would include -

- **the avoidance of the use of needles**, especially in paediatric practice, in nervous adults with a needle phobia and in mentally retarded patients;
- **patient allergy to the IV drug** chosen for the technique,
- if the **"hangover" (post operative sedation) effect of the IV drug were to be avoided**, as in out patient anaesthesia,
- induction of anaesthesia in patients with **compromised upper airways**, where IV induction may result in loss of control of the airway and possible consequent hypoxia in the patient and
- **if the patient prefers the technique** of inhalational induction.

The above list includes both relative and absolute indications for inhalational induction of anaesthesia. Of the volatile agents available, halothane is the agent of choice for inhalational induction of anaesthesia. This is so because halothane has a pleasant odour, is well accepted by patients and is economical. Due to its lack of pungency, it does not readily produce unwanted respiratory tract side effects, such as

coughing, laryngospasm and excessive secretions. Various studies, including one by Phillips, Brimacombe and Simpson [12] show that even though halothane is more soluble (higher B/G solubility coefficient) than isoflurane, it produces a faster inhalational induction. This is attributed to its lack of airway complications and smoother induction. However, since shortly after its introduction into clinical anaesthetic practice there have been concerns that halothane is able to produce a fulminant hepatitis in susceptible individuals [13].

Recently, the Committee on Safety of Medicines (CSM) in the United Kingdom published guidelines relating to the use of halothane [14]. This and other publications has resulted in the decline of the use of halothane in Britain and North America. Isoflurane is becoming the volatile agent of choice and methods are being sought to make this agent more patient-acceptable for use as an inhalational induction agent. One of the methods employed to make isoflurane more patient-acceptable has been to administer it by the technique of Rapid Inhalational Induction (RII).

## 1.5 CONVENTIONAL INHALATIONAL INDUCTION (CII) and RAPID INHALATIONAL INDUCTION (RII)

CII is the technique by which anaesthetic vapours and gases have been used to achieve anaesthetic induction since the discovery of ether. It involves the slow incremental increase of the concentration of the vapour or gas in the inspired gas as the patient breathes. This causes the patient to pass slowly through the stages of anaesthesia as described in Table 1. This also causes the patient to pass slowly through stage 2, the stage of excitement, with the complications related to this stage (see Table 1). As discussed, the less soluble the agent is the faster the agent will achieve adequate concentrations in the brain and exert its anaesthetic effect. It follows then that the less soluble the agent is the faster the various stages of anaesthesia will be achieved. Halothane (B/G solubility coefficient = 2,3) will therefore produce a faster inhalational induction than ether (B/G solubility coefficient = 12,1). Also, the time the patient spends in stage 2 of anaesthesia will be shorter for halothane than for ether, as examples. So, although halothane is used in the same manner as ether was originally used, the induction sequence is faster and more pleasant for the patient due to the improved physical properties of halothane over ether, as previously discussed.

RII is a technique originally described for the use of cyclopropane, an anaesthetic gas with a low B/G solubility coefficient [15]. The technique requires the patients to take 5 or 6 deep breaths of a high inspired concentration of cyclopropane. This produces a rapid increase in the alveolar concentration of the anaesthetic agent and subsequent loss of consciousness. Stage 3 of anaesthetic depth is achieved in a very short time and the complications related to stage 2 avoided. This technique is described more fully in Chapter 4. This technique would seem well suited to the use of isoflurane in that the physical properties of isoflurane should make it superior to halothane in terms of speed of induction. Also, if consciousness is rapidly lost, then the pungency of isoflurane will not be experienced by the patient for a prolonged time (ie. less so than if isoflurane were administered by CII). Isoflurane should also produce a more rapid induction and recovery than halothane as it is the least soluble of the volatile agents presently available for clinical use.

The use of both halothane and isoflurane have been investigated for RII (see Chapter 2). However, isoflurane has not been used for RII without the addition of either heavy premedication or nitrous oxide in the inspired gas to limit the airway side effects of the agent.

# CHAPTER 2

# LITERATURE REVIEW

The English language literature regarding Rapid Inhalational Induction (RII) is not extensive. This is because RII is a relatively new technique with a limited application.

In 1982 a study by Ruffle, Latta and Snider [16] introduced the concept of RII with one of the modern volatile agents, halothane, and compared the technique to conventional inhalational induction (CII). The more rapid onset of anaesthesia obtained by RII, as well as other advantages of the technique over CII were discussed. In a subsequent study the same authors studied the technique of anaesthetising patients with 4% halothane in oxygen ($O_2$) by RII that they had employed for the previous 5 years [17]. The study population consisted of healthy male and female volunteers who were anaesthetised with halothane in $O_2$. They were given 1,2,3 or 4% halothane in $O_2$. The volunteers took a vital capacity breath (VCB) of the particular concentration of halothane in $O_2$, and then held the breath for as long as possible. They then continued to breathe the same concentration of halothane in $O_2$ that had been administered for the VCB until unconsciousness ensued. Loss of consciousness (LOC) was defined as lack of response to verbal commands. All the volunteers had each of the halothane concentrations administered to them. They were allowed to wake up between the administrations of the different concentrations. During the induction sequence physiological variables such as heart rate (HR), blood pressure (BP) and arterial oxygen

saturation ($SpO_2$) were recorded. Inspired and expired gases were analysed on a breath by breath basis by means of a mass spectrometer.

The authors concluded that 4% halothane in $O_2$, administered in the manner described above, rapidly produces unconsciousness without significant impact on the physiological variable measured. The volunteers also found this to be a not unpleasant experience. The rapid LOC is ascribed to the rapid rate of rise of halothane in the expired gas, and by inference the alveolar gas, produced by this agent. Of interest is the fact that most of the study population experienced amnesia after the first VCB, although they responded to verbal commands for some time after this period and before LOC. The authors suggest this may account for the high degree of acceptance of the technique - as the subjects could not remember the induction sequence they did not find it unpleasant. 4% halothane in $O_2$ was found to be most effective for the technique of RII. This supported their previous practice of using this concentration in the preceding 5 years in healthy patients. The authors state that 2 - 4% halothane in $O_2$ is "effective, safe and well accepted by healthy young adults". They also state that RII is not useful or safe in patients with poor lung function or in senile, young or retarded patients who cannot co-operate with the manoeuvres required for RII.

In 1986 Wilton and Thomas [18] described a technique of RII, which they called the "single breath induction" technique. Their study population consisted of 100 unpremedicated outpatients. The patients' ages ranged from 17 - 90 years. The method of administration of the anaesthetic gas mixture was similar to that used by Ruffle and co-workers, but differed in the following aspects -

- the anaesthetic **gas mixture** contained 66% nitrous oxide ($N_2O$), 33% oxygen ($O_2$) and 4% halothane, and
- the mixture was administered to the patients by means of a modified Mapleson A **breathing system**, instead of the circle breathing system used by Ruffle and colleagues. (The details of the modified Mapleson A system are to be found in Chapter 4).

The rationale for using $N_2O$ in the anaesthetic mixture, as stated by these authors, is that $N_2O$ decreases the concentration of halothane required to induce anaesthesia and therefore shortens the induction period and will "minimise the cardiovascular depression that tends to occur with halothane-oxygen anaesthesia". These authors defined LOC as loss of the eyelash reflex, a level of anaesthesia deeper than that defined by lack of response to verbal command as defined by Ruffle and co-workers. Induction time (onset of the VCB to LOC) was not quantified by Ruffle and associates in actual time (they mention approximately 2 min. after a breath hold of 30-90 sec. or 5 breaths after the VCB). Ruffle and Snider [17], in a

separate study, compared induction time with RII to conventional inhalational induction (CII) and determined times of 112 sec. (RII) compared to 164 sec. (CII). Wilton and Thomas found that their technique produced an induction time of approximately 81-84 seconds.

This study by Wilton and Thomas [18] again demonstrated the small impact RII has on physiological variables such as HR and BP - the effect is comparable to that seen after a barbiturate intravenous (IV) induction. Ninety-one percent of the patients in this study sample found RII to be acceptable. This again is probably because most of the patients have no conscious recall after the VCB.

Of interest is the explanation given by the authors for the poor correlation between the period that the patient held the VCB and the induction time. The $N_2O$ in the inhaled mixture will ensure continued halothane uptake during the period of apnoea (breath-holding) by the so-called second gas effect (see Appendix, page 81). On the other hand, if the patient continues to breath the gas mixture and not hold his/her breath after the VCB, then the rate of rise of halothane concentration in the alveoli is assured (see "wash-in curves" in Chapter 1) by alveolar ventilation.

The above studies prompted an editorial in the Lancet [19] entitled "Inhalational Induction of Anaesthesia - New Inspiration". This editorial succinctly described the problems of CII; patients' fears of the anaesthetic mask, a slow onset of anaesthesia and a relatively high incidence of excitatory phenomena as the patient passes through the second stage of anaesthesia. It also emphasised the possible drawbacks of IV anaesthetic induction; namely possible marked hypotension, frequent post-induction apnoea and the "hangover" effect.

The mechanism of induction of anaesthesia by inhaled volatile agents was briefly described in the editorial. LOC occurs when an effective drug concentration is achieved in brain tissue. As the volatile anaesthetics are highly lipid soluble, there is a close correlation between their level in arterial blood and the brain. There is also (unless there is severe lung disease) a close relation between the alveolar concentration and the arterial blood concentration. Therefore, the rate of onset of anaesthesia is largely dependent on the rate of rise of the alveolar concentration of the anaesthetic agent. RII provides for this rapid rise in alveolar concentration, and subsequently a rapid onset of anaesthesia.

The author then goes on to review the studies described previously in this Chapter and concludes that RII offers advantages over CII (more rapid loss of consciousness) and IV induction (no venepuncture before the patient is asleep,

avoidance of the risk of anaphylaxis associated with IV agents, avoidance of the "hangover" effects seen with IV agents and a smooth transition from induction to maintenance of anaesthesia).

At the time of publication of this editorial, isoflurane and enflurane had not yet been used for RII and the author predicts that, because of their pungent "aroma", RII with these agents would be slower than that seen with halothane, despite the more rapid rate of rise of alveolar concentration associated with these agents (due to their lower B/G solubility coefficients). Mention is also made of the concern about hepatic damage following the administration of halothane.

The overall conclusions reached in this editorial were that RII offers some advantages over both CII and IV induction, but that the field of application of RII is rather limited. The limitations included: (i) RII cannot be recommended as the principal indication for inhalational induction in adults where there is anticipated difficulty in control of the upper airway, (ii) RII does not induce anaesthesia as fast as IV induction (83 sec. vs. 15-30 sec.) and (iii) a fully co-operative patient is required. There is also the concern about the use of halothane, in the face of reports on its hepatotoxicity.

Certain questions are prompted by this article - is it possible to use another volatile agent for RII, and how would it compare to halothane when used for RII ? Also, would one of the less soluble agents (enflurane or isoflurane) provide a faster RII than halothane?

The next article to appear in the literature was one by Loper and co-workers [20]. This study compared halothane and isoflurane for RII. The study population was made up of adults belonging to the American Society of Anesthesiologists (ASA) physical status I and II categories (see Appendix, page 81). They received a RII with 4,5 MAC equivalents of either halothane or isoflurane in oxygen as the carrier gas. The investigators acknowledged the pungency of the isoflurane vapour and consequently administered a relatively large dose (5mcg/kg) of fentanyl IV 5 min. prior to RII with either of the above agents in order to limit the cough reflex. During induction, with the vapour delivered from a circle absorber breathing system, HR, BP, $SpO_2$, end expired carbon dioxide (PE $CO_2$) and electroencephalographic (EEG) measurements were made.

Using the lack of response to verbal command as well as loss of the eyelash reflex as the end points, the authors found that time to LOC was significantly shorter with isoflurane (38 sec.) than with halothane (86 sec.). There were no significant differences in cardiovascular and respiratory parameters between the two groups. The EEG pattern showed a greater excitatory

phase when halothane was used compared to isoflurane. All the patients in the study group found RII to be acceptable, as determined at patient interview on the day after the anaesthetic. All the patients were amnesic for events in the induction sequence following the VCB containing the volatile agent.

This study then answered the questions prompted by the Lancet editorial. However, the study may be criticised on the following points. The dose of fentanyl administered prior to RII is relatively large and as pointed out in a letter to the editor by Lamberty [21], it is surprising that the patients "breathed at all afterwards!" Also, no mention is made of how the patients were "surveyed" on the day after the RII. Because of the fentanyl used in these patients, the induction times described cannot be extrapolated to the day-case anaesthesia situation, where rapid recovery is desirable. This study does not, therefore, describe the use of isoflurane for RII in patients who are to have short surgical procedures and in whom a rapid recovery is desired.

An article by Lamberty and Wilson [22] goes some way to clarifying the use of isoflurane for RII in unpremedicated patients, such as would present for day-case anaesthesia. They compared isoflurane for CII and RII in 72 ASA I and II patients presenting for day-case (outpatient) anaesthesia. Evaluation of complication rates between the two groups showed a lower

incidence of all the following complications in the RII group compared to the CII group; coughing, laryngospasm, breath holding, excitatory phenomena (movement) and airway secretions. Cardiovascular (CVS) stability was a feature of both groups.

The RII group received a VCB, from a modified Mapleson A breathing system, containing 2% isoflurane in 66% $N_2O$ and 33% of $O_2$. The CII group received 0,5% increments of isoflurane in 66% $N_2O$ in $O_2$ every 5 breaths in the induction sequence. The patients were not pre-oxygenated.

The authors also recognised the potential for isoflurane to cause airway complications due its pungency and used $N_2O$ in the inhaled anaesthetic mixture to limit the inspired concentration of isoflurane. They note the high degree of patient acceptance of RII (94%) compared to CII (74%). Once again, the rapid onset of amnesia for events in the induction sequence was demonstrated. Patients in the RII group had recall for a median 2 breaths, while those in the CII group had recall for a median 5 breaths in the induction sequence.

This study assessed the patient's co-operation with the techniques of RII and CII - ie how well they understood and complied with the maneouvres required during the induction. The findings show that there was less patient co-operation with RII than CII. This is not surprising, as in CII normal spontaneous respiration is all that is required, whereas with RII specific respiratory manoeuvres are required.

In their discussion, Lamberty and Wilson point out that the longer induction times predicted in the Lancet editorial [19] for RII with isoflurane was not confirmed. They also note the potential problems of halothane use (hepatic damage) and suggest that if isoflurane is to be used, then RII is a viable and safe technique with less complications than CII with isoflurane. They suggest that this lower complication rate is because the patient passes through the second stage of anaesthesia more rapidly with RII than with CII - akin to the effect of IV induction in taking the patient from being awake to stage 3 of anaesthesia rapidly. They do not make any attempt to determine induction times though, nor do they define LOC.

They also note that in the inductions which had to be abandoned, one in each group, both the patients were smokers and suggest that RII is not viable in smokers or patients who have other causes for airway irritability. This conflicts with the findings of Ruffle and co-workers [17], who advocate the technique for all patients, regardless of smoking history.

An editorial by Drummond [23] in the British Journal of Anaesthesia discusses the technique of RII, its implications and uses and poses some questions regarding the technique. Reference is made to the 1987 study of Ruffle and Snider [24], in which a variation of the technique of RII is described - the subjects take three VCB's interspersed with breath holds instead of the single VCB. This technique halved the time to LOC to

approximately 1 min., compared to the 2 min. period to LOC obtained by the technique described in the previous paper by Ruffle and co-workers [17].

The mechanism of action of production of LOC by RII is likened by Drummond to a "bolus", rather than an "infusion" technique (ie CII). If a VCB of 4 litres is taken by the subject and the inspiratory - expiratory halothane difference is 3%, then 120ml of halothane vapour has been taken up by the pulmonary circulation. This will produce a rapid rise in anaesthetic agent concentration in the arterial blood and consequently the brain. This results in rapid LOC. If loss of eyelash reflex is used as the end-point and isoflurane is the agent being used, the the time to LOC is approximately 38 sec. The author postulates that this time, which is almost as fast as IV induction, may be the fastest time possible using an inhalational induction technique.

Drummond also makes the point that for induction to proceed and for the patient to lose consciousness alveolar ventilation (VA) must continue - ie. anaesthetic agent must continue to be taken up. Two factors may interfere with continued alveolar ventilation and uptake of volatile agent; the first is respiratory depression by the volatile agent and the second is reflex apnoea and coughing due to reflexes elicited by the volatile agent causing airway irritation. The author discusses the possible problems due to airway irritation, when isoflurane is used. He also states that although 2% isoflurane administered

by RII is less irritant than isoflurane CII (quoting the paper by Lamberty and Wilson [22]), it may be that it is still more irritant than when halothane is used. He stated that there was no well-controlled trial comparing RII with halothane and isoflurane in unpremedicated patients. This statement forms the basis for the dissertation by this candidate.

The breath-holding part of RII is described as useful by Drummond because $CO_2$ is retained and provides a stimulus to respiration in the patient who may be apnoeic following RII.

He also states that, theoretically, $N_2O$ in the induction mixture may produce an increased incidence of excitation. This is because the less soluble and more rapidly acting $N_2O$ produces a light plane of anaesthesia (stage 2) with the accompanying restlessness, before the less soluble volatile agent produces stage 3 anaesthesia.

In his review of preceding studies of RII the author states that various end-points of RII (ie definitions of LOC) had been used in the various studies and that none of these were equivalent to surgical anaesthesia. He concludes the editorial with the words "there is no doubt regarding one advantage this method; prompt and full recovery".

The Candidate is unaware of any studies of RII reported in 1989. In 1990 there were only two references regarding the topic. The

first is a paper from Japan by Rowbottom and associates [25] comparing enflurane for RII and enflurane for CII. 4% enflurane in 67% $N_2O$ and $O_2$ taken by VCB was compared to CII with enflurane in 30 surgical patients. LOC was defined as loss of eyelash reflex and lack of response to verbal commands. All the patients were premedicated with atropine and secobarbitone. The authors found RII to produce a faster induction than CII (71 sec. vs. 132 sec.), and was acceptable in 87% of patients. There was no difference between the two techniques in the impact on physiological variables. There was a low incidence of airway irritation in both groups, probably due to the premedication, since enflurane has a very pungent odour. Of interest is the fact that only 50% of patients had amnesia after the VCB in the RII group. This is a much lower figure than that obtained in the studies using halothane and isoflurane quoted previously in this Chapter.

The other 1990 reference to RII is a letter by MacKenzie from Oxford [26] in which he reports a pilot study using 5% isoflurane in $O_2$ for RII in children aged 7 months to 13 years. $N_2O$ was omitted from the inhaled mixture to avoid the excitatory phenomena associated with its inclusion (see above). Older children were asked to breath three times deeply and younger children merely had the mask applied to their faces. Rapid times to LOC are described (45-60 sec.), but the criteria for definition of LOC are not mentioned. The author states that older children found the odour "particularly unpleasant", as no

doubt did the younger children who did not voice their opinions! This again highlights the problem of pungency associated with the use of isoflurane.

There are numerous other references [12,27] related to the pungency and airway complications of isoflurane. However, one recent study has shown that the simple manoeuvre of humidifying the carrier gas during CII with isoflurane decreased the incidence of respiratory complications [28].

The investigation by this candidate was undertaken to answer some of the questions raised by the above studies of RII.

# CHAPTER 3

# STUDY DESIGN-

# MATERIALS AND METHOD

## 3.1 STATEMENT OF THE PROBLEM

As discussed in Chapter 2, the literature review, there are various aspects of Rapid Inhalational Induction (RII) that require clarification. This study was designed to address the following aspects of RII -

1. To determine whether it is possible to administer isoflurane during RII to **unpremedicated** patients without inducing a high incidence of respiratory tract side effects.
2. To compare **halothane and isoflurane in equipotent doses** for RII in patients presenting for day-case anaesthesia.
3. To compare RII with **5% isoflurane** with the technique described by Lamberty and Wilson [22] (see Chapter 2), where **2% isoflurane is used in nitrous oxide ($N_2O$) and oxygen ($O_2$).**
4. To measure the impact on **heart rate (HR), blood pressure (BP) and arterial oxygen saturation ($SpO_2$)** produced in patients by the techniques of RII listed in (2) and (3) above.
5. To determine the **comparative side effects** observed when the techniques listed in (2) and (3) above are used.
6. To determine the relative **speeds of induction** when the above methods are used for induction of anaesthesia.

7. To survey the study participants as to the acceptability and immediate post-operative side effects of the above techniques.

The study would not make any attempt to address the question of emergence from anaesthesia.

## 3.2 THE NULL HYPOTHESES

These may be listed as follows -

1. It is not possible to administer isoflurane to **unpremedicated** patients during RII;
2. Isoflurane 5% does not produce a faster RII than halothane 3.5%.
3. 2% isoflurane in $N_2O$ and $O_2$ does not provide for a slower RII than when a higher concentration of isoflurane (5%) is used.
4. 3,5% halothane (4,5 MAC) does not produce a slower RII than either 2% or 5% isoflurane.
5. There will not be a higher incidence of restlessness in the patients receiving $N_2O$ in the inhaled mixture.
6. The incidence of respiratory tract side effects will be similar for all the groups entered into the study.
7. 2% isoflurane in $N_2O$ and $O_2$ will not produce the least effect on BP and HR, compared to the other two groups.

## 3.3 STUDY POPULATION AND PATIENT SELECTION

Sixty (60) ASA (American Society of Anesthesiologists) physical status I and II patients presenting for day-case dental surgery (extraction of wisdom teeth) at the Dental Hospital of the University of the Witwatersrand were entered into the study. Institutional Ethical Committee approval was obtained and informed consent was obtained from all the patients. The study was also approved by the Pharmaceutical and Therapeutics Committee of the University of the Witwatersrand (Clearance number 89/1/27).

All consenting patients were entered into the study. Exclusion criteria included the following -

- **any chronic pre-operative medication** ie. chronic medication for a pre-existing medical condition;
- mass less than **30 kilograms** (kg), to obviate the need to use different anaesthetic breathing systems;
- **ischaemic heart disease** - this was defined as any history of anginal attacks or previous myocardial infarction;
- age less than **12 years** or more than **65 years**;
- **compromised upper airway** eg. trismus, intra-oral abscess.

All other consenting patients were entered into the study group regardless of smoking history or degree of pre-operative

anxiety. All were given the choice of withdrawing from the study at any time (see the sample consent form).

The patients were admitted to the hospital either on the night before operation or on the morning of surgery. During the admission formalities, completed by the nursing staff, the patients were presented with a Consent Form and asked to peruse it. The candidate performed a pre-operative assessment on all the patients on the morning of surgery, and at this point asked the patients whether they would consent to enter the study and whether they had any questions arising from their study of the consent form. Written consent was then obtained from those who agreed to enter the study.

All the patients in the study group were randomly allocated to one of three groups on entering the Operating Theatre (OT). Randomisation was achieved by placing slips of paper labelled as follows in sealed envelopes -

- 2% iso/$N_2O/O_2$
- 5% iso
- 3,5% hal.

Twenty (20) of each of these slips of paper were placed in individual envelopes resulting in a total of 60 envelopes. The envelopes were then numbered from 1 to 60 and placed in random order. Random numbers were generated by a statistics program ("Epistat") on a Triton personal computer.

## ISOFLURANE STUDY CONSENT FORM

Sample

You are due to have an operation today/tomorrow. While the operation takes place you will be anaesthetised (put to sleep), so that you feel no pain and are not aware of what is happening. The usual method of putting patients off to sleep involves giving them an injection into a vein, of a short-acting anaesthetic medication. The effect of this medication wears off within a few minutes and the patient is then kept asleep by means of an anaesthetic vapour. He breathes this in and out for the duration of the operation. At the end of the operation the vapour is turned off and the patient regains consciousness.

The reason why the anaesthetic starts off with an injection is because the injection takes effect very quickly. In the past this avoided any unpleasantness the patient may have experienced from breathing pungent anaesthetic vapours, such as ether, before they lost consciousness. However, newer anaesthetic vapours are very potent and a new method has been developed whereby a single deep breath of these vapours can induce unconsciousness. The advantages of this technique are that the injection is not required and the patient wakes up faster at the end of the operation. The patient also has less of a "hangover" after the operation with this technique. The disadvantages are that the patient may find it uncomfortable to breathe from the anaesthetic mask before they are asleep or may find the smell of the anaesthetic vapour unpleasant.

I am presently conducting a trial into the use of two new anaesthetic vapours, halothane and isoflurane, for this new "single breath" technique. Both these vapours have been used in anaesthetic practice for a number of years and have been shown to be safe. I should be grateful if you would consider taking part in this trial. All that would be different from the anaesthetic that you would normally receive would be that you are not put off to sleep with an injection, but by means of taking a single breath of one of the above vapours from a mask. If at any stage you would prefer to be put off to sleep with an injection instead, or if you find the mask uncomfortable at all, then I will put you off to sleep in the normal fashion (with an injection).

I, the undersigned consent to take part/give consent for my child to take part in the above trial, as explained to me by Dr. van Heerden. I understand that if I do not wish to take part/do not wish my child to take part in this trial that this will in no way prejudice my anaesthetic care/the anaesthetic care of my child. I also understand that I may change my mind about entering/my child entering this trial at any stage without prejudice to myself/my child.

PATIENT/GUARDIAN .....
WITNESS .....
DATE .....

As each patient arrived in the OT, an assistant opened an envelope which indicated to him the vaporiser setting on the anaesthetic machine to be used for that particular patient. He then adjusted the vaporiser and gas flows as indicated by the random selection slip of paper, as described in the Methods section 3.5 below. The candidate was unaware of these settings.

The patients then received a RII in a random double blind fashion, in the manner described below (see Methods 3.5).

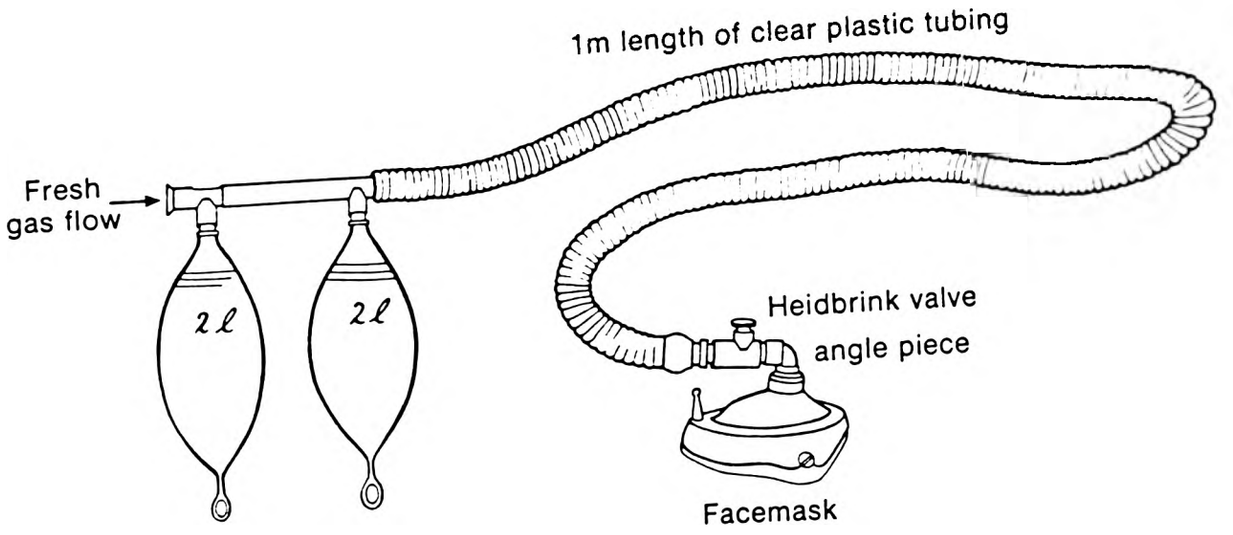
## 3.4 MATERIALS

Gas supplied from the anaesthetic machine was delivered to the patients via a modified Mapleson A breathing system. The modification consisted of the addition of a two litre (2 l) black rubber anaesthetic reservoir bag in series with the usual reservoir bag. The reason for the inclusion of this bag is to allow the breathing system to be able to meet the demand of a rapid vital capacity breath (VCB) by the patient. The modified breathing system is shown in Figure 2.

The anaesthetic machine was adjusted by an assistant to deliver one of the following gas mixtures (as indicated by the slip of paper in a sealed envelope - see Section 3.3 above) -

- 2% isoflurane in 67% $N_2O$ and $O_2$,
- 5% isoflurane in $O_2$ or
- 3,5% halothane in oxygen.

**Figure 2:** Modified Mapleson A breathing system



Total gas flow was set at 6 litres per minute (l/min). Once the settings had been made, the backbar (including the vaporiser) and the rotameters were covered with a green theatre towel. This made it impossible for the candidate to see which settings had been selected. In addition, all waste gas was actively scavenged to preclude the possibility of the candidate determining the anaesthetic mixture by smell.

Gas leaving the common gas outlet of the anaesthetic machine, and before entering the breathing system was humidified. Humidification was achieved by passing the gas through a hot water bath humidifier (Bennett Cascade 1 Humidifier, Puritan Bennett Corporation, USA) heated to approximately 60 degrees Celsius (°C). Dry gas at the common gas outlet had a temperature and relative humidity of 20°C and 15% respectively. These were increased to 27°C and 98% respectively by passage through the humidifier. Temperature and relative humidity were measured in a "bench-test trial" using a wet and dry bulb hygrometer placed in the stream of gas. After passage through the humidifier, the gas then entered the modified Mapleson A breathing system.

Each patient received a RII on the operating table in the manner described in Section 3.5 below. During the induction sequence the following were monitored -

- electrocardiogram (ECG) (Siemens Sirecust Monitor, Sweden)
- blood pressure (BP), recorded by means of continuous non-invasive finger probe (Finapress blood pressure monitor, BOC Health Care, USA)
- heart rate (HR)
- arterial oxygen saturation ($SpO_2$)
- time from the onset of the induction to loss of consciousness
- complications during the induction sequence.

Time was recorded to the nearest second (sec.) by means of a stopwatch. All the above observations were made by an assistant and recorded manually. The candidate carried out all the inductions.

## 3.5 METHODS

The patient was placed on the operating table, an intravenous (IV) cannula placed in a forearm vein and the monitoring equipment described above attached. All IV drugs required for intravenous induction of anaesthesia were immediately available.

The gas flows and the vaporiser were set by the assistant and baseline recordings of HR, BP and $SpO_2$ were made. The patient was then coached in the technique required for the RII as follows. Each patient was instructed to take as deep a breath as

possible. This was carried out with only the black rubber facemask and angle-piece applied to the patient's face. Once this had been carried out, the patient was then instructed to exhale as far as possible before taking another deep breath (the vital capacity breath = VCB) and holding this breath for as long as possible. Both the above manoeuvres were carried out with the patient breathing room air. Once the patient understood the above sequence, the same procedure was repeated with the patient breathing the selected anaesthetic mixture.

The breathing system was primed by allowing the 6l/min flow of carrier gas to flow through the system and then partially occluding the outlet of the system, until both reservoir bags were full, but not under tension. The outlet of the breathing system was connected to the angle piece already attached to the mask after the patient had exhaled to residual volume and before the patient took the VCB. The VCB that the patient then took contained the selected anaesthetic mixture. This breath was then held for as long as comfortable, before the patient resumed spontaneous respiration.

The time from the patient taking the VCB containing the anaesthetic mixture until the onset of loss of consciousness (defined below) was recorded by an assistant using a stopwatch.

Physiological parameters (HR, BP and $SpO_2$) were recorded manually during the induction sequence. Specific note was made of the baseline levels (taken once the patient was settled on

the operating table) and those at the time of loss of consciousness.

Loss of consciousness (LOC) was defined as lack of response to verbal commands, regular respiration and central pupils. This definition corresponds to the onset of surgical anaesthesia (stage 3) (as shown in Table 1, page 5). During the induction sequence the patient was asked by the candidate every ten seconds to open his/her eyes. When the patient no longer responded to these commands, the patient was observed for the onset or regular respiration. Once regular respiration had become established, the pupils were examined continuously. As soon as the pupils became central in position, the stopwatch was stopped. Time was recorded, representing the time to LOC.

In addition to the physiological parameters recorded any complications during the induction were also recorded. These complications included:

- **coughing**; this was deemed to have occurred if the patient made even a single cough. No differentiation was made between single or multiple coughs, unless the coughing was of such severity as to cause the induction to be abandoned - this was then recorded as an abandoned induction, with the reason stated as severe coughing;
- **laryngospasm**; being defined as any inspiratory stridor not due to airway obstruction by the tongue;

- **restlessness/patient movement**; being defined as patient movement requiring the patient to be physically restrained on the operating table;
- **desaturation**; being defined as a decrease in $SpO_2$ to below 90%;
- **secretions**; being defined as when these were audible in the airway.

If the procedure was abandoned the reason for this was noted.

Following the onset of LOC, suxamethonium was administered and the patient intubated. Anaesthesia was then maintained in all cases with 2% halothane in 66% $N_2O$ and 33% $O_2$, with the patient breathing spontaneously.

All the patients were visited by the candidate approximately two hours post-operatively. The candidate was unaware of which agent the patient had received. At this time they were asked -

- what their last recall in the induction sequence was;
- if they had experienced any nausea or vomiting post operatively, and
- whether they would choose a RII again for a future anaesthetic (as an estimate of the acceptability of the technique by the patient). All the study participants were interviewed post-operatively, including those in whom the induction sequence had to be abandoned due to the severity of complications.

The details described above during the induction sequence and for the post-operative interview were recorded manually on data sheets, an example of which is shown on the following page.

The data was then transferred to database files on the "Epistat" program on a Triton personal computer. These files were then used for the relevant statistical analyses.

## 3.6 STATISTICAL ANALYSIS

The following statistical tests were performed as appropriate, using the "Epistat" program on a Triton personal computer -

1. Analysis of variance (ANOVA). ANOVA was used to detect type 2 error when necessary (ie. to determine whether differences between groups were more significant than differences within groups). When ANOVA is used this is indicated in the relevant tables.
2. Paired and unpaired T-tests
3. Chi-squared tests (with Yates' correction when appropriate), and
4. Fischer's Exact test.

A p value of less than 0,05 was considered statistically significant. The results and the statistical tests performed to analyse the results are discussed in Chapter 4.

## RAPID INHALATIONAL INDUCTION STUDY

Sample

### DATA SHEET

Patient No .....

Age .....

Sex M F

Mass (kg) .....

ASA - 1 2 3

Procedure .....

Current medication .....

PMH - Smoker Y N
Recent URTI Y N
Chest disease Y N

### INDUCTION DETAILS

Agent - Hal 2% Iso in $N_2O/O_2$ 5% Iso

Complicated Y N

Complication -
- Coughing Y N
- Laryngospasm Y N
- Secretions Y N
- Excessive movement Y N

Abandoned Y N

Saturation ($SpO_2$) Baseline/LOC

Induction time (sec) (onset of VCB - LOC)

Number of breaths to LOC

Mean arterial pressure (MAP) Baseline/LOC

Heart rate Baseline/LOC

### POST-OP INTERVIEW

- Would repeat experience Y N
- Amnesia after 1st VCB Y N
- Nausea and vomiting Y N
- Headache Y N

# CHAPTER 4

# RESULTS

In the discussion of results obtained from this study, the study groups will be known as groups A, B and C. Group A received 3,5% halothane in oxygen, group B received 5% isoflurane in oxygen and group C received 2% isoflurane in $N_2O$ and $O_2$.

## 4.1 DEMOGRAPHIC DATA

The mean **ages** and standard deviations (SD) for the three groups, in years, are as follows - group A 25,40 (12); group B 25,15 (8,9) and group C 23,45 (6,4). These values are obtained from the raw data presented in Table 3. **Unpaired t-tests** and ANOVA did not reveal any significant differences between the means of these groups.

The **male to female ratios** in the three groups are as follows - group A, 12 males and 8 females; group B, 12 males and 8 females and group C, 14 males and 6 females. **Chi-squared** testing showed the groups to be comparable with regard to gender ratios (see Table 4).

The **mass**, mean (SD), of the three groups is shown in kilograms (kg) in Table 5. The values are as follows - group A, 64,35 (12); group B 62,65 (9) and group C 61,95 (9). **Unpaired t-testing** and ANOVA showed there to be no significant differences between the three groups with regard to the subjects' masses.

## Table 3.
## Subject ages in years.

| A. Halothane 3,5% n = 20 | B. Isoflurane 5% n = 20 | C. Isoflurane 2% $N_2O/O_2$ n = 20 |
|---|---|---|
| 14 | 17 | 14 |
| 16 | 18 | 16 |
| 16 | 18 | 17 |
| 18 | 19 | 18 |
| 19 | 19 | 19 |
| 21 | 21 | 20 |
| 21 | 21 | 21 |
| 21 | 21 | 21 |
| 22 | 24 | 23 |
| 22 | 24 | 24 |
| 22 | 25 | 24 |
| 22 | 25 | 24 |
| 23 | 27 | 24 |
| 23 | 27 | 25 |
| 26 | 27 | 26 |
| 28 | 29 | 27 |
| 34 | 33 | 33 |
| 34 | 34 | 34 |
| 38 | 38 | 36 |
| 69 | 55 | 38 |
| Mean 25,40 | 25,15 | 23,45 |
| +/- SD 12 | 8,9 | 6,4 |

| | Unpaired t tests. | ANOVA |
|---|---|---|
| A vs B p = | 0,940 | 0,917 |
| B vs C p = | 0,492 | 0,444 |
| A vs C p = | 0,526 | 0,609 |

## Table 4.
## Male/Female ratios.

| A. Halothane 3,5% n = 20 | B. Isoflurane 5% n = 20 | C. Isoflurane 2% $N_2O/O_2$ n = 20 |
|---|---|---|
| Male/Female | | |
| 12/8 | 12/8 | 14/6 |

Chi-squared test.

A vs B p = 0,747
B vs C p = 0,740
A vs C p = 0,740

## Table 5.
## Subject Mass in Kilograms

| | A<br>Halothane 3,5%<br>n = 20 | B<br>Isoflurane 5%<br>n = 20 | C<br>Isoflurane 2% $N_2O/O_2$<br>n = 20 |
|---|---|---|---|
| | 45 | 45 | 50 |
| | 47 | 52 | 51 |
| | 49 | 53 | 52 |
| | 50 | 55 | 53 |
| | 51 | 55 | 53 |
| | 54 | 56 | 54 |
| | 57 | 57 | 55 |
| | 64 | 58 | 55 |
| | 65 | 59 | 58 |
| | 65 | 60 | 60 |
| | 66 | 64 | 60 |
| | 67 | 65 | 65 |
| | 70 | 65 | 65 |
| | 72 | 68 | 70 |
| | 74 | 69 | 70 |
| | 75 | 71 | 70 |
| | 75 | 74 | 72 |
| | 76 | 75 | 74 |
| | 76 | 76 | 76 |
| | 89 | 76 | 76 |
| Mean<br>+\- SD | 64,35<br>12 | 62,65<br>9 | 61,95<br>9 |

| | Unpaired t tests | ANOVA |
|---|---|---|
| A vs B p = | 0,671 | 0,671 |
| B vs C p = | 0,857 | 0,857 |
| A vs C p = | 0,575 | 0,575 |

The number of **smokers** in each group was as follows - group A, 7 out of 20; group B, 7 out of 20 and group C, 8 out of 20. **Chi-squared testing** did not reveal any significant differences between the groups with regard to the number of smokers in each group. The p values obtained are shown in Table 6.

**American Society of Anesthesiologists (ASA) physical status** of the three groups is as follows - group A, 18 subjects ASA 1, and 2 subjects ASA 2; group B, 20 subjects ASA 1 and group C, 18 subjects ASA 1 and 2 subjects ASA 2. **Fischer's Exact Tests** showed there to be no significant differences between the groups with regard to physical status (see Table 7).

From the above, it is evident that the three groups are demographically comparable with regard to age, mass, gender ratio, ASA status and the number of smokers. This is due to the homogeneous, well-defined group of subjects (young patients presenting for day-case dental surgery) entered into the study. None of the subjects had any pre-existing respiratory pathology of note and none were receiving any medication pre-operatively.

## Table 6.
## Number of Smokers

| A<br>Halothane 3,5%<br>n = 20 | B<br>Isoflurane 5%<br>n = 20 | C<br>Isoflurane 2% $N_2O/O_2$<br>n = 20 |
|---|---|---|
| 7 | 7 | 8 |

Chi squared tests

A vs B p = 0,740
B vs C p = 1
A vs C p = 1

## Table 7.
## American Society of Anesthesiologists (ASA) Physical Status Classification

| | A<br>Halothane 3,5%<br>n = 20 | B<br>Isoflurane 5%<br>n = 20 | C<br>Isoflurane 2% $N_2O/O_2$<br>n = 20 |
|---|---|---|---|
| ASA 1 | 18 | 20 | 18 |
| ASA 2 | 2 | 0 | 2 |

Fisher's Exact Test

A vs B p = 0,243
B vs C p = 0,243
A vs C p = 0,697

## 4.2 THE INDUCTION PERIOD

Table 8 and Figure 3 depicts the raw data regarding the **speed of induction** in the three groups. The mean (SD) induction times in seconds are as follows - group A, 176 (36); group B 121 (50) and group C, 134 (41). **Analysis of variance (ANOVA)** and **unpaired t-tests** showed there to be a significant difference in induction times between group A and both groups B ($p = 0,0007$) and group C ($p= 0,003$). However, there is no significant difference in induction time between groups B and C ($p = 0,443$).

The **number of breaths to loss of consciousness** (LOC), mean (SD), in each group are as follows - group A, 30 (12); group B, 18 (12) and group C, 23 (8). The raw data from which these figures are derived are listed in Table 9 and Figure 4. As is the case with the speed of induction, there is a significant difference between the number of breaths to LOC between group A and group B ($p = 0,005$). There is no significant difference between groups A and C ($p = 0,06$) or B and C ($p = 0,139$). The p values were determined using **unpaired t-tests and ANOVA**.

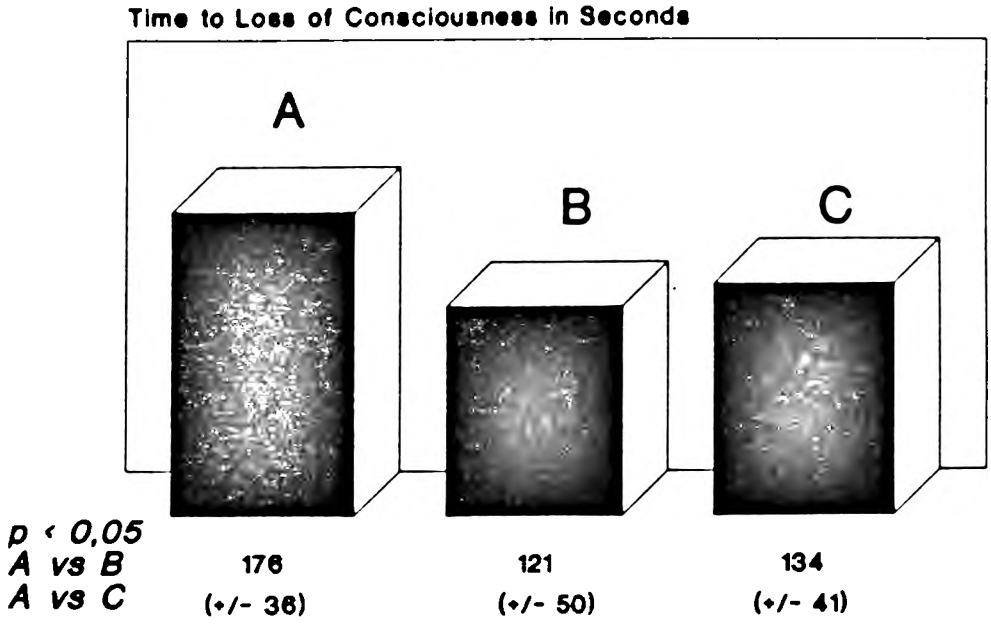
The data for both the speed of induction and the number of breaths to LOC include only those data obtained from subjects completing the induction sequence.

## Table 8.
## Speed of Induction
## (Time in seconds to loss of consciousness)

| | A<br>Halothane 3,5%<br>n = 17 | B<br>Isoflurane 5%<br>n = 18 | C<br>Isoflurane 2% $N_2O/O_2$<br>n = 16 |
|---|---|---|---|
| | 90 | 45 | 45 |
| | 120 | 60 | 90 |
| | 140 | 75 | 90 |
| | 158 | 76 | 120 |
| | 175 | 80 | 120 |
| | 176 | 83 | 122 |
| | 177 | 86 | 132 |
| | 180 | 89 | 132 |
| | 180 | 114 | 135 |
| | 180 | 120 | 135 |
| | 182 | 125 | 136 |
| | 183 | 135 | 142 |
| | 190 | 165 | 147 |
| | 191 | 172 | 180 |
| | 218 | 180 | 205 |
| | 221 | 182 | 210 |
| | 240 | 197 | |
| | | 202 | |
| Mean | 176 | 121 | 134 |
| +\- SD | 36 | 50 | 41 |

| | | | | | Unpaired t tests | ANOVA |
|---|---|---|---|---|---|---|
| A | vs | B | p | = | 0,0007 | 0,0007 |
| B | vs | C | p | = | 0,443 | 0,443 |
| A | vs | C | p | = | 0,003 | 0,003 |

# Speed of Induction
## Figure 3



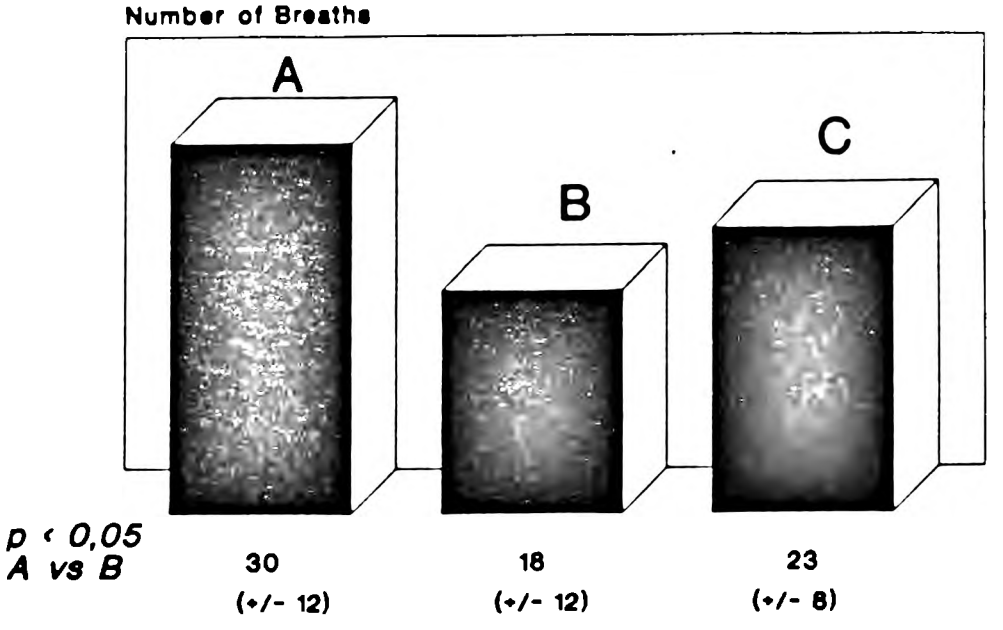
## Table 9.
## Number of breaths to loss of consciousness

| | A. Halothane 3,5% n = 17 | B. Isoflurane 5% n = 18 | C. Isoflurane 2% $N_2O/O_2$ n = 16 |
|---|---|---|---|
| | 7 | 3 | 15 |
| | 20 | 5 | 15 |
| | 20 | 0 | 15 |
| | 20 | 10 | 15 |
| | 24 | 10 | 17 |
| | 25 | 12 | 20 |
| | 25 | 13 | 20 |
| | 25 | 15 | 20 |
| | 28 | 15 | 24 |
| | 29 | 15 | 26 |
| | 30 | 15 | 26 |
| | 34 | 15 | 30 |
| | 40 | 20 | 31 |
| | 44 | 20 | 31 |
| | 45 | 28 | 35 |
| | 50 | 30 | 40 |
| | 50 | 35 | |
| | | 50 | |
| Mean | 30 | 18 | 23 |
| +/- SD | 12 | 12 | 8 |

| | Unpaired t tests | ANOVA |
|---|---|---|
| A vs B p = | 0,005 | 0,005 |
| B vs C p = | 0,139 | 0,139 |
| A vs C P = | 0,06 | 0,06 |

# Loss of Consciousness

## Figure 4



## 4.3 COMPLICATIONS DURING INDUCTION

Table 10(a) shows the **number of complicated inductions in each group.** There were 9 out of 20 complicated inductions in both groups A and B, and only 4 out of 20 complicated inductions in group C. **Chi-squared tests** (with Yates' correction) did not reveal any significant differences between the three groups with regard to total number of complicated inductions. There were also no significant differences between the **types of complications** during the induction sequence, between the groups. These are listed in Table 10(b). The p values obtained comparing the types of complications were determined by the **Fischer's Exact Test.**

There were no significant differences between the groups with regard to the **number of inductions which had to be abandoned,** as determined by **Fischer's Exact Test** The relevant p values are shown in Table 11. Of the 3 inductions which had to be abandoned in group A, 1 had to be abandoned due to uncontrolled coughing and 2 because of excessive movement, requiring restraint of the patient. In group B, both the abandoned inductions were due to uncontrolled coughing. In group C, 4 inductions were abandoned, all due to excessive patient movement and restlessness.

## Table 10.
## a). Complicated Inductions

| A. Halothane 3,5% n = 20 | B. Isoflurane 5% n = 20 | C. Isoflurane 2% $N_2O/O_2$ n = 20 |
|---|---|---|
| 9 | 9 | 4 |

Chi - squared tests.

A vs B p = 0,750
B vs C p = 0,177
A vs C p = 0,177

## Table 10.
## b). Types of Complications

| | A. Halothane 3,5% n = 9 | B. Isoflurane 5% n = 9 | C. Isoflurane 2% $N_2O/O_2$ n = 4 |
|---|---|---|---|
| Coughing | 5 | 3 | 0 |
| Secretions | 0 | 1 | 0 |
| Excessive movement | 5 | 6 | 4 |

Fisher's Exact Tests:

| 1. Coughing | 2. Secretions | 3. Excessive movement |
|---|---|---|
| A vs B p = 0,318 | A vs B p = 0,526 | A vs B p = 0,5 |
| B vs C p = 0,294 | B vs C p = 0,714 | B vs C p = 0,294 |
| A vs C p = 0,09 | | A vs C p = 0,176 |

# Table 11.
# Abandoned Inductions

| A. Halothane 3,5% n = 20 | B. Isoflurane 5% n = 20 | C. Isoflurane 2% $N_2O/O_2$ n = 20 |
|---|---|---|
| 3 | 2 | 4 |

**Fisher's Exact Test**

A vs B p = 0,499
B vs C p = 0,331
A vs C p = 0,499

Smokers were well represented within the subjects in whom inductions had to be abandoned due to the severity of complications. In group A, out of the three inductions abandoned, one of the subjects was a smoker. This was also true for both the inductions abandoned in group B and all the inductions abandoned in group C. If all the smokers from groups A, B and C are compared to the non-smokers from the same groups with regard to number of inductions abandoned, there is no significant difference ($p=0.09$ by Fisher's exact test - Table 12).

There were no episodes of **desaturation ($SpO_2$ <90%)** or **laryngospasm** in any of the groups. Excessive secretions complicated only one of the inductions - in group B.

## 4.4 CARDIOVASCULAR PARAMETERS DURING THE INDUCTION SEQUENCE

Table 13 and Figure 5 (**mean arterial pressure**), and Table 14 and Figure 6 (**heart rate**), show the raw data regarding the baseline and post-induction (at LOC) values for MAP and HR for the three groups. **Paired t-tests** and **ANOVA**, within groups, and **unpaired t-tests** and **ANOVA**, between groups, showed there to be no significant differences in the mean values for MAP, either between groups A, B and C or within groups A and B (baseline vs. post-induction). However, there was a significant decrease from baseline to post-induction MAP in group C ($p$ =

## Table 12.
## Abandoned Inductions.
## Smokers vs Non-smokers.

| | Not Abandoned | Abandoned |
|---|---|---|
| Smoker<br>n = 22 | 15 | 7 |
| Non-smoker<br>n = 38 | 36 | 2 |

**Fisher's Exact test**
Smokers vs Non-smokers

p = 0,09

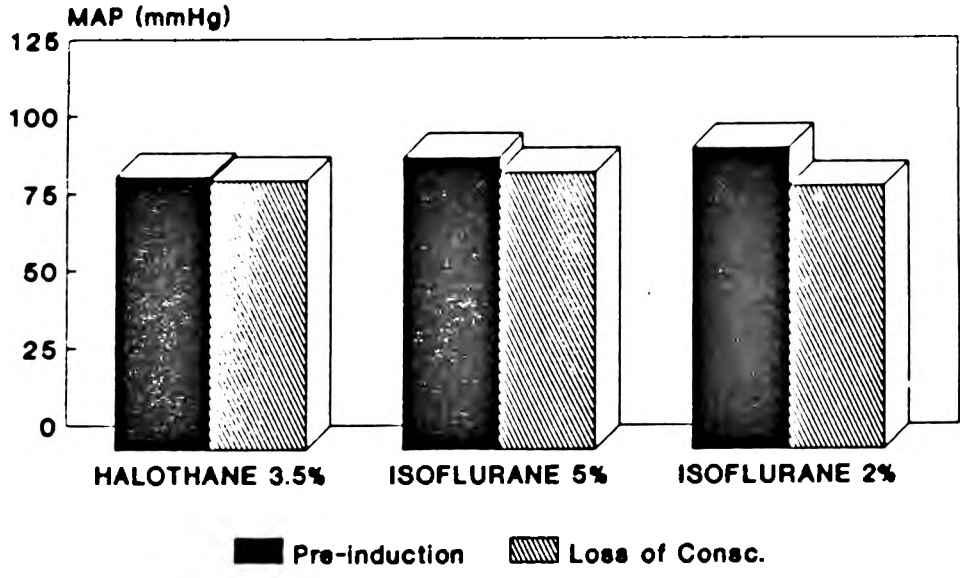
## Table 13.
## Mean Arterial Pressure (MAP)
## (1) Pre Induction
## (2) At loss of consciousness (LOC)

| | A Halothane 3,5% n = 17 | | B Isoflurane 5% n = 18 | | C Isoflurane 2% $N_2O/O_2$ n = 16 | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 1 | 2 | 1 | 2 |
| | 69 | 104 | 73 | 92 | 82 | 88 |
| | 72 | 78 | 81 | 92 | 83 | 67 |
| | 73 | 64 | 82 | 86 | 83 | 79 |
| | 76 | 85 | 83 | 68 | 86 | 76 |
| | 76 | 93 | 85 | 59 | 86 | 80 |
| | 81 | 72 | 86 | 82 | 90 | 88 |
| | 85 | 73 | 87 | 76 | 91 | 86 |
| | 86 | 78 | 88 | 84 | 92 | 83 |
| | 86 | 86 | 92 | 102 | 95 | 77 |
| | 88 | 77 | 94 | 80 | 97 | 97 |
| | 94 | 95 | 99 | 87 | 100 | 72 |
| | 95 | 84 | 100 | 103 | 106 | 93 |
| | 98 | 96 | 102 | 92 | 109 | 75 |
| | 100 | 90 | 102 | 110 | 111 | 100 |
| | 100 | 105 | 104 | 94 | 120 | 97 |
| | 107 | 115 | 107 | 92 | 121 | 97 |
| | 113 | 81 | 108 | 109 | | |
| | | | 123 | 102 | | |
| Mean | 88 | 86,8 | 94,2 | 89,4 | 97 | 84,7 |
| +\- SD | 13 | 13,3 | 12,4 | 13,5 | 13 | 10 |

| | Paired t tests. | ANOVA | | Unpaired t tests. | ANOVA |
|---|---|---|---|---|---|
| A1vsA2 | p = 0,708 | 0,765 | A1vsB1 | p = 0,166 | 0,166 |
| B1vsB2 | p = 0,114 | 0,277 | B1vsC1 | p = 0,527 | 0,527 |
| C1vsC2 | p = 0,0004 | 0,005 | A1vsC1 | p = 0,058 | 0,058 |
| | | | A2vsB2 | p = 0,568 | 0,568 |
| | | | B2vsC2 | p = 0,259 | 0,259 |
| | | | A2vsC2 | p = 0,609 | 0,609 |

# Mean Arterial Pressure (MAP).

## Figure 5



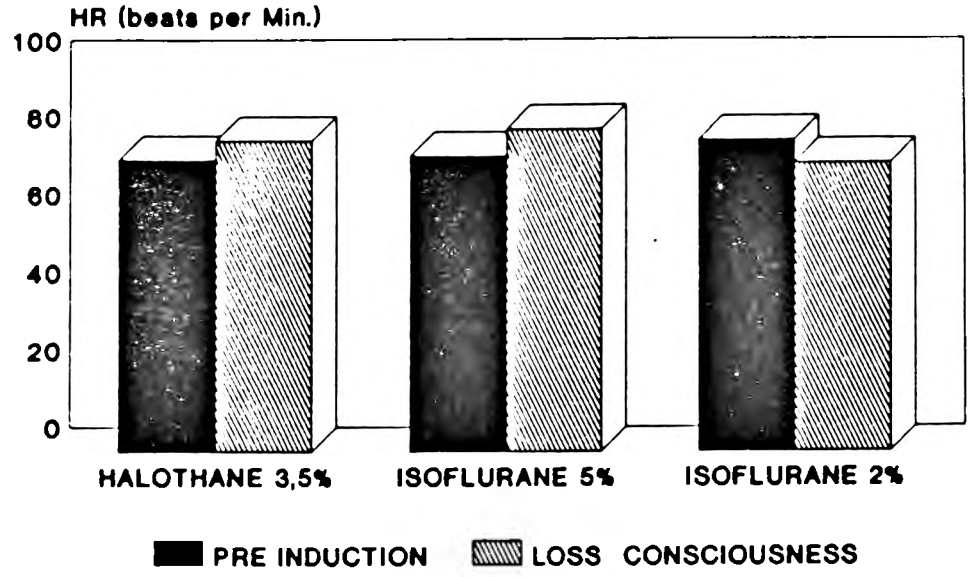
## Table 14.
## Heart Rate (HR)
## (1) Pre Induction
## (2) At loss of consciousness (LOC)

| | A<br>Halothane 3,5%<br>n = 17 | | B<br>Isoflurane 5%<br>n = 18 | | C<br>Isoflurane 2% $N_2O/O_2$<br>n = 16 | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 1 | 2 | 1 | 2 |
| | 59 | 66 | 52 | 53 | 61 | 61 |
| | 61 | 60 | 54 | 70 | 62 | 62 |
| | 61 | 74 | 58 | 67 | 63 | 75 |
| | 63 | 72 | 58 | 80 | 68 | 73 |
| | 63 | 81 | 60 | 49 | 69 | 60 |
| | 66 | 80 | 60 | 74 | 74 | 86 |
| | 69 | 95 | 67 | 78 | 75 | 61 |
| | 72 | 89 | 68 | 74 | 75 | 65 |
| | 74 | 81 | 70 | 80 | 75 | 68 |
| | 75 | 74 | 72 | 104 | 77 | 117 |
| | 78 | 76 | 82 | 85 | 84 | 76 |
| | 79 | 76 | 85 | 99 | 87 | 53 |
| | 81 | 72 | 86 | 91 | 88 | 75 |
| | 86 | 95 | 88 | 108 | 88 | 85 |
| | 88 | 100 | 91 | 90 | 96 | 53 |
| | 100 | 84 | 93 | 80 | 153 | 108 |
| | 104 | 92 | 113 | 117 | | |
| | | | 114 | 106 | | |
| Mean | 75 | 80 | 76 | 83 | 80 | 74 |
| +\- SD | 13 | 11 | 19 | 18 | 22 | 18 |

| | Paired t tests. | ANOVA | | Unpaired t tests. | ANOVA |
|---|---|---|---|---|---|
| A1vsA2 | p = 0,080 | 0,226 | A1vsB1 | p = 0,868 | 0,868 |
| B1vsB2 | p = 0,024 | 0,257 | B1vsC1 | p = 0,499 | 0,499 |
| C1vsC2 | p = 0,224 | 0,342 | A1vsC1 | p = 0,369 | 0,369 |
| | | | A2vsB2 | p = 0,577 | 0,577 |
| | | | B2vsC2 | p = 0,149 | 0,149 |
| | | | A2vsC2 | p = 0,230 | 0,230 |

# Heart Rate (HR).

## Figure 6



0,0004). Group B showed the only significant difference in HR (p = 0,024) with an increase from baseline to post-induction levels of HR. The data pertaining to the cardiovascular parameters includes only those data obtained from subjects who completed the induction sequence.

## 4.5 POST-OPERATIVE INTERVIEW

Table 15 lists the results of the post-operative interview. These results contain the responses of all the subjects included in the study, regardless of whether the induction had to be abandoned or not.

Most of the subjects had **amnesia** for events following the vital capacity breath (VCB) containing the anaesthetic mixture - 15 out of 20 in group A, 16 out of 20 in group B and 14 out of 20 in group C. There were no significant differences between the groups with regard to the incidence of amnesia as determined by **Fischer's Exact Test.**

Most of the subjects, 14 out of 20 in group A and 17 out of 20 in groups B and C, found the experience of RII not unpleasant and **were prepared to repeat the experience** for a subsequent anaesthetic.

## Table 15.
## Post operative interview

| | A<br>Halothane 3,5%<br>n = 20 | B<br>Isoflurane 5%<br>n = 20 | C<br>Isoflurane 2% $N_2O/O_2$<br>n = 20 |
|---|---|---|---|
| Amnesia after 1st Vital Capacity Breath (Number) | 15 | 16 | 14 |
| Would repeat experience (Number) | 14 | 17 | 17 |
| Headache (Number) | 3 | 1 | 1 |
| Nausea & Vomiting (Number) | 1 | 0 | 0 |

### Fisher's Exact Test

| | | |
|---|---|---|
| Amnesia | A vs B | p = 0,5 |
| | B vs C | p = 0,338 |
| | A vs C | p = 0,499 |
| Would repeat the Experience | A vs B | p = 0,225 |
| | B vs C | p = 0,669 |
| | A vs C | p = 0,225 |
| Headache | A vs B | p = 0.302 |
| | B vs C | p = 0,756 |
| | A vs C | p = 0,302 |
| Nausea and Vomiting | A vs B | p = 0,499 |
| | B vs C | p = 0,999 |
| | A vs C | p = 0,499 |

The incidence of post-operative complications was low - **headache** occurred in 1 subject in both groups B and C, and in 3 subjects in group C. **Nausea and vomiting** occurred in only 1 subject from group A. There were no significant differences between groups with regard to types of post-operative complications (headache or nausea and vomiting) (Table 15).

# CHAPTER 5

# DISCUSSION

# AND CONCLUSIONS

In essence, this study was undertaken to address one of the problems presented by the considerable prejudice developing against the use of halothane in Europe and North America [29]. The safety and efficacy of halothane as an agent for both conventional (CII) and rapid inhalational induction (RII) has been well proven [16,17,24]. However isoflurane is replacing halothane as the volatile agent of choice and has the reputation of being a difficult agent to use for CII [12,27]. Isoflurane has also been used for RII, but only when administered to heavily premedicated patients [20] or when the inspired concentration of the agent was limited by the addition of nitrous oxide ($N_2O$) in the inspired mixture [22]. Avoiding the emotive aspects of the decline of halothane as the volatile agent of choice for inhalational induction, the candidate wished to investigate the possibility of using isoflurane for RII.

RII as a technique is not new. It was introduced into clinical practice for use with cyclopropane in 1954 [15]. Although cyclopropane is still available in some countries, it is rarely used in clinical practice today because it is highly flammable. RII has therefore had to wait for the development of the fluorinated volatile agents with low B/G solubility to be revived. This revival occurred in 1982, when RII was described by Ruffle and co-workers [16] with halothane. As discussed in Chapter 2, the application of the technique of RII is limited, as is the literature regarding this technique. However, RII has

a definite place as an alternative to intravenous induction, as well as in the day-case setting.

A previous study by the candidate and others [28] showed that humidification of the carrier gas during inhalational induction with isoflurane decreased the respiratory tract side effects produced by the pungency of the agent. The question then arose whether it would be possible to administer a high concentration of isoflurane, as would be required for RII, if the carrier gas were humidified.

The three study groups in the present study were well matched as to demographic criteria as seen in Tables 3 to 7. Also, all the subjects were unpremedicated and presenting for very similar surgery by the same surgeon at the same hospital. All the anaesthetic inductions were carried out by the candidate. Interfering variables were reduced to a minimum and it can be assumed that any differences between the study groups are due to the different agents used. It should be noted that with regard to the demographic data none of the groups included patients who smoked more than twenty cigarettes per day. Although there is no supporting evidence, it may be argued that a smoker of up to 20 cigarettes per day should be classified as ASA physical status 2. The candidate chose to ignore this and only classify the subjects as physical status ASA 2 if systemic disease was present, whether this was due to cigarette smoking or not.

The results of the post-operative interview (Table 15) show that patient acceptance is high and that most patients would repeat the experience of RII in the future if the occasion arose. A very low incidence of post-operative complications occurs in these patients. These results may be criticised on the basis that they were obtained by interview and not by anonymous questionnaire. However, the answers were obtained by the candidate asking the subjects open-ended questions wherever possible eg."Are you experiencing any discomfort or any other problems now that the operation is over?". There were no significant differences between the three study groups with regard to post-operative complications, but the numbers involved are very small and a larger study would be necessary to obtain more meaningful results in this regard. It is impressive that 80% of all the subjects studied found the experience of RII not unpleasant, despite the fact that post-operative pain may have caused this response to be biased against a favourable answer. Before further discussion then, it would appear that the patients included in the study did not find the experience unpleasant. This is in keeping with the study by Lamberty and Wilson using isoflurane in $N_2O$ and oxygen ($O_2$) [22].

As anticipated from the physical properties (Table 2) of halothane and isoflurane, this study showed that halothane produces a significantly slower RII than isoflurane. This difference is significant whether isoflurane is administered in high concentration in oxygen (4,5, MAC) or as a lower

concentration in $N_2O$ and $O_2$. There is no significant difference in speed of induction between RII with 5% isoflurane in oxygen or 2% isoflurane in $N_2O$ and $O_2$ (Table 8, Figure 3). Presumably this is because the second gas effect [30] provided by $N_2O$ is sufficient to compensate for the more rapid rise in alveolar concentration produced by inhaling a higher concentration of isoflurane. Although isoflurane produces a faster onset of surgical anaesthesia than halothane when used for RII the following questions now arise -

- what, if any, is the clinical advantage of the increased speed of induction with isoflurane?, and
- would a larger study population show the same differences without the large standard deviations observed in this study? (Table 8)

It is the clinical impression of the candidate that patients who are not anxious and who are not smokers are better able to comply with the technique of RII, and in particular with holding the VCB containing the volatile agent. If the study had been designed to exclude all smokers and anxious patients it is possible that the wide standard deviations observed in induction time may well have not occurred. As no objective measure of anxiety was included in the study design, it is not possible, in retrospect, to exclude anxious subjects from the statistical

analyses. The findings of the study (Table 12) do not support the candidate's clinical impression that more inductions had to be abandoned in patients who smoke cigarettes.

The number of breaths that the subjects required to take before the onset of LOC (Table 9, Figure 4) support the findings described above regarding induction time (defined in chapter 3, page 40). This is not surprising, as the longer the induction time involved, the longer the subject would have to take additional breaths before LOC ensued. It is interesting though that there is no significant difference between the halothane group and the 2% isoflurane group with regard to the number of breaths before loss of consciousness - despite there being a small, but significant difference in induction times.

The definition of LOC chosen by the candidate for this study, namely no response to verbal command, regular respiration and central pupils coincides as far as possible with the definition of stage 3 of anaesthesia (Table 1), or surgical anaesthesia. This is not in keeping with any of the previous studies of RII [16-18,20,22,25], in that it is a relatively "soft" end point, rather than an end-point such as the loss of the eyelid reflex etc. previously used. The candidate preferred the use of stage 3 of anaesthesia as the definition of LOC, as this is a more clinically relevant definition. This is the point at which body surface surgery may commence as occurs in the day-case setting. More time is required to reach stage 3 of

anaesthesia than to reach the end-points as defined in the previous studies of RII. Therefore, the induction times and related measurements (number of breaths to LOC) obtained in this study are longer than those described in the studies by Ruffle and associates [16,17], Lamberty and Wilson [22] and Rowbottom and colleagues [25]. It should be noted though that a large proportion of patients have amnesia for events after the first vital capacity breath containing volatile agent (Table 15), and therefore, as far as the subject is concerned, he is no longer conscious after the first breath. This is in keeping with previous descriptions of this technique as the "single breath technique" [16,18]. If the candidate had access to a volatile agent analyser and automatic breath-by-breath data collection system it would have been possible to plot the rate of rise of volatile agent concentration in inhaled and exhaled gases and to correlate these levels with the onset of LOC as has previously been documented with halothane [17].

The cardiovascular stability of subjects who undergo RII is remarkable and well demonstrated by this study (Tables 13 and 14, Figures 5 and 6). The only significant decrease in mean arterial pressure (13%) occurred in subjects receiving 2% isoflurane in $N_2O$ and $O_2$. This degree of hypotension is similar to that seen when intravenous agents are used for induction of anaesthesia and it is unlikely that it represents a threat to the well-being of the patient. It may be prudent, however, to avoid this combination for RII in patients who have

ischaemic or valvular heart disease. It should also be noted that there is no tachycardia associated with this mild decrease in blood pressure. This also suggests that the decrease in blood pressure should not detract from the advantages of the technique of RII with 2% isoflurane in $N_2O$ and $O_2$. 5% isoflurane in $O_2$, when used for RII, produces a small (± 9%) but significant increase in heart rate, in keeping with the pharmacological action of this drug [3]. Again, this does not represent a threat to the cardiovascular safety of most patients.

Complications related to the airway appear to be common with RII in this study ie 45% in groups A and B and 20% in group C (Tables 10a and 10b). The candidate believes this is attributable not only to the technique of RII, but also to the rigid criteria by which the complications were defined. It will be noted that there were no significant differences between the study groups with regard to complication rate - this despite the poor reputation isoflurane has for producing respiratory tract irritation. The findings of this study suggest that humidification of the carrier gas does decrease the pungency of isoflurane to such a degree that the associated complication rate is similar to that seen when halothane is used. However, a further study would be required, comparing RII with isoflurane in humidified and non-humidified carrier gas, to clarify the effect of humidification on complication rate when isoflurane is used for RII. A similar study has shown the beneficial effect of humidification of the carrier gas for conventional inhalational

induction with isoflurane [28]. That the complications associated with RII were not severe is supported by the high acceptance rate of subjects for this technique regardless of the agent used (Table 15) and the small number of inductions which had to be abandoned due to the complications (Table 11).

The nature of the complications (Table 10b) encountered during RII is interesting in that the subjects in Group C (2% isoflurane in $N_2O$ and $O_2$) experienced only excessive movement/restlessness and not the expected complications of coughing and excessive secretions , as seen in the other two groups. This may be due to the presence of nitrous oxide in the inhaled mixture - $N_2O$ has a very low B/G solubility coefficient (Figure 1), but is not very potent (MAC=105%) [31]. As explained by Drummond [23], $N_2O$ may rapidly induce stage 2 (phase of excitement) of anaesthesia, before the concentration of isoflurane in the brain is sufficient to produce surgical anaesthesia. During this transient phase, while the $N_2O$ is exerting its effect and before the isoflurane has anaesthetised the patient sufficiently, the patient may exhibit all the features of stage 2 anaesthesia (shown in Table 1), including restlessness. The restlessness observed in the subjects receiving $N_2O$ in this study was of such severity as to result in the abandonment of all the inductions in which restlessness occurred. The inductions which had to be abandoned due to complications in the 5% isoflurane group were due to respiratory complications (coughing and excess secretions), and

those in the halothane group due to both excessive movement and respiratory complications. This may indicate that as 5% isoflurane results in a faster RII than halothane, the subject spends less time in stage 2 of anaesthesia and therefore exhibits less of the complications associated with that stage ie restlessness/excessive movement. It is important to note that not one episode of desaturation or laryngospasm occurred during this study. This, together with the already noted cardiovascular stability, attests to the safety of RII.

In conclusion then, it can be stated that RII is a safe technique, which is well accepted by patients regardless of whether halothane or isoflurane is used. 5% isoflurane in oxygen produces the fastest RII, with a low rate of complications and abandoned inductions. The speed of induction approaches that associated with intravenous induction. This makes RII a viable alternative to intravenous induction as well as to CII. The study also shows that isoflurane is a useful alternative to halothane for RII. 2% isoflurane in $N_2O$ and $O_2$ offers no advantage over 5% isoflurane in oxygen in terms of speed of induction, and it is associated with marked restlessness during induction of anaesthesia. This is probably due to the presence of $N_2O$ in the inhaled gas mixture. A cooperative subject is required to carry out RII successfully and therefore, the technique is not useful in children and unwilling subjects. Until proven otherwise, it would be better to avoid RII also in subjects who are anxious or who smoke cigarettes. This study

proves that it is not necessary to heavily premedicate subjects in order to tolerate RII with isoflurane. This, together with the speed of induction obtained when 5% isoflurane is used, makes RII a potentially useful technique for day-case anaesthesia. It may be argued whether the improved speed of induction with isoflurane compared to halothane is clinically significant and whether halothane would therefore be as useful as isoflurane in this role. As intravenous agents would not be required if RII were used, it is possible that the slightly longer induction provided for by RII compared to the intravenous agents would be offset by a shorter recovery period in the subject receiving only volatile agent and no IV agents. This provides the basis for further study (ie. RII vs IV induction).

# APPENDIX

## SOME DEFINITIONS

### MINIMUM ALVEOLAR CONCENTRATION (MAC)

The alveolar concentration of agent at one atmosphere needed to abolish movement in 50% of subjects in response to a noxious stimulus [32].

### SECOND GAS EFFECT - (related to nitrous oxide)

During induction of anaesthesia with anaesthetic gases and volatile agents, uptake of nitrous oxide exceeds the elimination of nitrogen. This increases the alveolar concentrations of other gases, including oxygen and volatile anaesthetic agents. The uptake of the other gases is then enhanced due to the increased alveolar:blood concentration gradient [30,33].

### ASA CLASSIFICATION OF PHYSICAL STATUS [34]

| Class | Physical status |
|---|---|
| I | A healthy patient with no systemic disease process |
| II | A patient with a mild to moderate systemic disease process caused either by the condition to be treated surgically or other pathological process and which does not limit the patient's activities in any way eg. mild diabetic, treated hypertensive, or heavy smoker |
| III | A patient with a severe systemic disturbance from any cause, and which imposes a definite functional limitation on him or her eg. ischaemic heart disease with a limited exercise tolerance, severe chronic obstructive airways disease with dyspnoea on exertion |
| IV | A patient with a severe systemic disease which is a constant threat to life eg. the chronic bronchitic who is dyspnoeic at rest, advanced chronic liver failure |
| V | A moribund patient who is unlikely to survive 24 hr with or without surgery |
| E | Emergency operation. Any patient in any of the above classes who is operated on as an emergency is regarded as being in poorer physical condition, and the letter E is prefixed |

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