THE EFFECTS OF MIGLITOL ON THE PHARMACOKINETICS OF PHENYTOIN IN HEALTHY VOLUNTEERS

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of
Master of Science in Medicine

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DECLARATION

I, Denise Richardt, declare that this dissertation is my own work. It is being submitted for the degree of Master of Science in Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

.....D Richardt.....

.....2nd.....day of .....December....., 1996

PUBLICATIONS AND PRESENTATIONS

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ABSTRACT

The interaction between miglitol, an α-glucosidase inhibitor used as an adjunct therapy in diabetes, and phenytoin, an anticonvulsant primarily used in the treatment of epilepsy, was studied over 26 days. Twenty-four healthy male volunteers took part in a placebo controlled, double blind, cross-over study in two phases, to determine the effects of multiple 100mg doses of miglitol on a single 400mg dose of phenytoin sodium. Miglitol or placebo was administered three times daily from Day 1 to Day 5. Phenytoin was administered as a single dose on Day 3 of each phase, after which blood samples were taken at regular intervals. A washout period of 14 days separated the two phases. No difference was found in the AUC(0-t_n), AUC(0-∞), C_{max}, t_{max}, $t_{½a}$, $t_{½\beta}$, β or K_a. Ethnic differences were found in AUC(0-t_n) and AUC(0-∞) with no differences between treatments in the groups. Miglitol therefore does not affect the pharmacokinetics of a single dose of phenytoin, however differences in phenytoin concentrations between ethnic groups were apparent.

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GLOSSARY OF ABBREVIATIONS

AE	=	Adverse event(s)
ALT	=	Alanine aminotransferase
AST	=	Aspartate aminotransferase
AUC(0-t_n)	=	Area under the plasma concentration curve
AUC(0-∞)	=	Area under the plasma concentration curve with extrapolation to infinity
BPM	=	Beats per minute
C_{MAX}	=	Maximum concentration
CRF	=	Case report form
CV	=	Coefficient of variation
ECG	=	Electrocardiograph
GEOMEAN	=	Geometric mean
GEOSTD	=	Geometric standard deviation
GGT	=	Gamma glutamyltranspeptidase
LDH	=	Lactate dehydrogenase
LOQ	=	Limit of quantification
MCH	=	Mean cell haemoglobin
MCHC	=	Mean cell haemoglobin concentration
MCV	=	Mean cell volume
n	=	number
OTC	=	Over the counter
SAIMR	=	South African Institute for Medical Research
SD	=	Standard deviation

t_{MAX} = Time to maximum concentration

$t_{½a}$ = Absorption half-life

$t_{½\beta}$ = Elimination half-life

K_a = Absorption rate constant

β = Elimination rate constant

CHAPTER 1

1.0 INTRODUCTION

The number of drugs at the disposal of the clinician in the treatment of illness and disease, has increased exponentially in the past two decades, not only in prescribed medications but also in over the counter preparations. All indications suggest that this trend will increase even further in the future (Brodie & Feely 1988; May, Stewart, Cluff 1974). The potential of these drugs to cause adverse events when used simultaneously, has led to the insistence by regulatory authorities for the conduction of drug-drug interaction studies during the initial development of the drug, before the medication is registered for general use (Muller & Gundert-Remy 1994). The study of drug interactions has therefore become an important aspect in the development and registration of new drugs (Kuhlmann 1994).

Phenytoin is an anticonvulsant which is widely used for the treatment of generalised tonic-clonic and partial seizures. Phenytoin is also used as prophylaxis against seizures after neurosurgery or head trauma (Bauer 1982). Furthermore, the antiarrythmic properties of this drug has led to its use in the treatment of ventricular arrythmias and after myocardial infarcts (Bigger & Hoffman 1991). Due to the narrow therapeutic range (10 - 20mg/ℓ) and non-linear kinetics of the drug, a small change in dose at steady-state may elicit a large increase in the plasma concentration (McInnes & Brodie 1988). Adverse events have been reported when phenytoin was used concurrently with preparations which delay its absorption from the gastro-intestinal tract (GIT) resulting in inadequate therapeutic levels e.g. antacids or certain foods (Nation, Evans & Milne 1990). Drug interactions mainly involve either induction or inhibition of the enzymes of the cytochrome P_{450} pathway eg. isoniazid and rifampicin respectively, or by competitive

displacement from plasma protein binding sites (Brennan, Dehijia, Kutt, Verebely, McDowell, 1970; Miller, Porter, Greenblatt, 1979; Nation *et al* 1990).

In this study, the potential interaction between miglitol and phenytoin was studied. Miglitol is an α-glucosidase inhibitor used as an adjunct in the treatment of diabetes mellitus (Kennedy, Gerich, 1987; Taylor, Barker, Bowey, Canfield, 1986). The local action of miglitol in delaying the breakdown of complex carbohydrates in the GIT, could result in a reduced absorption of phenytoin in the small intestine. This action is possibly due to the presence of increased amounts of food in the GIT for extended periods.

As a result of the above, the examination of the effects of miglitol on a single dose of phenytoin in healthy volunteers is necessary. This report will encompass the structure of the interaction study with respect to the drugs phenytoin and miglitol, the properties of both phenytoin and miglitol, their respective roles and possible concomitant use in diabetics. The methodology used to determine an interaction will be described and the conclusions reached will be discussed with reference to the methods and relevance to the population.

1.1 DEFINITION AND MECHANISM OF DRUG INTERACTIONS

The modern drug armantarium includes drugs with complex and powerful effects with the potential for one drug to change the action of another (Brodie & Feely, 1988). An alteration in activity, can either benefit the patient, or cause adverse effect which range from mild and innocuous to life-threatening. However, most interactions are predictable and therefore preventable, while a few are life-threatening (Gibaldi 1991; May, Stewart & Cluff 1977; McInnes & Brodie 1988).

Patients being treated on multiple drug regimens are particularly at risk, with the likelihood of interactions increasing with the number and type of drugs being administered (May *et al* 1974, 1977; Muller & Gundert-Remy 1994; Smith, 1966; Steel, Gertman, Crescenzi Anderson 1981). The elderly are among those most severely affected as they often suffer from a number of diseases (Brodie & Feely 1988; McInnes & Brodie 1988; Muller & Gundert-Remy 1994). It has also been reported by Beers, Storrie and Lee (1990) that this portion of the population appear to be exposed to more adverse drug interactions through medication received at routine visits to their emergency departments. However, the knowledge that two or more of the prescribed drugs interact does not necessarily contraindicate their use. Adjustment of doses in these cases may be more appropriate than discontinuing essential therapy (Kuhlmann 1994).

Decisions on which drug interactions have to be investigated are taken during drug development and primarily include a limited number of drugs which affect vital processes eg. respiration, cardiac rhythm, clotting, blood pressure, glucose homeostasis and central nervous system functioning. In addition these drugs will more than likely have narrow

therapeutic ratios (Brodie & Feely 1988; Kuhlmann 1994; McInnes & Brodie 1988). Phenytoin and miglitol which are the subject of the present study, fall into the latter two categories, ie glucose homeostasis and central nervous system functioning. Table 1.1 lists examples of these drugs.

Table 1.1 Drugs at risk of interaction (from Brodie & Feely, 1988)

Type of effect	Examples of drugs
Major effect on a vital process	Warfarin, chlorpromazine,morphine
Steep dose-response curve	Verapamil, levodopa, chlorpropamide
Concentration dependent toxicity	Digoxin, lithium, aminoglycosides, methotrexate
Loss of effect leads to a breakthrough of disease	Quinidine, prednisolone, sodium valproate
Patient dependent on prophylactic action	Oral contraceptive, cyclosporin
Saturable hepatic metabolism	Phenytoin, ethanol, theophylline

These studies are usually performed during Phase II and III once sufficient information regarding pharmacokinetics, efficacy, safety and tolerability have been gathered. However, the current trend is to evaluate potential interactions as early as possible during development, preferably before the start of Phase II studies (Versavel 1994). Depending on the information gathered in preclinical studies, drugs affecting vital processes or having very narrow therapeutic indices require testing at an early stage of the clinical trial period. In some instances such studies may be crucial to the further development of the drug (Muller & Gundert-Remy 1994).

1.1.1 Mechanisms of interactions

The effects of two or more concomitantly administered drugs may take several different forms:-

1. The drugs may reduce the desired therapeutic effects and enhance adverse effects.

2. The drugs may intensify the desired as well as the undesired effects.

3. The drugs may, via similar or opposing mechanisms of action appear to have an increased effect, these are however classified as potential interactions (Aronson & Grahame-Smith, 1981).

A true interaction has been described to be a state when the combined effects of the interacting drugs are greater or less than the arithmetic sum of their individual actions (McInnes & Brodie 1988). The majority of these true interactions have however been shown to occur through a relatively small number of specific basic mechanisms. The interpretation, prevention and treatment of these interactions require a knowledge and understanding of the mechanisms and sites involved (Gibaldi 1991, Kuhlmann 1994, McInnes & Brodie 1988).

A further general classification which requires attention is that of an interaction between drug A and drug B where drug A will precipitate the interaction by one of mechanisms mentioned above, and thus the effects of drug B are either reduced or increased. For example, erythromycin inhibits hepatic enzymes in the cytochrome P_{450} pathway and

thereby precipitates a reduction in the metabolism of theophylline and phenytoin (Porter & Pitlick 1994). This results in elevated concentrations of the affected drug in the serum, with the attendant adverse effects on the patient. In some instances, the combination of two drugs, e.g. phenytoin and phenobarbitone, interact so as to alter the effect each has on the body (Aronson & Grahame-Smith 1981).

1.1.2 Pharmaceutic interactions

The first site of interaction can occur between the various constituents of the drug during its formulation. These are classed as pharmaceutic interactions. Drugs mixed in an intravenous infusion device e.g heparin or benzylpenicillin, may interact with the infusion solutions causing a loss of activity, especially when the infusion is administered over a period of several hours (Aronson & Grahame-Smith 1981; McInnes & Brodie 1988). Aronson and Grahame-Smith quote the example of ampicillin which is stable for only 2 hours after mixing with saline and dextrose. In the stomach the chelation or complexing of drugs with stomach contents is well known e.g. tetracyclines and fluoroquinolones. The solubility of these compounds is then altered and consequently the absorption and bioavailability may change (Muck 1994). The bioavailability of phenytoin is also affected in this way (Cacek 1986, McInnes & Brodie 1988). Although these interactions are classified as pharmaceutical and can be predicted and avoided by *in vitro* investigations, they have pharmacokinetic effects as well (Wienbeck, Bigiel, Barnert 1994). The effects of food and antacids on the absorption of phenytoin will be discussed more fully in the section dealing with the drug *per se* (section 1.3.1.2).

1.1.3 Pharmacokinetic interactions

The second aspect to be dealt with is pharmacokinetic interactions. These may affect the processes of absorption, distribution, metabolism or excretion. The results of such interactions lead to alterations in the basic pharmacokinetic parameters of the drugs, ie. absorption and elimination half-lives, bioavailability, volume of distribution, renal clearance (leading to an alteration in the fraction excreted renally), and similarly hepatic clearance and faecal fractions (Aronson & Grahame-Smith 1981: Kuhlmann 1994). However, in drugs that show a high degree of interpersonal variation eg phenytoin, interactions may be difficult to predict.

As this project deals with a possible alteration in the absorption process, this aspect will be discussed in more detail. In Table 1.2, the general effects of a disturbance in absorption are described.

Table 1.2 Effects and implications of a disturbance in the absorption process (McInnes & Brodie 1988; Weinbeck *et al* 1994)

MECHANISM OF INTERACTION	EFFECT ON PHARMACOKINETICS
1. Luminal effects chelation - anionic exchange resins eg. cholestyramine binds acidic drugs complexes - antacids form insoluble complexes with tetracycline, iron, prednisolone	Decreased absorption
2. Delayed gastric emptying - anticholinergics, opioids	Decreased C_{max} and t_{max}. - drugs inactivated or degraded in gut - decreased total bioavailability - may increase overall bioavailability - increased time for absorption
3. Rapid gastric transit time	Increased bioavailability - water soluble drugs - formulations with low dissolution rate
4. Gut wall effects - mucosal damage produced by cytotoxic drugs - methotrexate, vinblastine	Reduced bioavailability of poorly soluble substances e.g. phenytoin
5. Alteration in bacterial flora - broad-spectrum antimicrobial agents	Disruption of enterohepatic cycling e.g. oral contraceptive Reduction of bacterial drug deconjugation e.g. digoxin
6. Alteration of composition and volume of GIT fluids	Disruption of absorption - ? miglitol

As can be seen from the above table, if the absorption of the drug is disturbed, the concentration at its site of action is reduced. Where the half-life of the drug is long, the change in the rate of absorption may have little clinical relevance if the relative bioavailability is unaffected. However, if the drug has a short half-life, a delay in absorption can be extremely relevant, as for example with some analgesics. Similarly an antimicrobial requires specific concentrations at the site of action and disturbances in this area can have serious clinical consequences (Aronson & Grahame-Smith 1988; Latocha 1994; McInnes & Brodie 1988). Versavel (1994) quotes the innocent use of

anticholinergics by patients with Parkinson's disease taking levodopa. The anticholinergics delay gastric emptying and result in a decrease in the absorption of levodopa.

1.1.4 Pharmacodynamic interactions

The effects of pharmacodynamic interactions are difficult to classify and while some effects may be utilised to the benefit of the patient, others are responsible for unexpected morbidity (Brodie & Feely 1988; McInnes & Brodie 1988). The most common interaction in this area is synergism between two drugs acting on the same system, organ or enzyme. This can be to the benefit of the patient e.g. gentamicin and penicillin in the treatment of bacterial endocarditis. However the converse is also true and the use of non-steroidal anti-inflammatory agents, especially the salicylates, combined with warfarin will lead to a potentiation of the anticoagulant effects of warfarin (Aronson & Grahame-Smith 1981; Brodie & Feely 1988; McInnes & Brodie 1988).

As a result of the increased awareness of drug interactions, many of these drug-drug interactions are now predictable and unwanted adverse events can be avoided by either adjusting the dosage or dosing interval regimen, or simply by avoiding the use of certain combinations.

The clinical relevance of such interactions must however be assessed using different criteria. For example, the relationship between beneficial effect and risk to the patient must be evaluated in each situation. Life threatening adverse effects such as arrhythmias and haemorrhages are more carefully monitored than others which cause only slight

discomfort to the patient (Adelmann 1994). Similarly, interactions between drugs which are often administered concomitantly and at the usual therapeutic doses are more relevant clinically than interactions between drugs at very high doses or rare combinations.

1.1.5 Factors influencing drug interactions

Other factors influencing the risk of interactions are:

- drugs with steep courses in the dose-response curve (Kuhlmann 1994);
- drugs with highly specific effects e.g. warfarin (Kuhlmann 1994);
- a summation of the same effect by two concomitantly administered drugs (Boston Collaborative Drug Surveillance Program 1972; Brodie & Feely 1988; McInnes & Brodie 1988);
- drugs with narrow therapeutic ranges especially when they are used in combination e.g. the oral antidiabetic - glibenclamide (Adelmann 1994; Versavel 1994);
- pharmacokinetics which are unpredictable or which have very high degrees of interpatient variations. e.g. phenytoin (McInnes & Brodie 1988);
- the effects of long term therapy with respect to enzyme induction or accumulation which are often synonymous with a higher risk of clinically relevant interactions e.g. carbamazepine (Kuhlmann 1994; Versavel 1994);
- simultaneous prescribing of several drugs by several physicians (this aspect is especially true in the elderly or illiterate population who are unable to recall their drug regimens) (Aronson & Grahame-Smith 1988; Kuhlmann 1994);
- the probability of self medication by the patient (Kuhlmann 1994).

In an effort to elucidate the potential problems associated with multiple drug therapy, interaction studies are undertaken during the development of the compound. However, appropriate design and analysis are vital if a true interaction or lack of interaction is to be adequately proven.

1.2 DESIGN OF INTERACTION STUDIES

1.2.1 Bioavailability versus bioequivalence

Drug interaction studies are commonly carried out where drugs are likely to be given concomitantly and Drug A affects the absorption of drug B, both drugs use the same metabolic pathway, e.g. cytochrome P_{450} enzymes, which have a narrow therapeutic range or compete for protein binding sites. These are in effect "lack of interaction" studies according to Steinijans, Hartman, Huber & Radtke (1992c). To prove no difference between the bioavailability with concomitant administration of Drug A + B (test) versus Drug A alone is not sufficient to protect the patient. In addition, bioequivalence must be proven for test versus reference i.e. that they differ only in the clinically accepted range of 80 - 125% of the ratio of test/reference with respect to the rate and extent of absorption (Gibaldi 1991; Kroboth 1986; Shargel & Yu 1993; Steinijans, Sauter, Jonkman, Schultz, Stricker, Blume 1992a).

To prove bioequivalence, the extent and rate of absorption of the interacting drugs are measured, whereas in bioavailability studies only the extent of absorption is considered (Gibaldi 1991; Shargel & Yu 1993). This is accomplished by determining the concentration of the drug in the circulation at frequent intervals following administration. The resulting values are viewed as a concentration versus time curve. The degree of

equivalence of the two drugs is determined by the amount of variance shown in the curves (Gibaldi 1991; Shargel & Yu 1993).

Conventionally, bioequivalence is confirmed when the following pharmacokinetic parameters which determine the rate and extent of absorption of the test drug are within 20 % of the reference product:

- the areas under the plasma concentration curve to the last measurable concentration [AUC(0-t_n)] and extrapolated to infinity [AUC(0-∞)],
- the maximum concentration achieved in the blood (C_{MAX})
- the time to reach maximum concentration (t_{MAX}) (Gibaldi 1991; Steinijans *et al* 1992a)

These pharmacokinetic parameters are calculated from the concentration versus time curves. A difference of no more than 20% in the preceding parameters to prove bioequivalence has been agreed upon by international regulatory authorities, the Food and Drug Administration (FDA) (Gibaldi 1991), the International Association of Pharmaceutical Technology (APV) which controls European standards (Schultz & Steinijans 1992). These guidelines are followed by the Medicines Control Council in South Africa.

The percentage difference required for equivalence can however vary, with a smaller difference being required for drugs with a narrow therapeutic window. The opposite is true for drugs with a large therapeutic index (Shargel & Yu 1993; Steinijans *et al* 1992a). The current requirements of demonstrating bioequivalence for the AUC to within 20% of the comparative product has however been challenged as being too lenient, and the use

of a 10% difference has been advocated, while the opposite is the case for C_{MAX}. In this instance it is considered that C_{MAX} values are more variable than AUC values and should therefore not be judged as stringently (Gibaldi 1991).

Pharmacokinetic parameters may be assessed by measuring the drug in either the plasma or the urine depending on the metabolism of the drug, however Gibaldi (1991) advocates that the measurements be extracted from blood data. Consequently, in the present study, plasma data was used to measure the equivalence parameters. Bioequivalence studies invariably use panels of healthy volunteers, but in certain circumstances e.g. cancer chemotherapy, where cytotoxic drugs are being evaluated, only affected patients can be used for ethical reasons (Gibaldi 1991).

1.2.2 Single versus multiple dose studies.

Drug interaction studies usually follow the cross-over design, where each volunteer receives both drug regimens. In this way interpersonal differences are controlled to a certain extent as each volunteer serves as his own control (Kroboth 1986; Steinijans *et al* 1992a, 1992c).

The studies are performed either as single, multiple or single/multiple dose studies. In the latter design multiple doses of Drug A is administered for about five half-lives. A single dose of Drug B is then given and blood concentrations monitored. This compromise takes advantage of the best aspects of single and multiple dose studies (Kroboth 1986). As the clearance of the drug is central to the calculation of the AUC (see relationship below), and clearance shows intra-individual variation, the study should

be kept as short as possible.

$$AUC(0\text{-}\infty) = F.D / Cl_{tot}$$

and $$Cl_{tot} = k.\ V_d$$

thus $$AUC(0\text{-}\infty) = F.D / k.V_d$$

where F = fraction of the dose absorbed; D = dose; k = elimination rate constant and V_d = volume of distribution (Shargel & Yu 1993, Steinijans *et al* 1992a).

An essential requirement in single dose studies is an adequate wash-out period between study periods to eliminate the possibility of carry-over effects into the second phase, of the drug given in the first phase of the study. At least 4 to 5 half-lives must be allowed between study periods. This is often a shortcoming in such studies leading to false positive or negative results. The washout period is however unnecessary in multiple dose studies where the change-over from one formulation to the other can take place at steady state (Steinijans *et al* 1992a). Further, sampling periods should be sufficiently long and regular to get reliable estimates of the terminal half-life, and to ensure that there are no gaps in the overnight sampling, where concentrations may have dropped below the level of quantification. These problems are again not encountered in multiple dose studies where sampling is done during a repetitive dosing cycle and concentrations are well above the limit of detection (Steinijans *et al* 1992a, 1992c).

Single dose studies are recommended where the effects of food are to be evaluated. In these studies, the volunteers are alternatively fasted and fed before receiving either the test or the reference drug (Kuhlmann 1995). In addition, where the drug to be investigated causes significant adverse effects, induces or inhibits enzymes, or has a very long half-

life, multiple-dose studies in healthy volunteers are discouraged. However, there are currently researchers who advocate the use of multiple dose studies as they are more indicative of the therapeutic situation and are able to detect interactions relating to metabolic processes, which are not possible in single dose studies (Rameis 1992). These studies also require fewer blood samples, are therefore more cost effective, and may require less sensitive analytical assay techniques, since plasma concentrations are relatively high (Steinijans *et al* 1992a).

The present study was conducted as a single dose study mainly because an interaction between phenytoin and miglitol is related to food and its breakdown in the GIT. Secondly, phenytoin has significant adverse effects, induces liver enzymes and shows non-linear kinetics resulting in either a long run-in period or bolus doses which will attain stable phenytoin levels at steady-state (Goff, Spunt, Bellur, Fischer 1984). In addition, the administration of bolus intravenous loading doses has been associated with serious adverse effects such as cardiac arrhythmias and hypotension (Earnest, Marx, Drury 1983). The infusion rate must therefore be strictly controlled and the patient closely monitored for toxicity. This limits its application in non-hospital situations (Goff *et al* 1984). The use of an oral loading dose is also problematic. Goff reports that although the toxic effects of phenytoin were reduced in his study, the administration of high loading doses resulted in slow, erratic and highly variable absorption. It is therefore preferable to conduct multiple-dose studies in patients whose seizures are controlled on phenytoin (Randinitis, Buchanan, Kinkel 1990). The multiple-dose studies conducted also offer the advantage of recording medication related adverse effects and control of seizures during the study period (Randinitis *et al*, 1990).

1.2.3 Statistical design and analysis

The importance of suitable statistical analysis was investigated by Smith, Krobboth and Juhl (1986). These researchers analyzed the results of drug interaction studies published during 1984 in which 62% of the investigators found no interaction. On closer inspection however, it appeared that the results were inconclusive as the number of patients evaluated in these studies were inadequate to predict a true change in drug action. These "failed" studies emphasise the importance in achieving a statistical power of at least 80% to ensure the detection of a 20% difference. This point is demonstrated by the pharmacokinetic study of three phenytoin sodium products carried out by Goff *et al.* in 1984. In their publication, they state that the statistical power in their study was limited by the small number of subjects and large intersubject variations. The significant differences among the treatment groups may thus have gone undetected.

The calculation of sample size has been debated at length because of its importance in maintaining the power of the study. This is vital if the risk to both patient and pharmaceutical company is to be kept to the minimum. Diletti, Hauschke and Steinijans (1992) have addressed this problem by investigating and reviewing the statistical methods used in these determinations, and have made recommendations which have been found acceptable by international regulatory authorities. These recommendations were followed in the present study.

The parametric analysis of AUC and C_{max} has been described by Steinijans and Hauschke (1992). This includes the application of a multiplicative model to the data with the assumption of a logarithmic normal distribution. This is only possible if the data is

transformed due to the "skewed distribution of the untransformed characteristics AUC and C_{max} with a long tail of higher values" (Steinijans & Hauschke 1992).

It is clear from the above remarks that the statistical analysis of pharmacokinetic data has become an extremely complex exercise which demands an above average statistical knowledge and expertise. So much so that this kind of biostatistics has become a specialised branch of statistics as a whole (Westlake, 1971, 1972).

1.3. PHENYTOIN

Although having existed since 1908, the use of phenytoin as an anticonvulsant drug was only recognized much later in 1938. The definitive property which singled out phenytoin from other anticonvulsants available at the time, was the lack of sedation at therapeutic doses. Today it remains one of the most widely used anticonvulsants for the treatment of generalised and partial seizures (Alldredge 1992; Rall & Schleifer 1991).

1.3.1 Chemical structure and physical properties

Phenytoin (also known as diphenylhydantoin, DPH) is a hydantoin derivative with the following chemical structure:-

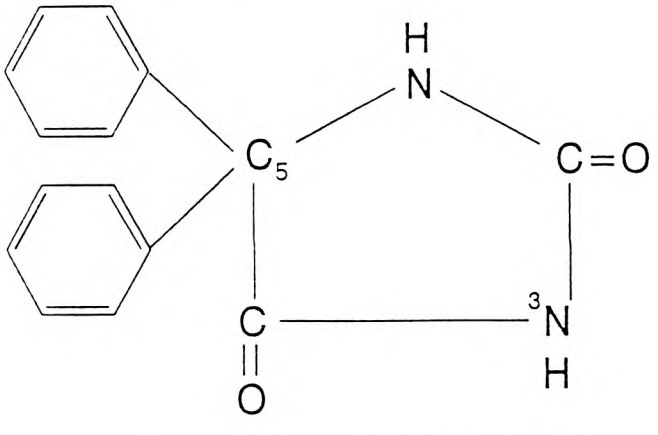

Figure 1.1 Chemical structure of phenytoin. (Porter & Pitlick 1995)

Similarities between the antiepileptic drugs as a whole, were reported by Porter and Pitlick (1995) to contribute to their antiepileptic activity. Of the approximately 16 antiepileptic drugs used most often, 13 have very similar basic chemical structures. These drugs have in common a heterocyclic ring structure with different substituents (Figure 1.2).

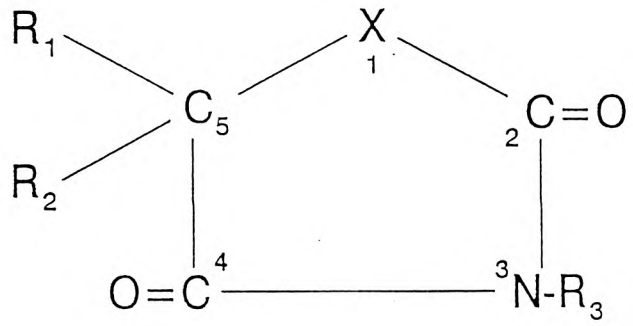

Figure 1.2. Basic antiepileptic heterocyclic ring structure (Porter & Pitlick 1995)

At the X position, the following substituents are found:-

-N- = hydantoin derivatives = phenytoin, mephenytoin

-C-N- = barbiturates

-C- = succinimides e.g. ethosuximide

The R_1, R_2 and R_3 positions vary within each subgroup. Very small changes in the structures of these drugs alter significantly the mechanism of action and clinical properties. Porter and Pitlick (1995) explain that the efficacy of an antiepileptic against partial seizures is determined by the presence of at least one phenyl ring in the hydrophobic region. However the addition of further groups in this region reduces solubility and in phenytoin two phenyl groups added at C_5 increase the antiepileptic

activity but also result in reduced solubility (Porter & Pitlick, 1995: Rall & Schleifer 1991).

Phenytoin is a weak acid with an apparent pK_a of 8.06 to 8.33. It is soluble in hot alcohol, slightly soluble in cold alcohol and the aqueous solubility is poor even in the small intestine, the major site of absorption. Phenytoin sodium occurs as a white hygroscopic salt which is freely soluble in water and warm propylene glycol, and soluble in alcohol. Because of its stability in propylene glycol, the injectable phenytoin sodium is combined in a sterile solution of 40% propylene glycol, 10% alcohol and water. The pH is adjusted to 12 as free phenytoin precipitates at a pH of 11.5 or less at which stage the injection should not be used (Alldredge 1992; Martindale 19??).

1.3.2 Mechanism of action

At therapeutic levels, phenytoin blocks neuronal sodium and calcium conductance in a similar manner to that of the local anaesthetics, resulting in a suppression of repetitive action potentials (Alldredge 1992; Porter & Pitlick 1995; Rall & Schleifer 1991). In high concentrations, i.e. above 10μM, phenytoin may indirectly affect GABA-mediated inhibition by decreasing the uptake of GABA, increasing the number of GABA receptors, increasing the breakdown of acetylcholine and suppressing excitatory amino acid release. At this concentration the drug delays K^+ outflow from the neuron, leading to an increased refractory period (Rall & Schleifer 1991). The drug also has an affect on the concentrations of various neurotransmitters, noradrenaline and serotonin by inhibiting their release, on dopamine by promoting the uptake and on monoamine oxidase by inhibiting its activity (Porter & Pitlick 1995).

The antiepileptic effects of phenytoin are accomplished without general depression of the central nervous system (CNS). From the above description of its effects on CNS neurons, the drug can limit the development of maximal seizure activity and reduce the spread of the seizure focus (Alldredge 1992; Rall & Schleifer 1991). Phenytoin does not have any affect however on the prodromal signs of a seizure nor does it eliminate the sensory aura which precedes the attack (Rall & Schleifer 1991).

1.3.3 Pharmacokinetic properties

The pharmacokinetics of phenytoin are dependent on its limited aqueous solubility, inactivation by microsomal enzymes, dose dependent elimination and formulation (Porter & Pitlick 1995; Rall & Schleifer 1992). Difficulties in predicting doses required by epileptic patients include variations in absorption and distribution, interindividual differences in the elimination rate, the non-linear kinetics of phenytoin, drug interactions and changes in these parameters due to other disease states (Gugler *et al.* 1992).

1.3.3.1 Absorption and bioavailability

Although the reported pK_a of phenytoin is 8.31, this has little effect in the acidic pH of the stomach due to the insolubility of the drug. Even in the alkaline environment of the proximal part of the small intestine, phenytoin is relatively insoluble, and it is the amount of fluid in the intestine and therefore the gastrointestinal dissolution which limits its absorption (Alldredge 1992; Gibaldi 1991; Marvel & Bertino 1991). The sodium salt preparation of phenytoin is usually slowly but completely absorbed from the GIT. However the bioavailability varies along with the formulation and shows marked interindividual variation (Alldredge 1992; Gibaldi 1991; Gugler *et al.* 1992; Martindale

1989; Rall & Schleifer 1992; Winter 1988). Particle size and excipients affect both the rate and extent of absorption (Manson, Beal, Magarey, Pollard, O'Reilly, Sansom 1975; Porter & Pitlick 1995; Smith & Kinkel 1976). In addition the drug undergoes enterohepatic cycling and is subjected to capacity limited metabolism which will be dealt with later in this report (Alldredge 1992; Marvel & Bertino 1991; Porter & Pitlick 1995; Rall & Schleifer 1991).

Due to the effects of a saturable metabolic and elimination process on bioavailability, the AUC of a single dose does not reflect the AUC at steady state or after the enzyme pathways have been saturated. At low systemic concentrations at the beginning of drug absorption, the rate of metabolism and elimination is first order and small dosage changes cause a proportional increase in the blood level. However, as more drug is absorbed either from a single or from multiple doses, the concentration of the drug increases to levels that saturate the enzymes involved in elimination. As the clearance of the drug from the body changes, the AUC increases disproportionally to the increase in the dose (Alldredge 1992; Gibaldi 1991; Shargel & Yu 1993).

The slow absorption rate leads to delays in the attainment of peak concentrations (C_{max}), even when loading doses of 1 gram are given, C_{max} will only be reached in 24 hours; if these doses are increased to 1600mg, the C_{max} can be delayed by up to 30 hours (Winter *et al.* 1988). This situation was researched in a study by Goff *et al.* (1984) and the use of divided oral doses was advocated instead of the usual intravenous bolus dose. In this study, C_{max} was achieved faster ie. within 6 hours as opposed to approximately 24 hours in a previous trial using the same loading dose. In addition, the use of the oral

formulation instead of the intravenous form resulted in fewer adverse effects (Goff *et al.* 1984).

The low water solubility of phenytoin also results in the precipitation and crystallization of the drug at the site of an intramuscular injection causing local tissue damage. The absorption from an intramuscular injection is in addition slow and erratic and for these reasons, this route of administration is avoided (Alldredge 1992; Porter & Pitlick 1995; Rall & Schleifer 1991).

The integrity of the intestinal mucosa plays a significant role in the uptake of drugs. Gibaldi (1991) describes the change in absorption which occurs when a malabsorption syndrome is present. This can be either a physical condition or may be drug induced as is the case with the cytotoxic drugs e.g. cisplatin, vinblastine and bleomycin. These drugs have been reported to cause epithelial damage to a degree where the absorption of phenytoin was impaired to an extent that serum levels were low and seizure control poor despite high oral doses of phenytoin (Gibaldi 1991).

Chronic alcoholism has been reported to lead to a "leaky gut" (Gibaldi 1991) in which case intestinal permeability has been shown to be elevated compared to controls. This increased permeability may persist for more than 2 weeks after the cessation of drinking and has led to the uptake of compounds which do not usually have absorbent properties. At the same time Gibaldi reports that studies on patients with histologic evidence of intestinal injury, have shown no difference in the intestinal absorption of drugs by passive diffusion. Surgical resection can however dramatically increase the doses of phenytoin

required to maintain adequate blood levels. In epileptic patients with an ileojejunal bypass, absorption was only 30 % of normal (Gibaldi 1991).

The effects of formulation on the bioavailability of phenytoin will be discussed in Section 1.3.4. The administration of phenytoin concomitantly with food, antacids and minerals has been the subject of many clinical trials which have led to controversies. These will be dealt with in the following section.

1.3.3.1.1 Effects of food, antacids and minerals on the bioavailability of phenytoin

The essential definition of bioavailability is the rate and extent to which therapeutically active ingredients reach the blood and become available at the site of action (Cacek 1986; Kuhlmann 1994; Shargel & Yu 1993). The absorption of phenytoin is a complex process dependant on factors such as the rate of disintegration and dissolution of the drug, as well as physiological properties such as the pH and properties of the gastrointestinal fluids and integrity of the membranes. In addition the passage time through the GIT will determine the relative and absolute bioavailability of phenytoin. Furthermore, according to Winter *et al.* (1988) bioavailability is affected by the capacity-limited metabolism of phenytoin.

It has been shown that the absorption of phenytoin is increased in the presence of food (Cacek 1986; ; Gugler *et al.* 1992; Kuhlamnn 1994; Randinitis *et al.* 1990). The reasons for this may be firstly that as phenytoin is poorly soluble and the presence of food in the stomach delays gastric emptying, a higher percentage of the drug may dissolve in the stomach before it passes through to the duodenum. This point is however

disputed by Goff *et al* (1984) who explain that phenytoin sodium is changed to phenytoin acid which precipitates in the acid medium of the stomach. Secondly, the duodenum is the primary site of absorption for phenytoin and here the increased contact time of the drug with the absorbent surface may lead to increased uptake (Kuhlamnn 1994). The increased absorption of poorly soluble drugs with food appears to be a generally accepted theory (Cacek 1986). An additional theory postulated by Melander in 1978, was that the enhanced absorption may in addition to increased drug dissolution, be due to increased splanchnic blood flow and saturation of first pass metabolism.

However, Randinitis *et al.* (1990) noted a slower rate of absorption in non-fasted compared to fasted subjects with the mean t_{max} and C_{max} values being 33% longer and 16% higher respectively in nonfasted subjects. The amount of drug absorbed as determined by the AUC(0-∞) was similar in both groups. It must be pointed out that Randinitis *et al.* administered the dose of phenytoin with milk during the meal and in addition the meal contained 8 ounces of milk. The fasting subjects received their dose of phenytoin with water.

The effects of antacids on the absorption of phenytoin have been described as variable. The overriding conclusion at present appears to support the conclusion that antacids may inhibit the absorption of phenytoin in a dose related relationship (Cacek 1986; Garnett, Carter, Pellock 1980). The mechanism of this inhibition has been proposed as being due to chelation to antacid cations, altered solubility of phenytoin in the duodenum or adsorption of the drug into the antacid preparation.The laxative effects of the antacid may also result in accelerated GIT motility and thus reduced phenytoin uptake (Cacek 1986).

With regard to the effects of minerals on phenytoin absorption, Cacek (1986) report that aluminium, calcium, copper and cobalt appear to chelate with phenytoin and thereby reduce its absorption in the GIT. It is therefore possible that the delay in absorption of phenytoin in the Randinitis *et al.* study (1990) was due to the chelation of phenytoin with or adsorption to the calcium in the milk.

1.3.3.1.2 Enteral feeding and phenytoin bioavailability

Alterations of phenytoin blood levels were first noted and reported by Bauer in 1982 where neurosurgery patients with head trauma were fed using nasogastric enteral food preparations (Osmolite®). These patients were also receiving oral phenytoin through the nasogastric tube for the treatment or prophylaxis of epilepsy caused by head trauma or neurosurgery. Although doses of phenytoin were adequate in therapeutic terms (300 to 400mg per day), subtherapeutic blood levels were being recorded. Even when dosing had been increased as high as 800 to 1200mg per day, levels of less than 2.5μg/ml were measured in two-thirds of the patients. On discontinuation of enteral feeding, the same patients showed signs and symptoms of toxicity.

Subsequent investigations showed that firstly, the enteral feeding solution inhibited the absorption of phenytoin (Hatton, 1984; Maynard, Jones, Guidry 1987; Guidry, Eastwood, Curry 1989). Maynard *et al.* established that the substitution of a meat based tube feeding (Compleat Modified®) instead of the protein hydrosylates (Osmolite®) led to an improved absorption of the drug. These findings were confirmed by Guidry *et al.* (1989) who propose that the major difference between the formulas is the quantity of dietary

fibre, the meat base containing 3.4 grams per 8 ounces while the protein hydrosylate formula contains none. They further postulate that the dietary fibre may either alter gastrointestinal transit time or bind and inactivate the substance in the feedings which bind phenytoin (Guidry *et al.* 1989).

Conversely, Krueger, Garnett and Comstock (1987) reported no difference in phenytoin absorption using a complex feeding formula (Ensure®). Subsequently in 1991, Marvel and Bertino conducted a controlled study evaluating an elemental (Vivonex TEN®) and complex enteral feeding formulation (Ensure®). They found no difference between the AUCs of phenytoin in either regimen compared to the control. These authors do not state the quantity of dietary fibre (if any) contained in the two products used in their study so no correlation can be made between the conclusions of Guidry *et al.* (1989) and Marvel and Bertino (1991).

In unpublished observations, Cacek (1986) proposed another possible mechanism whereby the phenytoin suspension physically may adhere to the feeding tube. It appears that the controversy has not been resolved and although Marvel and Bertino acknowledge that the situation is unresolved as regards the enteral feeding and the bioavailability of phenytoin, they can only offer possibilities as explanations (Marvel & Bertino 1991). Both of these studies were conducted according to strict criteria and the methodology appears sound. The results shown above emphasise once again the variability of absorption seen with phenytoin use and serve as a reminder of the interpatient differences which must be taken into account.

1.3.3.2 Distribution, Metabolism and Elimination of phenytoin

Once absorbed, phenytoin is rapidly distributed to the tissues and fat forms a storage site for the drug. In the blood, protein binding is approximately 90%, primarily to albumin. Conditions such as renal failure, hypoalbuminemia and the presence of displacing drugs, can alter protein binding, increasing the free fraction and volume of distribution. Phenytoin is also highly bound to brain proteins and the concentration in the cerebro-spinal fluid is proportional to that in the plasma (Alldredge 1992; Nation *et al.* 1990; Rall & Schleifer 1991).

The metabolism of phenytoin to 5-phenyl-5-hydroxyphenylhydantoin (*p*-HPPH) is an aromatic hydroxylation process as described in Figure 1.4, the 5-phenyl-5-hydroxyphenylhydantoin compound is in turn conjugated using glucoronic acid (Gibaldi 1991; Nation *et al.* 1990). The glucoronide conjugate and the para-hydroxylated metabolite *p*-HPPH, are excreted in urine and account for 60 to 90% of the total oral dose (Nation *et al.* 1990).

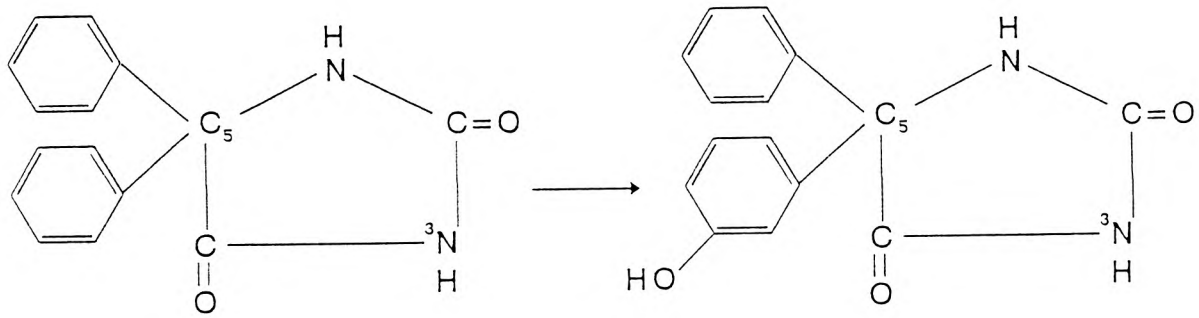

Figure 1.3 Aromatic hydroxylation of phenytoin to 5-phenyl-5-hydroxyphenylhydantoin (Gibaldi 1991).

Metabolism and elimination of phenytoin follow a non-linear model. At low doses, phenytoin clearance is first order, but as the concentration of the drug increases, the capacity-limited pathway involved in the metabolism of phenytoin utilizing the cytochrome P_{450} enzymes becomes saturated. This elimination is described by Michaelis-Menten kinetics where if C_p is the concentration in the plasma, then the elimination rate may be described as the change of concentration divided by the change in time

$$\text{Elimination rate} = - d\,C_p / d\,t$$

$$\text{thus:} \quad - d\,C_p / d\,t = V_{max} \,.\, C_p / K_m + C_p$$

$$\text{and} \quad \text{Rate of metabolism} = V_{max} \,.\, C_p / K_m + C_p$$

where V_{max} is the maximum elimination rate, K_m is the Michaelis constant, the concentration of the drug at which the rate of metabolism is one half of maximum. $1/K_m$ shows the affinity between the substrate (phenytoin) and the enzyme. It is the values of V_{max} and K_m which are dependent on the enzymatic process involved (Gibaldi 1991; Shargel & Yu 1993). Gibaldi quotes a study which suggested that the apparent K_m in patients is around 4mg/ℓ while the therapeutic range for the drug is 10 - 20mg/ℓ. Therefore when the drug concentration C_p is large in relation to K_m, saturation of the enzymes occur and the rate of elimination proceeds at a constant rate equal to V_{max}. The elimination then becomes a zero-order process.

$$- d\,C_p / d\,t = V_{max} \,.\, C_p / C_p = V_{max}$$

In phenytoin, because the drug tends to saturate the hepatic mixed function oxidases at higher therapeutic doses, the elimination kinetics of small doses are first-order, mixed at higher doses, and approach zero-order at very high therapeutic doses (Shargel & Yu 1993). Because the time required to decrease the concentration of the drug in the blood by 50% increases with increasing dose, the elimination half-life is dose-dependent or rather in the case of phenytoin, concentration-dependent. The calculation of the concentration half-life also stems from the clearance, therefore if

$$\text{Clearance}_{\text{phenytoin}} = V_{max} / K_m + C_p$$

and $$t_{½} = (0.693).\ V_d / Cl$$

substituting the values for clearance

$$t_{½\text{phenytoin}} = (0.693)\ .\ V_d\ .\ K_m\ .\ C_p / V_{max}$$

(Winter *et al.* 1988)

If patient specific values for V_{max} and K_m are not known, then population estimates of V_{max} = 7mg/kg/day for adults and K_m = 4 mg/ℓ may be used (Alldredge 1992).

1.3.4 Effects of formulation

Phenytoin is available in South Africa as a sodium salt in tablet and injectable forms or as a base in suspension (South African Medicines Formulary 1996). However, absorption and bioavailability vary markedly for the different pharmaceutical formulations (Tsai, Lai, Yang Huang, 1992; Rall & Schleifer 1991; Sansom, O'Reilly, Wiseman, Stern & Derham 1975; Winter 1988). The bioavailability of phenytoin is largely dependent on the manufacturing process and formulation can significantly alter bioavailability (Cacek 1986). Factors such as particle size, shape, salt form, dosage form

and product excipients can modify gastrointestinal absorption. Due to the narrow therapeutic index of 10 - 20 ml/ℓ, the bioavailability of phenytoin is crucial for the maintenance of therapeutic levels and the interchange of formulations can lead to therapeutic failure or intoxication (Gibaldi 1991; Koren, Brand, Daney, Halkin 1982; Tsai *et al.* 1992; Tyrer, Eadie, Sutherland, Hooper 1970).

An epidemic of phenytoin intoxication occurred when the excipient used in a phenytoin formulation was changed from calcium sulphate dihydrate to lactose (Tyrer *et al.*(1970). Patients were admitted to hospital in Brisbane Australia, following severe signs of intoxication. Ataxia of gait, double vision and vomiting were reported in these patients and 87% presented with phenytoin serum concentrations above 20μ/ml. 43% of these were in the range from 30 - 49μg/ml. The relationship between the change of excipient and the phenytoin concentration achieved in an epileptic patient is shown in figure 1.3. Similar evaluations were carried out in a further 3 patients with the same results. In all instances the preparation with the lactose excipient produced substantially higher serum phenytoin concentrations than with calcium sulphate (Tyrer *et al.* 1970). A subsequent cross-over study revealed that calcium sulphate produced lower blood levels of phenytoin than the combination of phenytoin and lactose (Gibaldi 1991). The presumption is that the change in excipient in the reformulated product led to a greater bioavailability and a higher incidence of adverse effects.

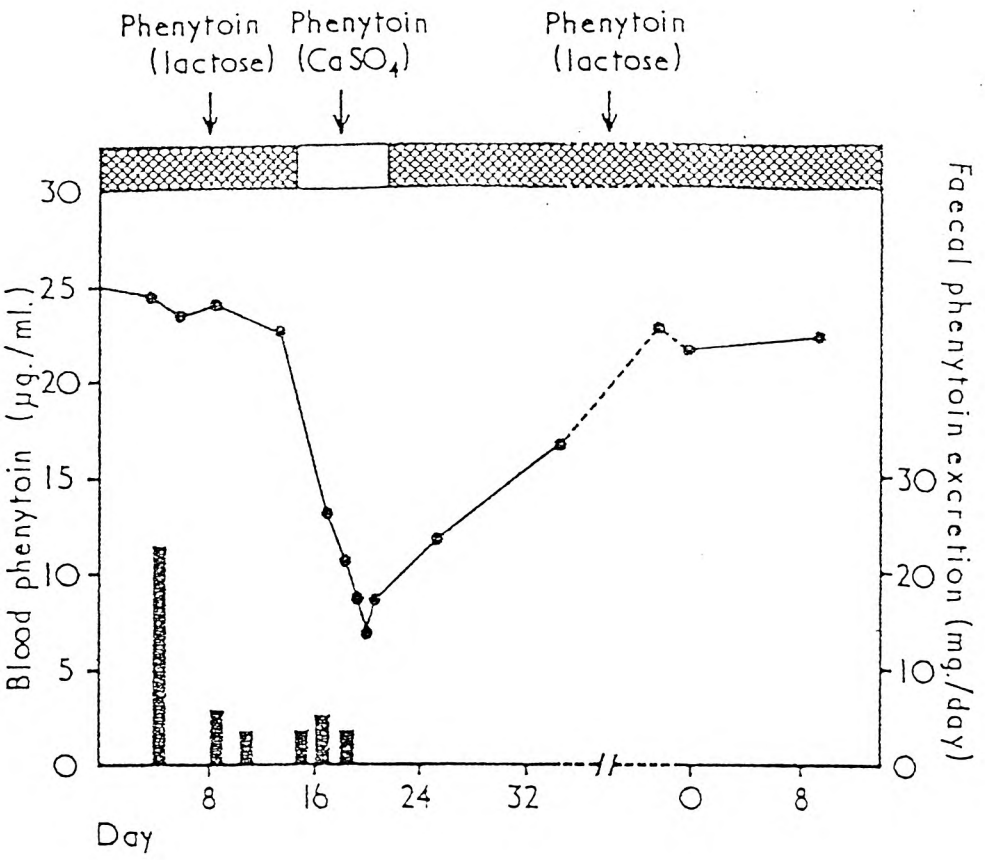

Figure 1.4 Blood phenytoin concentrations in a patient taking 400mg phenytoin per day. The excipients in the formulation are shown. Faecal excretion of phenytoin per day is represented by vertical columns (From Tyrer *et al.* (1970)

In 1986, Cacek reported that the differences in dissolution between various formulations have resulted in bioinequivalence between prompt and sustained release products. Over the past 20 years, the same conclusions have been reached by various researchers using the spectrum of phenytoin formulations. The differences between suspension and oral capsules or tablets was tested by Sansom, O'Reilly, Wiseman, Stern and Derham (1975). They compared a 300mg daily dose of capsules and tablets containing phenytoin sodium with a suspension containing the free acid form of phenytoin. The phenytoin plasma concentration of the suspension at steady state was double that of the capsules and tablets,

28.6 μg/ml versus 13.8, 15.9 and 18.1 μg/ml. They have ascribed the elevated plasma phenytoin concentrations resulting from the doses of suspension to the smaller particle size of the free acid in the suspension. Winter *et al* (1988) also report the same difference in the bioavailability of the acid to the sodium form of phenytoin.

In the same year that Samsom *et al* were carrying out their study, Manson, Beal, Pollard, O'Reilly and Sansom (1975) undertook an evaluation of phenytoin capsules versus tablets in epileptic children. Again the study was evaluated with phenytoin concentrations at steady state, and again considerable inter-patient variability was seen. The levels reached by the 100mg capsules were higher than those achieved by the 100mg tablets, while the converse was seen in the 30mg capsules and tablets. Interestingly the *in vitro* dissolution profiles for these products indicate that there are major dissolution differences between the 100 and 30mg capsules, this correlation was carried through into the results of the clinical trial (Manson *et al.* 1975).

Koren and colleagues (1982) observed an extremely low range of phenytoin concentrations measured at steady state, when they compared locally produced phenytoin sodium tablets with a reference formulation Dilantin®. This resulted in therapeutic failure even though the children in the study were taking adequate doses of phenytoin. Only 8 of 37 children had serum concentrations of phenytoin within the therapeutic range. In Taiwan the same trend was seen between local and international formulations (Tsai *et al.* 1992), with the two local products giving a consistent plasma concentration at steady state, of 13.4 mg/ℓ compared to the formulations from the United States of America (15.2mg/ℓ) and Japan (17.0mg/ℓ). In contrast, Smith & Kinkel (1977) compared single

250mg dose tablets phenytoin sodium to 250mg capsules in adults and found no difference in the AUC (43.28 versus 39.82 μg.h/ml).

The comparison as presented by Smith and Kinkel, of a single versus multiple dose study in phenytoin to compare the AUC has been rejected by Randinitis *et al.* (1990) and Gugler *et al.* (1992). The non-linear kinetics of phenytoin make the extrapolation of single to multiple dose values extremely difficult as well as being dependent on the patient group studied. At the time of publication, it appears that the Smith and Kinkel (1977) study was carried out to refute the claims made by Manson *et al.* (1975) as regards the blood levels achieved at specific times during the study. The study by Manson *et al.* was conducted at steady state in epileptic children, while the Smith and Kinkel study was a single dose study in healthy young male volunteers aged 23 to 43. Such a comparison seems unfair in view of the differences between the studies.

From the above reports, which represent but a few of the comparisons carried out over the past years, it is apparent that the bioavailability of phenytoin may not be guaranteed between formulations (SAMF 1995). A drug which presents with characteristics such as a variable bioavailability, poor solubility, a low therapeutic index and capacity-limited metabolism presents a unique set of problems to be faced by both the prescriber and researcher.

1.3.5 Adverse effects and toxicity

In the first 8 weeks of phenytoin therapy, signs of hypersensitivity which may include a rash, lymphadenopathy and haematologic alterations may appear. The rash may progress to Stevens-Johnson syndrome and phenytoin use may require discontinuation even if a mild hypersensitivity occurs (Alldredge 1992).

Acute, dose-related adverse effects of phenytoin include nystagmus, which occurs early in phenytoin usage, along with diplopia and ataxia. These can be minimised by a reduction in dose while maintaining seizure control. These effects usually occur with plasma concentrations greater than 20mg/ℓ (Winter 1988). Hirsutism occurs in young females, and again responds to a reduction in dose. Gingival hyperplasia and osteomalacia appear with long term use along with coarsening of the facial features and a mild peripheral neuropathy. Abnormalities in Vitamin D metabolism leads to osteomalacia with long term use, and low folate levels have been associated with megaloblastic anaemia (Alldredge 1992; Martindale 1989; Porter & Pitlick 1995; Rall & Schleifer 1991).

The signs and symptoms of phenytoin toxicity are related to the route of administration, dose and duration of exposure. The use of intravenous administration during status epilepticus or in the emergency treatment of cardiac arrhythmias, can preempt cardiac arrhythmias and/or hypotension and/or CNS depression (Alldredge 1992: Earnest *et al* 1983; Rall & Schleifer 1991). Acute oral overdose presents with signs indicative of cerebellar and vestibular disturbances. Toxicity as a result of chronic medication incorporate other CNS effects including those related to the cerebellar and vestibular systems. Behavioral changes, increased number of seizures, gingival hyperplasia,

osteomalacia and megaloblastic anaemia are also seen in chronic toxicity.

The effects of phenytoin on biochemical parameters are not apparent in all patients, but when present the following effects may be noted:

1. Increased serum alkaline phosphatase (ALP) or γ-glutamyl transferase (GGT)
2. Reduced protein-bound iodine (PBI) test values without lowered triiodothyronine (T_3) or symptoms of hypothyroidism
3. Decreased free thyroxine levels
4. Decreases in urinary 17-hydroxycorticosteroids and 17-ketosteroids
5. Increased excretion of urinary 6-β-hydroxycortisol
6. Lower than normal values for dexamethasone or metyrapone tests (Martindale 1989)

1.3.6 Drug interactions with phenytoin

Phenytoin is highly plasma protein bound and is a potent inducer of the enzymes in the cytochrome P_{450} pathway, and as such can enhance the metabolism of drugs which utilize the same pathway (Nation *et al.* 1990). At the same time the metabolism of phenytoin may be either induced or inhibited by drugs being metabolised by the same mechanisms.

1.3.6.1 Effects on gastrointestinal absorption of phenytoin

The first category of drugs which may interfere with phenytoin are those which affect gastrointestinal absorption. The effects of antacids and minerals has been considered in Section 1.3.1.2, as well as the reduction in phenytoin concentrations by the antineoplastic agents due to their effect on the gut mucosa.

Activated charcoal has been found to almost completely prevent the absorption of phenytoin, even when administered one hour after the dose. Sucralfate, a poorly absorbed complex of aluminium hydroxide and sulphated sucrose at a dose of 1g, reduced the AUC of phenytoin by 20%. Conflicting reports from other single dose studies suggest that the reduction may be nearer 10%, however, this remains to be clarified in multiple dose studies (Gibaldi 1991; Nation 1990). The concurrent administration of theophylline and phenytoin decreases the AUC Of phenytoin by 21% at steady state and it is postulated that theophylline decreases the absorption of phenytoin in some as yet undetermined way.

1.3.6.2 Plasma protein binding

In the section on distribution of phenytoin (section 1.3.3.2) mention was made of drugs which may influence the plasma protein binding of phenytoin and these will now be discussed further. In the presence of a displacing drug, an increase in the free fraction and volume of distribution is seen, resulting in increased clearance. However, this may not influence the therapeutic activity of phenytoin as the free concentration is not affected and therefore the therapeutic or toxic effect will remain the same (Alldredge 1992; Gibaldi 1991; Nation 1990). Valproic acid, another of the antiepileptics has this effect on the concentration but not on the therapeutic effect of phenytoin, as is seen in some of the sulfonamides, heparin and some of the non-steroidal anti-inflammatories, salicylate, phenylbutazone and ibuprofen. In addition, tolbutamide not only displaces phenytoin but also affects the metabolism of the drug by utilising the same pathway (Tassaneeyakul, Veronese, Birkett, Doecke, McManus, Miners 1992). The displacement of phenytoin by warfarin may lead to increased free fractions of the drug, however as stated above this increase may not be clinically relevant (Nation *et al.*1990)

In turn phenytoin indirectly affects the plasma protein binding of other agents. By increasing the plasma concentration of α_1-acid glycoprotein, phenytoin causes an associated decrease in the unbound fraction of lidocaine which binds preferentially to this protein (Nation *et al.* 1990; Ritchie & Greene 1991). In addition phenytoin stimulates the secretion of sex hormone binding globulin and this may lead to an alteration in the plasma binding of oral contraceptive steroids as well as an increase in the metabolism of this class of drugs (Alldredge 1992; Gibaldi 1991; Nation *et al.* 1990; Rall & Schleifer 1991).

1.3.6.3 Drugs increasing the metabolism of phenytoin

The inclusion of folic acid into the drug regimen of patients on phenytoin showing a folate deficiency has been the subject of research over the past 15 years. Nation *et al.* (1990) report on these findings as follows: the effects of folic acid are variable, however, in patients with depleted folate, supplementation with folic acid decreases serum phenytoin concentrations significantly which could lead to loss of seizure control (Nation *et al.* 1990).

Alcohol use in chronic alcoholics has a complex effect on the metabolism of phenytoin, with effects showing only during the initial ingestion phase and the withdrawal phase. In these phases the metabolism of phenytoin is increased, while moderate alcohol intake appears to have no effect on steady state concentrations (Alldredge 1992; Nation *et al.* 1990).

Finally, the use of dexamethasone to control cerebral oedema is routine in post-traumatic head injuries as is the use of phenytoin to control seizures in these patients. It has been

suggested that the concomitant use of these two drugs causes a decrease of almost 50% in phenytoin concentrations (Nation *et al.*,1990). Further studies must however be conducted to confirm these results as Rall and Schleifer (1991) and Gibaldi (1991) recount that while phenytoin enhances the metabolism of the corticosteroids there is no reciprocal effect on phenytoin by the corticosteroids.

1.3.6.4 Drugs inhibiting the metabolism of phenytoin

A serious interaction occurs between cimetidine and phenytoin with numerous reports of cimetidine-precipitated phenytoin intoxication. The mechanism of inhibition is thought to be the binding of the imidazole ring of cimetidine to cytochrome P_{450}, as related drugs like ranitidine have no effect on phenytoin (Gibaldi 1991; Nation *et al.* 1990).

1.3.6.5 Other anticonvulsants and phenytoin

According to Nation *et al.* (1990) and Rall & Schleifer (1991), studies dealing with the effects of phenobarbitone on the metabolism of phenytoin have produced conflicting results, while Gibaldi (1991) states that the effect on the metabolism of either drug is minimal. With respect to concomitant phenytoin and clonazepam therapy, phenytoin has been shown to stimulate the metabolism of clonazepam during long term treatment, resulting in a 50% lowering of the clonazepam plasma concentrations (Alldredge 1992; Gibaldi 1991; Nation *et al.* 1990).

Although primidone is converted to phenobarbital and phenyl-ethylmalonamide (PEMA), and although phenytoin has little effect on phenobarbitone *per se*, patients taking primidone and phenytoin together show a higher steady state concentration of derived

phenobarbitone than do controls using primidone alone. The same applies to the ratio of derived PEMA to primidone (Alldredge 1992; Gibaldi 1991; Nation *et al.* 1990).

Besides displacing phenytoin from plasma protein binding sites, valproic acid reduces the metabolism of phenytoin by inhibiting epoxide hydrolase. Epoxide hydrolase is an intermediate enzyme required to detoxify the unstable arene oxide metabolites which are formed during the hydroxylation of phenytoin to HPPH (Gibaldi 1991).

Reports on the effects of carbamazepine on phenytoin and vice versa are conflicting. As far as the influence of carbamazepine is concerned, most of the evidence suggests that the plasma concentration of phenytoin will increase with coadministration of the two drugs (Gibaldi 1991; Nation *et al.* 1990). In turn phenytoin causes an increase in the clearance of carbamazepine (Nation *et al.* 1990; Rall & Schleifer 1991)

1.3.6.6 Phenytoin and antituberculosis agents

An important interaction especially in the South African context is that of the antituberculosis agents and phenytoin. In 1970, Brennan *et al.* reported phenytoin intoxication in patients receiving concurrent antituberculosis therapy. It was established that phenytoin metabolism was inhibited by isoniazid (INH) in patients who were slow inactivators of INH, causing toxicity due to increasing serum levels of phenytoin. The toxicity occurred at therapeutic doses of phenytoin. The introduction of para-amino salicylic acid (PAS) and cycloserine to the regimens depressed the metabolism of phenytoin even further. No significant differences were noted with respect to body weight, age, race or liver function in these patients (Brennan *et al.* 1970)

Similarly, Miller *et al.* (1975) reported that 27% of patients taking INH and phenytoin concurrently developed symptoms of intoxication within 5 days. Recently Walubo and Aboo in Cape Town (1995), drew attention to the very large numbers of epileptic patients admitted due to phenytoin intoxication who were currently taking INH. These researchers state that roughly 50% of the South African population are slow acetylators of INH, ie. INH inhibits the para-hydroxylation of phenytoin. Given the rampant tuberculosis epidemic present in this country at the present time, and the large numbers of epileptic patients, there are likely to be many who are susceptible to phenytoin intoxication (Walubo & Aboo 1995).

Conversely, rifampicin induces the metabolism of phenytoin, thereby reducing the half-life and therapeutic levels. The magnitude of the decrease in metabolism was similar in patients taking rifampicin in combination with INH and ethambutol or alone, and was unaffected by acetylator status (Nation *et al.* 1990). It appears from this study that when phenytoin is given in combination with rifampicin and INH, the overall influence on metabolism is increased, while if phenytoin is given with INH alone, as is the case in prophylaxis, intoxication results in slow acetylators of INH. In both instances it is obvious that the plasma concentrations of phenytoin must be carefully monitored to maintain seizure control.

1.3.6.7 Anti-infective agents and phenytoin

Previously in this report, the sulfonamides were reported to displace phenytoin from plasma binding sites. In addition this class of drug increases the half-life of phenytoin to the extent of causing intoxication (Alldredge 1992). The mechanism proposed in this

instance is the inhibition of hepatic metabolism. A similar situation arises with the concomitant administration of trimethoprim and phenytoin (Nation *et al.* 1990). Caution has also been suggested with the use of phenytoin and chloramphenicol as reports have been published describing phenytoin toxicity due to inhibition of metabolism (Nation et al. 1990).

1.3.6.8 Analgesics and phenytoin

The administration of phenytoin to patients currently undergoing methadone treatment for drug withdrawal, may cause a decrease in the serum levels of methadone due to a phenytoin-induced increase in hepatic metabolism of methadone. A similar situation arises in the concomitant use of pethidine and phenytoin. In both cases higher doses of the analgesic are required (Nation *et al.*1990)

1.3.6.9 Theophylline and phenytoin

Enzyme induction caused by phenytoin is responsible for the increase in clearance and decrease in the half-life of theophylline. In some patients this decrease may be in the order of 50% requiring substantial increases in theophylline dose to approach therapeutic levels (Gibaldi 1991). Further, a combination of cigarette smoking and phenytoin had an additive effect on these parameters (*Nation et al.* 1990)

1.3.7 Uses of phenytoin

The primary indication for the use of phenytoin is in the prophylaxis and treatment of generalized tonic-clonic, simple and complex partial seizures. It is also used as emergency treatment in status epilepticus after diazepam has been administered.

Phenytoin may also be used in the treatment of trigeminal and related neuralgias, however, carbamazepine is the preferred treatment (Rall & Schleifer 1991). Phenytoin is further indicated for the prophylaxis and treatment of seizures resulting from traumatic head injuries or after neurosurgery (Bauer 1982; Guidry *et al.* 1989; Maynard *et al.* 1987). Phenytoin is also classified as a Class I_B antiarrythmic agent, where it is highly effective against ventricular arrhythmias, paroxysmal atrial flutter or fibrillation, and supraventricular arrhythmias especially those associated with digitalis toxicity. Phenytoin is also effective against ventricular arrhythmias after open-heart surgery and acute myocardial infarction (Bigger & Hoffman 1991).

1.3.8 Ethnic differences in phenytoin metabolism

The literature contains many examples of differences between the metabolising capacities in various populations. These comparisons are however difficult to extrapolate as the published parameters are not consistent for a drug like phenytoin with its non-linear kinetics. V_{max} is presented as mg/day or individualised as V_{max} in mg/kg/day, where the body weight of the patients is omitted. No extrapolation of these values to the population is therefore possible. Similarly plasma phenytoin concentrations or the concentration of the metabolite HPPH in urine are compared. The sole use of V_{max} (mg/kg/day) and K_m as parameters of comparison would enable the reader to discern salient differences between populations. That these variations exist seems without question and the role of genetics in phenytoin metabolism and intoxication seems to point to a familial deficiency in hydroxylation capacity (Vasco, Bell, Daly, Pippenger 1980). In Table 1.3, various publications have been reviewed in an effort to demonstrate the population groups in which genetic variations in metabolism may cause differences in dosing regimens.

Table 1.3 Comparison of genetic differences from published literature.

Population, Parameter measured, Result obtained	Authors, Year of Publication
Chinese: Singapore V_{max} = 499mg/day (415mg/day)* K_m = 2.31mg/ℓ (5.7mg/ℓ)*	Chan, Ti and Lee, 1990
Chinese: Taiwan No V_{max} or K_m recorded. Saturation of metabolism occurs at dosage = 4mg/kg. No difference found	Lai, 1985
South African Blacks (4 data sets averaged) V_{max} = 6.37mg/kg/day (7.22mg/kg/day)* K_m = 4.32μmol/ℓ (17.8μmol/ℓ)*	Miller, Rheeders, Klein, Suchet 1987
Mean plasma $t_{½}$ = 26.5 h (18.5 h)*	Arnold & Gerber 1969 in: Kalow 1982
Japanese V_{max} = not recorded no difference (411 mg/day) K_m = 3.66mg/ℓ (4.80mg/ℓ)*	Sheiner & Beal 1981 in: Kalow 1982
V_{max} = recorded: same as comparator (415mg/day) K_m = 3.8mg/ℓ (5.7mg/ℓ)*	Grasela, Sheiner, Rambeck, Boenigk, Dunlop, *et al.* 1983
Denmark versus Greenland Clearance of phenytoin urinary [HPPH] Danish = 17.0ml/min + Greenlanders = 66.5ml/min ++	Dam, Larsen, Christiansen 1977 in: Kalow 1982
Ghanaians versus Caucasians urinary [HPPH] > Caucasians < Ghanaians	Andoh, Idle, Sloan, Smith., Woolhouse 1982 in: Kalow 1982

* Comparator values in equal units

In genetic population studies conducted by Eichelbaum (1982), the impaired removal of drugs from the body was seen to be genetically dependent. The poor metabolizer, debrisoquin phenotype, was shown to be dependent on two allelic genes at a single gene locus and was homozygous for an autosomal recessive gene. Deficient hydroxylation of

phenytoin was found to be impaired in this phenotype as demonstrated by Sloan, Idle and Smith (1981). The data from this study suggested that metabolism of both debrisoquin and phenytoin were controlled by the same gene locus. It has also been established that an absence of a specific cytochrome P_{450} isoenzyme is involved in the production of the debrisoquin phenotype at the biochemical level. Similarly, genetic polymorphisms are also involved in other drugs which are oxidatively metabolised including phenytoin (Wedlund, Aslanian, McAllister, Wilkinson, Branch 1984).

However, later publications have disputed the relationship advocated by Sloan *et al.* (1981) between poor metabolizers of debrisoquin and deficiencies in phenytoin hydroxylation. A study carried out in the Japanese population established that in contrast to the Caucasian population, no poor metabolizers of debrisoquin were present in the sample population, even though the numbers of deficient hydroxylators of mephenytoin were six-fold higher than in Caucasian populations. It appears therefore that the two types are genetically distinct, with a definite difference being seen between Caucasian and Orientals (Nakamura, Goto, Ray, McAllister, Jacqz, Wilkinson, Branch 1985).

From the above discussion, it appears that deficiencies in phenytoin metabolism may in some population groups be detected by utilizing the debrisoquin metabolic status e.g Caucasians (Sloan et al 1981). However, in the Oriental population the same does not apply as shown above by Nakamura *et al.* (1985). It remains to be seen what genetic deficiencies are present in the black African population if the V_{max} and K_m are taken as indicators of enzyme activity in the cytochrome P_{450} pathway.

1.4 MIGLITOL

Close control of blood glucose concentrations reduces the long term complications of diabetes (Lasker 1993). The use of the antidiabetic preparations to maintain blood glucose levels is successful to a point, but the control of post prandial glucose remains the most resistant and most difficult period to stabilise. This is due partly to the imbalance between the slow absorption of subcutaneously administered insulin relative to the absorption in the GIT of dietary carbohydrates (Kennedy & Gerich 1987) and partly to the results of the slow absorption of insulin which increases the risk of late post prandial hypoglycaemia (Dimitriadis, Tessari, Go, Gerich 1985). The amount of available carbohydrate, as well as its characteristics, the presence of protein, fibre and fat in the meal are all important determinants in the rate of absorption of the carbohydrates. Physical abnormalities in the mucosa or enzyme deficiencies also play a role in carbohydrate metabolism, as well as the regular physiological mechanisms such as hepatic carbohydrate metabolism (Taylor *et al.* 1986).

The use of specific inhibitors of the α-glucosidase hydrolases is a novel manner to control carbohydrate digestion (Dimitriadis *et al.* 1985; Jenkins, Taylor, Goff, Fielden, Misiewicz, Sarson, Bloom, Alberti 1981; Walton, Sherif, Noy, Alberti 1979). Miglitol is a reversible inhibitor of intestinal α-glucosidases which has been developed for use as monotherapy or in combination with oral antidiabetic preparations in non-insulin dependent diabetics, or as an adjunct to conventional insulin therapy in insulin dependent diabetics (Kennedy & Gerich 1987).

The principal carbohydrate that is utilized directly by the cell is glucose. In order for all other sugars to be metabolized, they must be converted either to derivatives of glucose or to one of its metabolic intermediates. The principal nutrient carbohydrates of the average diet are the polysaccharide starch and the disaccharides sucrose and lactose. The use of starch and disaccharides by the body is restricted until hydrolysis has taken place and the compounds broken down into their component monosaccharides (Danishefsky 1980). For this process, the enzymes of the digestive system are required. Starch is digested by luminal α-amylase, while its products and the disaccharides are hydrolysed to glucose and fructose by intestinal brush border α-glucosidases at the surface of the intestinal cells. An inhibitor of α-glucosidases will reduce the amount of carbohydrates available for absorption and thus smooth the post prandial rise in blood glucose. (Taylor, Barker, Canfield 1983).

1.4.1 Chemistry and physicochemical properties

Miglitol is a derivative of deoxynojirimycin with modified side chains. Nojirimycin is synthesised by various species of *Streptomyces* and strains of *Bacillus*. Deoxynojirimycin is the reduced form of nojirimycin. The chemical structure of deoxynojirimycin and its modified derivative, N-hydroxyethyl-1-deoxynojirimycin (miglitol) is shown in Figure 1.6 (Taylor, Barker, Bowey, Canfield 1986).

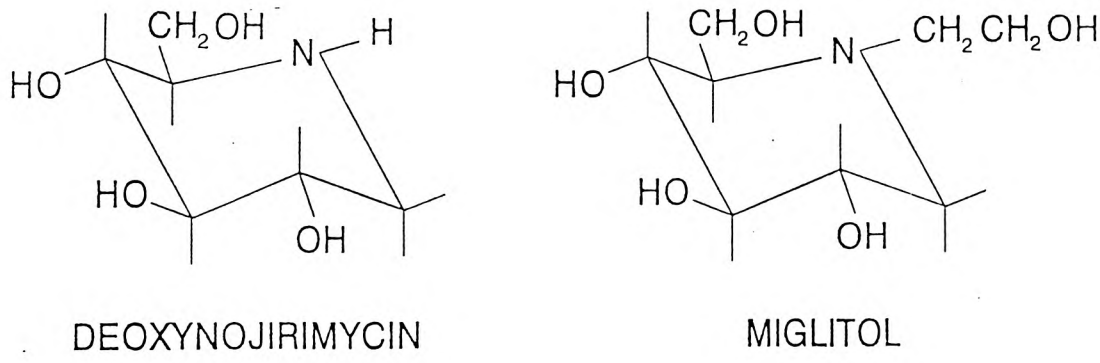

Figure 1.5 Chemical structure of deoxynojirimycin and miglitol (Taylor *et al.* 1986).

Miglitol occurs as a non-hygroscopic, white powder, readily soluble in water at room temperature. It is also soluble in 1N hydrochloric acid, 1N sodium hydroxide solution, gastric and intestinal juices. Miglitol is less soluble in organic solutions, is stable to heat and oxygen and slightly sensitive to light (Investigator's Brochure 1995)

1.4.2 Mechanism of action

Deoxynojirimycin and its derivative miglitol are potent inhibitors of mammalian intestinal brush border α-glucosidases. Miglitol acts reversibly to inhibit the α-glucosidases in the small intestine, thereby delaying the degradation and absorption of complex carbohydrates. Consequently, the post prandial glucose rise is reduced and the daily glucose curve smoothed. Miglitol selectively inhibits the degradation of complex carbohydrates, but not the absorbable monosaccharides glucose and fructose (Diabetes Control and Complications Trial Research Group (DCCT) 1993; Kennedy & Gerich 1987; Taylor *et al.* 1983, 1986).

By reducing post prandial hyperglycaemia, miglitol also decreases the amount of insulin released or required after a meal (Kennedy & Gerich 1987). The effect appears to be dose-dependent. While low doses of 25 and 50mg significantly reduced the postprandial increase in blood glucose and insulin, doses of 100 and 200mg abolished the increase almost completely. A study conducted by Kennedy & Gerich (1987) using 50mg doses of miglitol, has shown a significant reduction in the postprandial glucose concentrations despite a decrease of 20% in the insulin dose for that meal. Triglycerides were not affected (Cauderay, Tappy, Ternier, Jequier, Hillbrand, Felber 1985).

The action of miglitol takes place extrasystemically in the small intestine, but the drug is nevertheless absorbed to a small extent. Studies were carried out by Bollen, Vanderbroeck and Stamens (1988) to determine whether miglitol exerted an inhibitory effect on intracellular α-glucosidases, thereby affecting the degradation of glycogen. Even at very high concentrations there was no effect on hepatic glycogen content nor skeletal muscle glycogen (Bollen *et al.* 1988).

Miglitol causes a delay in carbohydrate absorption due to its inhibition of carbohydrate digestive enzymes. There are therefore increased amounts of undigested carbohydrates in the lower GIT segments. However, as miglitol is completely absorbed in the upper portions of the small intestine, undigested carbohydrates in the distal segments of the small intestine are completely digested and absorbed without inhibitory influences. Miglitol has no spasmolytic activity, does not interfere with the absorption of bile acids from the ileum nor does it have an influence on the charcoal transit time, a measure of GIT transit time (Bo-Linn, Santa-Ana, Morawski, Fordtran 1982; Bond, Currier, Buchwald, Levitt 1980).

1.4.3 Pharmacokinetic properties

1.4.3.1 Absorption

Miglitol is absorbed rapidly and completely in low doses, however, an increase in dose decreases the extent of absorption significantly. This indicates a dose-dependent saturation of the active transport mechanism in the proximal parts of the intestinal mucosa. Saturation of this transport system causes miglitol to become dependent on its luminal concentration for absorption (Investigators Brochure 1995).

1.4.3.2 Distribution, metabolism and excretion of miglitol

Miglitol is distributed heterogeneously to tissues and organs, being found mainly in the extracellular compartment with highest concentrations in the blood and well-perfused organs. The volume of distribution at steady-state is thus low. Miglitol does not undergo any metabolism, and is excreted unchanged via the kidneys at low doses. At higher doses, renal excretion decreases and faecal excretion increases in accordance with the higher concentrations found in the intestine. The elimination half-life is 2 - 4 hours (Investigators Brochure 1995).

1.4.4 Adverse effects.

The most frequently reported adverse effects with miglitol administration were dose-dependent and related to the GIT, i.e. flatulence, diarrhoea and abdominal pain (Kennedy & Gerich 1987). As explained in the mechanism of action (section 1.4.2) as the dose of miglitol increases, so do the amounts of undigested carbohydrates which reach the large bowel. There they are subjected to a fermentation process through interaction with intestinal flora. It is this interaction in the lower bowel which causes the gastric

discomfort (Lemcke, Loser, Folsch, Wohler, Creutzfeldt 1987; Bond *et al* 1980; Cauderay *et al.* 1985). No other adverse effects either physical, haematological or biochemical have been reported (Kennedy & Gerich 1987).

1.4.5 Uses of miglitol

Miglitol is indicated for the treatment of postprandial hyperglycaemia in non-insulin dependent diabetes mellitus (NIDDM). By way of the effects on blood glucose, miglitol also lowers glycated haemoglobin levels. The drug may be used alone or in combination with the sulfonylureas. Miglitol may also be used as an adjunct to diet and insulin to lower blood glucose and glycated haemoglobin in patients with insulin dependent diabetes mellitus (IDDM) (Dimitriadis *et al.* 1985; Kennedy & Gerich 1987). Miglitol may also be indicated for the treatment of patients with impaired glucose tolerance, since the improvement in glucose control may prevent the further development of NIDDM in these patients.

1.5 HYPERGLYCAEMIA AND DRUG BINDING

Glycosylation of proteins in diabetes is common but the long term physiological implications are as yet inconclusive. Nevertheless, research indicates that damage to membranes and joints by glycosylation of collagen, loss of control of cholesterol synthesis and utilization by glycosylation of low-density lipoproteins, and glycosylation of insulin (thereby reducing the effects of the compound) are but a few of the results of poorly controlled diabetes (Brownlee, Vlassara, Cerami 1984; Bunn, Gabbay, Gallop 1978; Kirschenbaum 1984).

The levels of nonenzymatically glycosylated proteins including albumin, have an influence on the binding of protein bound drugs (Kirschenbaum 1984; Shaklai, Garlick, Bunn 1984). Clinically these glycosylated proteins are used to indicate the period and degree of hyperglycaemia in a diabetic patient. The use of the life span of the protein indicates the period of over which glycosylation has occurred (Bunn, Gabbay, Gallop 1978; Ruiz-Cabello & Erill 1984). The proteins are measured as follows:

- glycosylated haemoglobin is used as an indicator of diabetic control for the period of 6 to 10 weeks before measurement (half-life of haemoglobin is 60 days)
- glycosylated albumin concentrations reflect short term control i.e. during the 2 to 4 weeks before measurement (half-life of albumin in serum is 14 days)
- glycosylated serum proteins eg transferrin, reflect recent control over the previous 1 to 2 weeks (half-life of transferrin in serum is 8 days)(Kemp, Creech, Horn 1984; Whitby, Smith, Beckett, Walker 1993).

Alterations in the binding of acidic drugs to nonenzymatically glycosylated proteins in diabetes were investigated by Ruiz-Cabello and Erill (1984). The patients used in the study had basal blood glucose levels above 120%. Binding was also measured in non-diabetic controls. Glycosylation of albumin resulted in an increase in the free fraction of sulfisoxazole, a weakly acidic drug, but there was however no related correlation with glycosylated haemoglobin. Diazepam which was tested under the same conditions was not affected.

As phenytoin is a weak acid bound primarily to albumin and α-globulins, a follow-up study using phenytoin was conducted by Kemp, Kearns and Turley (1987). Phenytoin concentrations used in this study were within the therapeutic range. Kemp *et al.* found that the free fraction of phenytoin in serum increased in a direct linear relationship to the extent of albumin glycosylation, which is similar to the results of the Ruiz-Cabello/Erill study. The degree of increase in the free fraction was of the magnitude of 50% in patient samples where the increase in glycosylation of albumin was from 5 to 25%. In contrast, a study carried out in healthy well controlled diabetics, did not yield the same results, as little change was found in the free fraction of phenytoin (McNamara, Blouin, Brazzell 1988). The alteration in binding of phenytoin in poorly controlled diabetics may have serious clinical effects as measurement of the total serum phenytoin concentration may underestimate the amount of free phenytoin in serum (Kemp *et al.* 1987).

CHAPTER 2

2.0 METHODS AND MATERIALS

2.1 PATIENTS AND PROCEDURES

2.1.1 Overall design and plan of the study

This was a double-blind, cross-over, placebo-controlled, randomised study in two phases. 24 healthy male volunteers were selected to participate in the study according to the inclusion and exclusion criteria (Section 2.1.2.1). On day 1, volunteers were randomised into two groups in a 1:1 balanced scheme, according to the randomisation code designed by the biostatistician (Appendix B Table B2).

Each volunteer received either miglitol 100mg or placebo three times daily with food for 5 days. On day 3 of each phase, each volunteer received 400mg phenytoin in a single dose. Blood samples were taken for a period of 96 hours after the phenytoin administration and assayed to determine pharmacokinetic values. The two phases were separated by a washout period of 14 days. The total duration of the study was 26 days.

The aims of the research program, the study protocol, amendment to the protocol and the informed consent for used in the study were approved in writing by the Human Ethics Committee of the University of the Witwatersrand prior to the start of the study (Appendix A).

2.1.2 Selection of healthy volunteers

Volunteers were selected according to the following inclusion and exclusion criteria:

2.1.2.1 Inclusion criteria

- healthy male volunteers aged between 18 and 45 years
- normal findings in the physical examination and normal laboratory values
- volunteers agreeing to attend the clinical unit for the each study period as requested
- volunteers willing and able to sign an informed consent form at the initial screening visit

2.1.2.2 Exclusion criteria

- volunteers with any concomitant, clinically significant disease or condition, including emotional disorders that were likely to interfere with the study or the volunteer's ability to complete the study
- volunteers participating in a trial with an investigational drug in the six weeks preceding the study
- volunteers with a history of non-compliance, alcoholism or drug abuse
- concomitant administration of any medication (including over-the-counter preparations such as Metamucil® resins or charcoal) which may significantly alter gastrointestinal motility or absorption
- history of hypersensitivity to the study drugs or related substances
- renal, hepatic, systemic, haematologic, metabolic, muscular or neuromuscular disease or metabolic disease
- volunteers with clinically significant abnormal values at the initial visit
- history of gastrointestinal disorders that could result in impaired absorption of the study drugs

- volunteers unable to understand or unwilling to sign the informed consent form.

2.1.2.3 Informed consent

Prior to entry into the study, the nature, purpose, procedures, expected duration, benefits and risks involved in the study were explained to each volunteer. They were then given the opportunity to ask questions, and were informed of their right to withdraw from the study at any time without prejudice. The volunteer then signed an informed consent statement in the presence of a witness.

2.1.2.4 Method of volunteer assignment

After the volunteer had satisfied all enrolment criteria and informed consent had been obtained, he was randomised to a treatment sequence designated by a study number, according to the randomisation list (Appendix B Table B2). When the volunteer reported to the clinical unit on day 1, he was issued with treatment medication to be taken according to the study plan. A daily dairy reflecting the times at which medication was taken, was filled in by the volunteer for the duration of the study period. Blinding was achieved by packing matching miglitol and placebo tablets in matching containers. A copy of the randomisation code was kept in the Department of Pharmacology in case of emergency, in which instant the code was to be broken and the volunteer treated accordingly.

2.2 DOSAGE AND DURATION OF TREATMENT

After the initial screening visit, the medication was administered orally according to the following dosage scheme:

Day 1 Start of Phase 1

Volunteer received, according to the randomisation plan, either miglitol 100mg (1 tablet) or placebo three times a day for five days with the first bite of each meal. Blood was taken every morning at 07h00 from day 1 to day 5 to determine plasma miglitol trough concentrations.

Day 3 Phenytoin 400mg was given as a stat dose immediately after the first meal of the day. Blood samples were taken for 96 hours after phenytoin administration (days 3 - 7). (See Appendix B Table B1 for the blood sampling times).

Day 6 - 19 Washout for 14 days.

Day 20 Start of phase II, the medication was crossed over and the volunteer received the alternate medication to phase I to be taken as before. Blood was again taken every morning at 07h00 from day 20 - 24 to determine plasma miglitol trough concentrations.

Day 22 Phenytoin 400mg stat dose was given immediately after the first meal of the day. Blood samples were taken for 96 hours after phenytoin administration (days 22 - 26)

In both phase I and II, all volunteers ate the same standardised meals from noon on day 2, the whole of day 3 until breakfast of day 4 (days 22, 23 and 24 of Phase II).

2.3 TREATMENT PROCEDURES

2.3.1 Pretreatment procedures

All volunteers were identified on study documentation by their study number and initials only. Within 2 weeks prior to administration of the first dose of phenytoin, the volunteers underwent the following procedures:

- medical history and demographics
- complete physical examination including blood pressure and heart rate
- ECG (interpretation by a cardiologist)
- chest X-ray
- laboratory test as listed below

  Haematology

  Full blood count with differential white cell and platelet count.

  Biochemistry

  Fasting serum glucose, uric acid, creatinine, urea, protein, albumin, total cholesterol, sodium, potassium, chloride, calcium. bicarbonate, phosphate, aspartate transferase (AST). alanine transferase (ALT), lactate dehydrogenase (LDH), gamma glutamine transferase (GGT), alkaline phosphatase (ALP) and total bilirubin.

  Urinalysis

  Dipstick analysis (Multistix®), 10SG glucose, bilirubin, ketones, blood, leucocytes, protein, urobilinogen, nitrites, pH and specific gravity.

Haematology and biochemical analysis was performed for the screening visit by the SAIMR, Johannesburg Hospital. Due to suspected laboratory errors in the screening

biochemistry assays, all biochemistry variables for the screening visit were reassessed by van Drimmelen Laboratories, Johannesburg, and all further biochemical assays were carried out by the same laboratory. Haematological assays were performed at the SAIMR for the duration of the study.

2.3.2 During treatment procedures

2.3.2.1 Observations and measurements

Four volunteers were assigned to each group and the same sequence was followed throughout the study. During the phenytoin administration period, volunteers were confined to the clinical unit in the Department of Pharmacology, and administration of the medication as well as blood sampling were staggered by 10 minutes. Again the same sequence was followed throughout the study.

No physical activity was allowed for the first 6 hours after phenytoin administration, volunteers were confined to bed except to void their bladders. Thereafter, limited activity was allowed, ie. walking in the Clinical Unit. No gymnasium work outs or jogging was allowed until the last blood sample had been taken.

2.3.2.2 Blood sampling - miglitol

All blood samples were taken with the volunteer in the supine position. Trough plasma samples (5ml each) were collected at 07h00 each morning before miglitol or phenytoin administration, on days 1 - 5 in phase I and days 20 - 24 in phase II. This was done to ascertain a base concentration and to assess miglitol regimen compliance. 5 samples per subject per treatment phase, were collected (total blood volume = 25ml per phase). The

blood was collected in heparin tubes and the samples centrifuged within 10 minutes at room temperature. Plasma was transferred into plastic tubes and frozen pending assay. Miglitol trough concentrations were assayed by Dr E. Brendel at the Bayer Institute of Clinical Pharmacology, Wuppertal, Germany.

2.3.2.3 Blood sampling - phenytoin

Venous blood samples were taken before phenytoin administration (0 hours), and after phenytoin administration at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 20, 24, 32, 40, 48, 56, 64, 72, and 96 hours (total 230mls per phase).

Phenytoin was administered sequentially to each volunteer in the group at 10 minute intervals according study number, ie. volunteer 1 received phenytoin at 07h00, volunteer 2 received phenytoin at 07h10 and so on.

The volunteers received 200ml tap water at 2 and 4 hours after drug administration and 200ml orange juice with their midday meal. From 5 hours after drug administration, water intake was permitted *ad libitum*. The volunteers remained recumbent for 6 hours after phenytoin administration, except for voiding their bladders. They remained in the clinical unit for all investigations up to blood sampling at 24 hours (07h00 on day 4 in phase I and day 23 in phase II). They were then permitted to leave the centre and returned for blood sampling as per the schedule, ie from 32 hours to 96 hours.

2.3.2.4 General procedures

Volunteers reported to the clinical unit on day 1 by 08h00. Medication, either miglitol or placebo according to the randomisation plan, was dispensed to them and blood samples were taken.

The volunteers returned to the clinical unit on the morning of day 2 for pre-dose plasma miglitol levels. At 12h00 on day 2, the volunteers commenced the controlled diet component of the study. From 12h00 on day 2 until 07h00 on day 4, meals were standardised for all participants.

On day 3, after staying at the clinical unit overnight, and having fasted since 22h00 on the previous evening, an indwelling venous catheter was inserted and pre-dose blood samples drawn. The miglitol or placebo tablet was taken with the first bite of breakfast. Immediately after finishing breakfast, the volunteers received 400mg phenytoin orally with 100ml tap water as described in Section 2.3.2.3. All procedures were staggered sequentially by 10 minutes, this included meals and vital signs.

After fasting from 22h00 on day 6, volunteers returned to the Clinical Unit at 07h00 on day 7 where laboratory investigations were carried out following the 07h00 blood sample, ie. 96 hours after phenytoin administration. Blood pressure and heart rate were monitored.

A fourteen day drug free period followed which served as a washout period for phenytoin and miglitol. Phase II commenced on day 20, and volunteers again reported to the clinical

unit as before to receive the next medication issue. Due to the cross-over design, volunteers received the alternate treatment to phase I. The entire sequence from day 1 to 7 was repeated on days 20 - 26. On day 22, all volunteers received 400mg phenytoin.

2.3.2.5 Monitoring for volunteer's compliance

Volunteers were considered non-compliant if they took prohibited medication, less than 95% or more than 105% of the required study medication.

2.3.2.6 Monitoring for adverse events

Biochemistry and haematological evaluations as well as physical examinations were performed on the final day of each phase (days 7 and 26). Blood pressure and heart rate were monitored during the study on days 3 to 7 in phase 1 and days 22 to 26 in phase 2 at 8, 16, 20, 24, 32, 40, 48, 56, 64, 72 and 96 hours. Volunteers were questioned with regard to adverse events before each blood sample was drawn. Any suspected adverse events were recorded in the case report form and the relationship to the study medication assessed according to the definition in the protocol (Appendix A). Adverse events were classified with respect to intensity (mild, moderate or severe), and whether the event was unexpected or serious.

2.3.3 Post-treatment procedures - observations and measurements

A volunteer who discontinued participation in the study before completion underwent a physical examination, which included blood pressure and heart rate. Blood was drawn for haematology, biochemistry and final pharmacokinetic sampling. Volunteers who completed the study successfully, underwent the same procedures after the final

pharmacokinetic blood sample had been drawn at 96 hours on days 7 and 26. Any abnormalities or adverse events were followed up until resolution in both instances.

2.4 CRITERIA FOR SAFETY AND TOLERABILITY EVALUATIONS

Physical examinations, laboratory testing and assessments as specified in the trial procedures (Section 2.3) were performed according to the study plan. Changes in laboratory values and vital signs compared to base line, as well as adverse experiences, were described in detail on the case report forms. This included signs and symptoms of the adverse event, time of onset and duration, whether treatment was discontinued, corrective measures, outcome and other possible courses of action.

2.5 ANALYSIS OF STUDY DRUGS

2.5.1 Determination of phenytoin serum concentrations

Blood samples were collected , centrifuged and aliqoted into two tubes. One tube was stored at -20°C pending batch analysis at the end of each phase. The second tube was stored at -70°C for the duration of the study to be used when needed. Phenytoin concentrations were determined using the Abbott TD_x assay method. 576 serum samples were analyzed at the end of phase I, and 576 samples at the end of phase II.

The Abbott TD_x system is an automated fluorescence polarization immunoassay which measures quantatively the concentration of bound and unbound phenytoin in serum.

Specificity

Cross reactivity was tested for compounds whose chemical structure or concurrent usage could cause concern over potential interference with the phenytoin assay. The reported values were determined with drug-free samples. Percent cross-reactivity = 100 x (measured concentration of phenytoin / concentration of the test compound). Represented data is shown in Appendix C.

Sensitivity

The lowest measurable level is defined as that concentration which can be distinguished from zero with 95% confidence; it was determined to be 0.5μg/ml.

Validation of the phenytoin assay

The accuracy and precision of the assay was ensured as follows:

1 The same batch number of the Abbott reagent for phenytoin was used in both cases.

2 The TD_X analyzer was calibrated before each run using Abbott calibrators.

3 For each carousel run of 20 specimens, 3 controls were used at concentrations of 2.5, 5.0, and 10.0μg/ml. These human serum standard calibrators were provided by Abbott Diagnostics, with exact assigned values. Interrun coefficients of variation were calculated.

2.5.2 Determination of miglitol concentrations in plasma

Samples

240 blood samples were collected in heparin tubes, centrifuged at room temperature within 10 minutes of collection, the plasma was separated and aliqoted into tubes and stored at -20°C. These samples were analyzed by Bayer, Wuppertal at the end of the study.

Methods

1. Apparatus and Materials

Auto-EIA system (Labsystems)

Centricon 10 microconcentrator ultrafiltrate vials, 2ml

Combiplate 8 microplates

Minisart RC membrane filter, 0.45 μm

Chromobond C18 extraction columns, 500mg, 3ml

2. Reagents

Miglitol reference substance, batch no. R 14-4

4-Nitrophenyl-α-D-glucopyranoside

Sucrase (prepared from porcine mucosa) batch no. SHV 5856/B 15

3. Solutions

a. NPG solution

18mg 4-Nitro-α-glucopyranoside (NPG) were dissolved in 50ml 0.1M phosphate buffer pH6.5

b. Sucrase solution

3mg sucrase were dissolved in 10ml 0.1M phosphate buffer pH6.5 and left in an ultrasonic bath for 3 minutes. Thereafter the solution was filtered through a 0.45μm membrane filter.

4. Assay procedure

1ml plasma was mixed with 1ml of 0.2M phosphate buffer pH 6 in an ultrafiltrate vial and then centrifuged at 7000rpm for 90 minutes. In a microplate 50μl of the ultrafiltrate were incubated with 50μl of the sucrase solution at 37°C for 35 minutes. Thereafter 100μl of the NPG solution were added and the mixture was further incubated at 37°C for 40 minutes. Then the enzymatic reaction was stopped by the addition of 100μl of 0.5M tris buffer pH 10.6. Thereafter the extinction of the solutions was measured photometrically at 405 nm (= extinction E_i).

The calibration was performed by linear regression using equation 1

$$[(E_{100} - E_0) / (E_i - E_0) - 1] = y = ax + b \qquad \text{eq.1}$$

where E_{100} is the extinction of a blank sample and E_0 is the extinction of the samples without the addition of the sucrase solution.

The limit of quantification was 0.1mg/l.

2.6 STATISTICAL AND ANALYTICAL PLAN

General

The demonstration that concomitant administration of miglitol and phenytoin did not affect the pharmacokinetics of phenytoin was handled as an equivalence problem

(Steinijans et al 1991). The treatment phenytoin + placebo serves as the reference situation, and phenytoin + miglitol as the test situation.

Sample size estimation

If the true mean difference (miglitol vs placebo) in a given pharmacokinetic variable is at the most 10%, and the coefficient of variation of the individual differences below 15%, then a sample size of 20 is adequate to rule out an interaction with respect to the variable (90% confidence interval of the "miglitol/placebo" mean ratio in the range 80% to 125%)(Hauschke et al 1990). Thus 24 subjects were enrolled into the study to finish with at least 20 evaluable subjects.

2.6.1 Criteria for the evaluation of a possible miglitol/phenytoin interaction

The following variables were calculated from plasma phenytoin concentrations determined over the 96 hour profile periods, by non-compartmental methods with respect to each volunteer and treatment:

- Maximum concentration (C_{max})
- Time to maximum concentration (t_{max})
- Area under the plasma concentration curve [AUC ($0\text{-}t_n$)] with extrapolation to infinity [AUC ($0\text{-}\infty$)]
- The elimination half-life ($t_{½\beta}$)
- Elimination rate constant (β)

C_{max}, [AUC ($0\text{-}t_n$)] and [AUC ($0\text{-}\infty$)] were normalised for dose per body weight.

The rate of absorption (K_a) and absorption half-life ($t_{½a}$) were calculated by one-compartmental methods from the plasma phenytoin concentrations for each volunteer.

2.6.2 Calculation of the pharmacokinetic variables

The individual plasma phenytoin concentrations, as well as the actual blood sampling intervals were tabulated for each subject, treatment and scheduled sampling time, together with the following descriptive statistics for each treatment and sampling time:

arithmetic mean

standard deviation

geometric mean

geometric standard deviation

coefficient of variation

standard error of the mean

maximum, minimum and median value

number of observations for each treatment

sampling time

Graphical representations were constructed for each individual plasma phenytoin concentration vs time profile, and of the mean concentration vs time profile.

The individual values of the various pharmacokinetic variables listed in section 2.6.1, were tabulated for each subject and treatment, together with descriptive statistics describe above for phenytoin concentrations.

Maximum concentration (C_{max})

C_{max} was read directly from the observed concentrations.

Time to maximum concentration (t_{max})

t_{max} was read directly from the observed concentrations as the blood sampling time corresponding to C_{max}.

Area under the plasma concentration vs time data pairs [AUC ($0\text{-}t_n$)]

AUC ($0\text{-}t_n$) was calculated according to the log-linear trapezoidal rule from 0h to the time to the last quantifiable concentration (t_n) after drug administration. Concentrations reported as "below the level of quantification" (BLOQ) during the absorption phase were substituted by zero before calculating AUC($0\text{-}t_n$). This was done to avoid an over-estimation of the area under the curve.

Area under the plasma concentration vs time data pairs with extrapolation to infinity [AUC ($0\text{-}\infty$)]

AUC ($0\text{-}t_n$) was extrapolated to infinity by adding C_n/β. Thus

$$AUC\ (0\text{-}\infty) = AUC\ (0\text{-}t_n) + C_n / \beta$$

where AUC($0\text{-}\infty$) is the area under the curve from 0h to infinity, β is the terminal rate constant, and C_n is the predicted concentration value at t_n.

Elimination half-life ($t_{½\beta}$) and rate of elimination (β)

The elimination half-life of phenytoin was calculated from the non-linear regression of a single exponential function ($Ce^{-\beta t}$) to the terminal phase of the untransformed plasma concentration vs time profile. Here β is the terminal rate constant. The regressions were done using the method of non-linear least squares. The terminal half-life was then calculated as $t_{½\beta} = (\ln 2) / \beta = 0.693 / \beta$

Absorption rate constant K_a

The absorption rate constant K_a was calculated using a curve fitting iterative program by Enzfitter for one-compartmental models. This program uses Marquardt's algorithm for minimizing the deviations between observed values and the concentration predicted by the one-compartmental model. The following equation was used in the determination of the K_a

$$[\ Dose / V_d \times (\ K_a / K_a - K_e\ )]\ \times\ [\ \exp(-K_e.X) - \exp(-K_a.X\ )]$$

where the dose of phenytoin was 400mg

Absorption half-life ($t_{½a}$)

The absorption half-life was calculated from the absorption rate constant as

$$t_{½a} = \ln 2 / K_a = 0.693 / K_a$$

2.6.3. Analysis of phenytoin/miglitol interaction

The test treatment (phenytoin + miglitol) was compared to the reference treatment (phenytoin + placebo) with respect to the following pharmacokinetic variables of phenytoin after logarithmic transformation of the data. Point estimates and 90% confidence intervals for the test/reference ratios of the true means of the variables were calculated.

- Maximum concentration (C_{max})
- Time to maximum concentration (t_{max})
- Area under the plasma concentration curve [AUC (0-t_n)] with extrapolation to infinity [AUC (0-∞)]

- The elimination half-life ($t_{½\beta}$)
- The rate of absorption (K_a)
- The rate of elimination (β)
- Absorption half-life ($t_{½a}$)

A pharmacokinetic interaction of miglitol with phenytoin occurred if the 90% confidence interval for the mean ratios was not included in the 80% to 125% range. The primary interaction parameters were:

(i) $AUC(0\text{-}t_n)_{norm}$ of phenytoin

(ii) $C_{max.norm}$ of phenytoin

All other variables were regarded as secondary parameters.

2.6.4 Statistical analysis

2.6.4.1 Statistical analysis of pharmacokinetic variables

Point estimates

The test/reference mean ratios of the pharmacokinetic variables were estimated by: the least squares method of the test/reference mean differences on the logarithmic scale, which were transformed to give point estimates for the test/reference ratios (Steinijans and Hauschke 1990). The conventional point estimates for the test/reference mean ratios are reported for all pharmacokinetic variables.

Confidence intervals

The confidence intervals for the test/reference mean ratios were calculated for the pharmacokinetic variables. The upper and lower limits of the conventional t-test based confidence intervals for the test/reference mean differences on the logarithmic scale, were transformed (antilog) to give these confidence intervals.

2.6.4.2 Analysis of safety and tolerability parameters

All continuous variables (demographics, vital signs, ECG, laboratory examinations) were tabulated for each subject and treatment. These variables were subjected to repeated measures ANOVA with treatment, between subject and within subject variability as the main effects. Where significant p values were found, the Bonferroni multiple comparison test was used to establish differences between screening, test and reference values. In situations where the number of comparisons was high, and the Bonferroni method reported to be too conservative, the Dunnett multiple comparisons test was used.

2.6.4.3 Analysis of ethnic differences in pharmacokinetic parameters

The data collected from the statistical analysis of the pharmacokinetic variables in 2.6.1, were used to assess ethnic variations between 13 black and 9 white volunteers. The data from the two coloured volunteers in the study were included in both groups to avoid bias.

The data were tabulated for each subject and variable, together with descriptive statistics for each treatment time:

arithmetic mean

standard deviation

standard error of the mean

maximum, minimum and median value

The two-tailed, students t-test for unpaired samples compared the means of the groups, and 95% confidence intervals were constructed from the differences of the means. If a significant difference in the standard deviations of the groups was noted, these were subjected to the Welch t-test for populations with unequal standard deviations. The data for each group, treatment and variable were tabulated along with the descriptive statistics described above.

CHAPTER 3

3.0 RESULTS

3.1 DEMOGRAPHICS AND BASELINE FEATURES

3.1.1 Number of healthy volunteers, actual dosage and duration of treatment

All subjects (n = 24) who entered the study were included in the analysis of pharmacokinetic results. One volunteer was discontinued in the second phase due to a protocol violation, but at a very late stage, with the result that all except for the last 3 phenytoin concentration values have been recorded. This did not affect the calculation of the pharmacokinetic parameters, and thus all 24 volunteers were declared evaluable and have been included in the analysis.

3.1.2 Demographic data

The mean values, standard deviations and ranges of the demographic data were as follows:

Table 3.1. Summary of demographic data (n = 24)

	AGE (Years)	WEIGHT (kg)	HEIGHT (cm)
Mean	23.5	69.4	171
SD	3.6	11.1	8.31
Range	19.3 - 31.1	53.2 - 96.5	151 - 183

The individual demographic data are tabulated in Appendix D (Table D1). The smoking and drinking habits of the subjects are listed in Appendix D (Tables D2-D3) as well as

any abnormal medical history if applicable. This was a randomised cross-over study. The two treatment groups were therefore identical with respect to baseline parameters.

3.2 PHARMACOKINETIC RESULTS

All subjects (n = 24) who entered the study were included in the analysis of the pharmacokinetic results. The actual dosage and duration of treatment was as planned (Section 2.2).

3.2.1 Plasma phenytoin concentrations

The plasma phenytoin concentrations (mg/ℓ) as reported for the various sampling times, are presented in Appendix E (Tables E1-E2).

In figure 3.1 the mean plasma concentration versus time curve for phenytoin + placebo and phenytoin + miglitol periods is shown. Graphical representations of the individual concentration versus time curves are shown in Appendix E (Figure E1).

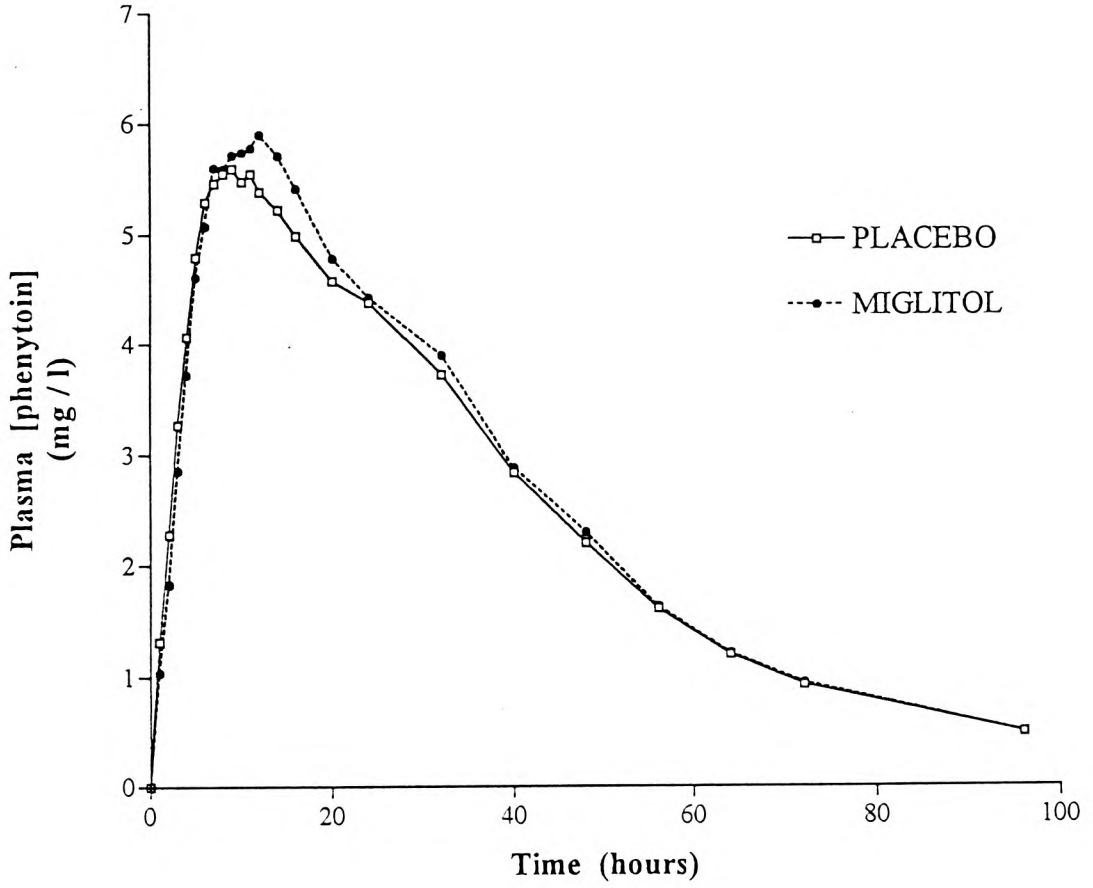

Figure 3.1. Mean plasma concentration versus time plot following a single 400mg dose of phenytoin sodium given concurrently with placebo (open circles) and with three times daily doses of 100mg miglitol (closed circles). Values are expressed as geometric means of the data (n = 24).

3.2.2 Pharmacokinetic variables

In Table 3.2, the geometric means, standard deviation and ranges of the pharmacokinetic variables are presented, as well as the point estimates and confidence intervals for placebo/miglitol mean ratios. The individual placebo/miglitol ratios of these variables are presented in Appendix E (Tables E3-E10). All the ratios for the above variables fall within the range of the confidence intervals. The individual pharmacokinetic variables C_{max}, t_{max}, AUC(0-t_n), AUC(0-∞), a, $t_{½a}$, β and $t_{½\beta}$ are tabulated in Tables 3.3 and 3.4.

In figure 3.2, the groups-by-period analysis is presented. No period effect was evident between the phases as there was no statistical difference between the AUCs for the treatments.

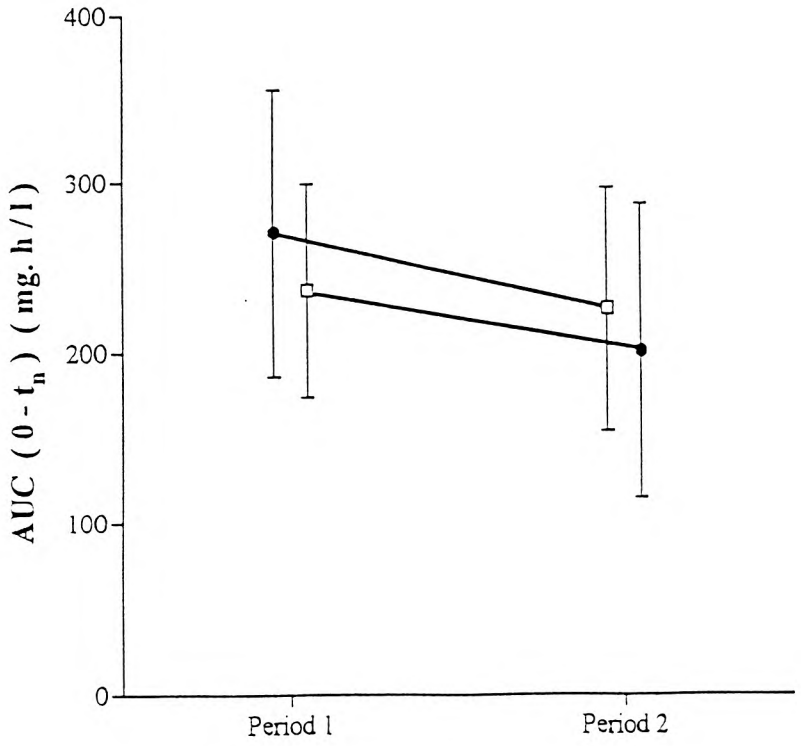

Figure 3.2 Groups-by-period plot for the primary character of extent AUC(0-t_n). Results are given for the geometric mean and standard deviation. Open squares = phenytoin + placebo; closed circles = phenytoin + miglitol

Table 3.2 Summary of pharmacokinetic data

		PHENYTOIN + PLACEBO			PHENYTOIN + MIGLITOL				
VARIABLE	**UNITS**	**Geometric**		**Range**	**Geometric**		**Range**	**Mean Ratio (%)[a]**	**90% Confidence Interval (%)[b]**
		Mean	SD		Mean	SD			
C_{MAX}	(mg/ℓ)	5.97	1.23	4.56 - 9.36	6.09	1.28	3.68 - 10.4	102	95.2 - 109
t_{MAX}	(h)	8.76	1.48	5.02 - 32.0	9.97	1.40	4.00 - 14.0	113	112.5 - 115
$AUC(0\text{-}t_n)$	(mg.h/ℓ)	221	1.34	126 - 354	224	1.39	123 - 430	101	95.3 - 108
$AUC(0\text{-}\infty)$	(mg.h/ℓ)	243	1.36	141 - 460	247	1.39	139 - 531	102	95.8 - 108
$C_{max,norm}$[c]	(kg/ℓ)	1.02	1.18	0.72 - 1.34	1.04	1.16	0.69 - 1.54	--	--
$AUC(0\text{-}t_n)_{norm}$[c]	(kg.h/ℓ)	38.0	1.29	25.1 - 69.4	38.4	1.29	23.3 - 61.8	--	--

[a] Estimate of "test/reference" mean ratio of log-transformed data.

[b] 90% conventional confidence interval for the "test/reference" mean ratio of log-transformed data.

[c] Normalised for dose per body weight.

Table 3.2 Summary of pharmacokinetic data (continued)

		PHENYTOIN + PLACEBO			PHENYTOIN + MIGLITOL				
VARIABLE	**UNITS**	**Geometric**		**Range**	**Geometric**		**Range**	**Mean Ratio (%)[a]**	**90% Confidence Interval (%)[b]**
		Mean	SD		Mean	SD			
$AUC(0-\infty)_{norm}$[c]	(kg.h/ℓ)	41.7	1.32	27.8 - 84.9	42.3	1.30	26.8 - 76.3	--	--
K_a	(h^{-1})	0.20	0.16	0.03 - 0.55	0.16	0.25	0.05 - 1.25	77	42.0 - 95.9
$t_{½a}$	(h)	3.42	2.07	1.25 -24.84	4.03	2.05	0.54 - 12.88	118	95 - 133
β	(h^{-1})	0.04	0.01	0.02 - 0.05	0.04	0.01	0.02 - 0.06	100	99.9 - 101
$t_{½\beta}$	(h)	18.9	1.31	13.3 - 36.6	18.9	1.32	12.4 - 36.2	99.5	91.9 - 108

[a] Estimate of "test/reference" mean ratio of log-transformed data.

[b] 90% conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data.

[c] Normalised for dose per body weight.

Table 3.3 Individual pharmacokinetic values for the period phenytoin + placebo.

Dose: 4 x 100mg phenytoin capsules

SUBJECT NO.	C_{MAX} (mg/ℓ)	t_{MAX} (h)	AUC(0-t_n) (mg.h/ℓ)	AUC(0-∞) (mg.h/ℓ)
1	4.76	14.07	163.478	174.876
2	9.36	8.02	309.815	330.241
3	7.11	9.05	234.782	246.619
4	7.71	8.10	348.747	376.146
5	6.74	8.98	225.573	240.108
6	4.56	6.02	151.059	169.321
7	5.01	10.02	214.904	232.725
8	7.35	10.98	260.637	289.103
9	4.68	7.13	170.647	182.017
10	6.50	11.02	165.671	186.083
11	6.72	6.00	251.163	274.885
12	4.71	5.02	152.552	162.225
13	4.88	14.00	181.542	198.862
14	6.79	5.08	225.805	243.159
15	5.39	10.00	246.476	271.986
16	6.21	32.00	354.279	459.720
17	4.72	7.05	125.925	141.286
18	6.09	7.00	215.532	241.536
19	7.04	9.00	261.768	285.860
20	5.23	6.02	165.291	171.609
21	7.91	7.05	225.927	242.638
22	6.90	10.02	332.498	361.788
23	5.05	9.02	329.861	403.350
24	4.81	9.28	217.148	230.022
Geom mean	5.97	8.76	221.472	243.154
SD	1.23	1.48	1.336	1.363

Table 3.3 Individual pharmacokinetic values for the period phenytoin + placebo. (continued)

Dose: 4 x 100mg phenytoin capsules

SUBJECT NO.	$t_{½\beta}$ (h)	β (h^{-1})	$t_{½a}$ (h)	K_a (h^{-1})
1	13.43	0.052	6.01	0.115
2	15.51	0.045	3.76	0.184
3	14.02	0.049	7.32	0.095
4	23.35	0.030	1.99	0.348
5	16.37	0.042	1.71	0.406
6	18.05	0.038	1.31	0.528
7	24.41	0.028	5.04	0.137
8	19.50	0.036	3.96	0.175
9	15.13	0.046	7.09	0.098
10	18.03	0.038	1.91	0.363
11	18.25	0.038	1.99	0.348
12	13.39	0.052	2.30	0.302
13	18.37	0.038	5.83	0.119
14	17.43	0.040	1.25	0.553
15	25.15	0.028	6.15	0.113
16	36.61	0.019	24.84	0.028
17	16.38	0.042	3.32	0.209
18	19.74	0.035	2.94	0.235
19	17.26	0.040	4.17	0.166
20	19.51	0.036	1.44	0.480
21	13.34	0.052	1.48	0.470
22	23.89	0.029	3.63	0.191
23	34.42	0.020	2.34	0.296
24	20.34	0.034	8.48	0.817
Geom mean	18.95	0.040	3.42	0.200
SD	1.31	0.01	2.07	0.016

Table 3.4 Individual pharmacokinetic values normalised for dose and body weight for the period phenytoin + placebo.

Dose: 4 x 100mg phenytoin capsules

SUBJECT NO.	$C_{MAX.norm}$ (kg/ℓ)	$AUC(0\text{-}t_n)_{norm}$ (kg.h/ℓ)	$AUC(0\text{-}\infty)_{norm}$ (kg.h/ℓ)
1	0.872	29.957	32.046
2	1.338	44.304	47.225
3	0.746	31.226	32.800
4	1.224	55.634	59.713
5	1.151	38.517	40.998
6	1.100	36.443	40.849
7	1.002	42.981	46.545
8	1.259	44.634	49.509
9	0.716	26.109	27.849
10	1.012	25.803	28.982
11	1.327	49.605	54.290
12	0.877	28.113	30.214
13	0.915	34.039	37.287
14	1.119	37.201	40.060
15	0.950	43.441	47.938
16	0.893	50.928	66.085
17	0.939	25.059	28.116
18	1.069	37.826	42.390
19	1.047	38.938	42.522
20	1.151	36.364	37.754
21	1.163	33.211	35.668
22	0.978	47.132	51.283
23	1.063	69.436	84.905
24	0.749	33.821	35.826
Geom mean	1.023	37.979	41.697
SD	1.176	1.289	1.322

Table 3.5 Individual pharmacokinetic values for the period phenytoin + miglitol.

Dose: 4 x 100mg phenytoin capsules

SUBJECT NO.	C_{MAX} (mg/ℓ)	t_{MAX} (h)	AUC(0-t_n) (mg.h/ℓ)	AUC(0-∞) (mg.h/ℓ)
1	5.28	8.00	205.702	224.191
2	8.61	9.00	317.516	336.436
3	7.57	12.25	240.263	256.580
4	6.68	11.03	315.311	334.298
5	6.23	7.02	181.196	193.579
6	4.84	4.00	188.482	205.976
7	5.27	10.03	199.452	222.310
8	5.90	14.00	251.148	275.941
9	7.66	12.00	255.699	272.346
10	7.58	5.12	228.338	241.482
11	4.93	14.03	234.112	257.756
12	3.68	9.02	125.118	143.733
13	6.34	11.00	177.234	200.610
14	6.31	12.00	203.543	217.546
15	5.90	12.03	242.336	274.112
16	7.12	14.00	429.856	530.989
17	4.42	12.00	122.524	141.132
18	5.37	7.00	193.974	213.229
19	10.37	11.00	354.267	371.290
20	4.65	7.00	124.551	138.652
21	7.86	9.25	224.500	235.266
22	7.36	14.00	384.973	426.466
23	4.55	14.00	254.806	302.676
24	5.78	12.00	206.290	225.255
Geom mean	6.09	9.97	224.164	246.751
SD	1.28	1.40	1.387	1.387

Table 3.5 Individual pharmacokinetic values for the period phenytoin + miglitol (continued).

Dose: 4 x 100mg phenytoin capsules

SUBJECT NO.	$t_{½\beta}$ (h)	β (h^{-1})	$t_{½a}$ (h)	K_a (h^{-1})
1	25.26	0.027	6.46	0.107
2	21.81	0.032	5.82	0.119
3	16.51	0.042	7.76	0.089
4	20.20	0.034	8.09	0.086
5	13.38	0.052	6.44	0.108
6	18.49	0.037	0.54	1.283
7	19.52	0.036	3.66	0.190
8	25.41	0.027	6.83	0.101
9	15.09	0.046	4.39	0.158
10	14.77	0.047	1.69	0.410
11	25.85	0.027	3.00	0.231
12	16.22	0.043	4.16	0.167
13	16.59	0.042	4.51	0.154
14	15.66	0.044	5.69	0.123
15	19.58	0.036	12.88	0.054
16	36.18	0.019	4.21	0.165
17	17.20	0.040	8.43	0.082
18	19.02	0.036	1.98	0.351
19	12.38	0.056	2.01	0.345
20	14.74	0.047	3.08	0.225
21	12.81	0.054	2.84	0.244
22	25.15	0.028	5.45	0.127
23	32.04	0.022	6.71	0.103
24	17.25	0.040	1.16	0.600
Geom mean	18.86	0.040	4.03	0.160
SD	1.32	0.010	2.05	0.025

Table 3.6 Individual pharmacokinetic values normalised for dose and body weight for the period phenytoin + miglitol.

Dose: 4 x 100mg phenytoin capsules

SUBJECT NO.	$C_{MAX.norm}$ (kg/ℓ)	$AUC(0\text{-}t_n)_{norm}$ (kg.h/ℓ)	$AUC(0\text{-}\infty)_{norm}$ (kg.h/ℓ)
1	0.968	37.695	41.083
2	1.231	45.405	48.110
3	1.007	31.955	34.125
4	1.060	50.056	53.070
5	1.064	30.939	33.054
6	1.168	45.471	49.692
7	1.054	39.890	44.462
8	1.010	43.009	47.255
9	1.172	39.122	41.669
10	1.181	35.564	37.611
11	0.974	46.237	50.907
12	0.685	23.303	26.770
13	1.189	33.231	37.614
14	1.040	33.534	35.841
15	1.040	42.712	48.312
16	1.023	61.792	76.330
17	0.880	24.382	28.095
18	0.942	34.043	37.422
19	1.543	52.697	55.229
20	1.023	27.401	30.503
21	1.155	33.001	34.584
22	1.043	54.570	60.452
23	0.958	53.637	43.713
24	0.900	32.130	35.803
Geom mean	1.043	38.440	42.314
SD	1.160	1.292	1.303

3.2.3 Safety and tolerability evaluation

3.2.3.1 Clinical laboratory variables

Summaries of the laboratory examinations are given in Appendix E. Table F1 = normal reference ranges; Tables F2-F4 = descriptive statistics for the variables at screening; Table F5 = frequencies of abnormal values , after treatment with phenytoin + placebo, and after treatment with phenytoin + miglitol respectively. As no clinically significant differences were found between the treatment periods, the results of the ANOVA are not reported.

3.2.3.1.1 Haematology

A summary of the haematological variables measured at screening and after the placebo and miglitol periods, is presented in Table 3.7.

The mean erythrocyte count and mean haematocrit for both placebo and miglitol periods were significantly different from screen values, however these differences were not clinically relevant as neither fell below the normal reference range. Although neutropenia was noted in 4 of 24 volunteers at screening; 8 of 24 volunteers at the end of the miglitol period and 2 of 24 at the end of the placebo period, these results did not reach significance.

The ranges for the parameters which show values either above or below the normal reference range are indicated by asterisks where appropriate. These abnormalities were not considered clinically relevant, and all volunteers showing abnormalities were followed up after the study when they returned to normal pre-study levels.

Table 3.7 Summary of laboratory values for haematology (n = 24)

VARIABLE	UNITS	SCREEN		PHENYTOIN + PLACEBO		PHENYTOIN + MIGLITOL	
		Mean	Range	Mean	Range	Mean	Range
Leucocytes	x $10^9/\ell$	6.18	4.20 - 10.30*	6.34	3.10* - 11.20*	6.00	3.30* - 9.00
Erythrocytes	x $10^{12}/\ell$	5.15	4.36** - 6.05	4.91#	4.22** - 5.61	4.91#	4.11**- 5.74
Haematocrit	%	0.45	0.39** - 0.51	0.43#	0.38** - 0.51	0.43#	0.37** - 0.49
Platelets	x $10^9/\ell$	233.63	168 - 192	230.25	169 - 322	232.00	125.00** - 313
Neutrophils	x $10^9/\ell$	3.36	1.68** - 7.00	3.09	0.68** - 6.83	2.77	0.13** - 4.54
Eosinophils	x $10^9/\ell$	0.16	0.00 - 0.65*	0.17	0.00 - 0.72*	0.18	0.00 - 0.63*
Basophils	x $10^9/\ell$	0.04	0.00 - 0.18*	0.03	0.00 - 0.16*	0.03	0.00 - 0.18*
Lymphocytes	x $10^9/\ell$	2.15	0.97** - 3.01	2.52	1.28** - 5.25*	2.48	1.26** - 4.80*
Monocytes	x $10^9/\ell$	0.47	0.17** - 0.93*	0.53	0.18** - 1.01*	0.53	0.22 - 1.08*

* Above Normal Range

** Below Normal Range

\# Statistically but not clinically significant - within normal reference range

3.2.3.1.2 Biochemistry

A summary of the mean biochemical variables measured at screen, and after the placebo and miglitol periods is contained in Table 3.8. Although a number of these variables showed a statistical difference in treatment periods compared to screen, all values were within normal reference ranges and therefore not clinically significant. The variables which showed statistical but not clinical relevance are flagged.

Table 3.8 Biochemistry laboratory results (n = 24)

VARIABLE	UNITS	SCREEN		PHENYTOIN + PLACEBO		PHENYTOIN + MIGLITOL	
		Mean	Range	Mean	Range	Mean	Range
Sodium	mmol/ℓ	140.5	135 - 144	138.8#	136 - 143	139#	137 - 144
Potassium	mmol/ℓ	4.45	4.0 - 5.0	4.1#	3.6 - 4.6	4.1#	3.8 - 4.5
Chloride	mmol/ℓ	102.6	100 - 109	105.5#	101 - 109	105.8#	102 - 112
Urea	mmol/ℓ	4.86	3.10 - 7.40	5.10	3.10 - 9.00*	4.53	2.80 - 7.90**
Creatinine	μmol/ℓ	96.9	78 - 108	89.9#	73 - 130	89#	73 - 119
Uric Acid	mmol/ℓ	0.40	0.28 - 0.56*	0.38	0.23 - 0.56*	0.37	0.22 - 0.51*
Calcium	mmol/ℓ	2.46	2.28 - 2.63*	2.38#	2.17 - 2.55	2.40#	2.19 - 2.67*
Phosphate	mmol/ℓ	1.00	0.78 - 1.40	1.28#	0.96 - 1.60*	1.26#	0.90 - 1.68*
Protein	g/ℓ	77.3	69 - 85*	73.4#	68 - 85*	73.7#	66 - 85*
Albumin	g/ℓ	52.5	43 - 60	46.0#	41 - 53*	46.7#	42 - 52*
ALP	μ/ℓ	84.4	45 - 164*	77.6#	41 - 147*	77#	44 - 128*

* Above Normal Range
** Below Normal Range
\# Statistically but not clinically significant - within normal reference range

Table 3.8 Biochemistry laboratory results (n = 24) (continued)

VARIABLE	UNITS	SCREEN		PHENYTOIN + PLACEBO		PHENYTOIN + MIGLITOL	
		Mean	Range	Mean	Range	Mean	Range
GGT	U/ℓ	28.6	13.0 - 91.0*	34.2	11.0 - 151.0*	32.5	14.0 - 87.0*
AST	U/ℓ	28.8	14.0 - 140.0*	21.8	10.0 - 33.0	20.8	13.0 - 30.0
ALT	U/ℓ	25.4	7.0 - 68.0*	23.6	10.0 - 50.0*	20.8	9.0 - 37.0
Cholesterol	mmol/ℓ	4.2	2.4 - 6.0	4.2	2.5 - 5.8	4.1	2.5 - 6.1
Glucose	mmol/ℓ	5.1	3.9 - 6.4	4.4#	2.9 - 8.2*	4.6	3.3 - 6.2
HCO_3	mmol/ℓ	27.5	21.9 - 36.0*	22.9#	16.6 - 27.1	22.4#	15.4 - 27.2
Total Bilirubin	μ/mol/ℓ	13.2	5.0 - 33.0*	9.8	4.0 - 19.0*	9.8	5.0 - 19.0*
LDH	U/ℓ	187.3	118.0 - 345.0*	154.6#	91.0 - 206.0	155.3#	111.0 - 214.0

* Above Normal Range

** Below Normal Range

\# Statistically but not clinically significant - within normal reference range

3.2.3.2 Adverse Events

The most commonly reported adverse events reported during the study are summarised in Table 3.9. The complete record of adverse events is tabulated in Appendix F (Table F6).

Table 3.9 Frequency of adverse events in volunteers

EVENT	NUMBER *Mild*	%	NUMBER *Moderate*	%	NUMBER *Severe*	%
Phenytoin + Placebo						
Flatulence	8	33	0	0	0	0
Diarrhoea	5	21	0	0	0	0
Headache	4	17	2	8	0	0
Abdominal Pain	3	13	0	0	0	0
Nausea	2	13	0	0	0	0
Phenytoin + Miglitol						
Diarrhoea	13	54	3	13	0	0
Flatulence	11	46	4	17	1	4
Stomach Cramps	3	13	1	4	0	0
Headache	3	13	0	0	0	0
Heartburn	2	8	0	0	0	0

3.2.3.3. Vital signs and physical examinations

No significant differences from baseline were detected during the study. A graphical representation of the systolic and diastolic blood pressure during both study periods is presented below in Figure 3.3. Mean values for blood pressure, heart rate and physical examinations are presented in Appendix F (Table F7).

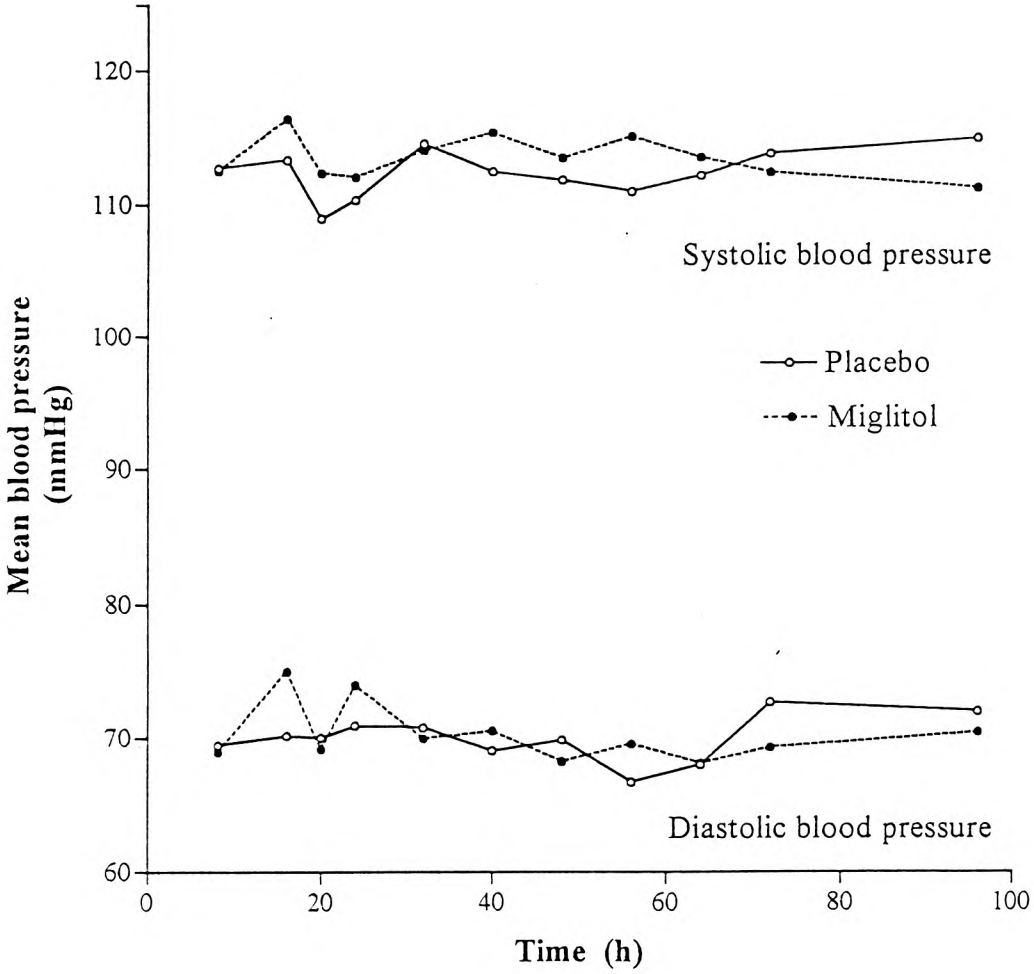

Figure 3.3 Graph of systolic and diastolic blood pressure for phenytoin + placebo (open circles) and phenytoin + miglitol (closed circles) study periods. (n = 24)

3.3 ETHNIC DIFFERENCES IN PHARMACOKINETIC PARAMETERS

The pharmacokinetic data with respect to the two ethnic groups are presented in Table 3.10. Statistically significant differences in AUC(0-t_n), AUC(0-∞) and C_{max}, were found between the groups. No difference was found between treatment values for the individual group. In Figures 3.4 and 3.5 the graphs of the ranges and medians for AUC(0-t_n) and C_{max} are shown.

Table 3.10 Pharmacokinetic comparison of ethnic differences

VARIABLE		UNITS	BLACK (n = 11)#		WHITE (n = 7)#		P
			Mean	Range	Mean	Range	
AUC (0 - t_n)	**Placebo**	mg.h/ℓ	**253.75**	165.67 - 354,28	**197.09**	125.93 - 329.86	0.022*
AUC (0 - t_n)	**Miglitol**	mg.h/ℓ	**263.33**	177.23 - 429.86	**194.66**	122.52 - 255.70	0.018*
AUC (0 - ∞)	**Placebo**	mg.h/ℓ	**280.26**	186.08 - 459.72	**216.81**	141.29 - 403.35	0.041*
AUC (0 - ∞)	**Miglitol**	mg.h/ℓ	**288.87**	193.58 - 530.99	**215.30**	138.65 - 302.68	0.031*
C_{MAX}	**Placebo**	mg/ℓ	**6.72**	4.81 - 9.36	**5.29**	4.56 - 7.91	0.004*
C_{MAX}	**Miglitol**	mg/ℓ	**7.00**	5.37 - 10.37	**5.36**	3.68 - 7.86	0.004*
t_{MAX}	**Placebo**	h	**10.04**	1.02 - 32.00	**7.90**	5.021 - 14.07	0.329
t_{MAX}	**Miglitol**	h	**10.71**	5.12 - 14.00	**10.15**	4.00 - 14.03	0.623

Vol 21 + 22 = Coloured - included in both groups

* $p < 0.05$

Table 3.10 Pharmacokinetic comparison of ethnic differences (n = 24) (Continued)

VARIABLE		UNITS	BLACK (n = 11)#		WHITE (n = 7)#		P
			Mean	Range	Mean	Range	
$t_{½\beta}$	**Placebo**	h	**19.93**	13.34 - 36.61	**18.79**	13.34 - 34.42	0.633
$t_{½\beta}$	**Miglitol**	h	**19.10**	12.38 - 36.18	**19.52**	12.81 - 32.04	0.861
$t_{½a}$	**Placebo**	h	**5.29**	1.25 - 24.84	**3.71**	1.31 - 8.48	0.409
$t_{½a}$	**Miglitol**	h	**5.16**	1.16 - 12.88	**4.28**	0.54 - 8.43	0.440

Vol 21 + 22 = Coloured - included in both groups

* $p < 0.05$

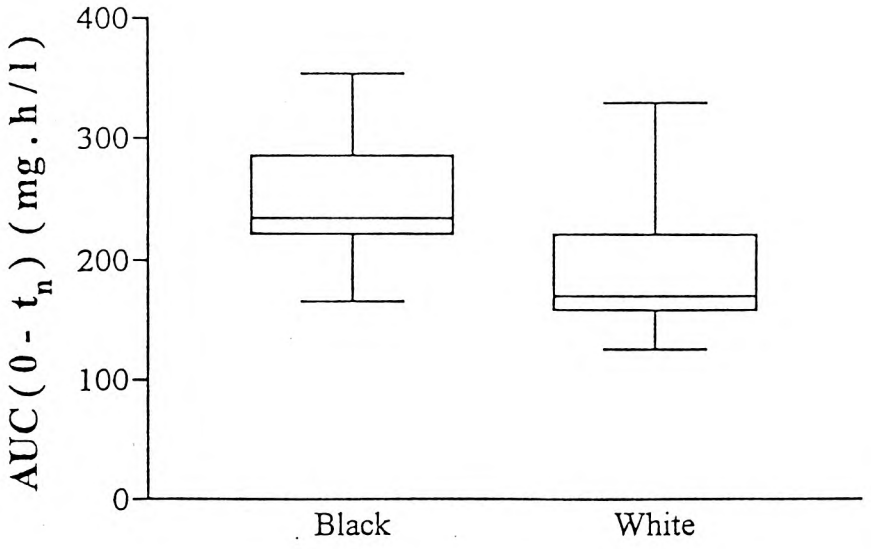

Figure 3.4a Comparison of the area under the plasma concentration curve to 96 hours in black versus white volunteers after a single 400mg dose of phenytoin during the placebo phase (p = 0.022)

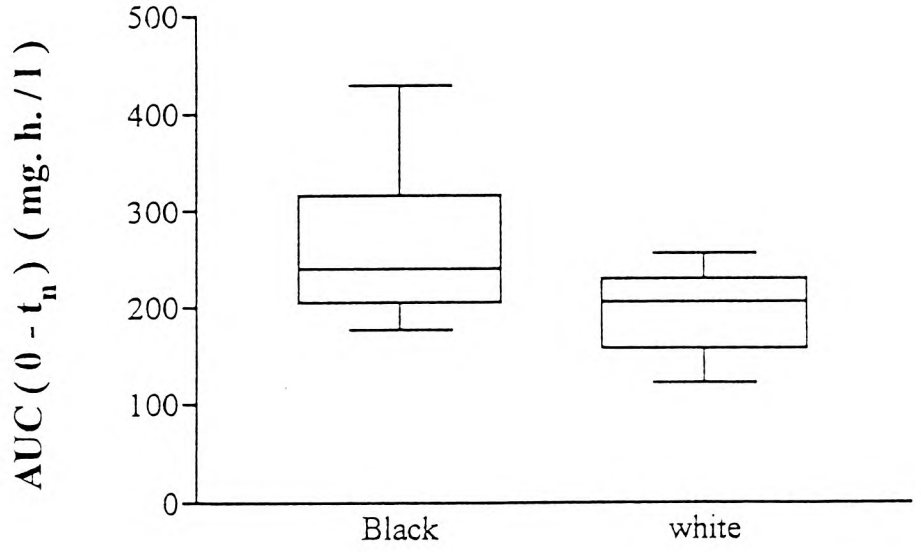

Figure 3.4b Comparison of the area under the plasma concentration curve to 96 hours in black versus white volunteers after a single 400mg dose of phenytoin during the miglitol phase (p = 0.018)

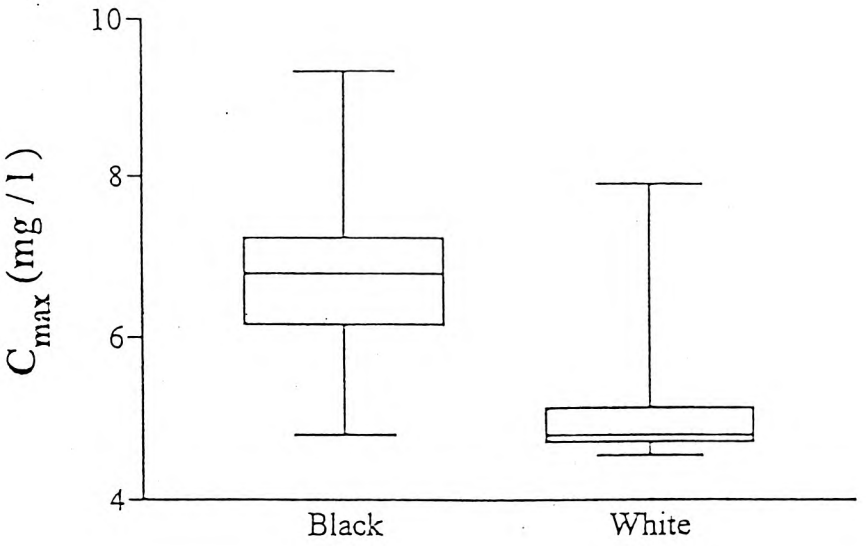

Figure 3.5a Comparison of the maximum concentration (C_{MAX}) in black versus white volunteers after a single 400mg dose of phenytoin during the placebo phase (p = 0.004)

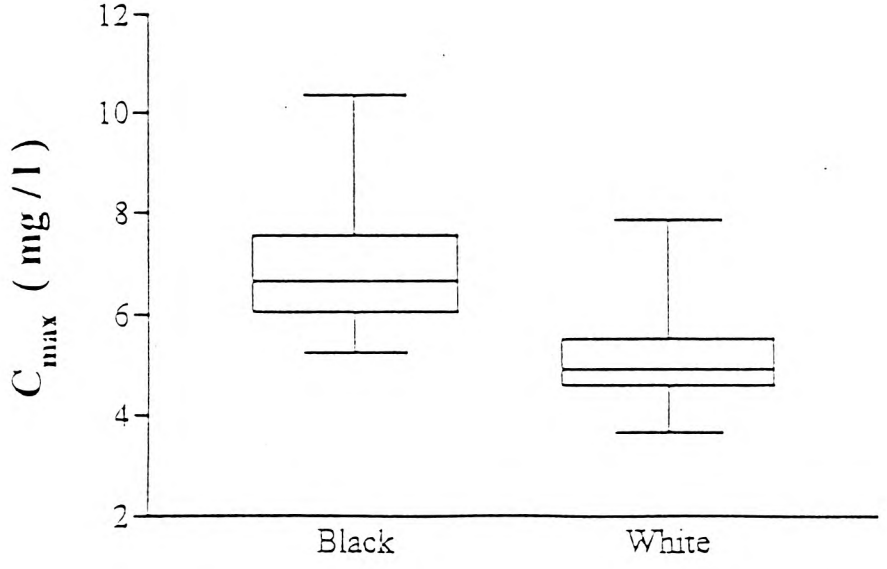

Figure 3.5b Comparison of the maximum concentration (C_{MAX}) in black versus white volunteers after a single 400mg dose of phenytoin during the miglitol phase (p = 0.004)

3.4 VALIDATION OF LABORATORY STANDARDS FOR PHENYTOIN AND MIGLITOL ASSAYS

3.4.1 Phenytoin assays

The coefficient of variation for the assays performed by the TD_X method was as follows:

Phase I		Phase II	
Concentration mg/l	**Coefficient of variation %**	**Concentration mg/l**	**Coefficient of variation %**
2.5	8.80	2.5	5.02
5.0	4.63	5.0	3.10
10.0	2.61	10.0	2.88

3.4.2 Miglitol assays

The coefficient of variation measured during miglitol assays are as follows (assays were carried out in one batch and there are therefore one set of validation data):

Concentration mg/l	Coefficient of variation %
0.3	4.5
0.8	2.9
2.0	5.6

CHAPTER 4

4.0 DISCUSSION

The results from this study show that the combination of phenytoin and miglitol does not alter the pharmacokinetics of phenytoin. These results reflect the bioequivalence of the two drug regimens with respect to the rate and extent of absorption. A conclusion that no interaction exists may be made equally well regarding the distribution and elimination rate of phenytoin with and without miglitol.

4.1 PHARMACOKINETIC VARIABLES

The AUC of phenytoin determined by measurements up to 96 hours post administration, showed no variation in both the phenytoin plus placebo and phenytoin plus miglitol situation (placebo 224mg.h/ℓ vs miglitol 221mg.h/ℓ). Nor did the extrapolation to infinity of the AUC display any differences between the two regimens (miglitol 247mg./ℓ vs placebo 243mg.h/ℓ). C_{max} was consistent during both periods, i.e. miglitol - 6.09mg/ℓ and placebo - 5.97mg/ℓ, the only difference being seen in the slight extension of the range in the test period (miglitol range 3.68 to 10.4mg/ℓ, placebo 4.56 - 9.36mg/ℓ).

t_{max} did however show a degree of variation, but this difference did not reach significance (9.97 hours for miglitol compared to 8.76 hours during the placebo period). Part of this discrepancy could be explained by the presence of the outlier, whose t_{max} for the placebo period (32 hours) produced a skewed data set. If the t_{max} of this volunteer is removed from the analysis of both miglitol and placebo data sets, a normal distribution and no variation is seen. It must also be borne in mind that the measurement of t_{max} is a directly observed value. An outlier may have a considerable influence on the results of such a

variable. Similar results were found for t_{max} in a study by Gugler *et al.*(1992), although the range (2.9 to 8.9 hours) was not as extensive as that in the present study (placebo 5.0 to 32.0 hours; miglitol 4.0 to 14.0 hours). A significant difference in the Gugler study compared to the results under review in this report, is the variation in the time of administration of phenytoin. The volunteers in the Gugler study received their dose one hour after breakfast, whereas in the present study, phenytoin was given within 5 minutes of breakfast. As has been discussed previously, food appears to have the effect of increasing the absorption of phenytoin (Kuhlmann 1994), by reviewing the data for t_{max} in the present study this does not seem the case.

The elimination rate constant and absorption and elimination half-lives of phenytoin were also in harmony with the results of the AUC, C_{max} and t_{max}, showing no difference between the two treatments. Although no significant difference was seen in the absorption rate constant (placebo $0.20h^{-1}$; miglitol $0.16h^{-1}$), the range was extended in the miglitol phase ($0.05 - 1.25h^{-1}$) compared to $0.03 - 0.55h^{-1}$ in the placebo period. The confidence interval for this parameter (42.0% to 95.9%) therefore did not fall within the range for bioequivalence (80.0% - 125%). Again this could be due to an outlier with a K_a of $1.25h^{-1}$. This difference however had no effect on the overall bioequivalence of the study. A similar result was reported in the study by Gugler *et al.* (1992), where the absorption of the single dose showed marked intersubject variation.

The conclusion from the above variables which comprise the rate and extent of absorption as prescribed by the literature (Schultz & Steinijans, 1992) is that miglitol has no effect on either the rate or extent of the absorption of phenytoin and therefore the two regimens

evaluated are bioequivalent. The importance of determining both interaction or lack of interaction between drugs has been described by Steinijans *et al* (1992c). This is especially the case when one of the drugs has a narrow therapeutic index as has phenytoin. In effect a lack of interaction, if all of the preconditions for the study have been met (Steinijans *et al* 1992a), indicates to the clinician that an alteration in the dosing regimen of the drugs tested will be unnecessary. Strict adherence to the experimental design as laid down by the regulatory authorities limits the potential risk to 5%, the level of significance in bioequivalence studies (Schultz & Steinijans 1992; Westlake 1972).

As this was a single dose study of an orally administered form of phenytoin, the absolute bioavailability, F, could not be established. Thus the calculation of total clearance and volume of distribution was abandoned due to the reliance of these variables on F by the equations

$$Cl_{tot} = F.Dose / AUC(0\text{-}\infty) \quad \text{and} \quad V_{d\beta} = F.Dose / \beta.AUC(0\text{-}\infty)$$

It could be argued that as no difference in the AUCs was seen between placebo and miglitol periods, the assumption could be made that the relative bioavailability of the formulation in both instances was the same and therefore F was equal to 1. However, as discussed previously, the bioavailability of phenytoin is variable, not only from product to product but also from batch to batch (Tsai et al 1992; Tyrer et al 1970). Furthermore, Gugler *et al.* (1992) found that the values for absolute bioavailability were different in the single versus the multiple dose regimen (70% - single dose; 86%. - multiple doses) when compared to the intravenous dose. From this data it is clear that

the bioavailability from a single dose study underestimates the true bioavailability. The difference in the data for the single versus multiple dose bioavailabilty, demonstrates further the non-linear elimination of phenytoin even in low concentration ranges as is seen in single dose studies (Gugler *et al.* 1992).

Also of importance in the results of this study, was the lack of interference by food on the absorption of phenytoin with and without miglitol. It must be remembered however, that the volunteers in this study were on a strictly controlled diet in which none of the constituents were reported to have an influence on the absorption of phenytoin. In the general population, unrestricted diets containing those foods and minerals which alter the bioavailability of phenytoin may indeed have a deleterious effect on the absorption of phenytoin (Cacek 1986; Garnett *et al.* 1980; Winter *et al.* 1988). This effect will not be enhanced by the addition of miglitol to the patients drug regimen.

4.2 TRIAL DESIGN

In deciding on the appropriate study design, a number of potential problem areas must be dealt with as described previously. This was a single dose study and as such, the short-comings of this kind of study had to be obviated (Steinijans *et al.* 1992a). The interindividual variability in the clearance of some drugs which led historically to the two-period change-over design avoids the problems associated with carry-over effects or period-treatment interactions, as appropriate washout periods are effected as part of the trial design (Haushke *et al* 1992; Steinijans *et al.* 1992a). In this study no period effect was seen (Figure 3.3), indicating that the washout period was sufficiently long to eliminate any carry-over of drug effect into the follow-on phase.

The second most significant problem incurred in single-dose studies is the estimation of a sufficiently long sampling period in order to minimise the extrapolation of AUC to infinity. The extrapolation should never exceed 20% of the AUC to the last sampling time (Sauter *et al* 1992). In this study the problem was obviated, as the actual sampling period of 96 hours covered 91% of the AUC to infinity in both phases. In addition to the calculation of the AUC, the length of the sampling time is an important factor in the estimation of the terminal half-life.(Steinijans *et al* 1989).

A further problem cited in short term studies, is the lack of overnight samples and the possibility of drug concentrations lying below the limit of detection (Steinijans *et al.* 1992a). Again, this problem was averted by continual sampling for the first 24 hours after administration of the drugs, and thereafter at eight-hourly intervals for the following 72 hours. Even allowing for the large variation in patient metabolism and elimination of phenytoin, the majority of the volunteers showed quantifiable blood concentrations up to the 72 hour sample. Thereafter, as expected, most concentrations tended to lie below the limit of quantification.

Unfortunately, single dose studies do not reflect the recommended use of the drug by the patient, and for this reason as advocated by Rameis (1992), a follow-up study of phenytoin at steady state in combination with placebo and miglitol should be considered. In defence of the single-dose study however, it has been recommended by Steinijans *et al* (1989) that the effects of food or enteral formulations may be successfully investigated in these studies, and the results used as a basis for further research.

4.3 STATISTICAL PLAN AND EVALUATIONS

As is the practice in bioequivalence studies, logarithmic transformation of the data was carried out before statistical testing to ensure a true indication of the central tendency of the data (Dawson-Saunders and Trapp 1990; Steinijans & Hauschke 1992). This transformation is essential due to the large variations in the data which is routinely seen in such studies. As described by Steinijans *et al* (1992c), a multiplicative model is the fundamental pharmacokinetic relationship which is assumed for the determination of equivalence characteristics. This model has been based on empirical evidence and the recommendations and guidelines of the International Association of Pharmaceutical Technology (APV), and has been adopted by international regulatory authorities (Schultz & Steinijans 1992).

The inclusion of 90% confidence intervals in the bioequivalence range instead of the more conservative 95% intervals has been explained by Dawson-Saunders and Trapp (1990) and Steinijans and Hauschke (1992), in that 90% intervals when included in the bioequivalence range of 80 - 125%, represent a narrower range of the desired effect and therefore limit the consumer risk to 5% (Westlake 1982). This approach has been adopted by the APV and the Food and Drugs Administration (FDA). Finally, the power of the study was conserved by the evaluation of the data from all of the volunteers, ensuring that a power of more than 80% was retained and the results can therefore be reported with confidence.

In summary, the study plan met the requirements of international specifications in both design and statistical analysis and averted the stumbling blocks commonly encountered in single dose studies.

4.4 INTERETHNIC DIFFERENCES IN PHARMACOKINETIC PARAMETERS

The principle parameters used in the establishment of bioequivalence, ie AUC(0-t_n) with extrapolation to infinity and C_{max}, showed marked differences between the population groups but none between the treatment groups (Figures 3.4 & 3.5). Thus, bioequivalence was carried through in all parameters, but with different values in each group. The AUC(0-t_n) for the black volunteers was larger by 22% in the placebo period and 26% greater in the miglitol period (Figure 3.4). The same variation existed in the value of the AUC extrapolated to infinity where the differences were repeated with the black volunteers exceeding the AUCs of their white counterparts by 22% in the placebo period and 25.5% in the miglitol period. C_{max} showed the same distribution with increases in the black volunteers of 21% in the placebo phase and 23% in the miglitol period (Figure 3.5).

In summary, the black volunteers had an elevated AUC and C_{max}, while the AUC and C_{max} in the white group was reduced. The AUC and C_{max} are regarded as measures of absorption, therefore phenytoin was more readily absorbed by the black group. At this point, it must be emphasised that the numbers of black to white volunteers were small by statistical standards, and may not reflect the true differences between the groups. However, the volunteers also represent a homogenous population and differences such as these require further evaluation.

The significant differences found between the black and white volunteers has underlined the differences in population groups described in the literature (Chan *et al* 1990; Kalow 1982). Genetic variations in the hydroxylation of phenytoin have been described earlier in this document, as well as the ethnic distribution of such variations. Reduced ability of the cytochrome P_{450} enzymes to hydroxylate phenytoin into its metabolites, has been demonstrated in Japanese (Nakamura *et al.* 1985), Chinese (Chan *et al.* 1990) and to some extent in South African blacks (Miller *et al.* 1987). The genetic observations assessed in the Japanese, Chinese and Caucasian populations do not appear to have been evaluated in the South African context. This remains an area for concerted research in terms of the large numbers of black patients with epilepsy being treated at clinics and emergency rooms.

Although forming a homogenous whole the differences between the ethnic groups are apparent, from the variations in their socio-economic backgrounds, their origins - whether rural or urban which could have influenced their physical development, to the variations in their genetic makeup. In a study conducted by Miller *et al* (1988) in epileptic patients at an outpatient clinic at Baragwanath Hospital, Johannesburg, a difference was measured in the K_m of the black patients compared to generally accepted population values. The black patients had a lower rate of metabolism for phenytoin and it was thus recommended that lower doses of the drug may be appropriate. Similar results were obtained by Valodia, Folb and Seymour (1996) in the black and coloured population in Cape Town, with the exception that these researchers discovered that a decrease in the values of V_m had more influence on the elimination of phenytoin than K_m. If these variations are indicative of the black population as a whole, lower doses of

phenytoin would be required to achieve the same plasma concentrations as in the white population. Tsai *et al* (1992) have reported similar ethnic differences in the kinetics of phenytoin, between the Chinese population in Taiwan and Caucasians. The Chinese patients showed a lower volume of distribution and slower rates of clearance than their Caucasian counterparts. However, these researchers did not evaluate V_m or K_m. Unfortunately, the results of the present single dose study cannot be utilized to calculate V_m or K_m as steady state data is required. No assumptions with regard to these parameters can thus be made.

Further aspects of this problem are those related to genetic inheritance. The polymorphic characteristics in the alleles which control the hydroxylation of phenytoin in different ethnic groups as described by Gibaldi (1991), Meir (1985), Nakamura (1985) and Sloan (1981), has been mentioned previously. p-Hydroxylation is the major metabolic pathway in phenytoin, and defects in this pathway lead to high plasma concentrations of phenytoin. This characteristic is inheritable as shown by Vasco *et al* (1980) in a family where the half-life of phenytoin ranged from 29 to 43 hours compared to a normal range of around 14 hours.

Drug elimination rates are important as is metabolism in its various forms. Variations in intrinsic capacity for drug metabolism can be categorised as follows: the amounts of accessible enzymes, for example through enzyme induction, or as is the case with phenytoin, by the lack of accessible enzymes; the molecular structure of enzymes which differ as in the cytochrome P_{450} enzymes; enzyme activity which may be modified by cofactors, inhibitors or activators. This point is effectively demonstrated in a study on

Japanese and European epilepsy patients (Grasella *et al* 1983). The Michaelis-Menten constant K_m, appears to be 23% less in Japanese patients, possibly due to the existence of allelic differences in cytochromes linked to phenytoin metabolism (Kalow 1982). Adjusting for age did not improve the predictability of either the maximum elimination rate (V_{max}), or the K_m. The coefficient of variation for these parameters ranged from 10 - 20% for the V_{max} and around 50% for the K_m. These results are exactly opposite to those obtained by Valodia *et al* (1996) in South African blacks and coloureds.

A link between the inability to remove debrisoquin (a sulphate used as an antihypertensive) from the blood, and a reduction in the p-hydroxylation of phenytoin, has been reported by Eichelbaum in 1982, but at that stage no cross over studies had been performed to confirm the concurrent conditions (Eichelbaum 1982). Poor metabolizers of debrisoquin, where metabolism is significantly inhibited by a lack of enzymes of the cytochrome P_{450} type, have been associated with similar irregularities in the metabolism of mephenytoin in the Asian population. However, when they were compared to Caucasians, they were found to be 6-fold more likely to carry the defective alleles for the hydroxylation of phenytoin than Caucasians who were in addition poor metabolizers of debrisoquin. No evidence of debrisoquin insufficiency in metabolism was apparent in the Japanese sample population. There do not appear to be comparable studies on South Africa blacks to establish the existence of the polymorphism in these communities.

The therapeutic implications of the abovementioned abnormalities is an increased responsiveness to phenytoin, with elevated serum levels at therapeutic doses. Population numbers may not be relevant if only 8% have such a deficiency. However, in a

population of 60 million, this may amount to 5 million affected persons. Pharmaceutical companies develop and produce their compounds in their country of origin, these products are then distributed throughout the world on the assumption that all groups will react in the same manner. In this respect, the present study has served to highlight the variability in populations outside of the original site of drug development. The results of this, although not statistically correct with respect to significant numbers of subjects, indicate that there may be reason for concern in the prescribing of phenytoin to black patients on the same basis as to Caucasians.

Similar sentiments were expressed by Eichelbaum (1982), who questioned the validity of extrapolating the kinetics and metabolic data obtained in one population group to other ethnic groups in different geographical regions. In the same year, Kalow raised the issues of ethnic differences in drug metabolism in terms of the introduction of drugs into countries other than the place of origin. Safety testing is frequently required by governments before registration, but knowledge is lacking regarding how many and which specific reactions or metabolic pathways should be investigated. The prevalence and significance of population variation requires consideration on a number of strata.

4.5 OUTLIERS - EVALUATION AND IMPORTANCE

The interpersonal variations in the absorption, metabolism and elimination of phenytoin were clearly demonstrated in this study. As described previously in this report, genetic defects in the cytochrome P_{450} hydroxylation of phenytoin may exist in the volunteers on this trial (Eichelbaum 1982, Grasela 1983, Kalow 1982). As the incidence of this type

of polymorphic hydroxylation does not appear to have been described in a South African context, the possibility cannot be discounted.

The importance of such outliers may lie in the fact that they represent a type of subject for whom the relevant bioavailability of the product is markedly different from the majority of the population. They should thus be included in the statistical evaluations unless scientific evidence or explanations warrant their exclusion (Spilker 1991). In addition, they may indicate a genetic variation in the population of the metabolism of the drug, which would require investigation to establish the presence of polymorphic drug oxidation in the population.

4.6 SAFETY AND TOLERABILITY

No significant adverse events were reported during the study, and the statistically significant laboratory abnormalities were not clinically relevant (Tables 3.7 to 3.9). All biochemical, haematological and urinary parameters were within normal reference ranges. A reduction in the number of erythrocytes and haematocrit has been ascribed to the amount of blood taken for kinetic measurements (approximately 310mls). Biochemical disturbances were mild, attributed to the effects of phenytoin and returned to pre-study levels on follow-up. No other abnormalities were noted in physical findings. The study was therefore concluded successfully with respect to safety measures.

4.7 ASPECTS RAISED IN THE STUDY REQUIRING FURTHER RESEARCH

Miglitol has been proven in this single dose study to have no influence on the kinetics of a single dose of phenytoin. However, this is not a true indication of the therapeutic setting with multiple doses of phenytoin and the resultant non-linear kinetics of the drug. Further studies should be undertaken to establish whether the same results are seen in patients at steady state of both drugs. The issues in a study of this kind are of an ethical and practical nature. Ethically it does not seem appropriate to subject healthy volunteers to a drug which may alter their mental functions in a significant way, add to this the difficulty and length of time required to attain steady state; volunteer compliance may then become an important issue. To conduct such a study in controlled epileptics where a possibility exists that miglitol may alter the serum concentrations of phenytoin in however small a way seems irresponsible. It has been established in the literature that patients who are poor hydroxylators of phenytoin may, due to the non-linear kinetics of phenytoin, experience toxic symptoms with only very slight serum increases of the drug. As has been discussed, the therapeutic window for phenytoin is small, and the concentration difference at which either toxic symptoms are seen or seizures occur is slight. Close monitoring preferably in a hospital setting would be required for the conduction of such a study.

Arising from the interethnic variations seen in this study, it seems appropriate that an investigation be carried out in the black and coloured populations to determine the existence and frequency of the alleles responsible for poor metabolism of debrisoquin and whether this abberation is connected to poor hydroxylation of phenytoin in the South African context. Following on from the interethnic differences is the evaluation of the

kinetics of phenytoin in the black population. There appears to be sufficient evidence to question whether the standards and therapy regimens developed in Caucasian models are appropriate for extrapolation to black South Africans. The point is taken however that epilepsy is treated with a great deal of success in South Africa, but this may be attributable to the skills of the clinicians involved rather than adherence to the prescribed literature.

In the same context, clinicians should be made more aware of the serious consequences of the potential interaction between phenytoin and isoniazid. In a country where tuberculosis is rampant, increased vigilance with respect to this interaction should be encouraged. The incidence of slow acetylators should also be investigated, as the quoted reference of 50% of the population appears to be excessive, and there does not appear to be adequate sources in the literature to elucidate the point.

Finally, the existence of genetic abnormalities will need to be taken into account when conducting Phase 1 drug studies. In Phase 1 studies the numbers of subjects selected are small and normal as regards the physical and biochemical characteristics. If in a study the majority of the subjects belong to one extreme group, false data will unwittingly be obtained. The need to establish "metabolic phenotypes " as well as normality in the usual parameters may be relevant in drug trials especially where metabolism of the drug is via vulnerable enzyme pathways.

4.8 CONCLUSIONS

Miglitol as it is used as an adjunct to diabetic therapy, may safely be added to an epileptic's drug regimen if the patient is taking phenytoin. However, it must be remembered that this single dose study has not reflected the true situation when patients are at steady state for both drugs. The need for multiple dose studies has been discussed as well as the ethical and practical problems involved. The issues of genetic variations in the metabolism of phenytoin seen in the volunteers taking part in this study, has raised essential areas of prospective research which should be investigated to ensure that patients are not at risk when exposed to drug regimens developed in other geographic regions.

APPENDICES

APPENDIX A
HUMAN ETHICS APPROVAL

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS (MEDICAL)
Ref: R14/49 (Registry)

CLEARANCE CERTIFICATE PROTOCOL NUMBER M931113

PROJECT	A randomised,double-blind,cross-over trial to determine the effects of multiple doses of miglitol (BAY m 1099) on the pharmacokinetics of a single dose of concomitantly administered phenytoin sodium in healthy male volunteers.
INVESTIGATORS	Professor I Havlik
DEPARTMENT	Experimental and Clinical Pharmacology
DATE CONSIDERED	931126

DECISION OF THE COMMITTEE

Approved unconditionally
Informed Consent Document approved.

DATE 940118 CHAIRMAN .....
(Professor P E Cleaton-Jones)

* Guidelines for written "informed consent" attached where applicable.

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DECLARATION BY INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10001, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorised to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee.

18/11/1994 SIGNATURE .....

APPENDIX B
STUDY PROCEDURES TABLE B1

PROCEDURES AND BLOOD SAMPLING TIMES

Day	Hours after phenytoin dose	Total plasma phenytoin	Trough plasma Miglitol	Laboratory & Procedures
screen day				X, PE, BP, HR, #, H
1 & 20			X	
2 & 21			X	
3 & 22	0	X	X	
	1	X		
	2	X		
	3	X		
	4	X		
	5	X		
	6	X		
	7	X		
	8	X		BP, HR
	9	X		
	10	X		
	11	X		
	12	X		
	14	X		
	16	X		BP, HR
4 & 23	20	X	X	BP, HR
	24	X		BP, HR
	32	X		BP, HR
	40	X		BP, HR
5 & 24	48	X	X	BP, HR
	56	X		BP, HR
	64	X		BP, HR
6 & 25	72	X		BP, HR
7 & 26	96	X		X, PE, BP, HR
14 days washout from day 6 to day 19				

Code: X - Venous blood taken, HR - Heart rate, BP - Blood pressure, # - ECG and Chest X-Ray
PE - Physical examination, H - Medical history and demographics

RANDOMISATION LIST

1	Miglitol	(Phase 1)	-	Placebo	(Phase 2)
2	Placebo	(Phase 1)	-	Miglitol	(Phase 2)
3	Miglitol	(Phase 1)	-	Placebo	(Phase 2)
4	Placebo	(Phase 1)	-	Miglitol	(Phase 2)
5	Placebo	(Phase 1)	-	Miglitol	(Phase 2)
6	Miglitol	(Phase 1)	-	Placebo	(Phase 2)
7	Placebo	(Phase 1)	-	Miglitol	(Phase 2)
8	Miglitol	(Phase 1)	-	Placebo	(Phase 2)
9	Placebo	(Phase 1)	-	Miglitol	(Phase 2)
10	Miglitol	(Phase 1)	-	Placebo	(Phase 2)
11	Miglitol	(Phase 1)	-	Placebo	(Phase 2)
12	Placebo	(Phase 1)	-	Miglitol	(Phase 2)
13	Placebo	(Phase 1)	-	Miglitol	(Phase 2)
14	Miglitol	(Phase 1)	-	Placebo	(Phase 2)
15	Placebo	(Phase 1)	-	Miglitol	(Phase 2)
16	Miglitol	(Phase 1)	-	Placebo	(Phase 2)
17	Placebo	(Phase 1)	-	Miglitol	(Phase 2)
18	Miglitol	(Phase 1)	-	Placebo	(Phase 2)
19	Miglitol	(Phase 1)	-	Placebo	(Phase 2)
20	Placebo	(Phase 1)	-	Miglitol	(Phase 2)
21	Miglitol	(Phase 1)	-	Placebo	(Phase 2)
22	Miglitol	(Phase 1)	-	Placebo	(Phase 2)
23	Placebo	(Phase 1)	-	Miglitol	(Phase 2)
24	Placebo	(Phase 1)	-	Miglitol	(Phase 2)

APPENDIX C

LABORATORY METHODS - PHENYTOIN - TDx ASSAY

CROSS REACTIVITY DATA FOR PHENYTOIN ASSAY

TEST COMPOUND	CONCENTRATION ADDED (μg/ml)	CONCENTRATION FOUND (μg/ml)	% CROSS REACTIVITY
p-Hydroxy-phenylphenyl-hydrantoin (HPPH)	0.10	NR**	-
	1.00	ND*	-
	10.00	1.29	12.9
	100.00	5.32	5.3
	1000.00	NR**	-
Mephenytoin	0.10	NR**	-
	1.00	ND*	-
	10.00	ND*	-
	100.00	2.10	2.1
	1000.00	7.65	0.8
5-ethyl-5-Phenylhydrantoin	0.10	NR**	-
	1.00	ND*	-
	10.00	ND*	-
	100.00	0.44	0.4
	1000.00	2.31	0.2

NR** Not reported
ND* None detected; less than the sensitivity of the assay

The following compounds showed less than 1% cross-reactivity when tested with the phenytoin assay:

Amitriptyline	Amobarbital
Carbamazepine	Carbamazepine-10, 11-Epoxide
Chlorazepate	Chlordiazepoxide
Chlorpromazine	Diazepam
Ethosuximide	Ethotoin
Glutethimide	Imipramine
Methsuzimide	2-Phenyl-2-Ethylmalonamide (PEMA)

Pentobarbital	Phenobarbital
p-Hydroxy Phenobarbital	Primidone
p-Hydroxyphenyphenylhydrantoin Glucoronide	
Promethazine	Secobarbital
Valproic Acid	

APPENDIX D

DEMOGRAPHIC DATA FOR VOLUNTEERS

APPENDIX D

TABLE D1

I. Demographic data

Subject	Age (years)	Sex	Weight (kg)	Height (cm)	Race
1	21.34	Male	73.30	176.00	White
2	26.20	Male	57.20	151.00	Black
3	26.61	Male	53.20	169.00	Black
4	23.25	Male	63.50	180.00	Black
5	22.19	Male	68.30	162.00	Black
6	22.17	Male	96.50	177.00	White
7	20.08	Male	80.00	174.00	White
8	19.28	Male	68.50	167.00	Black
9	23.08	Male	61.20	176.00	White
10	23.10	Male	62.30	163.00	Black
11	20.24	Male	79.00	180.00	White
12	19.79	Male	74.50	182.00	White
13	30.22	Male	75.00	172.00	Black
14	31.12	Male	65.90	166.00	Black
15	21.85	Male	70.50	175.00	Black
16	30.84	Male	57.50	156.00	Black
17	28.65	Male	79.60	183.00	White
18	24.61	Male	70.20	174.00	Black
19	23.64	Male	59.50	163.00	Black
20	22.15	Male	88.00	181.00	White
21	20.50	Male	58.80	175.00	Coloured
22	21.67	Male	56.70	165.00	Black
23	20.08	Male	84.20	169.00	White
24	21.20	Male	62.30	169.00	Coloured
MEAN	23.50		69.40	171.04	
MEDIAN	22.18		68.40	173.00	
GEOMEAN	23.25		68.59	170.84	
STDERR	0.73		2.26	1.70	
STD	3.60		11.08	8.31	
GEOSTD	1.16		1.17	1.05	
CV	15.33		15.97	4.86	
MIN	19.28		53.20	151.00	
MAX	31.12		96.50	183.00	
N	24	24	24	24	24

APPENDIX D

TABLE D2

II. Smoking and drinking habits

Subject	Smoker	Amount	Alcohol	Amount
1	Nonsmoker<1		YES	=<7drinks/week
2	Nonsmoker<1		NO	
3	Nonsmoker<1		YES	=<7drinks/week
4	Nonsmoker<1		NO	
5	Nonsmoker<1		NO	
6	Nonsmoker<1		YES	=<7drinks/week
7	Nonsmoker<1		YES	=<7drinks/week
8	Nonsmoker<1		NO	
9	Nonsmoker<1		YES	=<7drinks/week
10	Nonsmoker<1		NO	
11	Nonsmoker<1		YES	=<7drinks/week
12	Nonsmoker<1		YES	=<7drinks/week
13	Nonsmoker<1		YES	=<7drinks/week
14	Nonsmoker<1		NO	
15	Nonsmoker<1		NO	
16	Smoker	2cigp/d-stopped	NO	
17	Nonsmoker<1		YES	=<7drinks/week
18	Nonsmoker<1		NO	
19	Nonsmoker<1		YES	=<7drinks/week
20	Nonsmoker<1		YES	=<7drinks/week
21	Nonsmoker<1		NO	
22	Nonsmoker<1		YES	=<7drinks/week
23	Nonsmoker<1		YES	=<7drinks/week
24	Nonsmoker<1		NO	
N	24	1	24	13

APPENDIX D

TABLE D3

Medical history

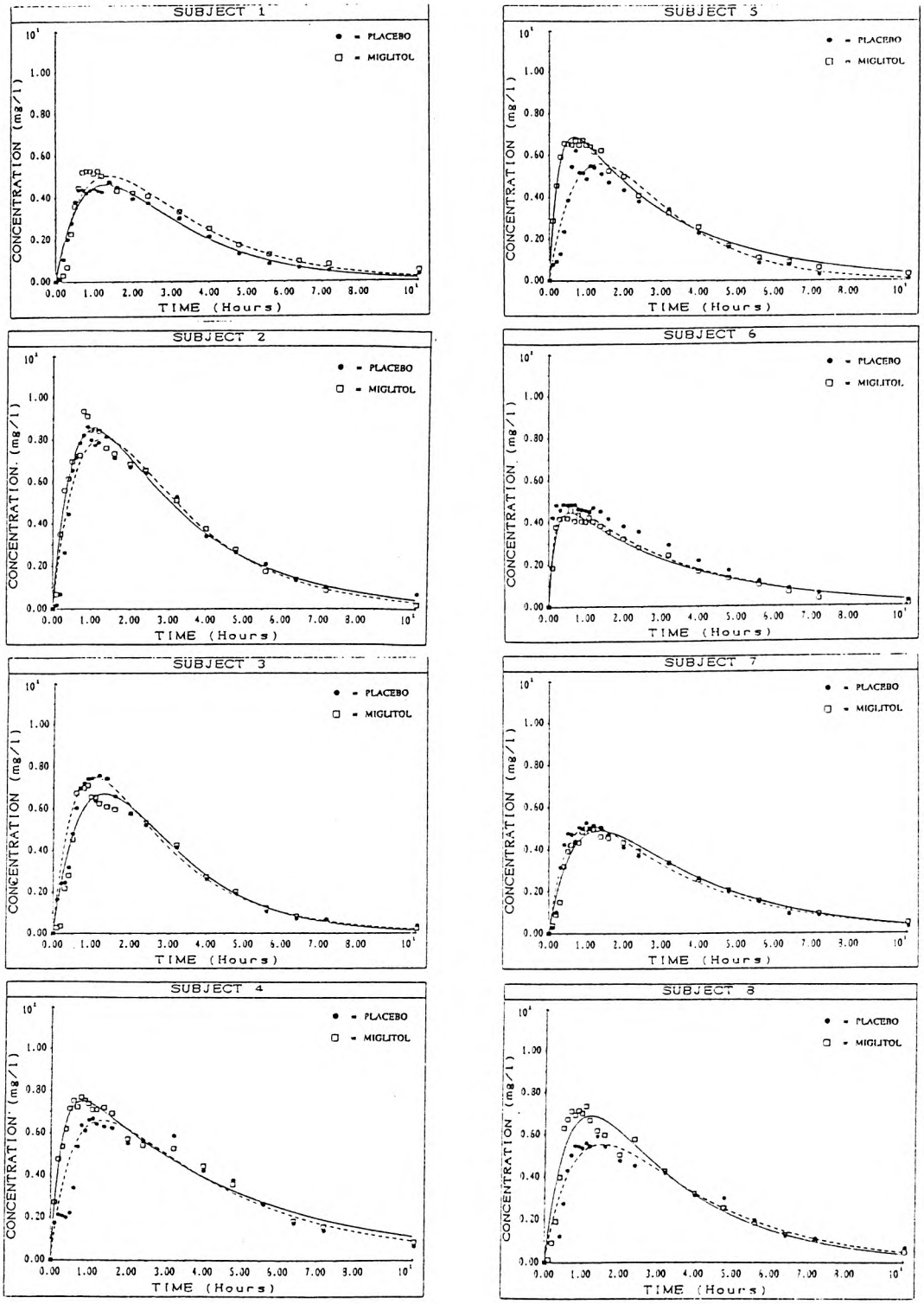
Subject	Allergy	Drug intolerance	Surgery	Hepatic disorders	Renal/ urologic disorders	Neurological disorders	Other disorders
1	Bermuda grass	Possibly penicillin	Appendectomy				
2					Previous STD 1986		
3						Migraines 1991 - Stress	
4			Traditional circumcision 1984				
7	Mild pollen		Tendon repair R hand Tonsillectomy 1982	Neonatal juandice 1974		25% hearing deficiency	
10							Mild acne-current
11					Kidney infection 1993		
12		Neonatal erythromycin 1974	Achilles tendon lengthening 1984				
15							Bilharzia 1991
19			Tonsillectomy 1980				

APPENDIX E

PHARMACOKINETIC DATA FIGURE E1

INDIVIDUAL PLASMA PHENYTOIN CONCENTRATION VERSUS TIME GRAPHS

AFTER A SINGLE 400MG DOSE OF PHENYTOIN

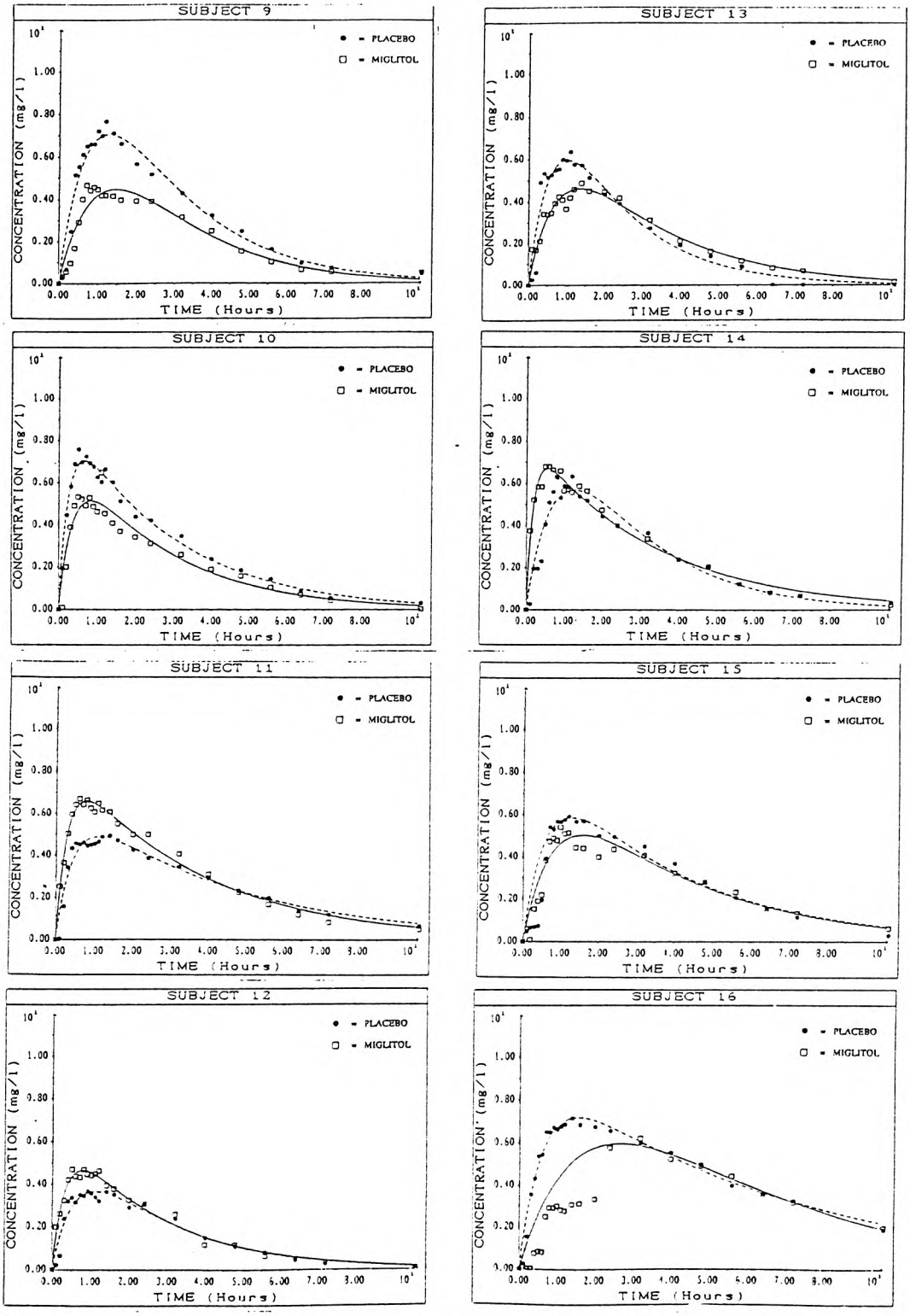


APPENDIX E

PHARMACOKINETIC DATA FIGURE E1

INDIVIDUAL PLASMA PHENYTOIN CONCENTRATION VERSUS TIME GRAPHS

AFTER A SINGLE 400MG DOSE OF PHENYTOIN

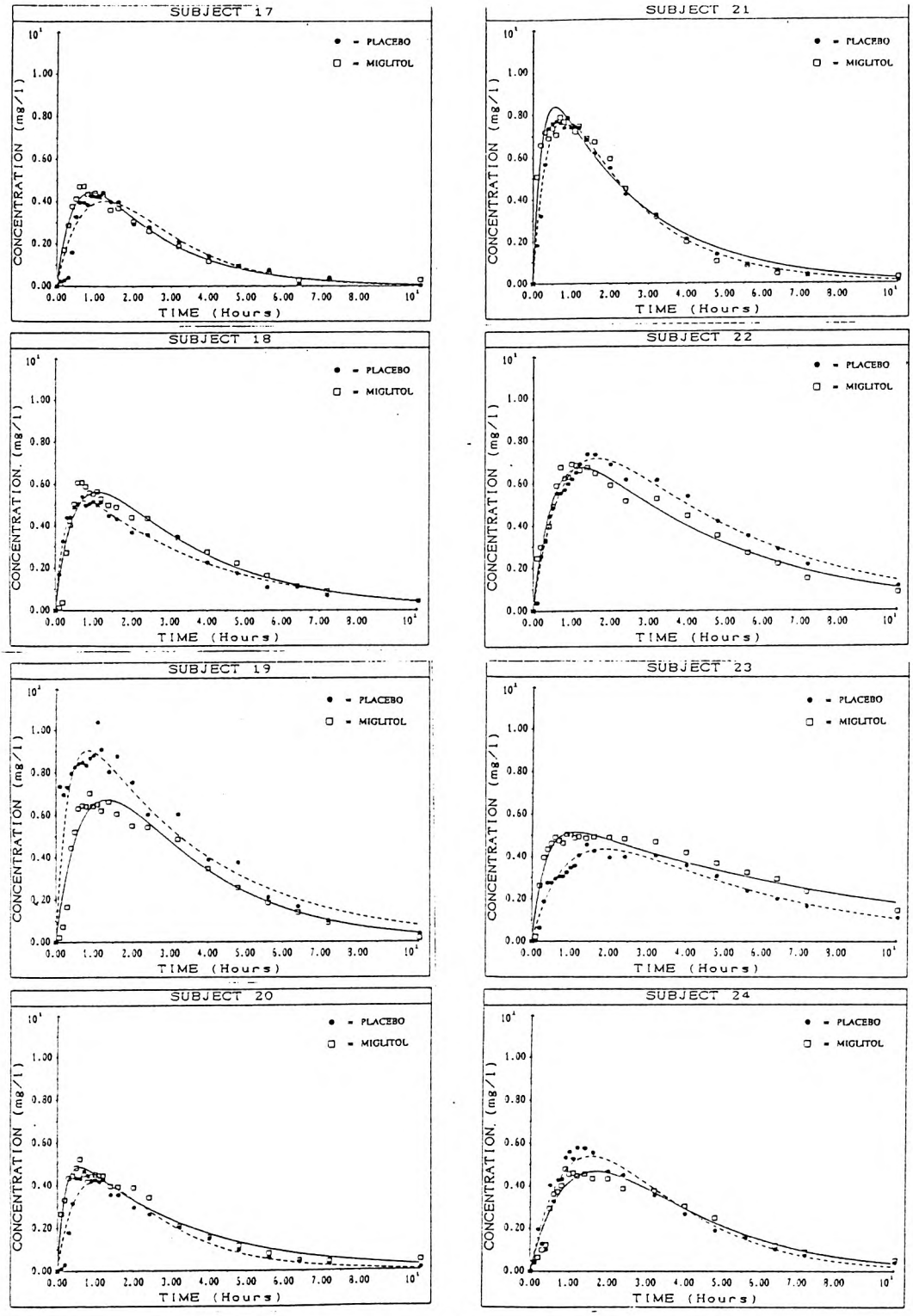


APPENDIX E

PHARMACOKINETIC DATA FIGURE E1

INDIVIDUAL PLASMA PHENYTOIN CONCENTRATION VERSUS TIME GRAPHS

AFTER A SINGLE 400MG DOSE OF PHENYTOIN



APPENDIX E

PHARMACOKINETIC DATA TABLES

APPENDIX E

TABLE E1

Individual plasma phenytoin concentrations (mg/ℓ) for the period phenytoin + placebo.

Dose: 4 x 100mg phenytoin capsules

Lower limit of quantification (LLOQ) = 0.5mg/ℓ

* = Below limit of quantification (BLQ) values in data were substituted with half the LLOQ value

SUBJECT NO.	0 h	1 h	2 h	3 h	4 h	5 h
1	.000	BLQ	1.050	2.020	2.800	3.820
2	.000	.690	3.510	5.600	6.150	6.970
3	.000	BLQ	BLQ	2.180	2.810	4.530
4	.000	2.720	4.760	5.350	6.190	7.150
5	.000	2.900	4.560	5.930	6.580	6.540
6	.000	1.860	3.790	4.170	4.210	4.190
7	.000	BLQ	.910	1.510	3.210	3.930
8	.000	BLQ	.910	1.910	3.990	6.310
9	.000	BLQ	.570	.980	1.690	2.930
10	.000	BLQ	2.000	3.900	4.920	5.330
11	.000	2.540	3.650	5.050	5.970	6.440
12	.000	2.000	2.620	3.240	4.220	4.710
13	.000	1.730	1.670	2.110	3.420	3.380
14	.000	3.760	5.210	5.840	5.840	6.790
15	.000	.610	BLQ	1.520	1.910	2.200
16	.000	BLQ	BLQ	BLQ	.780	.860
17	.000	BLQ	1.710	2.880	3.770	4.140
18	.000	BLQ	BLQ	2.720	4.050	5.050
19	.000	BLQ	.740	1.670	4.460	5.210
20	.000	2.680	3.330	4.350	4.450	4.820
21	.000	5.080	6.590	7.190	6.910	7.380
22	.000	2.460	2.990	3.280	3.990	4.930
23	.000	BLQ	2.650	3.970	4.350	4.620
24	.000	BLQ	.660	1.000	1.230	2.960
MEAN			2.287*	3.276*	4.079	4.800
SD			1.824	1.859	1.678	1.658
GEOM MEAN			1.486	2.652	3.642	4.423
GEOM SD			2.903	2.134	1.721	1.596
CV%			79.748	56.744	41.133	34.536
SEM			.372	.379	.342	.338
MIN	.000	BLQ	BLQ	BLQ	.780	.860
MAX	.000	5.080	6.590	7.190	6.910	7.380
MEDIAN	.000	.430	1.855	3.060	4.130	4.765
n	24	24	24	24	24	24

APPENDIX E

TABLE E1

Individual plasma phenytoin concentrations (mg/ℓ) for the period phenytoin + placebo.

(continued)

Dose: 4 x 100mg phenytoin capsules

Lower limit of quantification (LLOQ) = 0.5mg/ℓ

* = Below limit of quantification (BLQ) values in data were substituted with half the LLOQ value

SUBJECT NO.	6 h	7 h	8 h	9 h	10 h	11 h
1	4.370	4.390	4.230	4.360	4.420	4.320
2	7.210	7.270	9.360	9.120	8.470	8.490
3	6.740	6.960	6.970	7.110	6.550	6.540
4	7.540	7.220	7.710	7.540	7.390	7.100
5	6.510	6.710	6.510	6.740	6.510	6.420
6	4.560	4.060	4.350	4.040	4.020	4.220
7	4.230	4.350	4.330	4.850	5.010	4.920
8	6.730	7.120	6.930	7.150	7.020	7.350
9	4.020	4.680	4.430	4.580	4.480	4.190
10	5.220	4.930	5.300	4.880	4.640	6.500
11	6.720	6.430	6.650	6.260	6.070	6.490
12	4.390	4.340	4.700	4.490	4.430	4.510
13	3.470	3.930	4.250	4.100	3.660	4.200
14	6.790	6.620	6.280	6.580	5.640	5.720
15	3.830	4.710	4.860	4.770	5.390	5.080
16	.840	2.500	2.920	2.910	3.000	2.820
17	4.700	4.720	4.360	4.250	4.410	4.220
18	6.070	6.090	5.880	5.590	5.530	5.650
19	6.310	6.440	6.400	7.040	6.420	6.510
20	5.230	4.540	4.160	4.420	4.510	4.450
21	7.070	7.910	7.690	7.450	7.450	7.210
22	5.900	6.760	6.260	6.310	6.900	6.840
23	4.900	4.740	4.630	5.050	5.010	4.880
24	3.630	3.740	4.030	4.810	4.570	4.620
MEAN	5.291	5.465	5.550	5.600	5.479	5.552
SD	1.579	1.434	1.532	1.492	1.371	1.377
GEOM MEAN	4.939	5.272	5.354	5.413	5.315	5.384
GEOM SD	1.563	1.325	1.315	1.307	1.289	1.294
CV%	29.841	26.239	27.605	26.636	25.017	24.795
SEM	.322	.293	.313	.304	.280	.281
MIN	.840	2.500	2.920	2.910	3.000	2.820
MAX	7.540	7.910	9.360	9.120	8.470	8.490
MEDIAN	5.225	4.835	5.080	4.965	5.200	5.365
n	24	24	24	24	24	24

APPENDIX E

TABLE E1

Individual plasma phenytoin concentrations (mg/ℓ) for the period phenytoin + placebo.

(continued)

Dose: 4 x 100mg phenytoin capsules

Lower limit of quantification (LLOQ) = 0.5mg/ℓ

* = Below limit of quantification (BLQ) values in data were substituted with half the LLOQ value

SUBJECT NO.	12 h	14 h	16 h	20 h	24 h	32 h
1	4.280	4.760	4.510	3.950	3.750	3.030
2	8.410	7.610	7.350	6.850	6.560	5.110
3	6.240	6.090	5.960	5.740	5.320	4.260
4	7.100	7.200	6.930	5.740	5.430	5.280
5	6.180	6.250	5.270	5.000	4.090	3.250
6	4.030	3.820	3.500	3.220	2.790	2.440
7	4.940	4.630	4.550	4.340	3.930	3.370
8	6.680	6.190	5.990	5.040	5.780	4.280
9	4.200	4.160	3.980	3.930	3.900	3.160
10	4.550	4.100	3.710	3.430	3.110	2.600
11	6.160	6.070	5.500	4.980	4.990	4.070
12	4.650	3.950	3.790	3.250	3.080	2.590
13	4.590	4.880	4.510	4.470	4.190	3.130
14	5.580	5.870	5.640	4.740	3.990	3.370
15	5.130	4.430	4.410	4.000	4.360	4.080
16	2.760	3.070	3.110	3.330	5.760	6.210
17	4.350	3.610	3.690	3.060	2.600	1.870
18	5.300	5.000	4.910	4.420	4.380	3.440
19	6.200	6.630	6.050	5.480	5.420	4.850
20	4.440	3.950	3.910	3.880	3.420	2.080
21	7.480	6.910	6.730	5.930	4.520	3.200
22	6.610	6.740	6.470	5.920	5.170	5.280
23	4.940	4.860	4.920	4.900	4.830	4.690
24	4.490	4.580	4.360	4.350	3.890	3.770
MEAN	5.387	5.223	4.990	4.581	4.386	3.725
SD	1.298	1.274	1.188	1.012	1.025	1.109
GEOM MEAN	5.237	5.074	4.856	4.475	4.268	3.566
GEOM SD	1.278	1.281	1.269	1.249	1.273	1.358
CV%	24.104	24.399	23.818	22.090	23.371	29.781
SEM	.265	.260	.243	.207	.209	.226
MIN	2.760	3.070	3.110	3.060	2.600	1.870
MAX	8.410	7.610	7.350	6.850	6.560	6.210
MEDIAN	5.035	4.870	4.730	4.445	4.275	3.405
n	24	24	24	24	24	24

APPENDIX E

TABLE E1

Individual plasma phenytoin concentrations (mg/ℓ) for the period phenytoin + placebo.

(continued)

Dose: 4 x 100mg phenytoin capsules

Lower limit of quantification (LLOQ) = 0.5mg/ℓ

* = Below limit of quantification (BLQ) values in data were substituted with half the LLOQ value

SUBJECT NO.	40 h	48 h	56 h	64 h	72 h	96 h
1	2.130	1.290	.820	.640	BLQ	BLQ
2	3.770	2.790	1.750	1.380	.860	BLQ
3	2.730	2.030	1.230	.840	.620	BLQ
4	4.450	3.590	2.660	1.870	1.610	.860
5	2.600	1.670	1.100	.880	.610	BLQ
6	1.660	1.330	1.010	.680	BLQ	BLQ
7	2.570	2.060	1.560	1.130	.950	.520
8	3.230	2.550	1.820	1.300	1.010	BLQ
9	2.510	1.530	1.020	.660	.550	BLQ
10	1.910	1.590	1.050	.710	BLQ	BLQ
11	3.110	2.250	1.670	1.190	.840	BLQ
12	1.810	1.170	.660	.520	BLQ	BLQ
13	2.120	1.600	1.150	.810	.660	BLQ
14	2.380	2.050	1.230	.840	.680	BLQ
15	3.230	2.810	2.340	1.530	1.330	.630
16	5.220	4.920	4.450	3.570	3.180	1.990
17	1.170	.940	.650	BLQ	BLQ	BLQ
18	2.740	2.240	1.640	1.130	.890	BLQ
19	3.450	2.560	1.840	1.390	.910	BLQ
20	1.560	1.170	.820	BLQ	BLQ	.510
21	1.980	1.040	.840	BLQ	BLQ	BLQ
22	4.480	3.540	2.700	2.180	1.510	.850
23	4.190	3.690	3.250	2.950	2.360	1.460
24	3.050	2.500	1.590	1.190	.900	.510
MEAN	2.835	2.205	1.619	1.172*	.884*	
SD	1.030	.991	.912	.809	.715	
GEOM MEAN	2.660	2.011	1.424	.943	.671	
GEOM SD	1.448	1.550	1.655	2.010	2.147	
CV%	36.331	44.949	56.366	69.030	80.851	
SEM	.210	.202	.186	.165	.146	
MIN	1.170	.940	.650	BLQ	BLQ	BLQ
MAX	5.220	4.920	4.450	3.570	3.180	1.990
MEDIAN	2.665	2.055	1.395	1.005	.760	.250
n	24	24	24	24	24	24

APPENDIX E

TABLE E2

Individual plasma phenytoin concentrations (mg/ℓ) for the period phenytoin + miglitol.

Dose: 4 x 100mg phenytoin capsules

Lower limit of quantification (LLOQ) = 0.5mg/ℓ

* = Below limit of quantification (BLQ) values in data were substituted with half the LLOQ value

SUBJECT NO.	0 h	1 h	2 h	3 h	4 h	5 h
1	.000	BLQ	BLQ	.700	2.300	3.600
2	.000	BLQ	.680	2.620	4.440	6.530
3	.000	1.640	2.420	2.450	3.180	4.780
4	.000	1.720	2.130	2.060	1.990	2.210
5	.000	BLQ	.910	1.270	2.360	3.860
6	.000	4.220	4.810	4.580	4.840	4.800
7	.000	BLQ	1.010	3.150	4.230	4.760
8	.000	BLQ	.590	.560	1.210	2.740
9	.000	BLQ	.670	2.480	5.140	5.530
10	.000	1.920	4.470	5.820	6.870	7.580
11	.000	BLQ	1.570	3.420	4.330	4.560
12	.000	BLQ	.640	2.370	3.180	3.370
13	.000	BLQ	.590	4.900	5.320	5.130
14	.000	BLQ	1.950	1.950	2.300	4.060
15	.000	BLQ	.650	.680	.730	1.950
16	.000	BLQ	1.550	3.560	4.320	5.350
17	.000	BLQ	BLQ	BLQ	1.580	3.270
18	.000	1.680	3.240	4.390	4.390	4.890
19	.000	7.340	6.960	7.300	7.960	8.260
20	.000	BLQ	BLQ	1.780	3.150	4.320
21	.000	1.820	3.230	5.670	7.370	7.610
22	.000	BLQ	2.540	3.320	4.450	4.830
23	.000	BLQ	.640	1.880	2.760	2.760
24	.000	BLQ	1.950	1.270	1.000	4.030
MEAN			1.831*	2.851*	3.725	4.616
SD			1.697	1.838	1.950	1.643
GEOM MEAN			1.219	2.200	3.177	4.337
GEOM SD			2.602	2.285	1.861	1.444
CV%			92.650	64.468	52.352	35.600
SEM			.346	.375	.398	.335
MIN	.000	BLQ	BLQ	BLQ	.730	1.950
MAX	.000	7.340	6.960	7.300	7.960	8.260
MEDIAN	.000	.250	1.280	2.465	3.705	4.660
n	24	24	24	24	24	24

APPENDIX E

TABLE E2

Individual plasma phenytoin concentrations (mg/ℓ) for the period phenytoin + miglitol.

(continued)

Dose: 4 x 100mg phenytoin capsules

Lower limit of quantification (LLOQ) = 0.5mg/ℓ

* = Below limit of quantification (BLQ) values in data were substituted with half the LLOQ value

SUBJECT NO.	6 h	7 h	8 h	9 h	10 h	11 h
1	4.480	5.220	5.280	5.270	5.170	5.280
2	7.150	7.850	8.220	8.610	7.990	7.730
3	6.020	6.950	7.200	7.420	7.430	6.340
4	3.400	5.340	6.350	6.120	6.600	6.680
5	5.450	6.230	5.180	5.160	4.870	5.490
6	4.820	4.820	4.620	4.580	4.530	4.490
7	4.700	4.390	5.040	4.990	5.270	5.000
8	4.290	5.010	5.460	5.420	5.340	5.590
9	6.110	6.500	6.590	6.590	7.200	6.990
10	6.970	7.230	6.920	6.750	6.260	6.030
11	4.510	4.600	4.430	4.490	4.540	4.650
12	3.140	3.510	3.450	3.680	3.580	3.380
13	5.250	5.470	5.530	5.980	5.930	6.340
14	5.080	5.590	6.260	5.300	5.880	5.830
15	3.910	5.380	5.260	5.640	5.640	5.740
16	5.440	6.490	6.480	6.700	6.620	6.760
17	3.940	3.940	3.830	4.250	4.210	4.260
18	5.030	5.370	4.960	5.060	5.150	4.990
19	8.420	8.480	8.330	8.660	8.810	10.370
20	4.300	4.650	4.440	4.180	4.230	4.150
21	7.710	7.600	7.400	7.860	7.390	7.420
22	5.530	5.540	5.700	5.980	6.190	6.500
23	2.960	3.060	3.050	3.240	3.460	3.560
24	3.270	4.290	4.330	5.330	5.600	5.260
MEAN	5.078	5.563	5.596	5.719	5.745	5.785
SD	1.438	1.379	1.404	1.431	1.375	1.510
GEOM MEAN	4.891	5.398	5.424	5.551	5.588	5.608
GEOM SD	1.323	1.288	1.296	1.285	1.275	1.289
CV%	28.307	24.793	25.080	25.023	23.928	26.112
SEM	.293	.282	.287	.292	.281	.308
MIN	2.960	3.060	3.050	3.240	3.460	3.380
MAX	8.420	8.480	8.330	8.660	8.810	10.370
MEDIAN	4.925	5.375	5.370	5.375	5.620	5.665
n	24	24	24	24	24	24

APPENDIX E

TABLE E2

Individual plasma phenytoin concentrations (mg/ℓ) for the period phenytoin + miglitol.

(continued)

Dose: 4 x 100mg phenytoin capsules

Lower limit of quantification (LLOQ) = 0.5mg/ℓ

* = Below limit of quantification (BLQ) values in data were substituted with half the LLOQ value

SUBJECT NO.	12 h	14 h	16 h	20 h	24 h	32 h
1	5.050	4.710	4.340	4.240	4.100	3.340
2	7.860	8.140	7.140	6.700	6.420	5.280
3	7.570	7.430	6.560	5.770	5.190	4.140
4	6.410	6.300	6.230	5.510	5.610	5.870
5	5.410	5.110	4.700	4.340	3.800	3.450
6	4.680	4.500	4.150	3.790	3.540	2.910
7	5.150	5.050	4.720	4.100	3.690	3.350
8	5.440	5.900	5.410	4.740	4.520	4.170
9	7.660	7.100	6.610	5.650	5.160	4.270
10	6.650	6.020	5.120	4.400	4.220	3.470
11	4.870	4.930	4.690	4.250	3.870	3.440
12	3.200	3.640	3.510	2.900	3.060	2.380
13	5.740	5.710	5.120	4.340	3.900	2.720
14	6.310	5.360	5.170	4.420	3.990	3.650
15	5.900	5.640	5.670	4.960	4.920	4.480
16	6.840	7.120	6.820	6.720	6.540	6.000
17	4.420	3.980	3.990	2.930	2.790	2.090
18	5.130	4.480	4.330	3.690	3.560	3.490
19	9.080	8.030	8.760	7.530	6.010	6.010
20	4.270	3.540	3.540	2.960	2.630	2.010
21	7.400	6.830	6.190	5.480	4.250	3.270
22	6.900	7.360	7.330	6.870	6.170	6.150
23	4.050	4.550	4.270	3.950	3.980	4.040
24	5.780	5.750	5.560	4.680	4.520	3.550
MEAN	5.907	5.716	5.414	4.788	4.435	3.897
SD	1.406	1.343	1.320	1.268	1.107	1.213
GEOM MEAN	5.744	5.563	5.267	4.631	4.305	3.720
GEOM SD	1.277	1.271	1.269	1.303	1.284	1.368
CV%	23.795	23.491	24.381	26.490	24.954	31.120
SEM	.287	.274	.269	.259	.226	.248
MIN	3.200	3.540	3.510	2.900	2.630	2.010
MAX	9.080	8.140	8.760	7.530	6.540	6.150
MEDIAN	5.760	5.675	5.145	4.410	4.160	3.520
n	24	24	24	24	24	24

APPENDIX E

TABLE E2

Individual plasma phenytoin concentrations (mg/ℓ) for the period phenytoin + miglitol.

(continued)

Dose: 4 x 100mg phenytoin capsules

Lower limit of quantification (LLOQ) = 0.5mg/ℓ

* = Below limit of quantification (BLQ) values in data were substituted with half the LLOQ value

SUBJECT NO.	40 h	48 h	56 h	64 h	72 h	96 h
1	2.530	1.730	1.260	.950	.810	.520
2	3.400	2.660	2.100	1.320	1.000	.700
3	2.600	1.900	1.050	.690	.680	BLQ
4	4.220	3.780	2.620	1.740	1.390	.640
5	2.280	1.590	.830	.740	BLQ	BLQ
6	2.170	1.690	1.200	.850	.610	BLQ
7	2.640	2.000	1.490	.910	.850	BLQ
8	3.120	3.000	1.960	1.230	1.120	.680
9	3.230	2.480	1.630	.980	.730	BLQ
10	2.370	1.850	1.440	.880	.550	BLQ
11	2.950	2.320	1.970	1.350	1.180	.630
12	1.490	1.090	.800	BLQ	BLQ	BLQ
13	1.900	1.360	.860	MISSING	MISSING	MISSING
14	2.380	2.000	1.220	.790	.640	BLQ
15	3.670	2.830	2.050	1.550	1.130	BLQ
16	5.530	4.970	3.980	3.560	3.260	1.880
17	1.400	.960	.760	BLQ	BLQ	BLQ
18	2.250	1.740	1.080	1.080	.680	BLQ
19	3.870	3.740	2.090	1.650	.990	BLQ
20	1.490	.980	.590	BLQ	BLQ	BLQ
21	2.120	1.370	.890	.590	BLQ	BLQ
22	5.380	4.190	3.500	2.850	2.140	1.130
23	3.580	3.080	2.360	1.990	1.640	1.110
24	2.680	1.890	1.530	1.000	.720	BLQ
MEAN	2.885	2.300	1.636	1.193*	.929*	
SD	1.089	1.053	.856	.791	.695	
GEOM MEAN	2.705	2.090	1.451	.970	.734	
GEOM SD	1.441	1.563	1.642	1.996	2.040	
CV%	37.744	45.765	52.351	66.273	74.808	
SEM	.222	.215	.175	.165	.145	
MIN	1.400	.960	.590	BLQ	BLQ	BLQ
MAX	5.530	4.970	3.980	3.560	3.260	1.880
MEDIAN	2.620	1.950	1.465	.980	.730	BLQ
n	24	24	24	23	23	23

APPENDIX E

TABLE E3

Individual ratios with respect to placebo

Phenytoin pharmacokinetic variable: C_{MAX} (mg/ℓ)

Dose: 4 x 100mg phenytoin capsules

Treatment A: Phenytoin + placebo

Treatment B: Phenytoin + Miglitol

Subject	A	B	B/A	Sequence
1	4.760	5.280	1.109	B A
2	9.360	8.610	.920	A B
3	7.110	7.570	1.065	B A
4	7.710	6.680	.866	A B
5	6.740	6.230	.924	A B
6	4.560	4.840	1.061	B A
7	5.010	5.270	1.052	A B
8	7.350	5.900	.803	B A
9	4.680	7.660	1.637	A B
10	6.500	7.580	1.166	B A
11	6.720	4.930	.734	B A
12	4.710	3.680	.781	A B
13	4.880	6.340	1.299	A B
14	6.790	6.310	.929	B A
15	5.390	5.900	1.095	A B
16	6.210	7.120	1.147	B A
17	4.720	4.420	.936	A B
18	6.090	5.370	.882	B A
19	7.040	10.370	1.473	B A
20	5.230	4.650	.889	A B
21	7.910	7.860	.994	B A
22	6.900	7.360	1.067	B A
23	5.050	4.550	.901	A B
24	4.810	5.780	1.202	A B
GEOMETRIC MEAN	5.966	6.085	1.020	
GEOMETRIC SD	1.231	1.275	1.212	
n	24	24	24	

APPENDIX E

TABLE E4

Individual ratios with respect to placebo

Phenytoin pharmacokinetic variable: t_{MAX} (h)

Dose: 4 x 100mg phenytoin capsules

Treatment A: Phenytoin + placebo

Treatment B: Phenytoin + Miglitol

SUBJECT	A	B	B/A	Sequence
1	14.070	8.000	0.568	B A
2	8.020	9.000	1.122	A B
3	9.050	12.250	1.353	B A
4	8.100	11.030	1.361	A B
5	8.980	7.020	0.782	A B
6	6.020	4.000	0.664	B A
7	10.020	10.030	1.000	A B
8	1.0980	14.000	1.275	B A
9	7.130	12.000	1.683	A B
10	11.020	5.120	0.465	B A
11	6.000	14.030	2.338	B A
12	5.020	9.020	1.797	A B
13	14.000	11.000	0.786	A B
14	5.080	12.000	2.362	B A
15	10.000	12.030	1.203	A B
16	32.000	14.000	0.438	B A
17	7.050	12.000	1.702	A B
18	7.000	7.000	1.000	B A
19	9.000	11.000	1.222	B A
20	6.020	7.000	1.163	A B
21	7.050	9.250	1.312	B A
22	10.020	14.000	1.397	B A
23	9.020	14.000	1.552	A B
24	9.280	12.000	1.293	A B
GEOMETRIC MEAN	8.760	9.970	1.243	
GEOMETRIC SD	1.480	1.40	0.507	
n	24	24	24	

APPENDIX E

TABLE E5

Individual ratios with respect to placebo

Phenytoin pharmacokinetic variable: AUC(0-t_n) (mg.h/ℓ)

Dose: 4 x 100mg phenytoin capsules

Treatment A: Phenytoin + placebo

Treatment B: Phenytoin + Miglitol

SUBJECT	A	B	B/A	Sequence
1	163.478	205.702	1.258	B A
2	309.815	317.516	1.025	A B
3	234.782	240.263	1.023	B A
4	348.747	315.311	.904	A B
5	225.573	181.196	.803	A B
6	151.059	188.482	1.248	B A
7	214.904	199.452	.928	A B
8	260.637	251.148	.964	B A
9	170.647	255.699	1.498	A B
10	165.671	228.338	1.378	B A
11	251.163	234.112	.932	B A
12	152.552	125.118	.820	A B
13	181.542	177.234	.976	A B
14	225.805	203.543	.901	B A
15	246.476	242.336	.983	A B
16	354.279	429.856	1.213	B A
17	125.925	122.524	.973	A B
18	215.532	193.974	.900	B A
19	261.768	354.267	1.353	B A
20	165.291	124.551	.754	A B
21	225.927	224.500	.994	B A
22	332.498	384.973	1.158	B A
23	329.861	254.806	.772	A B
24	217.148	206.290	.950	A B
GEOMETRIC MEAN	221.472	224.164	1.012	
GEOMETRIC SD	1.336	1.387	1.205	
n	24	24	24	

APPENDIX E

TABLE E6

Individual ratios with respect to placebo

Phenytoin pharmacokinetic variable: AUC(0-∞) (mg.h/ℓ)

Dose: 4 x 100mg phenytoin capsules

Treatment A: Phenytoin + placebo

Treatment B: Phenytoin + Miglitol

Subject	A	B	B/A	Sequence
1	174.876	224.191	1.282	B A
2	330.241	336.436	1.019	A B
3	246.619	256.580	1.040	B A
4	376.146	334.298	.889	A B
5	240.108	193.579	.806	A B
6	169.321	205.976	1.216	B A
7	232.725	222.310	.955	A B
8	289.103	275.941	.954	B A
9	182.017	272.346	1.496	A B
10	186.083	241.482	1.298	B A
11	274.885	257.756	.938	B A
12	162.225	143.733	.886	A B
13	198.862	200.610	1.009	A B
14	243.158	217.546	.895	B A
15	271.986	274.112	1.008	A B
16	459.720	530.989	1.155	B A
17	141.286	141.132	.999	A B
18	241.536	213.229	.883	B A
19	285.860	371.290	1.299	B A
20	171.609	138.652	.808	A B
21	242.638	235.266	.970	B A
22	361.788	426.466	1.179	B A
23	403.350	302.676	.750	A B
24	230.022	225.255	.979	A B
GEOMETRIC MEAN	243.154	246.751	1.015	
GEOMETRIC SD	1.363	1.387	1.188	
n	24	24	24	

APPENDIX E

TABLE E7

Individual ratios with respect to placebo

Phenytoin pharmacokinetic variable: $t_{½\beta}$ (h)

Dose: 4 x 100mg phenytoin capsules

Treatment A: Phenytoin + placebo

Treatment B: Phenytoin + Miglitol

Subject	A	B	B/A	Sequence
1	13.433	25.262	1.881	B A
2	15.514	21.810	1.406	A B
3	14.016	16.506	1.178	B A
4	23.350	20.198	.865	A B
5	16.366	13.383	.818	A B
6	18.052	18.490	1.024	B A
7	24.408	19.515	.800	A B
8	19.496	25.412	1.303	B A
9	15.125	15.092	.998	A B
10	18.031	14.765	.819	B A
11	18.249	25.847	1.416	B A
12	13.388	16.223	1.212	A B
13	18.371	16.590	.903	A B
14	17.431	15.662	.899	B A
15	25.146	19.058	.758	A B
16	36.607	36.175	.988	B A
17	16.377	17.202	1.050	A B
18	19.744	19.024	.964	B A
19	17.262	12.376	.717	B A
20	19.511	14.737	.755	A B
21	13.342	12.813	.960	B A
22	23.892	25.154	1.053	B A
23	34.421	32.041	.931	A B
24	20.340	17.520	.861	A B
GEOMETRIC MEAN	18.946	18.855	.995	
GEOMETRIC SD	1.307	1.324	1.262	
n	24	24	24	

APPENDIX E

TABLE E8

Individual ratios with respect to placebo

Phenytoin pharmacokinetic variable: β (h^{-1})

Dose: 4 x 100mg phenytoin capsules

SUBJECT	A	B	B/A	Sequence
1	0.052	0.027	0.519	B A
2	0.045	0.032	0.711	A B
3	0.049	0.042	0.871	B A
4	0.030	0.034	1.122	A B
5	0.042	0.052	1.238	A B
6	0.038	0.037	0.974	B A
7	0.028	0.036	1.286	A B
8	0.036	0.027	0.750	B A
9	0.046	0.046	1.000	A B
10	0.038	0.047	1.236	B A
11	0.038	0.027	0.711	B A
12	0.052	0.043	0.808	A B
13	0.038	0.042	1.105	A B
14	0.040	0.044	1.100	B A
15	0.028	0.036	1.285	A B
16	0.019	0.019	1.000	B A
17	0.042	0.040	0.952	A B
18	0.035	0.036	1.029	B A
19	0.040	0.056	1.400	B A
20	0.036	0.047	1.306	A B
21	0.052	0.054	1.038	B A
22	0.029	0.028	0.966	B A
23	0.020	0.022	1.100	A B
24	0.034	0.040	1.176	A B
GEOMETRIC MEAN	0.040	0.040	1.000	
GEOMETRIC SD	0.010	0.010	1.000	
n	24	24	24	

APPENDIX E
TABLE E9

Individual ratios with respect to placebo
Phenytoin pharmacokinetic variable: $t_{½a}$ (h)
Dose: 4 x 100mg phenytoin capsules

Treatment A: Phenytoin + placebo
Treatment B: Phenytoin + Miglitol

SUBJECT	A	B	B/A	Sequence
1	6.010	6.460	1.075	B A
2	3.760	5.820	1.548	A B
3	7.320	7.760	1.060	B A
4	1.990	8.090	4.065	A B
5	1.710	6.440	3.766	A B
6	1.310	0.540	0.412	B A
7	5.040	3.660	0.726	A B
8	3.960	6.830	1.725	B A
9	7.090	4.390	0.619	A B
10	1.990	1.690	0.885	B A
11	2.300	3.000	1.508	B A
12	2.300	4.160	1.809	A B
13	5.830	4.510	0.774	A B
14	1.250	5.690	4.552	B A
15	6.150	12.880	2.094	A B
16	24.840	4.210	0.169	B A
17	3.320	8.430	2.539	A B
18	2.940	1.980	0.673	B A
19	4.170	2.010	0.482	B A
20	1.440	3.080	2.139	A B
21	1.480	2.840	1.919	B A
22	3.630	5.450	1.501	B A
23	2.340	6.710	2.867	A B
24	8.490	1.160	0.137	A B
GEOMETRIC MEAN	3.420	4.030	1.178	
GEOMETRIC SD	2.070	2.050	0.990	
n	24	24	24	

Individual ratios with respect to placebo
Phenytoin pharmacokinetic variable: K_a (h^{-1})
Dose: 4 x 100mg phenytoin capsules

Treatment A: Phenytoin + placebo
Treatment B: Phenytoin + Miglitol

SUBJECT	A	B	B/A	Sequence
1	0.075	0.007	0.093	B A
2	0.184	0.119	0.647	A B
3	0.095	0.089	0.937	B A
4	0.348	0.086	0.247	A B
5	0.406	0.108	0.266	A B
6	0.528	1.283	2.430	B A
7	0.137	0.190	1.387	A B
8	0.175	0.101	0.577	B A
9	0.098	0.158	1.612	A B
10	0.363	0.410	1.129	B A
11	0.348	0.231	0.664	B A
12	0.302	0.167	0.552	A B
13	0.119	0.154	1.294	A B
14	0.553	0.123	0.222	B A
15	0.113	0.054	0.478	A B
16	0.028	0.165	5.893	B A
17	0.209	0.082	0.392	A B
18	0.235	0.351	1.494	B A
19	0.166	0.345	2.078	B A
20	0.480	0.225	0.469	A B
21	0.470	0.244	0.519	B A
22	0.191	0.127	0.665	B A
23	0.296	0.103	0.348	A B
24	0.817	0.600	0.736	A B
GEOMETRIC MEAN	0.200	0.160	0.800	
GEOMETRIC SD	0.016	0.025	1.562	
n	24	24	24	

APPENDIX F

SAFETY AND TOLERABILITY

TABLE F1

Standard safety data: Normal reference ranges

	Units	From	To
Leucocytes	$\times 10^9$/l	3.92	9.88
Erythrocytes	$\times 10^{12}$/l	4.89	6.11
Haematocrit	%	0.43	0.55
Platelets	$\times 10^9$/l	137.00	373.00
Neutrophils	$\times 10^9$/l	2.00	7.50
Eosinophils	$\times 10^9$/l	0.04	0.40
Basophils	$\times 10^9$/l	0.00	0.10
Lymphocytes	$\times 10^9$/l	1.50	4.00
Monocytes	$\times 10^9$/l	0.20	0.80
Sodium	mmol/l	133.00	147.00
Potassium	mmol/l	3.50	5.30
Chloride	mmol/l	96.00	112.00
Urea	mmol/l	2.50	7.50
Creatinine	µmol/l	53.00	130.00
Uric acid	mmol/l	0.18	0.42
Calcium	mmol/l	2.10	2.55
Phosphate	mmol/l	0.80	1.50
Protein	g/l	63.00	79.00
Albumin	g/l	35.00	50.00
Total bilirubin	µmol/l	3.40	17.10
ALP	U/l	38.00	111.00
GGT	U/l	0.00	65.00
AST	U/l	0.00	43.00
ALT	U/l	0.00	43.00
LD	U/l	117.00	230.00
Cholesterol	mmol/l	0.00	6.00
Glucose	mmol/l	2.50	6.40
HCO_3	mmol/l	20.00	30.00

Standard safety data: Descriptive statistics - Screening

		Screening				
	Units	Mean	SD	Min	Max	Total
Leucocytes	$\times 10^9$/l	6.18	1.58	4.20	10.30	24
Erythrocytes	$\times 10^{12}$/l	5.15	0.39	4.36	6.05	24
Haematocrit	%	0.45	0.03	0.39	0.51	24
Platelets	$\times 10^9$/l	233.63	39.81	168.00	292.00	24
Neutrophils	$\times 10^9$/l	3.36	1.34	1.68	7.00	24
Eosinophils	$\times 10^9$/l	0.16	0.14	0.00	0.65	24
Basophils	$\times 10^9$/l	0.04	0.05	0.00	0.18	24
Lymphocytes	$\times 10^9$/l	2.15	0.52	0.97	3.01	24
Monocytes	$\times 10^9$/l	0.47	0.20	0.17	0.93	24
Sodium	mmol/l	140.46	2.28	135.00	144.00	24
Potassium	mmol/l	4.45	0.32	4.00	5.00	24
Chloride	mmol/l	102.63	2.00	100.00	109.00	24
Urea	mmol/l	4.86	1.00	3.10	7.40	24
Creatinine	µmol/l	96.92	8.48	78.00	108.00	24
Uric acid	mmol/l	0.40	0.06	0.28	0.56	24
Calcium	mmol/l	2.46	0.09	2.28	2.63	24
Phosphate	mmol/l	1.00	0.16	0.78	1.40	24
Protein	g/l	77.33	4.50	69.00	85.00	24
Albumin	g/l	52.46	4.64	43.00	60.00	24
Total bilirubin	µmol/l	15.75	7.80	8.00	38.00	24
ALP	U/l	84.42	29.73	45.00	164.00	24
GGT	U/l	28.63	19.11	13.00	91.00	24
AST	U/l	28.79	24.42	14.00	140.00	24
ALT	U/l	25.42	14.01	7.00	68.00	24
LD	U/l	320.21	95.29	118.00	494.00	24
Cholesterol	mmol/l	4.25	0.87	2.40	6.00	24
Glucose	mmol/l	5.06	0.61	3.90	6.40	24
HCO_3	mmol/l	27.45	3.17	21.90	36.00	24

Standard safety data: Descriptive statistics
Phenytoin + placebo

	Units	Phenytoin + placebo Mean	SD	Min	Max	Total
Leucocytes	$\times 10^9$/l	6.34	1.74	3.10	11.20	24
Erythrocytes	$\times 10^{12}$/l	4.91	0.37	4.22	5.61	24
Haematocrit	%	0.43	0.03	0.38	0.51	24
Platelets	$\times 10^9$/l	230.25	41.38	169.00	322.00	24
Neutrophils	$\times 10^9$/l	3.09	1.23	0.68	6.83	24
Eosinophils	$\times 10^9$/l	0.17	0.16	0.00	0.72	24
Basophils	$\times 10^9$/l	0.03	0.05	0.00	0.16	24
Lymphocytes	$\times 10^9$/l	2.52	0.84	1.28	5.25	24
Monocytes	$\times 10^9$/l	0.53	0.22	0.18	1.01	24
Sodium	mmol/l	138.83	1.79	136.00	143.00	24
Potassium	mmol/l	4.13	0.26	3.60	4.60	24
Chloride	mmol/l	105.46	2.21	101.00	109.00	24
Urea	mmol/l	5.10	1.40	3.10	9.00	24
Creatinine	µmol/l	89.92	12.15	73.00	130.00	24
Uric acid	mmol/l	0.38	0.08	0.23	0.56	24
Calcium	mmol/l	2.38	0.10	2.17	2.55	24
Phosphate	mmol/l	1.28	0.18	0.96	1.60	24
Protein	g/l	73.38	4.12	68.00	85.00	24
Albumin	g/l	46.09	3.12	41.00	53.00	23
Total bilirubin	µmol/l	9.82	4.44	4.00	19.00	24
ALP	U/l	77.58	24.44	41.00	147.00	24
GGT	U/l	34.17	28.58	11.00	151.00	23
AST	U/l	21.79	5.79	10.00	33.00	24
ALT	U/l	23.58	8.79	10.00	50.00	24
LD	U/l	154.58	27.56	91.00	206.00	24
Cholesterol	mmol/l	4.18	0.69	2.50	5.80	24
Glucose	mmol/l	4.42	0.99	2.90	8.20	24
HCO_3	mmol/l	22.85	2.65	16.60	27.10	24

Standard safety data: Descriptive statistics
Phenytoin + miglitol

		Phenytoin + miglitol				
	Units	Mean	SD	Min	Max	Total
Leucocytes	$\times 10^9$/l	6.00	1.53	3.30	9.00	24
Erythrocytes	$\times 10^{12}$/l	4.91	0.40	4.11	5.74	24
Haematocrit	%	0.43	0.03	0.37	0.49	24
Platelets	$\times 10^9$/l	232.00	52.03	125.00	313.00	24
Neutrophils	$\times 10^9$/l	2.77	1.18	0.13	4.54	24
Eosinophils	$\times 10^9$/l	0.18	0.17	0.00	0.63	24
Basophils	$\times 10^9$/l	0.03	0.06	0.00	0.18	24
Lymphocytes	$\times 10^9$/l	2.48	0.87	1.26	4.80	24
Monocytes	$\times 10^9$/l	0.53	0.22	0.22	1.08	24
Sodium	mmol/l	139.00	1.50	137.00	144.00	24
Potassium	mmol/l	4.13	0.16	3.80	4.50	24
Chloride	mmol/l	105.75	2.45	102.00	112.00	24
Urea	mmol/l	4.53	1.14	2.80	7.90	24
Creatinine	µmol/l	89.00	10.90	73.00	119.00	24
Uric acid	mmol/l	0.37	0.08	0.22	0.51	24
Calcium	mmol/l	2.40	0.11	2.19	2.67	24
Phosphate	mmol/l	1.26	0.18	0.90	1.68	24
Protein	g/l	73.71	4.99	66.00	85.00	24
Albumin	g/l	46.73	2.91	42.00	52.00	22
Total bilirubin	µmol/l	9.80	4.27	5.00	19.00	24
ALP	U/l	77.00	22.98	44.00	128.00	24
GGT	U/l	32.46	17.37	14.00	87.00	24
AST	U/l	20.75	4.93	13.00	30.00	24
ALT	U/l	20.79	7.75	9.00	37.00	24
LD	U/l	155.25	26.36	111.00	214.00	24
Cholesterol	mmol/l	4.08	0.86	2.50	6.10	23
Glucose	mmol/l	4.59	0.68	3.30	6.30	24
HCO_3	mmol/l	22.40	2.77	15.40	27.20	24

APPENDIX F
TABLE F5

Standard safety data: Frequencies of abnormal values

Below: Number of volunteers with values below normal reference range
Above: Number of volunteers with values above normal reference range
Total: Total number of subjects

	Units	Screening			Phenytoin + placebo		
		Below	Above	Total	Below	Above	Total
Leucocytes	$\times 10^9$/l		1	24	1	1	24
Erythrocytes	$\times 10^{12}$/l	5		24	12		24
Haematocrit	%	3		24	12		24
Platelets	$\times 10^9$/l			24			24
Neutrophils	$\times 10^9$/l	4		24	2		24
Eosinophils	$\times 10^9$/l	4	1	24	6	1	24
Basophils	$\times 10^9$/l		2	24		2	24
Lymphocytes	$\times 10^9$/l	3		24	2	2	24
Monocytes	$\times 10^9$/l	1	2	24	1	3	24
Sodium	mmol/l			24			24
Potassium	mmol/l			24			24
Chloride	mmol/l			24			24
Urea	mmol/l			24		2	24
Creatinine	µmol/l			24			24
Uric acid	mmol/l		6	24		8	24
Calcium	mmol/l		4	24			24
Phosphate	mmol/l	2		24		3	24
Protein	g/l		7	24		1	24
Albumin	g/l		14	24		1	23
Total bilirubin	µmol/l		7	24		1	24
ALP	U/l		5	24		2	24
GGT	U/l		2	24		2	23
AST	U/l		1	24			24
ALT	U/l		2	24		1	24
LD	U/l		20	24	2		24
Cholesterol	mmol/l			24			24
Glucose	mmol/l			24		1	24
HCO_3	mmol/l		2	24	4		24

APPENDIX F

TABLE F5

Standard safety data: Frequencies of abnormal values (continued)

Below: Number of volunteers with values below normal reference range
Above: Number of volunteers with values above normal reference range
Total: Total number of subjects

	Units	Phenytoin + miglitol		
		Below	Above	Total
Leucocytes	$\times 10^9$/l	1		24
Erythrocytes	$\times 10^{12}$/l	10		24
Haematocrit	%	10		24
Platelets	$\times 10^9$/l	2		24
Neutrophils	$\times 10^9$/l	8		24
Eosinophils	$\times 10^9$/l	4	3	24
Basophils	$\times 10^9$/l		5	24
Lymphocytes	$\times 10^9$/l	2	1	24
Monocytes	$\times 10^9$/l		4	24
Sodium	mmol/l			24
Potassium	mmol/l			24
Chloride	mmol/l			24
Urea	mmol/l		1	24
Creatinine	µmol/l			24
Uric acid	mmol/l		7	24
Calcium	mmol/l		2	24
Phosphate	mmol/l		2	24
Protein	g/l		4	24
Albumin	g/l		4	22
Total bilirubin	µmol/l		1	24
ALP	U/l		2	24
GGT	U/l		2	24
AST	U/l			24
ALT	U/l			24
LD	U/l	1		24
Cholesterol	mmol/l		1	23
Glucose	mmol/l			24
HCO_3	mmol/l	4		24

Number of volunteers experiencing adverse events

Treatment: Phenytoin + placebo

Event	Count Mild	%	Count Moderate	%	Count Severe	%	Count Total	%
Number of patients with adverse events							17/24	71
Flatulence	8	33	0	0	0	0	8/24	33
Headache	4	17	2	8	0	0	6/24	25
Diarrhoea	5	21	0	0	0	0	5/24	21
Abdominal pain	3	13	0	0	0	0	3/24	13
Nausea	3	13	0	0	0	0	3/24	13
Cramps - stomach	2	8	0	0	0	0	2/24	8
Blocked nose	1	4	0	0	0	0	1/24	4
Dizziness	1	4	0	0	0	0	1/24	4
Irritable / anxious	1	4	0	0	0	0	1/24	4
Leukopaenia	1	4	0	0	0	0	1/24	4
Rash - both forearms	1	4	0	0	0	0	1/24	4

Treatment: Phenytoin + miglitol

Event	Count Mild	%	Count Moderate	%	Count Severe	%	Count Total	%
Number of patients with adverse events							22/24	92
Diarrhoea	13	54	3	13	0	0	16/24	67
Flatulence	11	46	4	17	1	4	16/24	67
Cramps - stomach	3	13	1	4	0	0	4/24	17
Abdominal pain	1	4	2	8	0	0	3/24	13
Headache	3	13	0	0	0	0	3/24	13
Belching	1	4	1	4	0	0	2/24	8
Heartburn	2	8	0	0	0	0	2/24	8
Blood / protein in urine	1	4	0	0	0	0	1/24	4
Dizziness	1	4	0	0	0	0	1/24	4
Drowsiness	1	4	0	0	0	0	1/24	4
Hiccoughs	1	4	0	0	0	0	1/24	4
Leukopaenia	1	4	0	0	0	0	1/24	4
Motor vehicle accident	1	4	0	0	0	0	1/24	4
Motorbike accident	0	0	1	4	0	0	1/24	4
Nasal congestion	1	4	0	0	0	0	1/24	4
Nausea	1	4	0	0	0	0	1/24	4
Rash - left arm	1	4	0	0	0	0	1/24	4
Sweating	0	0	1	4	0	0	1/24	4
Tiredness	1	4	0	0	0	0	1/24	4

APPENDIX F

TABLE F6

Number of volunteers experiencing adverse events

Events occurring before treatment

Event	Count Mild	%	Count Moderate	%	Count Severe	%	Count Total	%
Leukopaenia	1	4	0	0	0	0	1/24	4

Events occurring after both treatments

Event	Count Mild	%	Count Moderate	%	Count Severe	%	Count Total	%
Leukopaenia	2	8	0	0	0	0	2/24	8

APPENDIX F

TABLE F7

Vital signs

Means of heart rate, systolic and diastolic blood pressure (mmHg) for period phenytoin + placebo

TIME (hours)	SYSTOLIC (mmHg)		DIASTOLIC (mmHg)		HEART RATE (beats/minute)	
	MEAN	SD	MEAN	SD	MEAN	SD
Screening	118.33	8.00	72.25	7.22	61.50	6.69
+8	113.08	9.15	70.00	8.61	69.17	10.04
+16	113.92	11.52	70.88	9.97	67.71	9.58
+20	110.13	16.15	70.92	11.21	63.83	10.32
+24	111.13	12.85	71.54	9.26	64.83	9.53
+32	114.79	6.99	71.17	7.01	74.42	12.45
+40	112.92	9.66	69.58	8.59	64.58	10.56
+48	112.21	8.53	70.21	6.67	70.08	10.53
+56	111.25	6.80	67.08	6.74	70.38	10.09
+64	112.50	7.66	68.33	6.37	66.67	8.16
+72	114.17	8.17	73.13	7.78	69.00	8.11
+96	115.50	11.29	72.63	9.36	71.71	11.23

APPENDIX F

TABLE F8

Vital signs

Means of heart rate, systolic and diastolic blood pressure (mmHg) for period phenytoin + miglitol

TIME (hours)	SYSTOLIC (mmHg)		DIASTOLIC (mmHg)		HEART RATE (beats/minute)	
	MEAN	SD	MEAN	SD	MEAN	SD
Screening	118.33	8.01	72.25	7.22	61.50	6.69
+8	113.17	11.86	69.83	11.11	66.42	9.55
+16	116.95	11.42	75.58	9.37	67.58	10.78
+20	113.13	12.98	70.08	11.70	63.42	9.98
+24	112.67	11.63	74.58	9.41	42.50	9.44
+32	114.37	8.51	70.42	7.51	66.08	10.79
+40	115.83	10.39	71.25	10.03	67.33	10.68
+48	113.96	9.89	68.54	5.96	69.33	12.13
+56	115.63	10.87	70.00	7.94	72.54	12.74
+64	113.91	8.91	68.48	6.82	66.35	9.68
+72	112.83	8.90	69.78	7.90	68.48	6.79
+96	111.65	9.29	70.87	7.62	70.09	10.29

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