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Pharmacokinetics of Propofol in Cats

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DEDICATIONS

To my husband Dirk

Thank you for putting up with my studies and late night call's

To my mother Annette

Thank you for "standing in" for me when life was going a bit crazy,

which was MOST OF THE TIME

To my children

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To my All Mighty God

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LIST OF ABBREVIATIONS

Abbreviation	Description
AUC (min.µg/mℓ)	Area under plasma concentration curve
A (µg/mℓ)	Distribution phase intercept
B (µg/mℓ)	Distribution and elimination phase intercept
C (µg/mℓ)	Elimination phase intercept
α (min^{-1})	Distribution constant
ß (min^{-1})	Distribution and elimination phase constant
σ (min^{-1})	Elimination constant
K10-HL (min)	Terminal elimination constant half life
α-HL (min)	Distribution half life
ß-HL (min)	Distribution half life
Σ-HL (min)	Elimination half life
i.v.	Intravenous
MRT (min)	Mean residence time
V_C (L/kg)	Volume of central distribution
V_{SS} (L/kg)	Volume of distribution at steady state
Cl (mℓ/kg/min)	Total body clearance

SUMMARY

Since the introduction of the lipid emulsion formulation in 1986, propofol has become established for induction as well as for maintenance of anaesthesia in veterinary practice[1] including cats[2;3-8]. Propofol is rapidly metabolized by hepatic glucuronidation in most species and it has also been shown to undergo extrahepatic metabolism[9-13], so that total body clearance may exceed liver blood flow in certain species.

Because of their highly carniverous diet, cats are little exposed to antiherbivory compounds so that they have become deficient in UGP-glucuronosyltransferase (UGT)[14]. Consequently, a number of drugs are eliminated slowly[15;16], often giving rise to prolonged half-lives of the parent drugs. Cats are therefore sensitive to the adverse effects of many drugs and toxins that are normally glucuronidated before elimination. It is therefore likely that the disposition of propofol may differ markedly from that of humans and other animal species[17].

Adam *et al*[18] reported that for the cremophor propofol formulation in cats, volumes of distribution were smaller and elimination halflives were longer than those of pigs, rats and rabbits. In addition, pulmonary uptake has been demonstrated to occur in cats,[19] however propofol's pharmacokinetics have not been studied formally. The purpose of this study was to determine the pharmacokinetic behaviour of propofol after single intravenous injections.

In comparison with man, the apparent central volume of distribution in domestic cats is small (0.56L.kg^{-1} body weight vs. 0.228L.kg^{-1}) for the human pharmacokinetic parameter set of Marsh *et al*[20] and the clearance (0.0086 L.kg^{-1}.min^{-1} vs. 0.027 L.kg^{-1}.min^{-1}) is approximately 2½ times slower in cats when compared with humans.

Slow clearance should not influence recovery from anaesthesia following standard induction doses, because the early decreases in blood concentrations are predominantly due to redistribution of drug to various tissues (similar to the disposition of thiopentone which exhibits a slow total body clearance[21]. However it is possible that drug may accumulate within the body after prolonged infusions, resulting in delayed recovery times. This phenomenon is best described by calculating "context-sensitive" decrement-times by computer simulation[22-24].

Computer software♣ were used to calculate the 20%, 50% and 80% context-sensitive decrement times for the cat pharmacokinetic model. For comparative purposes, similar calculations were performed for an adult human male (weight 70 kg) using the pharmacokinetic parameter-set of Marsh *et al*[20].

Assuming that recovery from anaesthesia occurs after a 50% decrease in blood concentrations has taken place, it is apparent from the 50% context-senstive decrement-time graph that for infusions lasting up to 20 minutes (during which concentrations are kept constant), recovery can be expected to be rapid and predictable. However if infusions are administered for longer than 20 minutes, the recovery times of the "average" cat increase rapidly, reaching a plateau of 36 minutes, while recovery times of the human remain short, albeit increasing slowly.

Awakening times become dramatically prolonged and unpredictable in both cats and humans if propofol concentrations are required to decrease by 80% for recovery to occur. Under these circumstances the 80% decrement time after a two-hour infusion is approximately two hours in cats and 45 minutes in humans.

♣ TIVA Trainer version 8, author Frank Engbers, Leiden University Medical Centre

On the other hand, if dosing is conservative, so that blood concentrations need to decrease by only 20% for awakening to occur, then recovery times are short and predictable, being only a few minutes, regardless of the duration of the preceding infusion.

These findings are in accordance with those of Pascoe *et al*[25] who reported that cats took longer to recover after a short (30 min) infusion than after a long (150 min) infusion. In their crossover study, the propofol infusion rates were adjusted so that the cats were maintained at a light level of anaesthesia at which they responded sluggishly to pedal stimulation. It is therefore likely that propofol concentrations were kept steady and were similar during the 30-minute as well as during the 150-minute infusions. Delayed recovery has also been reported when propofol was administered to cats on consecutive days[26].

Conclusions and clinical relevance:

We recommend that propofol infusions be administered to cats only for fairly short procedures and that for prolonged surgery, maintenance of anaesthesia should be accomplished using other drugs. In order to decrease the propofol dose, premedication and analgesic supplements should be co-administered to provide "balanced" anaesthesia.

CHAPTER 1

INTRODUCTION

Propofol (2.6-di-ispropylphenol) is a rapidly metabolized non-barbiturate sedative/hypnotic anaesthetic drug that is administered intravenously to small animals to induce sedation and anaesthesia[27]. Due to its limited solubility in aqueous solutions, it is formulated in an aqueous oil-in-water emulsion RAPINOVENT® Shering, PROPOFLOW® Abbott, DIPRIVAN® AstraZeneca, PROPOFOL® Fresenius Kabi, containing 10 mg/mℓ propofol in a glycerol, egg lecithin and soybean oil.

Currently there are no pharmacokinetic studies reported for the lipid formulation of propofol in cats. The understanding of the pharmacokinetics of propofol in cats is essential for its improved clinical use and safety.

1.1 Objective of the present study

The objective of this study was to investigate the pharmacokinetics of propofol in the cat after a single intravenous infusion.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

Joubert[1] showed in a survey amongst the veterinarians in South-Africa that alphaxalone/alphadolone (Saffan®) was the most commonly used anaesthetic agent for induction and maintenance for routine sterilization in cats. This was followed by thiopentone, ketamine and propofol, with or without various premedication drugs[1]. With the discontinuation of alphaxalone/alphadolone from the South-African market, propofol became the most commonly used agent for induction in cats[28].

Propofol appears to offer a clinically useful alternative to thiopentone and ketamine[29] as it is associated with smooth induction and recovery from anaesthetia in the clinical situation[30;31]. After intravenous administration, rapid redistribution to other tissues occurs, resulting in a rapid decrease of blood and brain concentrations. Metabolic clearance is also rapid. No allergic-type reactions were seen in contrast to alphaxalone/alphadalone[31]. No adverse effects were reported when propofol was accidentally injected perivascularly[6]. The lack of tissue irritation if given peri-vascularly gives it distinct advantage over thiopentone[31].

The pharmacological and pharmacokinetic properties of the formulation dissolved in CremophorEL have been studied in animals[18;32]. In 1983 propofol was re-formulated as an oil in water emulsion (Diprivan) which has the same anaesthetic, haemodynamic and pharmacokinetic properties as the Cremophor-El formulation[33-35].

The pharmacodynamic effects of propofol are well described in cats[31;36;37] and humans[29]. However, despite the use and increasing popularity of propofol for induction and maintenance of general anaesthesia in cats over the past 15 years, no reports on its pharmacokinetics could be found. An understanding of the pharmacokinetic features of propofol in cats will facilitate its optimal and rational use.

2.2 Chemical and physical characteristics

Propofol 2.6 di-isopropyl (ICI 35868) is a sterically-hindered alkyl phenol, chemically unrelated to barbiturate, steroid, imidazole or eugenol agents (Figure 1)[33].

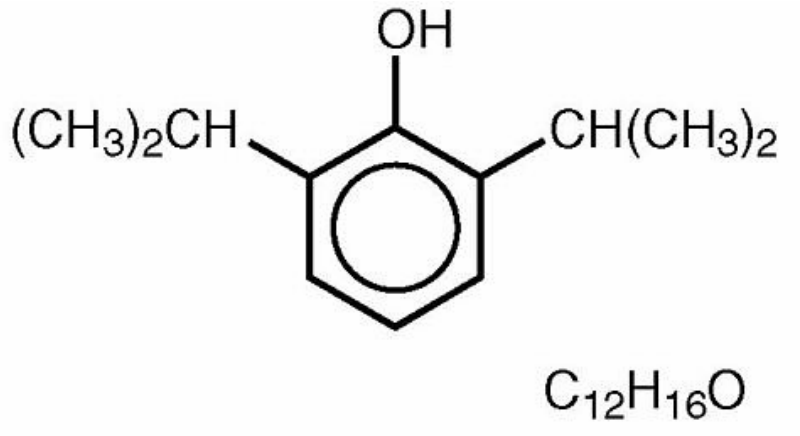

Figure 1 Structural formula of propofol.

The group of hindered phenolic compounds, of which propofol is one, exist as oils at room temperature. Propofol is a weak organic acid with a pKa of 11, so that it is almost entirely un-ionised at pH 7.4[38]. It has a molecular weight of 178. In common with other acidic drugs it is extensively bound to plasma albumin, leaving a free fraction of only 2% over a wide range of drug concentrations. Propofol is formulated as a 1% aqueous solution in 10% soybean oil, 2.25% glycerol and 1.2% purified egg phosphatide emulsion[33].

2.3 Pharmacokinetic properties

Table 1 Summary of pharmacokinetic parameters in different animal species.

Refe-rence	Species	Dose	Compart ments	T½α (min)	T½ß (min)	T½γ (min)	Vd_{ss} mℓ.kg^{-1}	Vd_{area} mℓ.kg^{-1}	$Cl_ß$ mℓ.min^{-1} .kg^{-1}
[39]	Dog	7 mg/kg	3	4.2	31	303	1140		76
	Rat	9.3 mg/kg	3	3.5	33	383	996		72
	Pig	2.5 mg/kg	2	4.9	57		620		76
	Rabbit	5 mg/kg	2	2.1	17		460		337
[40]	Dog	6.5 mg/kg	2 and 3		90.0		6598	4889	58.6
[41]	Dog (mixed breeds)		2	7.671	122.04		9.748		114.8
[41]	Dog (greyhounds)		2	10.9	175.6		6.289		54
[42]	Goat	4 mg/kg/min	2	0.705	15.46		2560	6235	275
[43]	Dog	0.4 mg/kg/min			4862		6040		34.4
[44]	Horse	0.5 mg/kg			.69		894		33.1

$T_{½}$ α, $T_{½}$ β and $T_{½}$ γ = Plasma concentration half-lives of the α, β and γ decay curves. VD_{ss} = Apparent volume of distribution at steady state. Vd_{area} = Apparent volume of distribution based on area under the curve (AUC). $Cl_β$ = Clearance total body.

The pharmacokinetic parameters of propofol that have been studied in various animal species are summarized in Table 1[41-43;45].

2.3.1 Propofol blood concentration versus time profile

In all species, following a single rapid intravenous injection, propofol blood concentrations decrease curvilinearly with time. The pharmacokinetic profile of propofol is usually described by the sum of two or three exponential functions that describe: (1) fast distribution from blood into tissues; (2) rapid metabolic clearance from blood; and (3) slow return of the drug from a poorly perfused deep compartment (probably fat tissue) into blood[34].

Propofol's fast onset and short predictable duration of action are due to a rapid penetration of the blood-CNS barrier and distribution to the central nervous system (CNS), followed by redistribution from the CNS to tissue depots such as muscle and fat[29]. Due to the fast redistribution and efficient elimination, the blood concentration after intravenous injection of a single dose of 2.5mg/kg^{-1} propofol declines within ten minutes to less than 1 µg.mℓ$^{-1}$, the mean value at awakening from anaesthesia occurs in humans[29;35].

The propofol concentration at wakening, following both single and multiple infusions in dogs (about 4 µg.mℓ$^{-1}$) was double that following a bolus dose (about 2 µg.mℓ$^{-1}$). This may possibly indicate acute tolerance to propofol[39].

Where the sampling period in humans was of adequate duration (i.e. 12-24 h post administration), the data were best described by a tri-exponential function. Shorter duration of sampling resulted in description by two exponential phases[29;35;39]. However, in some individuals even when the sampling period was sufficient (> 12 h), only two exponential phases could be determined[29;46]. In goats the blood propofol concentration time profile is best described by a bi-exponential decline[42]. The mean elimination half-life in goats is short (15.5 min), the volume of distribution at steady state large (2.56 ℓ/kg), and the clearance rapid (275 mℓ.min^{-1}.kg^{-1}). No propofol could be detected in any of the goats after 120 minutes, indicating that a bi-exponential decline is appropriate in goats[42]. Dogs premedicated with acepromazine also showed a bi-exponential decline[47], but the use of a lower induction dose and sampling for only three hours, was indicated as the reason for the results. Zoran *et al*[41] also described a two-compartmental model in all the studied dogs when comparing mixed-breed dogs and Greyhounds.

The blood sampling schedule[48] and timing[49] of the first sample can have an important influence on the estimated volume of the central compartment. One of the assumptions of conventional compartmental models is instantaneous and complete mixing between venous and arterial systems. These models cannot accurately describe the initial distribution and transit through the lungs in the first minute after injection. For drugs with a fast onset of action, this is an important shortcoming, because onset of effects may occur before mixing is complete[12].

2.3.2 Plasma Protein Binding

Plasma protein binding of propofol is very high (96-98%) in all species[39]. It is primarily bound to albumin (95%) and it has been demonstrated that only very low albumin concentrations can modify propofol binding. Binding to α1-acid glycoprotein is relatively weak (54%). Plasma protein binding of propofol is similar in both young and elderly patients[50;51].

In vitro data demonstrated that propofol was uniformly distributed within human blood, but its distribution within dog blood favored plasma (overall eryhtrocyte/plasma ratio 0.6), whilst distribution in the rabbit (ratio 13.7) and rat (ratio3.8) blood favored the formed elements[39].

Most researchers measure total blood concentrations of propofol because drug concentrations in plasma are lower than in blood, indicating that the drug is intimately associated with the red blood cells (RBC). Nevertheless, it is assumed that the propofol associated with the RBC is an integral part of the central compartment and is active and available for distribution to other tissues.

Although propofol is extensively bound to the plasma proteins, this does not seem to inhibit its rapid clearance and extensive tissue distribution. The classic displacer drugs also do not affect its plasma protein binding[51]. Hiraoka has reported that total body clearance of propofol was unaffected by changes in protein binding because the hepatic extraction ratio of propofol is very high indicating that hepatic clearance was blood flow- limited[52].

2.3.3 Distribution

A highly lipophilic drug such as propofol would be expected to distribute rapidly and extensively from blood into tissues; the high estimated volume of the central compartment (Vc) and the very high apparent volume of distribution at steady state (Vd_{ss}) being consistent with this prediction[34].

2.3.3.1 Influence of cardiac output

After drug injection, any given drug molecule must make a first pass through the heart and lungs subsystem, before appearing in systemic arterial blood. Thereafter it is distributed to the body organs including those responsible for drug elimination after which it is recirculated.

During the first pass through the heart and lungs subsystem, the drug is essentially added to a stream of blood flowing at a rate determined by the cardiac output (CO)[53]. Avram *et al*[54] suggested that the pharmacokinetics of intravenous anaesthetics are influenced by their initial disposition. Upton *et al*[53] reported that cardiac output is a determinant of the initial concentration of propofol after the administration of a short IV infusion.

Traditional pharmacokinetic compartment models do not include cardiac output as a variable for calculating the predicted drug concentrations[12;34;55;56]. The recirculatory model of Kuipers's *et al*[12], indicates that CO is a determinant of total distribution volume, elimination clearance and some distribution clearances. Pulmonary distribution volume was independent of CO.

Changes in CO are likely to influence liver blood flow and therefore will influence the elimination clearance (Cl_{EI}) of drugs with high hepatic extraction ratios such as propofol[12]. Altering cardiac output had a profound effect on both arterial and brain concentrations of propofol[57]. The influence of CO on the distribution rate is readily understood that, as tissue perfusion increases, more drug is presented to the tissues per unit of time, increasing the tissue uptake[12]. An increase in CO will increase (Cl_{EI}) in drugs with a hepatic blood flow-limited clearance[57]. The initial arterial concentrations of propofol after IV administration were shown to be inversely related to CO. This implies that CO is an important determinant of the induction dose for anaesthesia with propofol[53].

2.3.4 Elimination

Since propofol is eliminated only by metabolism[58], the liver would be expected to be the organ predominantly responsible for the clearance of propofol[34;35]. However, total body clearance of propofol may exceed liver blood flow, and hence extra-hepatic metabolism and/or extra renal elimination (e.g. via the lungs) cannot be excluded[29;34;46].

Evidence for this is provided by the detection of propofol metabolites during the anhepatic phase of orthotopic liver [59;60]. Hiraoka[11] showed significant extraction by the liver and kidneys with the hepatic and renal extraction ratio being approximately 0.9 and 0.7 respectively. The generally accepted estimates for hepatic and renal blood

flow are 21 and 18ml/kg/min respectively[61]. The sum of the calculated hepatic and renal clearance is 31ml/kg/min, which is similar to the total body clearance of propofol measured[52;62;63].

2.3.4.1 Metabolism

In healthy human volunteers, following a sub-anaesthetic dose of ^{14}C-propofol (mean dose 0.47 mg/kg), only 0.3% of the dose was recovered in the urine as unchanged drug[38] indicating that the primary elimination pathway is via metabolism. In humans, metabolism is primarily via glucuronidation to propofol glucuronide[64].

Unchanged propofol accounts for 94% of the radioactive material in blood two minutes after injection, but due to a very rapid metabolism, at ten minutes the value drops to 39%, at 30 minutes to 20%, at one hour to 14%, and 5% at eight hours[38].

The best-known instance of species differences in drug metabolism is the inability of cats to form glucuronides of certain foreign compounds[65;66]. The glucuronyl transferase enzyme usually responsible for the glucuronidation of simple planar phenolic compounds is UGT1A6. The gene responsible for the production of this enzyme has been classified as a pseudogene in cats and the protein it produces is likely not to be functional[14]. A significant proportion of the drug in humans is hydroxylated (to 2-4 diisopropyl-1-4quinol) via various cytochrome P450's and these in turn are glucuronidated (to 4-(2,6 diisopropyl-1-4quinol)-sulphate (4-QS), 1 or 4-(2-6 diisopropyl-1-4quinol)-glucuronide 1-QG and 4-QG). The cytochrome that is mainly involved in this process in humans is cytochrome P4502B6[67], but this specific cytochrome has not been identified in cats.

In cats low molecular weight phenolic compounds are glucoronidated slowly resulting in prolonged half-lives, or metabolized by alternative pathways, such as the easily saturable sulphating pathway. This results in prolonged half-life of the parent drug[16]. Consequently, cats are very sensitive to the adverse effects of many drugs and toxins that are normally glucuronidated before elimination.

Interestingly, other species differences exist, with regard to propofol glucuronidation. Human liver microsomes exhibit greater glucuronidation activity than rabbits, followed by rats[68]. This is in agreement with *in vivo* rat studies that indicate that sulphate conjugates are predominantly excreted in rat urine[68]. Extrahepatic metabolism was investigated using lung and kidney microsomes by the same group. Animal kidney microsomes were able to glucuronidated propofol. No propofol glucuronidation was demonstrated in the lungs of humans, rats or rabbit[68].

The lungs are pharmacologically active organs and affect the blood concentrations of drugs given intravenously. The lungs can take up, retain, metabolize and delay the release of many drugs[69]. One of the assumptions of conventional compartmental models is instantaneous complete mixing in the central compartment. Such models cannot accurately describe the initial distribution and transit through the lung in the first minutes after injection[12;48;69-71]. This can lead to serious errors in estimating pharmacokinetic parameters of traditional pharmacokinetic models, especially with regard to the apparent central volume of distribution[71].

The mixing period may be better described with models that allow for recirculation[69]. The recirculatory model described by Kuipers[12] can better describe the initial mixing and the transit through the lungs that occur in the first minutes after injection.

Studies in rats have shown that lungs play a major role in the formation of sulphate and glucuronide conjugates of phenol[72]. The high total body clearance ($Cl_{TB)}$ in rats may indicate that pulmonary conjugation is involved in propofol's clearance[39;58].

Because the lung receives the entire cardiac output, even a small pulmonary extraction ratio can account for significant clearance. Following pulmonary retention, the drug may return to the blood from the lung at a rate not yet determined or a portion is metabolized by the lung tissues[19].

Extensive first pass elimination of propofol in the lungs has been reported in sheep, cats and rats[73;19;74;75]. However the role of lungs in the metabolism of propofol in humans is controversial[9;10]. Dawidowicsz *et at* [9] reported higher propofol concentration in blood from the right atrium than from the radial artery due to oxidative pulmonary metabolism of propofol during propofol infusion.

The calculated pulmonary extraction ratio was approximately 0.3 – 0.4 and it was demonstrated that human lungs take part in the elimination of propofol by transforming the drug to 2,6-diisopropyl-1,4-quinol[9]. By contrast He *et al*[10] reported no pulmonary extraction at pseudo-steady state. Le Guellec *et al*[68] also determined that propofol glucuronidation does not occur in human lung microsomes.

Hiraoka[11] concluded that the lungs do not contribute to the extra-hepatic clearance of propofol in humans, supporting the report of He *et al*[10]. In Upton's *et al*[76] recirculating kinetic and dynamic model of propofol in man, the best fit was found assuming a lung extraction ratio of 10% and kidney extraction ratio of 30%.

Uridine diphosphate glucuronosyltransferase (UGT) isoforms are expressed in the kidney and the brain[77]. Recent studies also demonstrated a higher rate of propofol glucuronidation in human kidney than in human liver[11].

Uptake and disposition of highly lipid soluble drugs such as propofol into well-perfused organs is frequently assumed to be flow-limited, and changes in organ blood flow induced by the drug itself can alter its own organ distribution.

There are marked disequilibria between propofol concentrations in blood and brain after rapid administration of propofol, and the time-course of the effects of propofol on cerebral blood flow (CBF) and anaesthetic effects are closely related to the time-course of propofol concentrations in the brain but not the arterial blood[78].

Zhang[77] reported that the brain may be a major pathway of extra-hepatic metabolism as expression of UGT isoforms in the brain suggested the possibility of glucuronidation of propofol in the brain. Hiraoaka[11] disagree, as they found no difference between the arterial and internal jugular venous bulb blood concentrations of propofol.

2.3.4.2 Clearance

Propofol's clearance is approximately ten times faster than that of thiopentone in humans because of its high metabolic clearance rate[79]. Total body clearance (Cl_B) is rapid in humans (1.91 $m\ell^{-1}min^{-1}kg^{-1}$)[35], dogs, rats and pigs (50-80 $m\ell.min^{-1}.kg^{-1}$) and even faster in rabbits (340 $m\ell^{-1}min^{-1}kg^{-1}$)[39].

Total body clearance (Cl_B) of propofol following a bolus dose to dogs is about double the estimate of liver blood flow (41 $m\ell^{-1}min^{-1}kg^{-1}$) predicted, whilst for the rat Cl_B is similar to the estimated value (69 $m\ell^{-1}min^{-1}kg^{-1}$)[39].

2.3.4.3 Excretion

Eighty-eight percent of ^{14}C-propofol is excreted glucuronidides in the urine, while in faeces it is less than 2%. Less than 0.3% of propofol is excreted unchanged. The remainder consists of the one and four sulphate conjugates[33;46].

Propofol was cleared by conjugation of the parent molecule or its quinol metabolite; hydroxylation of an isopropyl group also occurred in rat and rabbit. Biliary excretion leading to entero-hepatic recirculation and in turn increased sulfate conjugation, occurred in rats and dogs, but not rabbits, resulting in a marked interspecies variation in drug clearance and metabolite profiles[58].

2.4 Pharmacokinetic Interactions

Co-administration of premedication, neuromuscular blocking agents and other anaesthetics could theoretically change the pharmacokinetic profile of propofol. However, only minor clinically insignificant interactions have been reported[29].

2.4.1 Halothane

Inhalation anaesthetics such as halothane, that decrease hepatic blood flow, would be expected to prolong the elimination half-life of propofol[29;63]. Cockshott *et al* 1987[35] reported that the use of halothane decreased V_C and V_{SS} of propofol in humans by 16% and 36%, respectively. Clearance remained unaffected but $t_{½ß}$ and $t_{½α}$ are reduced by 24% and 35%, respectively. Maintenance of anaesthesia with halothane and nitrous oxide had no effect on pharmacokinetics of propofol in the dog[45].

In cats the first pass uptake of propofol is 61.3% and decreases dramatically to 38.8% when exposed to 1.5% halothane[19]. The exact mechanism remains unclear, but changes in pulmonary blood flow, in capillary surface area due to lung inflation, in arterial blood gas tension, as well as a direct effect of halothane on pulmonary endothelium may be the cause[19].

2.4.2 Fentanyl

As in the case of halothane, Cockshott *et al*[85] found that fentanyl reduced V_C (47%) and V_{SS} (46%) of propofol, as well as in its $t_{½\beta}$ and $t_{½}$ by 24% and 27%, respectively. However, unlike halothane, pre-treatment with fentanyl also reduced the clearance value of propofol by 32% in humans[29;63]. Cats pre-treated with fentanyl also show a reduction in pulmonary uptake. This finding may directly reflect inhibition of pulmonary drug uptake by the presence of a previously administered, highly accumulative drug[19].

2.4.3 Medetomidine

Medetomidine, an α_2-adrenergic receptor agonist can cause profound cardiovascular effects[80] which, at least at high doses, may be expected to alter pharmacokinetics of other drugs by reduction of cardiac output and, hence, liver bloodflow.

2.5 Clinical Implications

The rapid onset of hypnotic agents are determined their physicochemical characteristics. A high diffusible fraction (an un-ionized free drug fraction), good lipid solubility and minimal lipid buffering in the CNS are required for a rapid crossing of the blood-brain barrier and production of an hypnotic effect[29]. The pharmacokinetic properties of propofol, especially its rapid and extensive distribution, indicates that it exhibits the appropriate characteristics to readily cross all cell membranes, including the capillaries in the CNS[29]. However, hysteresis was observed in concentration-effect

studies. The blood propofol concentrations at the onset of unconsciousness were always higher than the steady state concentration necessary to maintain CNS depression, and were directly related to the speed of injection.

Whatever the physiological or physicochemical bases for hysteresis (delayed blood-brain diffusion, delayed receptor binding or initial binding on inactive sites), they remain difficult to assess[29]. In the pharmacokinetic-pharmacodynamic model of Schüttler *et al*[81], an effect compartment was included, with a blood-brain equilibration half-life of about three minutes, to provide for an adequate mathematical description of the occurrence of hysteresis[82].

Ludbrook *et al*[67] observed significantly shorter induction times following slow injection compared with fast injection of the same dose of propofol. On the other hand, the percentage of successful inductions decreased when a similar dose was injected even more slowly, probably because a greater fraction of the drug had already distributed elsewhere than in the CNS.

A high propofol concentration gradient is necessary to produce rapid induction of anaesthesia. But as high blood propofol concentrations may produce important cardiovascular side effects, a slower injection speed of a somewhat larger amount might be preferable[29;46].

It is important to determine the contribution of each organ to total propofol clearance in order to adjust the dosage for certain disease states or specific surgical procedures[11]. When a drug is extensively metabolized, dosage reduction is generally recommended for patients with severe hepatic dysfunction since it is the most likely site of metabolism. If only 60% of total body clearance is contributed by the liver, 40% must be extracted by organs other than the liver[11]. Many studies indicate that the total body

clearance of propofol is similar in individuals with renal failure, hepatic cirrhosis and in healthy subjects[83].

Understanding the factors that determine the offset of drugs effect is essential to clinical practice. The short duration of action of propofol indicates that the drug-receptor complexes are readily broken when the concentration gradient is reversed so that the duration of action is related to the rapid decay of blood drug concentrations[29]. Using compartmental models it is impossible to intuitively predict how blood concentrations will vary with time. Shafer *et al*[84] and Hughes *et al*[23] demonstrated how essential computer simulations are in this situation. These simulations have clearly shown that predictions of the relative recovery times of different IV drugs, based on comparisons of terminal elimination half-times, may be erroneous and that recovery times are influenced by the duration of anaesthetic administration[85].

The termination of effects of most anaesthetic agents is due to redistribution from the brain to the tissues during the initial exponential phases of the blood concentration-time curve, and is generally much faster than the elimination rate of the drug. After repeated administration, the duration of effect is gradually prolonged until steady state is reached, indicating that accumulation has occurred. At steady state, a distribution equilibrium has been achieved and the rate of disposition of drug effect exactly equals the rate at which drug is being irreversibly removed from the body by metabolism and excretion. At that time the elimination half-life is representative of the duration of effect[29].

It takes 4 half-lives to reach 90% of steady state. For propofol, related to its long terminal half-life, continuous administration for nearly 24 hours is necessary to obtain distribution equilibrium and produce a significant delay of recovery from anaesthesia in humans[29]. Moreover, the long terminal half-life of propofol does not reflect elimination.

More than 70% of the administered dose is eliminated during the first and second exponential phases[29].

To maintain a defined level of sedation or unconsciousness during a propofol infusion, most of the administered amount will have to compensate for the clearance and fast distribution of the drug and not its accumulation in the remote peripheral compartment[29]. A better understanding of the clinical observations is now possible. The very rapid recovery from a bolus injection is mainly related to the very short initial redistribution half-life[29].

After repeated injections or short-term infusions a slight delay in recovery compared with single bolus administration is the result of the gradual distribution equilibrium in the second compartment[29]. Duration of effect is then governed by the second exponential phase, during which the half-life is mainly determined by rapid elimination by bio-transformation[29].

Intermittent doses have been used to keep cats anesthetized for longer periods with no apparent effect on recovery times[6]. A 90 min infusion resulted in rapid recoveries[86]. This is surprising as smaller volumes of distribution and longer elimination half times have been reported for propofol in cats compared to other species (rat, rabbit and pigs)[18]. The data from Morgan *et al*[6] suggest than none of the cats were kept under anaesthesia for longer than 30 minutes, which is not long enough to show the results obtained by Pascoe *et al*[25] that showed prolonged anaesthesia with propofol in healthy cats may be associated with delayed recovery.

Prolonged anaesthesia with propofol in healthy cats resulted in delayed recovery[25;26]. These effects have been attributed to a relative lack of glucuronide conjugation in feline hepatic metabolism[16]. Without this metabolic pathway, phenolic compounds can cause

oxidative injury to red blood cells. Feline hemoglobin is particular susceptible to drug-induced oxidative injury resulting in Heinz body formation and methemoglobinemia[26].

Bley's[87] recent study indicated that repeated propofol-associated short-duration anaesthesia does not lead to clinically relevant hematolgic changes or prolonged recoveries, which may be due to lower induction doses used. The duration of drug effect is a function of both pharmacokinetic and pharmacodynamic variables[88].

Following infusions, the length of anaesthetic administration influences the rate at which concentrations of anaesthetic decreases after discontinuation[85]. When selecting a suitable agent for TIVA (total intravenous anaesthesia), a number of pharmacokinetic parameters should be evaluated. The concentration at steady state is used to determine the initial bolus dose required to induce anaesthesia prior to the commencement of the continuous infusion rate. None of the anaesthetic agents used for TIVA follow a single compartment model. In a multi-compartment model, the elimination half-life gives a poor indication of the expected time of recovery following the termination of an infusion[23;84].

Recovery from anesthesia is determined by the pharmacokinetic principles that govern the rate of decrease in drug from the effect compartment once drug administration is terminated, as well as by the pharmacodynamics of the drug. Although the terminal elimination half-life is often interpreted as a measure of how short or long lasting a drug is, the rate at which drug decreases is dependent on both elimination and redistribution of the drug from the central compartment. The contribution of both redistribution and elimination toward the rate of decrease in drug concentration varies according to the duration for which the drug has been administered[23;84].

The time for the plasma concentration to decrease by 50% from an infusion that maintains a constant concentration, has been termed the "context-sensitive half-time"[23] with the context being the duration of the infusion. The 50% decrease was chosen both for tradition (e.g., half-lives are the time for a 50% decrease with a one-compartment model) and because, very roughly, a 50% reduction in drug concentration appears to be necessary for recovery after the administration of most intravenous hypnotics at the termination of surgery. Depending on circumstances, decreases other than 50% may be clinically relevant.

Context-sensitive decrement times are fundamentally different from the elimination half-life. With mono-exponential decay, each 50% decrease in concentration requires the same amount of time, and this time is independent of how the drug is given. This is not true for the context-sensitive half-time. First, as the name is intended to imply, the time needed for a 50% decrease is absolutely dependent on how the drug was given, with infusion duration being the context to which the name refers. In addition, small changes in percent decrement can result in surprisingly large increases in the time required.

Context-sensitive decrement times focus on the role of pharmacokinetics in recovery from anesthesia. Pharmacodynamics plays an important role in recovery as well. Bailey[88] used integrated pharmacokinetic/pharmacodynamic models to define the "mean effect time" as the average time to responsiveness after maintenance of anesthesia at the 90% probability of unresponsiveness. The mean effect time demonstrates that when drugs have a very shallow concentration-versus-response relationship, concentrations must decrease by a significant fraction to provide adequate emergence. This delays recovery from anesthesia. In contrast, recovery is hastened by a steep concentration-versus-response relationship, in which emergence from

anesthesia occurs after a relatively small fractional decrease in concentration. Most intravenous hypnotics have a fairly steep concentration-versus-response relationship.

The distribution rates between different compartments, as well as the elimination half-life determines the plasma concentrations and hence the rate at which plasma concentrations decline and the rate of recovery. In order for an agent to redistribute, space must be available in the body for the agent to redistribute into. The apparent volumes of distribution provide an indication of the quantity of agent required to saturate the peripheral compartments before recovery becomes solely dependant on the elimination half life[23;84]. The discrepancy between context-sensitive half-time and elimination half-life reflects the important role of drug redistribution, from blood and highly perfused organs to less well-perfused sites for drug disposition. The elimination half-life is a parameter derived from pharmacokinetic modeling and is an estimate of the time needed for drug metabolism or elimination from the body[89]. If kinetics are well described by one –compartment model, then the elimination half-life and the context-sensitive half-time is identical[89]. For example, propofol and sufentanil have long elimination half-times, however their context-sensitive half-times remain short, this is in contrast with thiopentone and fentanyl[23].

2.6 Clinical uses of propofol in cats

2.6.1 Sedation

Propofol unlike thiobarbiturates, does not cause stage two excitement and as a result, is useful for sedation in sub-anaesethic doses in animals[90]. Oral examinations may be performed, sutures removed and ears inspected. Due to the rapid metabolism, animals can be discharged sooner and safer than by using thiopentone. This becomes very valuable in MRI and CT scanning where a patient has to keep absolutely still even in the noisy surroundings.

Propofol infusions do not cause adrenocortical suppression and if prolonged recoveries[25;26] is taken into account in cats, it can still be useful for ICU sedation[90]. Unlike thiobarbiturates, propofol, due to its extensive redistribution, can be safely used in species with a glucuronide deficiency, like sight hounds[41] and cats.

2.6.2 Induction

In animals, propofol was used initially as an induction agent only, but its clinical uses have been extended to include maintenance of anaesthesia and sedation in intensive care patients. Induction is rapid with few excitatory effects[41]. For induction with propofol, dogs premedicated with acepromazine maleate required 4.3mg/kg and unpremedicated dogs required 6.9mg/kg. Premedicated cats required 7,1mg/kg and unpremedicated cats required 7.8mg/kg[30].

Brearly 1988[31] has shown that acepromazine maleate premedication had no effect on induction doses in cats. The rate of administration is a significant determinant in the severity of side effects associated with its use[90]. A conservative and recommended approach is to administer the calculated induction dose during 90 seconds. Smaller dogs and cats may require a higher body weight related dose, as observed with thiopentone and ketamine/midazolam[90].

Ludbrook *et al*[78] has shown that there are marked disequilibria between propofol concentrations in the blood and brain after rapid administration of propofol to sheep. The time-course of the effects of propofol on cerebral blood flow (CBF) and anaesthetic effects is closely related to the time-course of propofol concentrations in the brain but not in the arterial blood.

2.7 Conclusions or research question

Over 40 years ago, it was recognized that the domestic cat differed significantly from other animals in the ability to form glucuronide conjugates of certain xenobiotics, particularly low molecular weight phenolic derivates[65]. Cats metabolized these agents slowly, resulting in prolonged half-lifes[14;26;91].

Dose regimens for maintenance of anaesthesia are most frequently derived from compartmental models fitted to the time course of drug concentrations in blood, and these generally allow relatively accurate prediction of blood concentrations and depth of anaesthesia[29].

In clinical practice propofol is used in cats for bolus induction and maintenance infusions, however no pharmacokinetic study has been reported for the current formulation of propofol in cats. An understanding of the pharmacokinetics of propofol in cats is essential for its improved clinical use and safety.

CHAPTER 3

MATERIALS AND METHODS

3.1 Experimental animals

Institutional ethics committee approval for the study was obtained from the Faculty of Veterinary Science, University of Pretoria (Protocol number 36.50036). Six adult domestic shorthair cats (two sterilized females and four castrated males) obtained from the Onderstepoort Teaching Animal Unit (OTAU) were used. These were clinically healthy cats used for student training. A full clinical examination was performed on each animal to evaluate the health status. Body weights (3.4-4.8 kg, mean 3.9 kg), temperature, pulse, respiration, and haematological parameters were recorded prior to anaesthesia. Food was withheld from all animals overnight and not premedicated.

3.2 Experimental design

Cats were housed according to the standard operating procedures as set out by the OTAU unit and returned to the same unit after full recovery from the anaesthetic. Cats were induced with 5% isoflurane with a fresh gas flow of 10 ℓ oxygen per minute in a perspex induction chamber. As soon as consciousness was lost, the cats were oro-tracheally intubated and connected to an Ayres T-piece (with Jackson Rees modification) (GRS Medical) breathing circuit. Anaesthesia was maintained with 3% isoflurane in an oxygen fresh gas flow of 1.5-ℓ/min oxygen for maintenance for placement of a central venous line.

A 5.5 F paediatric multi-lumen central venous catheter (Arrow Howes^{TM}, Arrow Inc., Reading, PA, USA) was placed in the jugular and secured. The distal port was used for injection of propofol and the proximal port for sampling. The cats were allowed an hour to recover from the inhalation anaesthetic before induction with propofol.

Four mg/kg propofol (Diprivan™, AstraZeneca) was given by an infusion pump (Perfusor™, Bbraun, Melsungen,Germany). The calculated dose was administered over 60 seconds via the distal port of the multi lumen catheter. The cats were placed on a warm, water-circulating blanket and kept covered until they had fully recovered, after which they were allowed to resume their normal activities. Food and water were freely available.

3.3 Blood collection

Blood samples were collected just prior to administration and thereafter at 2, 5, 10, 15, 30, 60, 90, 120, 180, 240, 360 and 540 minutes after the end of the propofol infusion. One and a half mℓ blood was collected in 5-mℓ potassium oxalate evacuated tubes (Venoject) (Terumo) and kept in the fridge at 4°C prior to centrifugation within four hours.

Waste samples were returned to the cats and flushed with an equal volume of Ringer Lactate (Intramed) to maintain circulating volume and to keep the catheter patent. Blood samples were centrifuged at 3000 rpm for 15 minutes at 4°C and the plasma transferred to polycarbonate tubes. Plasma samples were stored at -20°C until analyzed for propofol content.

3.4 Determination of propofol in plasma

Plasma samples were analyzed for propofol content within three weeks of blood collection. Propofol concentrations in plasma were determined using a validated high-performance liquid chromatographic (HPLC) with UV detection method described by Vree *et al*[92] with thymol as internal standard. The method was validated for specificity, sensitivity, accuracy, precision, extraction efficiency and method suitability.

Saturated ammonium sulphate (133 µL) and 400 µL thymol (160 µg.ml^{-1} in acetonitrile) were added to 400 µL plasma in a mini test tube. These mini test tubes were capped and the contents mixed for 30s in a multi-tube vortex mixer. The mixtures were centrifuged at 10 800 rpm for 10 min. The organic layer was transferred to the insert fitted into the vial, and the vial capped.

A 100 µL aliquot organic phase was removed for direct injection into a high-pressure liquid chromatograph (PerkinElmer LS 30 Luminescence Spectrometer, PerkinElmer Life & Analytical Sciences Inc. Waltham, Massachusetts USA). Analysis was performed on a 150 x 4.6 mm column (Phenomenex Synergi 4 µ Max-RP 80Ă, 150 x 4.6 mm, Separations code number 00C4337-EO; Guard column: Phenomenex SecurityGuard holder and cartridges, Separation code number KJO-4282 and cartridges AJO-6074, Torrance,CA). The eluent consisted of acetronitrile, water and trifluoro-acetic acid (600:400:1 ml). Propofol and thymol were detected by fluorescence at 310 nm after excitation at 276 nm. Runtime was 10 min and flow rates alternated between 1.2 and 2.4 ml.min^{-1}.

Typical chromatograms of extracts containing propofol are shown in figure 2.

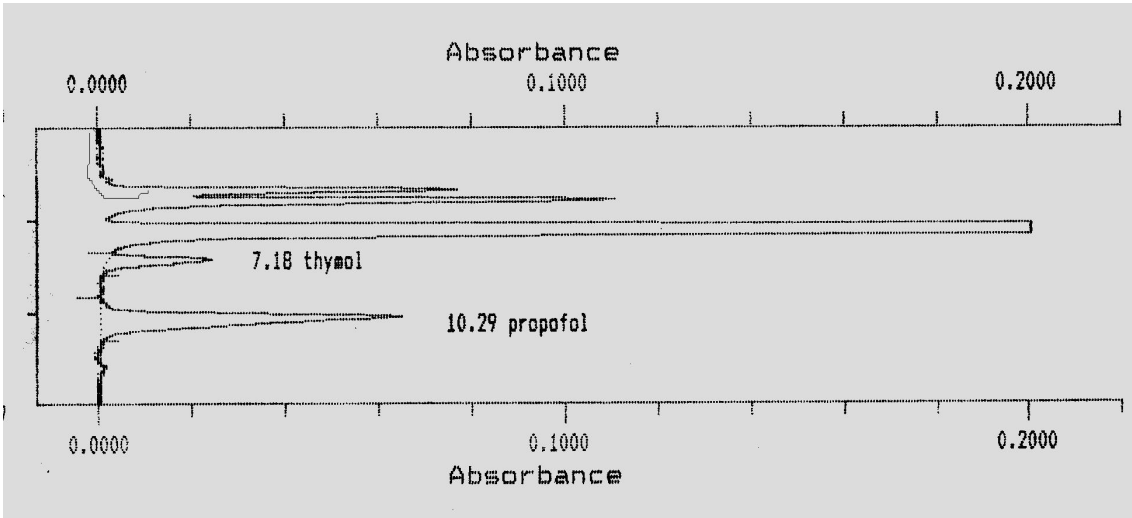

Figure 2 Typical chromatograms of extracts containing propofol.

Chromatographic peak height ratios were used to calculate propofol concentrations. Standard curves were computed by adding pure propofol (Sigma-Aldrich (Pty) Ltd., Aston Manor, South-Africa, Cat no 12.660-8, Lot #03904BU-462) to drug-free pooled plasma to make up concentrations of 5.0, 3.0, 2.0, 1.0, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1, 0.05 µg/mℓ.

Linear regression was used with plasma propofol concentration as the dependant variable and the ratios of the propofol and internal standard chromatographic peaks as the independent variable.

Propofol concentrations in test serum were calculated using the obtained regression equation. The lower limit of detection was 60 ng/ml. Control samples were prepared (containing propofol 0.3, 1.5 and 3.0 $\mu g.ml^{-1}$) without internal standard. These received the same treatment as the samples and were alternately inserted after every five samples for every analytical run.

The coefficient of variation of the peak area ratios for these control samples did not vary by more than 10% for both the intra-day and inter-day runs.

3.4.1 Recovery

Recovery was tested by addition of propofol to pooled experimental samples at different expected concentrations. Recovery for the range 0.06-5.98 µg/mℓ varied between 81-96% over the concentration examined.

3.4.2 Accuracy

These were determined from the initial calibration curves and from in vitro control samples. Analyses were done six times to increase the precision and to arrive at the same answer each time. The linear correlation coefficient provided a measure of how

well the calibration points fit a straight line. Precision was accepted if the coefficient of variance (CV) of the mean concentrations of propofol measured for each sample concentration was ≤ 10%.

Each day replicate analyses of 0.598 µg/mℓ - 5.98 µg/mℓ of the spiked plasma, representing a range of low, medium and high values were performed. Intra-day and inter- day accuracy and precision were determined from the results of the in vitro studies. Reproducibility of the method was established from the intra-day and inter-day variation.

3.4.3 Repeatability

The repeatability of the results were determined by comparing the linear calibration curves which were run on each day of analysis and sample analysis on the same day and on different days of analysis. Repeatability of real samples was not attempted due to the limited sample volumes available.

3.5 Pharmacokinetic analysis

Non-linear compartmental analysis of the propofol plasma data was performed using WinNonlin (Version 1.1, Statistical Consultants, Inc., New York, USA) computer software program. Primary pharmacokinetic parameters were derived from a three-compartmental analysis with IV-infusion over one minute input, first order output, using macro-constants as primary parameters (Model 19) and yielding the micro constants (K10, K12, K21, K13 and K31), the partial exponents (α, ß and λ) and the coefficients (A, B and C). Mean residence time (MRT) was determined by means of non-compartmental analysis using the following formula: MRT = AUC/AUMC where AUC refers to aria under the curve.

CHAPTER 4

RESULTS

The plasma propofol concentrations in cats (n=6) after intravenous infusion over a period of one minute at a dose of 4 mg/kg are given in Table 2 and graphically illustrated in Figure 2.

Results are expressed as mean ±standard deviation (±SD). Concentrations decreased rapidly during the first 10 to 15 minutes, followed by slower declines. In five out of the six animals, secondary increases in concentration occurred during the first 10 minutes.

Mean recovery times after the 4mg/kg dose were 11 ±3 min to awakening, (judged by a blinking response to touching the medial canthus) and 33 ±2 min to sternal recumbence.

Table 2 Plasma concentrations (µg/mℓ) of propofol in cats (n=6) after intravenous infusion at 4 mg/kg over 1 min.

Time (min)	Propofol plasma concentrations (µg/mℓ) in cats						Mean ± SD 3.9 ± 0,5kg
	1 3.4kg	2 3.6kg	3 4.2kg	4 4kg	5 3.4kg	6 4.8kg	
2	12.86	9.24	2.86	4.00	4.23	3.56	6.11 ± 3.99
5	4.70	2.68	4.14	8.11	5.67	4.00	4.88 ± 1.26
10	4.26	3.22	3.69	6.51	4.75	3.13	4.26 ± 0.72
15	3.51	3.10	2.78	4.99	3.69	2.54	3.44 ± 0.87
30	2.29	2.11	1.75	3.60	2.43	1.59	2.30 ± 0.72
60	1.60	0.46	0.74	2.45	0.92	1.01	1.20 ± 0.72
90	0.93	0.46	0.47	0.86	0.59	0.59	0.65 ± 0.20
150	0.67	0.27	0.38	0.46	0.39	0.31	0.41 ± 0.14
180	0.61	0.18	0.17	0.29	0.27	0.22	0.29 ± 0.16
240		0.15	0.14	0.24	0.22	0.16	0.18 ± 0.05
360	0.16	0.11	0.12	0.28	0.25	0.09	0.17 ± 0.08
540	0.13	0.09	0.06	0.18	0.14	0.06	0.11 ± 0.04

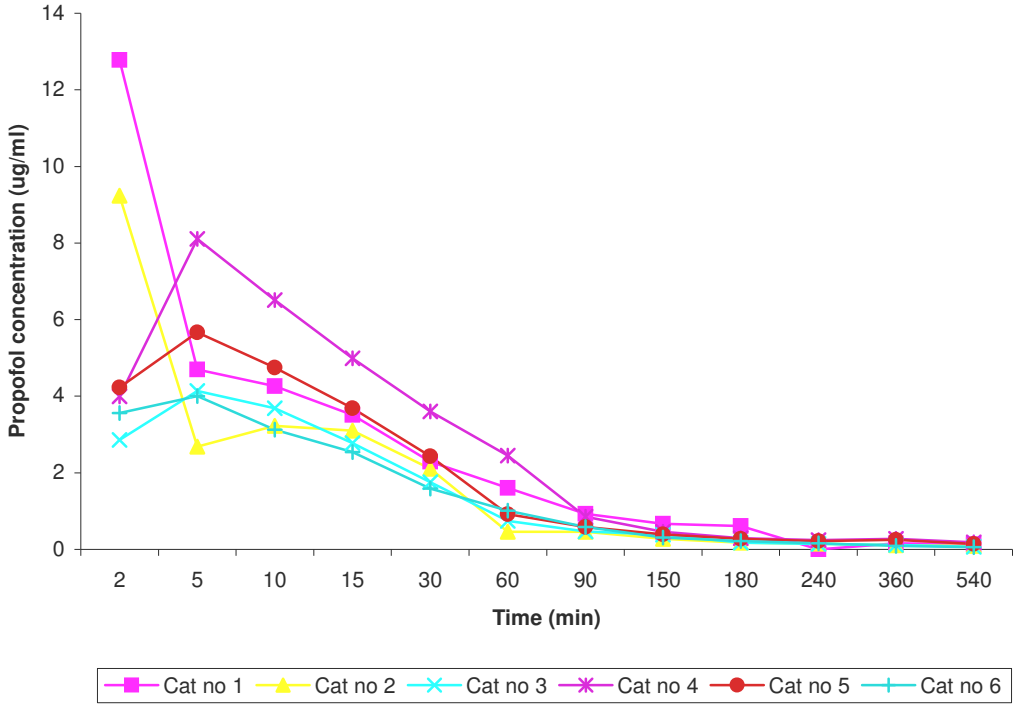

Figure 3 Propofol concentrations in plasma in healthy cats after 4 mg/kg intravenous infusion over one minute.

Secondary increases in propofol plasma concentrations occurred in four cats (#3, 4, 5, 6) between five and ten minutes after intravenous infusion. Cat #1 showed a monotonic drug plasma concentration versus time curve following intravenous administration. Two cats (#1 and #2), showed markedly higher propofol plasma concentrations at two minutes in comparison to other cats.

A relatively high variability in propofol concentrations in plasma (CV % of 40.5 ± 13.8) was observed between cats. Akaike's information criteria[93], based upon the mean values of the final estimate of the associated pharmacokinetic parameters and lack of systemic deviations around the fitted disposition curve, was used to determine the number of exponential terms that best described the data.

The plasma concentration versus time profile of propofol was best fitted to a three-compartmental mammillary open model (Figure 3). The least squares regression lines illustrated in the semi-logarithmic plot in Figure 5 represents the distribution and elimination phases of the tri-exponential disposition curve. The mean values of the rate constants and their standard deviations of the movement of propofol between the various compartments are given in Figure 4.

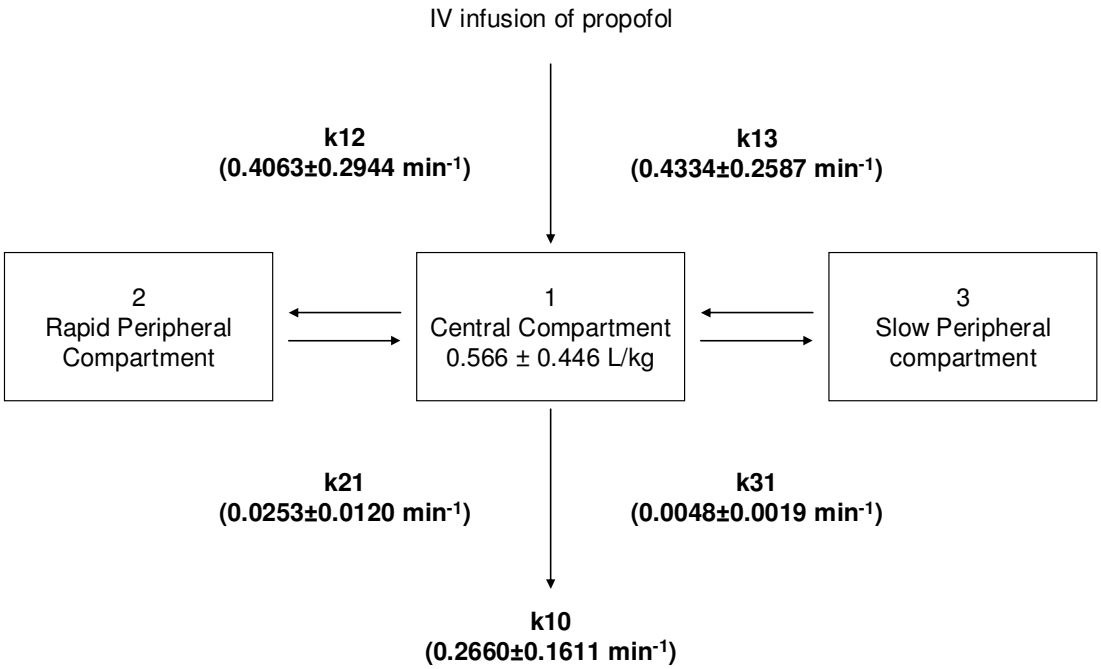

Figure 4 Three-compartment mammillary open model based of propofol administered by intravenous infusion in cats.

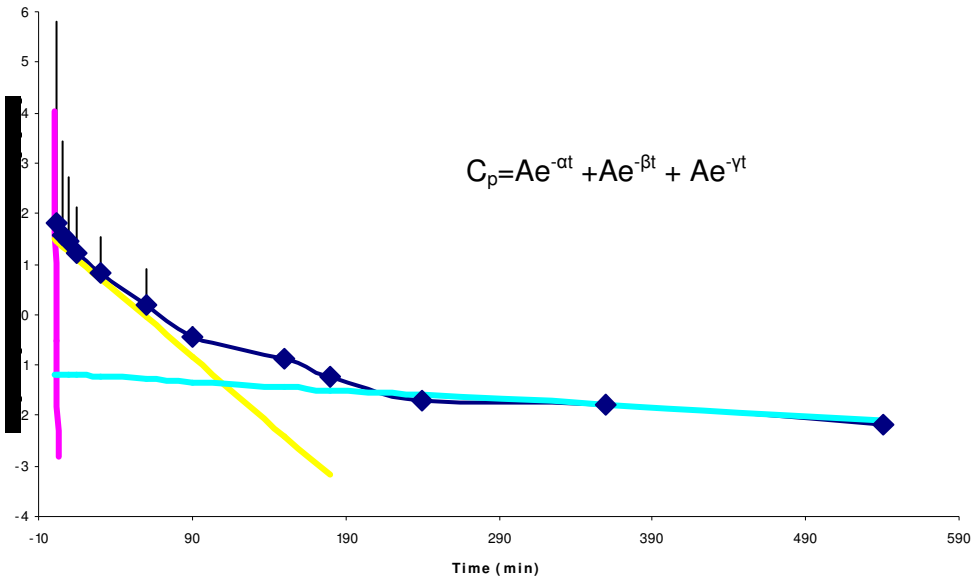

Figure 5 Semi-logarithmic graph of the mean ± SD propofol plasma concentration versus time profile in cats (n=6) administered by IV infusion over 1 min at 4 mg/kg. The least squares regression lines that represent the distribution and elimination phases of the tri-exponential disposition curve are shown.

The pharmacokinetic parameters of propofol in six cats are given in Table 3. The descriptive statistics of the various pharmacokinetic parameters are given in Table 4.

Table 3 Pharmacokinetics of propofol in cats after IV infusion determined using a three-compartmental non-linear open model.

Pharmacokinetic variable	Cat No.						Mean ± SD
	1	2	3	4	5	6	
AUC (min.µg/mℓ)	493.47	1249.0	269.34	831.5	439.8	341.29	604.1 ± 370.9
A (µg/mℓ)	357.11	1013.3	-17.16	73.76	31.28	3.047	243.55 ± 401.3
B (µg/mℓ)	3.88	3.55	20.70	-67.61	-26.32	1.0070	-10.8 ± 31.7
C (µg/mℓ)	1.64	0.09	0.354	0.413	0.46	0.0526	0.5017 ± 0.5847
α (min^{-1})	2.78	3.82	0.0167	0.012	0.019	0.0401	1.113 ± 1.722
ß (min^{-1})	0.045	0.024	0.018	0.011	0.017	0.0092	0.0208 ± 0.0128
γ (min^{-1})	0.0069	0.0001	0.0022	0.0007	0.0015	0.0003	0.0018 ± 0.0022
K10-HL (min)	0.94	0.85	47.92	87.89	56.21	57.6	41.90 ± 34.5
T½α (min)	0.25	0.18	41.40	58.65	36.41	17.28	25.69 ± 23.73
T½ß (min)	15.535	29.16	37.93	61.57	39.70	75.0	43.15 ± 21.69
T½γ (min)	117.17	6531.2	315.57	1001.7	460.6	2059.34	1747.6 ± 2445.5
MRT (min)	99.24	6297.7	275.51	1030.9	459.1	1401.5	1594.0 ± 2355.4
V_C (L/kg)	0.011	0.039	1.03	0.610	0.74	0.974	0.5663 ± 0.4463
Vd_{SS} (L/kg)	0.81	20.17	4.09	4.96	4.18	16.4	8.44 ± 7.86
$Cl_β$ (mℓ/kg/min)	8.1	3.9	15	4.8	9.1	11.7	8.6 ± 4.3
Regression (%)	0.97	0.99	0.97	0.93	0.98	0.99	0.97 ± 0.02

Values are expressed as mean ± standard deviation. A, B and C = Y-intercepts of the extrapolated decay curves. α, β and γ = Slopes of the lines representing the rapid distribution phases, and the elimination phase.

Vc = Volume of the central compartment. $T_{½}$ α, $T_{½}$ β and $T_{½}$ γ = Plasma concentration half-lives of the α, β and γ decay curves. K_{12}, K_{21} and K_{13} = Transfer rate constants between indicated compartments. Kel = Elimination constant. Vd = Volume of distribution related to the area under the curve. VD_{ss} = Apparent volume of distribution at steady state. $Cl_β$ = Clearance. AUC = area under the curve. R = Best-fit calibration lines of peak area ratios versus concentration.

The non-linear regression analysis of the experimental data showed that the plasma concentration-time profile could be adequately described by a tri-exponential expression of $C_p = Ae^{-\alpha t} + Ae^{-\beta t} + Ae^{-\gamma t}$. C_p is the concentration of the drug in plasma at time t the disposition curve, which described the decline in plasma concentration of propofol as a function of time were determined by least square linear regression.

The pharmacokinetics in cats showed rapid distribution (T½ α and T½ ß) to the peripheral compartments with a long terminal half-live (T½ γ). Steady state volume of distribution (Vd_{SS}) was very large. Total body clearance (Cl) of propofol was slow resulting in a long mean residence time (MRT) in the body.

Table 4 Descriptive statistics of propofol intravenous pharmacokinetics in cats.

Pharmacokinetic variable	SEM	Min	Max	Median	Range
AUC (min.µg/mℓ)	151.437	269.341	1249.021	466.640	979.681
A (µg/mℓ)	163.815	-17.163	1013.296	52.568	1030.459
B (µg/mℓ)	12.942	-67.613	20.705	2.278	88.317
C (µg/mℓ)	0.239	0.053	1.644	0.384	1.592
α (min^{-1})	0.703	0.012	3.816	0.030	3.804
ß (min^{-1})	0.005	0.009	0.045	0.018	0.035
γ (min^{-1})	0.0019	0.0001	0.006	0.001	0.006
K10-HL (min)	14.102	0.851	87.891	52.063	87.040
T½α (min)	9.689	0.182	58.647	26.848	58.466
T½ß (min)	8.854	15.525	75.000	38.815	59.474
T½γ (min)	998.357	117.166	6531.17	731.160	6414.004
MRT (min)	961.6	99.2	6297.7	745.0	6198.5
V_C (L/kg)	0.1857	0.0039	1.0267	0.6737	1.0228
Vd_{SS} (L/kg)	3.209	0.805	20.169	4.567	19.364
$Cl_β$ (mℓ/kg/min)	1.8	3.2	14.9	8.6	11.6

CHAPTER 5
DISCUSSION

The use of intravenously administered drugs and safe clinical anaesthesia requires an understanding of the relationship between administered dose and pharmacological effect. Since the introduction of the lipid emulsion formulation in 1986, propofol has become established for induction as well as for maintenance of anaesthesia in veterinary practice[1], including cats[2;4-8;94].

Propofol is rapidly metabolized by hepatic glucuronidation in most species and it has also been shown to undergo extrahepatic metabolism[9;10;13;73] so that total body clearance may exceed liver blood flow in certain species. Because of their highly carniverous diet, cats are little exposed to antiherbivory compounds so that they have become deficient in UGP-glucuronosyltransferase (UGT)[14]. Consequently, a number of drugs are eliminated slowly[16] often giving rise to prolonged half-lives of the parent drugs. Cats are therefore sensitive to the adverse effects of many drugs and toxins that are normally glucuronidated before elimination. It is therefore likely that the disposition of propofol may differ markedly from that of humans and other animal species[95].

This is the first pharmacokinetic report of the current formulation of propofol in cats. In a previous study by Adam (1978)[18] the pharmacokinetics of propofol (ICI35868) in Cremophor-EL was described in four cats. The pharmacokinetic parameters reported here, differ from previous published research[18] because of different formulations, difference in sampling times[18] as well as lung clearance of the emulsion formula[19;32]. Adam *et al*[18] reported that for the cremophor propofol formulation, volumes of

distribution were smaller and elimination half-lives were longer than those of pigs, rats and rabbits.

Initial evaluation of propofol in a range of animal species showed that intravenous administration produced rapid onset of anaesthesia with induction times similar to those of thiopentone[32]. In contrast to thiopentone, animals regained coordination more rapidly following propofol administration[32].

5.1 Compartmental analysis

Although some investigators have proposed two-compartment models, most data sets have required three-compartment solutions. The tri-exponential decline of propofol concentration in the blood of cats is similar to the tri-exponential decline described in dogs[45] and humans[35].

Best fits were obtained by three-compartmental models in part due to the ability to measure low propofol concentrations that occurred after some hours. The completeness of the disposition curve depends not only on the frequency and duration of blood sampling, but also on the sensitivity of the analytical method used for quantitative determination of plasma drug concentrations[96].

The secondary increases in propofol concentrations observed in cats # 3,4,5,6 in this study, at five to ten minutes after intravenous infusion is not explained by conventional compartmental pharmacokinetics, where a monotonic decline would have been expected. In comparison, Kanto[29] has shown a tenfold decrease in the first 10-20 minutes in humans.

Plasma samples obtained during the first minute may reveal an initial increase, followed by oscillations, eventually followed by a monotonic decrease[97]. According to the 3-compartment mammillary model, blood samples obtained at two or more minutes after intravenous administration drug concentration should decrease monotonically over time.

Propofol has a large oil/water partition coefficient (K) of about 4700[98]. Because of the fat partitioning, propofol is taken up into adipose tissue where uptake and release occurs slowly [70]. A fraction of the dose is sequestered and then released from the lungs. This may explain the early increases in propofol plasma concentrations in five of the six cats.

A further explanation for this unusual pharmacokinetic profile could be the result of the administration by constant intravenous infusion. Levitt *et al* (2005)[70] have shown that the pharmacokinetics of propofol following constant rate infusion or after rapid bolus injection is not the same in the same subject. They ascribed the differences to either early recirculation, propofol induced changes in hepatic blood flow or pulmonary sequestration[70]. They suggest that pulmonary sequestration is the major factor responsible for these differences. Propofol is formulated as a lipid emulsion because it has a low aqueous solubility. In some subjects, up to sixty percent of the emulsion bolus is sequestered in its first pass through the lung and then slowly released[70].

Pulmonary sequestration of the bolus dose with slow release provides an explanation for the increase of plasma concentration at early time points. As the sequestered dose is slowly released, an increase in drug blood concentration at later time points may occur[70]. Sequestration is dependent on the concentration of propofol in the emulsion when it is mixed with the venous blood at the injection site[70].

The occurrence of propofol plasma concentration "peaks" observed during the early phase of concentration-decline after rapid administration, has been mentioned in a previous publication[99] and are particularly likely to occur when sampling venous blood. In an editorial, Krejcie and Avram[100] coined the term "front-end" kinetics when commenting on studies of chronically instrumented sheep by Upton and coworkers[53].

Firstly, drug is mixed in the venous flow before entering the pulmonary circulation through which it must undergo a first-pass before entering the systemic circulation. The lungs may delay the passage of drugs and even remove significant proportions[9;10:73].

The systemic circulation then distributes drug to various organs (including the targeted organ) through which it is again subjected to a first-pass before being returned to the venous flow for recirculation. The liver is mainly responsible for metabolism and elimination of propofol, however some extra-hepatic metabolism (notably the lungs and kidneys) does occur[11;13].

It is apparent that the traditional two (or three)-compartment mammillary models that are used to express the disposition of intravenously administered drugs, are inadequate to describe the early pharmacokinetics and pharmacodynamics of short, rapid infusions. These models assume that drugs distribute immediately and homogeneously within a "well-stirred" central compartment, before undergoing distribution to peripheral compartments. After injection, the decreasing arterial plasma concentrations are described by an expression that consists of the sum of two or more exponential terms. This "polyexponential" model misspecifies the early time course of drug concentration, because it assumes the central compartment to be homogeneous rather than a complicated system of organs in series and parallel[97].

Because traditional compartmental models are represented by monotonic functions, recirculatory oscillations cannot be described by conventional compartmental models.

Hybrid models that incorporate circulatory physiology (including lung kinetics and recirculation phenomena) into compartmental models satisfactorily predict the early time course of propofol concentrations in the circulation and the brain[76]. The simplest model consists of two compartments, the lungs and the rest of the body[101]. Drug administration is into the "lung" compartment (which receives the total cardiac output) and clearance is from the "body" compartment.

These models have been developed further and expanded to include cerebral blood flow and dynamics. They are able to simulate the complex effects of circulatory changes on the pharmacokinetics and pharmacodynamics of propofol in sheep,[53;102] as well as in humans[76].

Various studies have indicated that cardiac output has a particularly important influence on blood drug concentrations, according to the same principle by which dilution of injected tracer is used to measure cardiac output[53;56]. As cardiac output decreases, peak arterial concentrations increase in response to a bolus dose and the area under the arterial concentration-time curve increases. Propofol has been shown to decrease cardiac contractility, heart rate and blood pressure in cats[103]. Therefore it is possible that the late occurrence of recirculatory peaks in our experiments may have been partly due to cardiovascular depression after a large, rapidly-administered propofol dose, leading to decreased cardiac output and a slow circulation time. However as no haemodynamic variables were recorded, it is not possible to conjecture further in this regard.

The secondary peak observed in cat #2 occurred at the same time of assuming sternal recumbency. This peak could be the result of ambulation and food intake, as these can produce large changes in muscle blood flow, whereby sequestered propofol is released into the circulation[29]. Secondary peaks have also been reported in human and other animal studies[41;104]. Propofol is known to be a direct venodilator, therefore during recovery, when the dynamics of the peripheral circulation are returning to the pre-anaesthetic state, there may be influx of propofol from peripheral tissues[41].

5.2 Distribution

The rapid-distribution half-life ($T_{1/2\alpha}$) (mean 25.69 ± 23.73 min) of the propofol emulsion formulation was longer in comparison with Adam's 1980[18] study of the cremorphor formulation, that showed a very rapid $T_{1/2\alpha}$ of 5.8 ± 0.4 min in cats using ICI 35 868 (2% Propofol in 10% Cremophor-L). This discrepancy is most likely due to individual variation between cats as described in humans[29]. The half-life of the initial phase of the disposition curve, which is comprised of distribution/redistribution correlates with the duration of clinical anaesthesia[96]. However, since the first sampling point was at two minutes, this exponential has been based on a small number of points and its value may not be accurate. After intravenous administration to cats, rapid redistribution to less well-perfused tissues occurs, resulting in a rapid fall in blood and brain concentrations[105].

The large V_{dss} (mean of 8.44 ℓ/kg) indicates that propofol is extensively distributed from blood to the tissues and correlates well with the results of humans[29] and dogs[41;45]. This would be expected of a highly lipophyllic anaesthetic agent. Lipid solubility may be more important than the degree of ionisation in determining the rate as well as the pattern of distribution, which is ultimately limited by blood flow to tissues. Organs with high perfusion rates, such as heart, brain, liver and kidneys, achieve higher drug

concentrations than skeletal muscle and adipose tissue. Equilibrium between deep and peripheral compartments and blood is rapidly attained[96].

The apparent volume of the central compartment or initial volume of distribution (V_C) was relatively small (mean of 0.57 ℓ/kg) and is in contrast to the relatively large initial volume of distribution reported for propofol in humans[82]. In a three-compartmental model, V_C is that volume in which a drug appears to mix instantaneously after administration, but before it redistributes throughout the remaining volume. The estimate of V_C is therefore affected by the time the first blood sample is collected after drug administration because the drug is distributed more extensively with the passage of time. Similarly the sampling site (e.g. arterial versus venous)[29] and the physiological state (e.g. variation in cardiac output)[106] will affect conventional estimates of the V_C of IV anaesthetics, because it is based on infrequently collected blood samples, beginning after the peak plasma concentrations of the drug have begun to wane. From the central compartment drugs are distributed to the rapidly (fast) and slow equilibrating volumes of distribution (V_f and V_S, respectively) by a process called inter-compartmental clearance.

These clearances are volume-independent estimates of drug transfer that are determined by blood flow and transcapillary permeability[100]. This also explains the reduced dose requirements of patients in hemorrhagic shock because the fraction of the dose received by the brain is very large and the rate of removal is very slow because of the reduced blood flow to other tissues[100]. The traditional compartmental models fail to account for the variability in drug distribution and including mixing within the vascular volume and flow (both cardiac output and its peripheral distribution)[100].

A common problem has been highly variable estimates of the central volume, which appears to relate to time and site of the first blood sample[102]. Because three-

compartment models based on drug concentration histories obtained after rapid intravenous administration do not characterize V_C accurately, target-controlled infusions based on them produce concentrations exceeding the target[107].

5.3 Elimination half-life

Following the mixing time (up to two minutes) within the blood volume, further distribution of propofol is very rapid. The second exponential phase half-life (mean 43.15 ± 21.69 minutes) mirrors the high metabolic clearance of propofol also seen in humans[29]. ICI 35 868 was eliminated in 55 ± 3 minutes, but sampling was only done for two hours[18]. The third exponential phase (1747 ± 2445.5 minutes) describes the slow elimination of a small proportion of the drug that remained in the poorly perfused tissues. This long elimination is related to the slow release of propofol from high lipophilic tissue compartments.

Anaesthetic drugs are rarely given for sufficient time duration to attain steady state, limiting the importance of elimination half-life[97]. At the conclusion of anaesthesia, the issue of importance to the clinician is how soon the plasma concentration decreases by 50% or 80% to a concentration at which the patient wakes up, rather than the slope of the plasma concentration-time curve when elimination phase is reached many hours later[97].

Context sensitive half-time determines the rapidity with which plasma concentration decrease by 50%[108]. As early as 1955, Hartiala reported that cats metobolize phenolic compounds slowly[65], Court *et al*[14] demonstrated that the UGT1A6 gene is deficient in domestic cats, as well as in a margay (*Leopardus wiedii*). Therefore the fairly slow declines in plasma propofol concentrations that occurred after the initial rapid distribution phase, probably resulted from slow clearance of the drug.

Slow clearance should not influence recovery from anaesthesia following standard induction doses, because the early decreases in blood concentrations are predominantly due to redistribution of drug to various tissues, similar to the disposition of thiopentone which exhibits a slow total body clearance[21]. However it is possible that drug may accumulate within the body after prolonged infusions, resulting in delayed recovery times. This phenomenon is best described by calculating "context-sensitive" decrement-times by computer simulation[22-24].

If drug is infused according to a regimen that achieves and maintains a constant plasma concentration, when the infusion is discontinued, drug concentrations decrease exponentially. If the duration of the infusions is increased, would the times taken for the concentrations to decrease by a certain fixed proportion (say 50%) be constant, or would these "decrement-times" increase as the duration of the infusion increases? This question is not easily answered by looking at the pharmacokinetic parameters, as there are complex interactions between the inter-compartmental and total-body clearances during prolonged infusions. In fact drug elimination half-lives have no relevance to the behaviour of drug concentrations after infusion[22-24].

Simulation computer software♣ were employed to calculate the 20%, 50% and 80% context-sensitive decrement times for the cat pharmacokinetic model. For comparative purposes, similar calculations were performed for an adult human male (weight 70 kg) using the pharmacokinetic parameter-set of Marsh *et al*[20]. These are presented in figure 5.1 while figure 5.2 to 5.4 compares the decrement times to those that typically occur in humans. Assuming that recovery from anaesthesia occurs after a 50% decrease in blood concentrations has taken place, it is apparent from the 50% context-senstive decrement-time graph that for infusions lasting up to 20 minutes (during which concentrations are kept constant), recovery can be expected to be rapid and

♣ TIVA Trainer version 8, author Frank Engbers, Leiden University Medical Centre

predictable. However if infusions are administered for longer than 20 minutes, the recovery times of the "average" cat increase rapidly, reaching a plateau of 36 minutes, while recovery times of the human remain short (< 8min; upper graph of figure 6), albeit increasing slowly. Awakening times become dramatically prolonged and unpredictable in both cats and humans if propofol concentrations are required to decrease by 80% for recovery to occur. Under these circumstances the 80% decrement time after a two-hour infusion is approximately two hours in cats and 45 minutes in humans (middle graph of figure 6). On the other hand, if dosing is conservative, so that blood concentrations need to decrease by only 20% for awakening to occur, then recovery times are short and predictable, being only a few minutes, regardless of the duration of the preceding infusion (lower graph of figure 5.1).

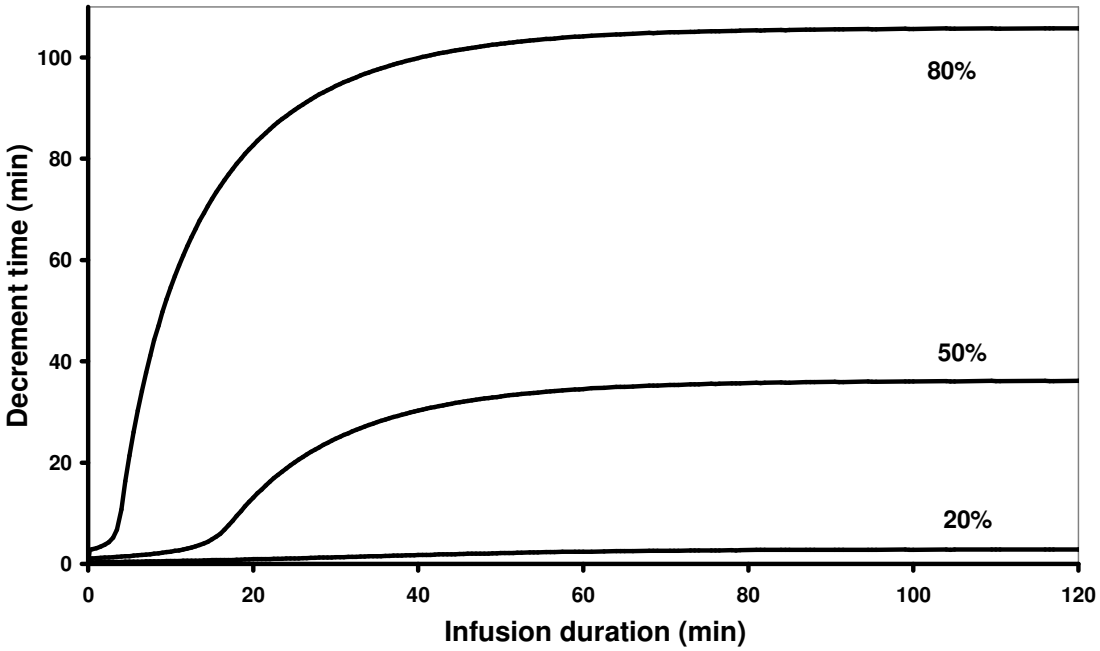

Figure 6 Context-sensitive decrement times for propofol for cats receiving infusions lasting up to 120 minutes. It is assumed that drug plasma concentrations are kept constant during each infusion. Lower, middle and upper plots depict the 20%, 50% and 80% decrement times respectively.

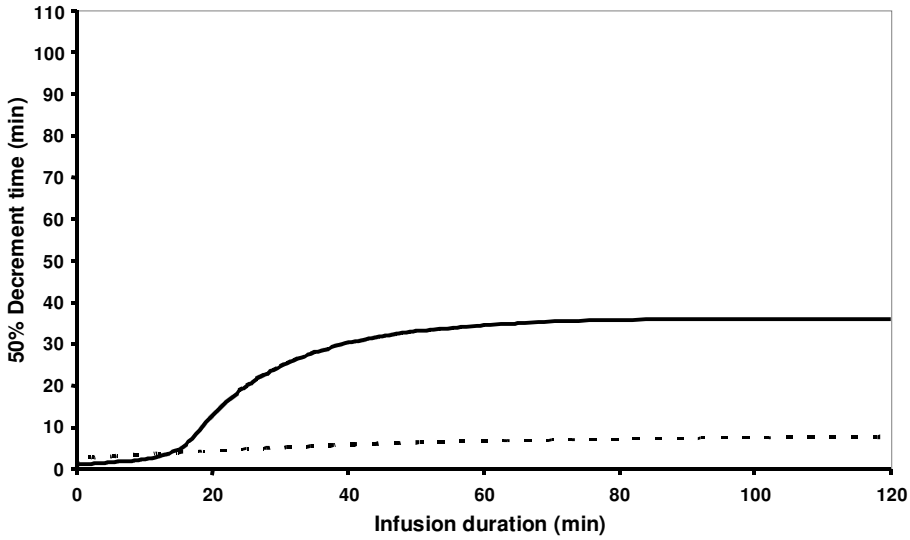

Figure 7 50% Context-sensitive decrement times for propofol for infusions lasting up to 120 minutes in cats (solid lines) and humans (dotted lines).

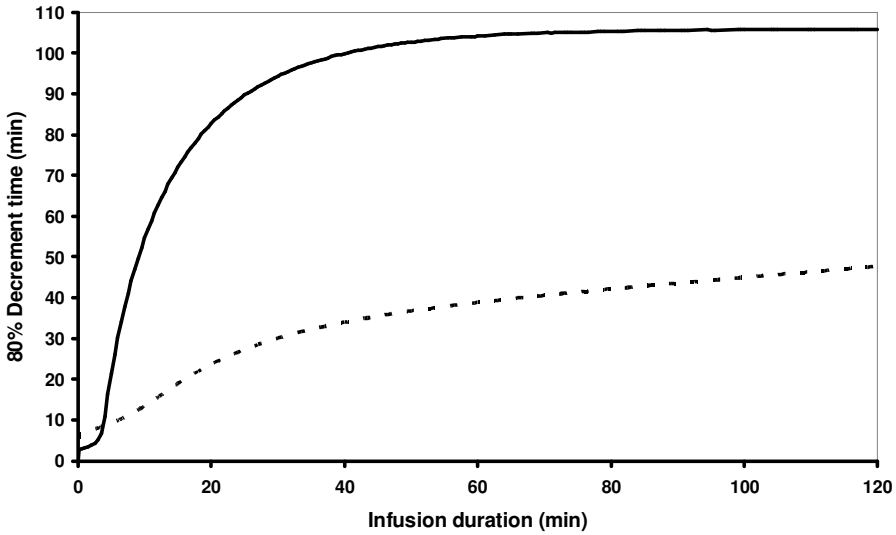

Figure 8 80% Context-sensitive decrement times for propofol for infusions lasting up to 120 minutes in cats (solid lines) and humans (dotted lines).

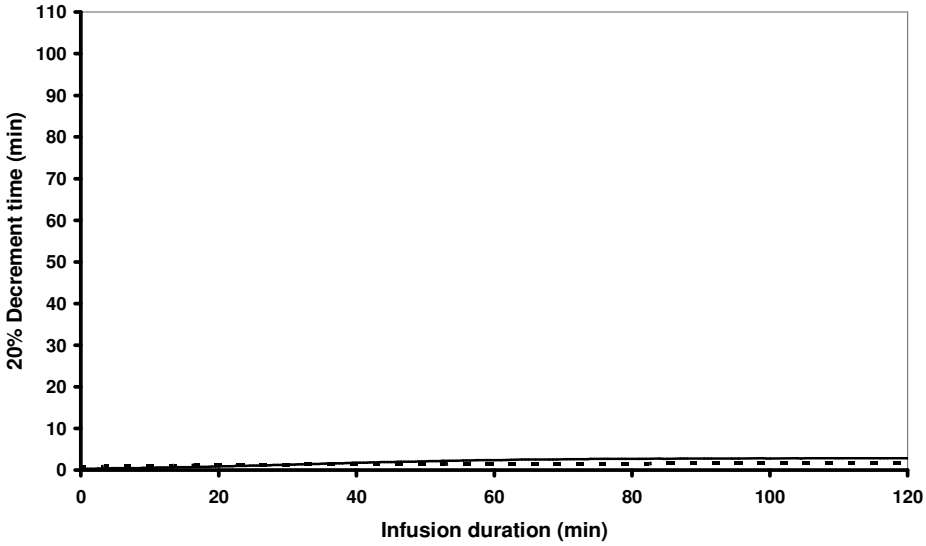

Figure 9 20% Context-sensitive decrement times for propofol for infusions lasting up to 120 minutes in cats (solid lines) and humans (dotted lines).

Our findings are in accordance with those of Pascoe *et al*[25], who reported that cats took longer to recover after a short (30 min) infusion, than after a long (150 min) infusion. In this crossover study, the propofol infusion rates were adjusted so that the cats were maintained at a light level of anaesthesia at which they responded sluggishly to pedal stimulation. It is therefore likely that propofol concentrations were kept steady and were similar during the 30-minute as well as during the 150-minute infusions. Delayed recovery has also been reported when propofol was administered to cats on consecutive days[26].

5.4 Clearance and metabolism

Compared with the high values for body clearance in humans (mean 25-31 /mℓ/min/kg)[35] and goats (mean 275 mℓ/min/kg)[42], the clearance values in all cats was extremely low (Mean 8.6 ± 43 mℓ/min/kg). This is also much less than the clearance of 76 mℓ/kg/min reported in dogs[39].

Drugs that are extensively metabolized by the liver, the elimination process obeys first-order kinetics. Interspecies comparisons of their rates of excretion should use intrinsic clearance, and not half-life as the parameter of choice[96]. Intrinsic clearance is distinctive for any particular drug in a given situation such as it reflects only the inherent ability of the organ (e.g. hepatic metabolic activity) to remove the drug[96]. The cat's limited capacity to metabolize xenobiotics and particularly the glucuronidation defect is a significant determinant of the pharmacokinetic behaviour of drugs and could account for the lower clearance.

Total hepatic blood flow in most animal species is assumed to approximate 25% of the cardiac output at resting conditions. Hepatic blood flow in the cat is ± 21 /mℓ/kg/min[109]. In many species the hepatic extraction ratio of propofol appears to be nearly one, which means that the elimination clearance is hepatic flow limited and will change with changes in cardiac output and hepatic blood flow[52].

In the cat, however the elimination clearance relative to hepatic blood flow is low enough to suggest that the hepatic extraction ratio of propofol in cats is substantially less than one. This implies that the elimination clearance of propofol in cats is probably restricted, which in turn means that elimination clearance will not change as cardiac output and hepatic blood flow change.

Total body clearance of propofol is dependant on metabolism, being rapidly metabolized by specific cytochrome P450 enzymes[39]. Elimination is almost exclusively by means of metabolism, since excretion of unchanged drug in urine and faeces is negligible[29;110]. Carnivores have a deficiency in the glucuronide pathway and this deficit manifested to its most extreme degree in cats. The formation of phenol glucuronide conjugates proceeds 65-100 times faster in most species relative to the cat[105:19].

The major part of the compound not glucuronidated, is converted to sulphate conjugates, which is a much slower reaction. In addition, as a further compensation for its glucuronidation deficiency, the cat also synthesizes some unusual conjugates, notably phosphate and glycyltaurine derivates[105].

Hepatic metabolism conjugates propofol to glucuronides and sulphates which, being water-soluble are readily excreted in the urine. In the cat considerable first pass retention of propofol occurs in the lung (61%). It is uncertain whether all of the propofol is released back into the circulation, or if some lung metabolism of the compound occurs.

Dose regimens for maintenance of anaesthesia are most frequently derived from compartmental models fitted to the time-course of drug concentrations in blood, and these generally allow relatively accurate predictions of blood propofol concentrations and depth of anaesthesia[29].

Earlier recommendations suggested that propofol must be given by rapid intravenous injection, otherwise rapid redistribution will prevent anaesthetic concentrations being achieved in the brain[105]. In clinical practice this often leads to apnoea, especially in the cat and more recent publications prefer slow IV induction over a minute or two to give the body time to respond and achieve haemodynamic stability. Dose regimens using conventional compartmental pharmacokinetic modeling based on the concentration of propofol in blood may fail to accurately predict propofol brain concentrations and anaesthetic effects following rapid administration. It is important to take these factors into account when dose protocols are advised[78].

A limitation of this study is that venous blood sampling as opposed to arterial blood was done[49]. No earlier samples (prior tot 2 min) were obtained which resulted in the initial distibution phase to be poorly characterized. Nevertheless, this preliminary pharmacokinetic study serves to demonstrate that the disposition of propofol differs in cats from other species and that these findings have implications for veterinary clinical practice.

We conclude that this preliminary pharmacokinetic study serves to demonstrate that the disposition of propofol in cats differ from other species, notably man. It was found that propofol and that its pharmacokinetic profile, with slower metabolism and low body clearance might not be a suitable agent for total intravenous anaesthesia (TIVA) in this species either by incremental dosing or continuous i.v. infusion, as accumulation with prolonged recoveries is likely and need to be investigated.

It is recommend that propofol infusions be administered to cats only for fairly short procedures and that for surgeries that are expected to be prolonged, maintenance of anaesthesia should be accomplished using other drugs. In order to decrease the propofol dose, premedication and analgesic supplements should be co-administered to provide “balanced” anaesthesia. Further research is required to determine the relationships between propofol concentration and their effects with regards to hypnosis and anaesthesia in cats.

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