Computer simulations of propofol infusions for total intravenous anaesthesia in dogs

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ABSTRACT

The volatile anaesthetic agents halothane, isoflurane and enflurane are all chlorofluorocarbons and according to international treaties, their emission into the atmosphere will be prohibited from the year 2030. The agents desflurane and sevoflurane are fluorinated hydrocarbons and act as greenhouse gases. The future of veterinary anaesthesia could be dependent on the development of total intravenous anaesthesia. Drugs utilised in total intravenous anaesthesia (TIVA) should have a short duration of action and no tendency to accumulate in the body. Propofol has been the dominant agent used. Computer technology has enabled targeted plasma concentration controlled infusions to replace manual infusion regimens. This study simulated the pharmacokinetics of various infusion regimens similar to those used in clinical practice using previously published pharmocokinetic data. Bolus doses of 0, 4, 6 and 8 mg/kg were simulated in combination with infusion rates of 0, 0.2, 0.3 and 0.4 mg/kg/min for either 240 or 1440 min. The computer was also programmed to maintain a steady state plasma concentration based on the previous simulated data. Generated data were then compared with published data. Changes in the context-sensitive half-life for propofol were also evaluated. Results showed that the generated data were similar to published data. A decrease in plasma concentration to levels associated with a light plane of anaesthesia was evident even when the highest bolus dose and infusion rate were used. There was a slow rise in plasma concentration when only an infusion was used. A lightening of anaesthetic plane may be evident early in the course of TIVA and careful monitoring of anaesthetic depth is required. As the duration of the infusion increased, plasma concentration steadily rose but achieved 95 % of the steady state by 204 min. The most dramatic changes in plasma concentration occurred in the first hour of an infusion. Similarly, the infusion rates decreased most in the first 70 min. Most changes in anaesthetic depth are likely to occur early in the course of TIVA and careful observation of anaesthetic depth is required.

Key words: computer-controlled infusions, pharmacokinetics, propofol, simulations, total intravenous anaesthesia

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INTRODUCTION

In order to maintain general anaesthesia either volatile anaesthetics or intravenous agents can be used. The volatile anaesthetic agents halothane, isoflurane and enflurane are all chlorofluorocarbons and according to international treaties, their emission into the atmosphere has to be controlled[21]. The 1992 Copenhagen Conference concluded that their emission into the atmosphere will be prohibited in the year 2030[21]. The newly introduced volatile anaesthetic agents desflurane and sevoflurane are fluorinated hydrocarbons that are less destructive to the ozone layer but are more effective greenhouse gases than carbon dioxide[21]. It is anticipated that legislation to control their emission into the atmosphere will be devised in the near future[21]. Thus in future veterinary anaesthesia could be dependent on the development of total intravenous anaesthesia.

Total intravenous anaesthesia (TIVA) is a technique that allows for the continuous administration of an intravenous anaesthetic agent to maintain an adequate depth of anaesthesia to allow for surgery. The concept of the minimum alveolar concentration (MAC) as used with inhalational anaesthesia has been replaced with the concept of a minimum infusion rate (MIR). MIR is defined as the infusion rate of an intravenous agent at which 50 % of patients are unresponsive to a surgical stimulus.

Drugs utilised in TIVA should have a short duration of action and no tendency to accumulate in the body. The 1st reports of TIVA in veterinary medicine started to appear in 1987[12,35]. Propofol has been the dominant agent in these studies[12]. Propofol has been utilised for the maintenance of anaesthesia through the administration of multiple bolus doses[24,35] or as a constant rate infusion[1,5,9,12,13,16,19,20,25,29,32,33]. The induction doses have varied between 3 and 7.5 mg/kg and the infusion rates from 0.2 to 0.8 mg/kg/min. The mean induction dose of propofol used in these studies for unpremedicated patients was 5.81 mg/kg and for premedicated patients was 3.68 mg/kg. The induction doses and infusion rates of propofol used in various studies are given in Tables 1 and 2. The recommended induction dose of propofol is 6 mg/kg in unpremedicated patients and 4 mg/kg in premedicated patients[11]. Acetylpromazine[9,12,29,35,36] or medetomidine[13,32] have been used as premedications and the concomitant use of a CRI (constant rate infusion) of an opioid has been investigated[4,8,14]. During infusion studies, when the anaesthetic depth was inappropriate, either the infusion rate[9,16,19] was adjusted or an additional bolus dose[12,24,35] of propofol was given. Several studies have indicated that with a constant rate of infusion of propofol, the plasma propofol concentration rises with time[5,13,20,25]. Glowaski and Wetmore suggested a simple protocol for the infusion of propofol:[10] following the induction of anaesthesia with propofol, an infusion rate of 0.2 mg/kg/min should be used for non-invasive procedures, 0.3 mg/kg/min for slightly invasive procedures and 0.4 mg/ kg/min for moderately invasive procedures[10]. Recovery from propofol anaesthesia has been shown to occur when plasma concentrations are between 0.98 and 4.1 μg/mℓ (Table 3)[2,5,13,26,39]. The plasma concentration of propofol at recovery from anaesthesia has been shown to increase with increasing duration of the infusion[5].

Computer simulation models can be used to guide the administration of intravenous anaesthetic agents and make predictions about the pharmacokinetics and pharmacodynamics of different infusion rates. Computers using mathematical

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Table 1: **Induction dose and infusion rate for propofol infusion studies.**

Parameter Study:	Hall & Chambers[12]	Watkins *et al.*[35]	Morgan & Legge[24]	Fonda[9]	Vainio[33]	Watney & Pablo[36]	Robertson *et al.*[29]		Keegan & Greene[#,16]	Thurmon *et al.*[32]
Premedication							Greyhounds	Non-Greyhounds		
Acetylpromazine[1]	0.05	0.02–0.04	Not stated	0.05			0.025	0.025		
Atropine[1]	0.02	0.02	Not stated	0.03			0.02	0.02		0.044
Medetomidine[1]					0.04					0.030
Propofol induction										
Premedicated[1]	4.89	3.80	4.55	3.00*	4.00*	3.8	4.0	3.2		2
Unpremedicated[1]		5.95	6.50			2.2			5*	
Propofol infusion										
Premedicated[2]	0.3–0.4*	0.38	0.26	0.26–0.4[+]	0.15*		0.4	0.4	–	0.165
Unpremedicated[2]	–	0.80	0.41	–	–				0.44	

[1]Dose in mg/kg. [2]Dose in mg/kg/min.
*A preset quantity of propofol was administered or preset administration rate was used and hence the dose was not titrated to a clinical effect.
[+]Infusion was changed according to the surgical requirements of the patient.
[#]Infusion time was 2 hours.

Table 2: **Induction doses and infusion rates used in pharmacokinetic studies.**

Parameter Study:	Cockshott *et al.*[5]		Nolan *et al.*[26]	Reid & Nolan[28]	Nolan & Reid[25]	Zoran *et al.*[39]		Hall *et al.*[13]		Mandsager *et al.*[20]
Propofol	Single bolus	Induction and infusion				Greyhound	Mixed breed	Unpremedicated	Medetomidine	
Induction[1]	7	7	6.5	4	4	5.28	5.44	6.29	5.28	10
Infusion[2]	–	0.466		–	0.4			0.4	0.2	0.4

[1]Doses in mg/kg. [2]Dose in mg/kg/min.

Table 3: **Reported recovery concentration and times of propofol in pharmacokinetic studies.**

Parameter Study:	Cockshott *et al.*[5]		Nolan *et al.*[26]		Reid & Nolan[28]	Nolan & Reid[25]	Zoran *et al.*[39]		Hall *et al.*[13]	Mandsager *et al.*[20]		Beths *et al.*[2]	
Model	Beagle		Mixed breed	Mixed breed	Mixed breed	Beagle	Greyhound	Mixed breed	Mixed breed	Greyhound		Mixed breed	Greyhound
Recovery concentration[1]													
Extubation						2.3						1.6	2.1
Head lift						2.1							
Sternal recumbency	2	4.1	1.15				1.6	1.05					
Standing			0.98				1	<1					
Walking									2.2	1.03			
Recovery times[2]													
Extubation				3		7.6				183[3]	21.4	8.8	8.2
Head lift						10.4				335	35.4		
Sternal			18	12	31*	20.8	16.7	10.88		398	51.8		
Standing			24	51.5		30.7	21.7	14.63		557	67		
Walking			26						174	160			

[1]Recovery concentrations are in µg/mℓ. [2]Recovery times in minutes. [3]Administered chloramphenicol to this group, which delayed recovery.
*Infusion of 60 minutes.

Table 4: **Reported recovery following the administration of propofol for TIVA. Recovery times are given to standing.**

Parameter	Study:	Watkins *et al.*[35]	Morgan & Legge[24]	Fonda[9]	Vainio[33]	Robertson *et al.*[29]	Keegan & Greene[16]	Thurmon *et al.*[32]
Recovery times								
Single dose								
Premedicated		22 min	40 min	–	–			–
Unpremedicated		18 min	24 min	–	–			–
Infusion								
Premedicated		25 min	33 min	12–18 min	15–25 min*	63 min*	28 min*	79.3 min*
Unpremedicated		22 min	33 min	–	–		– 32 min†	

†Infusion time was 2 hours.
*Infusion of 60 minutes.

models enable the simulation of pharmacokinetics under normal physiological conditions and do not always represent a true clinical picture of what may happen in a diseased or compromised patient. However, the information obtained from simulation may help predict and explain clinical observations. Recently, Beths *et al.* validated a pharmacokinetic model of propofol for use with a computer-assisted infusion to maintain plasma concentrations of propofol[2]. The pharmacokinetic program used in this study was P K Sim[2].

A pharmacokinetic infusion program, Stelpump by J F C Coetzee and R Pina (Department of Anesthesiology, Faculty of Medicine, University of Stellenbosch, Tygerberg; e-mail: jfc@sun.ac.za) is available as shareware and thus freely available to all clinicians. It can be programmed with any set pharmacokinetic parameters and can be used to drive 2 pumps simultaneously. Each pump can then infuse 2 different agents each with their own set of pharmacokinetic values. It has not been used in veterinary clinical studies but has been used in human clinical medicine[6]. The intention of this study was to evaluate the suitability of Stelpump in dogs. Theoretical simulation using various infusion protocols of propofol were performed so that the predicted plasma concentrations of propofol and recovery times could be compared with published data. If valid data were generated, the clinical use of such a program could be considered. Clinically relevant doses of propofol were simulated. The secondary intention was to compare simulated data to clinical practice and current recommendations.

Computer simulation

The validated computer pharmacokinetics of propofol by Beths *et al.*[2] (Table 5) were entered into Stelpump. Induction doses of 0, 4, 6 and 8 mg/kg and infusion rates of 0.0, 0.2, 0.3, 0.4 and 0.5 mg/kg/min were used. The 20 simulated infusions were run for 240 min and 1440 min. Recovery was assumed to occur when a plasma concentration of either 1 or 2 μg/mℓ was reached. The time required for the plasma concentration to fall to the recovery concentration was calculated by the computer program and recorded every 5 min. The computer simulation automatically recorded the predicted plasma concentration and pump rate every 10 seconds. In the 2nd part of the study, the computer was programmed to maintain the steady state values achieved at 1440 min from time 0. This meant that the computer administered a bolus followed by a decreasing infusion rate. The model used was a 10 kg, 1-year-old male dog. Bolus doses were administered at a rate of 0.333 mℓ/s (1200 mℓ/h). The bolus dose was immediately followed by the constant rate infusion. The propofol concentration was 10 mg/mℓ. The delta T for the simulation was 10 seconds and all simulations were run in real time.

Table 5: **Pharmacokinetic parameters constructed from a computer model by Beths *et al.*** V_c, Volume of central compartment, Cl, clearance; K_{ab}, equilibration constant between compartments.

Parameter	Value
V_c (l/kg)	0.780
Cl (mℓ/kg/min)	54.6
K_{10} (min)	0.07
K_{12} (min)	0.0365
K_{21} (min)	0.0312
K_{13} (min)	0.0049
K_{31} (min)	0.0011

A statistical comparison between predicted plasma concentrations of different infusion regimens was made using an ANOVA analysis with Dunn's method in pairwise comparison (SigmaStat 2.0, Jandel Corporation, San Rafael, CA). Statistical significance was set at $P < 0.05$. Computer-generated data were broken down into 15-minute intervals so that a time frame could be determined when groups were no longer statistically different. For interpretation and comparison of generated data between different infusion regimens, data were normalised to a percentile. The predicted plasma concentration and pump rate after 240 or 1440 min of simulation was used as the expected value. After normalisation, data could be compared between different induction doses in combination with infusion rates. Linear regression and correlation using the Pearson product moment correlation were used to determine if changes were time and infusion rate related. Descriptive statistics were used as required.

Results of computer simulation

After the administration of a single bolus dose of propofol at 4, 6 or 8 mg/kg, the plasma concentration rapidly declined. The graphed curve was similar to that found in pharmacokinetic studies. Plasma concentrations decreased to below 2 μg/mℓ after 9, 13.5 and 17 min and below 1 μg/mℓ after 16, 23 and 28 min for bolus doses of 4, 6 and 8 mg/kg of propofol, respectively (Fig. 1). After 240 min statistical significance between the groups had been lost ($P > 0.05$) and all predicted plasma concentrations were below 0.02 μg/mℓ for all bolus doses. An increased predicted plasma concentration in relation to larger bolus doses was evident during the 1st

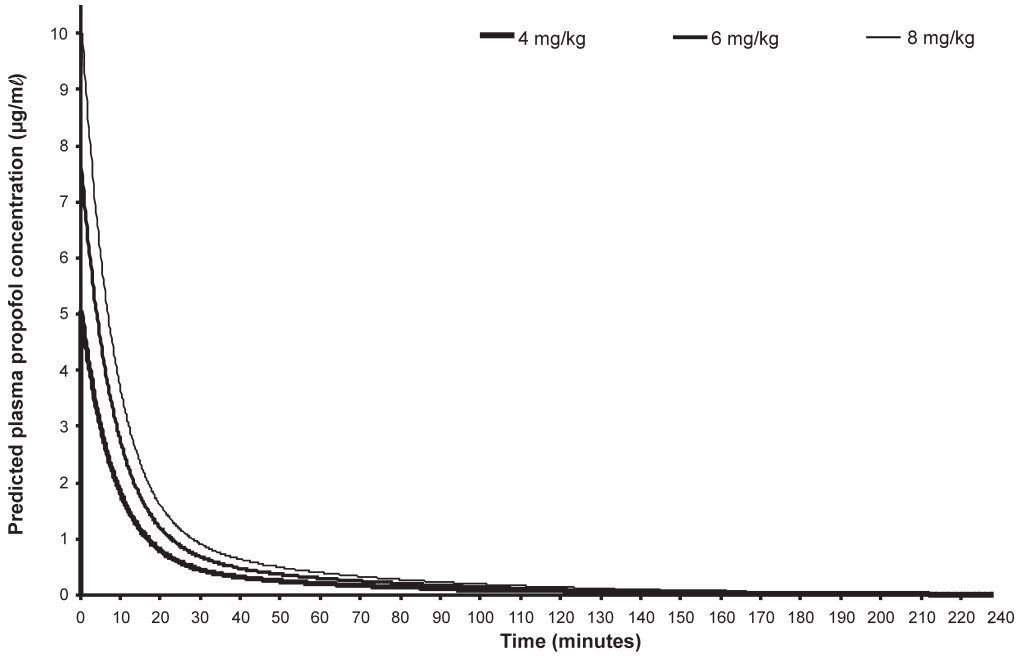

Fig. 1: **Predicted plasma concentration of propofol following a single bolus dose of propofol at 4, 6 and 8 mg/kg. A rapid decline in predicted plasma concentration is evident and similar to that found in a pharmacokinetic trial. A difference in plasma concentration is evident between the different bolus doses until 120 minutes after the administration of propofol.**

60 min with no difference evident after 120 min.

When CRIs of 0.2, 0.3, 0.4 and 0.5 mg/kg/min were simulated without a bolus dose, 25 % of final concentration was achieved in 4.5 min, 50 % at 13 min, 80 % at 57 min, 90 % at 111.5 min and 95 % by 204 min. After 240 min, concentrations were just over 95 % of concentrations achieved at 1440 min with a 5 % increase in plasma concentration over the remaining 1200 min (Fig. 2). The plasma concentration changed by less than 1 % over the last 460 min when simulated for 1440 min. The concentrations achieved at 240 and 1440 min are shown in Table 6. When the CRI infusion was plotted as percentage of its final concentration after 1440 min, all the graphs were superimposable with no statistical significance ($P > 0.05$). When a bolus dose of propofol was immediately followed by a CRI, the predicted plasma concentration increased initially in response to the bolus dose before decreasing below predicted plasma concentrations at 1440 and 240 min. Most troughs were reached between 15 and 30 min. Plasma concentrations then steadily rose for the remainder of the simulation (Fig. 3). After 120 min, the constant rate infusion had the greatest effect on the predicted plasma concentration (98 % at 120 min and 99 % at 240 min). The bolus dose administered had no statistical effect ($P > 0.05$) on the plasma concentration beyond 240 min. There was a significant difference between different infusion rates ($P < 0.05$) after 60 min.

When the simulation was programmed to maintain a steady-state concentration based on predicted plasma concentrations after 1440 min of a constant rate infusion,

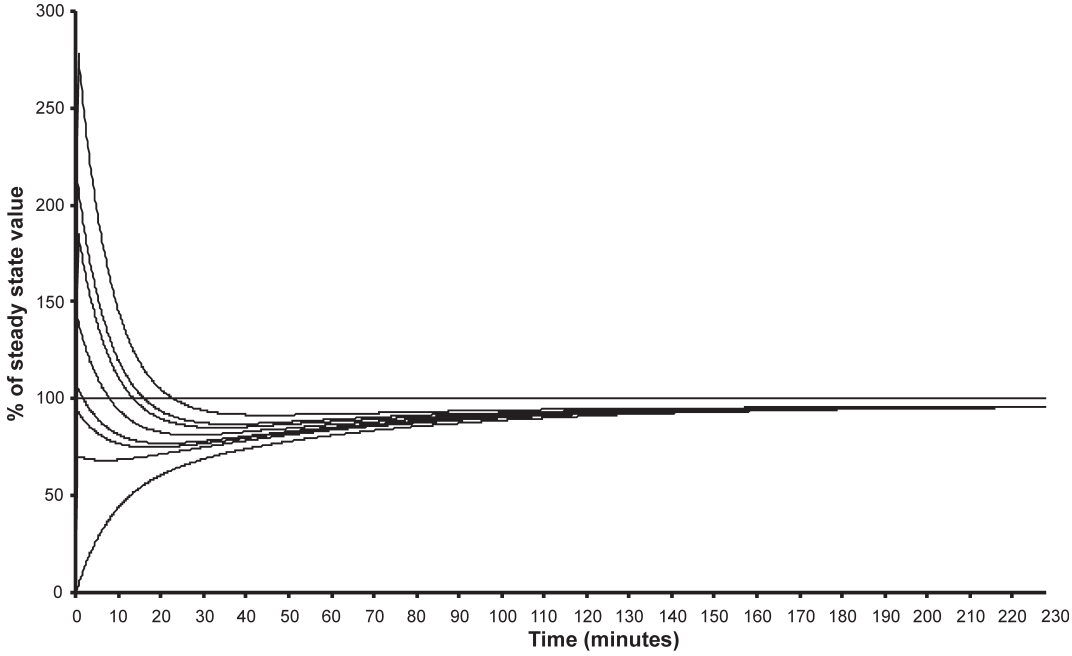

Fig. 2: **Predicted plasma concentrations graphed as a percentage of steady state values after 1440 minutes graphed over 240 minutes Plasma concentrations fall rapidly after the bolus administration, reaching trough levels between 15 and 30 minutes before increasing in response to the CRI. The graph starting from 0 represents a CRI without a bolus dose.**

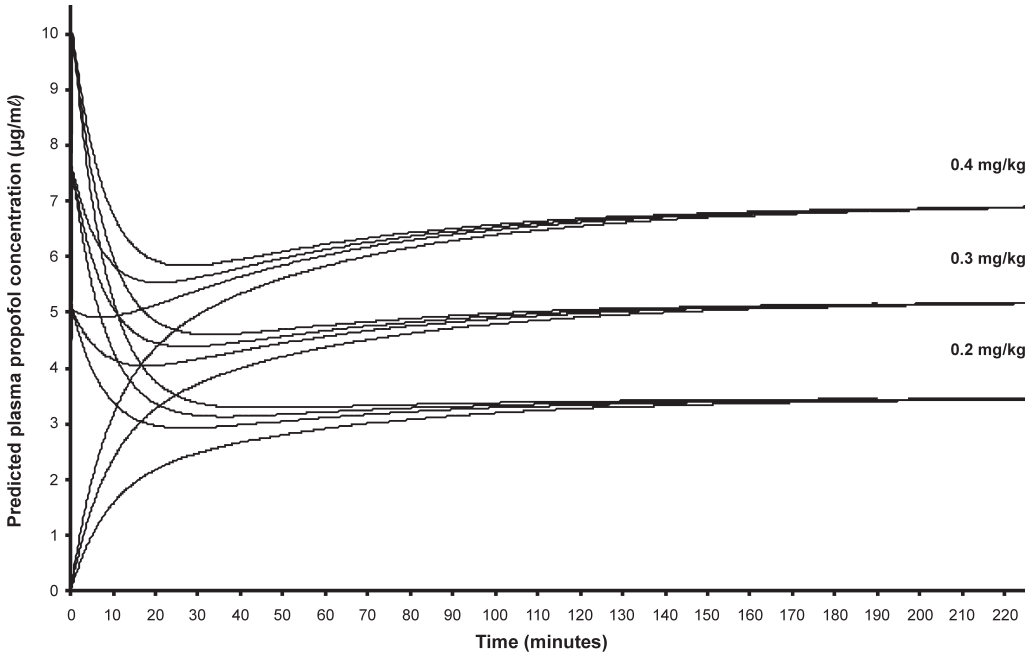

Fig. 3: **Predicted plasma concentration of propofol after a different constant rate infusion. This graph was constructed following the administration of 0, 4, 6 and 8 mg/kg of propofol as a bolus dose combined with an infusion rate of 0.2, 0.3 and 0.4 mg/kg/min. From this graph it is evident that with time the predicted plasma concentration becomes dependent on the constant rate infusion and that the initial bolus dose has little influence on plasma concentrations after 120 minutes.**

pump rates decreased rapidly initially. A 10 % decrease in pump rate was evident after 11 min, a 20 % decrease by 30 min and a 30 % decrease by 74 min. A further 4 % decrease was evident after 240 min and 5 % decrease by 1440 min. Infusion rates are given in Table 7. When the pump rates were graphed as percentage of their final rate after 1440 min, the graphs were superimposable and independent of infusion rate (Fig. 4).

Predicted recovery time was decreased by an increase in the set recovery concentration (2 μg/mℓ concentration had a shorter recovery time than 1 μg/mℓ). The infusion rate and duration of the infusion was positively correlated with an increase in recovery time ($P < 0.05$). The mean time for recovery after 5 min of an infusion was 14.4 ± 5.6 min that increased to 33.4 ± 21.9 min at 240 min for both recovery concentrations. The recovery time after 5 and 240 min of an infusion at recovery concentration of 2 μg/mℓ were 9.75 ± 2.2 and 19 ± 11.5 min and for 1 μg/mℓ 19.0 ± 3.4 and 47.5 ± 21.0 min, respectively. The recovery times started to plateau after 240 min (Fig. 5).

Table 6: **Predicted plasma concentration of propofol at 240 and 1440 minutes. The concentration achieved at 1440 minutes was considered to a steady state value.**

Infusion rate	Concentration at 240 min (µg/mℓ)	Steady state at 1440 min (µg/mℓ)
0.2 mg/kg/min	3.45	3.6
0.3 mg/kg/min	5.17	5.41
0.4 mg/kg/min	6.89	7.21
0.5 mg/kg/min	8.63	9.01

DISCUSSION

The exponential decline of propofol following the administration of a single bolus dose is similar to what has been reported in pharmacokinetics studies[5,28,39]. Routine clinical practice indicates that even when an induction agent is followed by a maintenance agent the animal usually reaches a lighter anaesthetic plane before going back to a surgical plane of anaesthesia. In fact, over 50 min are required to achieve 80 % of propofol steady state values. The slow rise in plasma concentration following the start of CRI is evident when CRI without a bolus dose is used (Fig. 3). After the administration of a large bolus dose (8 mg/kg) and a high infusion rate (0.4 mg/kg), plasma concentrations fall from a peak of 10.04 μg/mℓ to 5.84 μg/mℓ after 27 min before returning to steady state values of 6.91 μg/mℓ at 240 min.

Before this observation can be interpreted further, an idea of the MIR required to maintain anaesthesia is needed. In the initial study by Hall and Chambers, it was shown that a CRI of 0.5 mg/kg/min

Table 7: **Infusion rates to maintain target plasma concentrations. Infusion rates are given in mg/kg/min. The final infusion rate at 1440 minutes is equal to the infusion rate used to create the target plasma concentrations. At all time intervals before 1440 minutes infusion rates were higher.**

Target plasma concentration (µg/mℓ)	Infusion rate (mg/kg/min)					
	0.5 min	11 min	30 min	74 min	240 min	1440 min
3.6	0.31	0.285	0.250	0.220	0.206	0.200
5.41	0.47	0.425	0.376	0.330	0.312	0.300
7.2	0.62	0.566	0.500	0.438	0.415	0.400
9.01	0.78	0.710	0.626	0.55	0.518	0.500

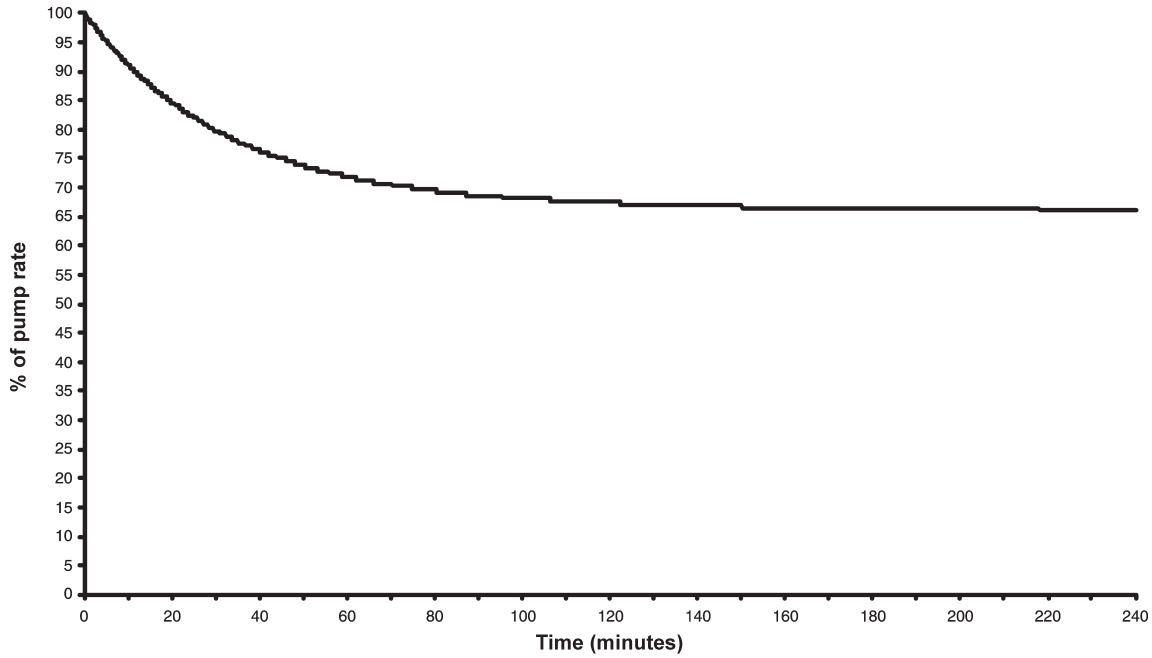

Fig. 4: **Pump rates graphed as a percentage of final pump rates after 1440 minutes graphed over 240 minutes. A rapid decrease in pump rate is evident in the 1st 60 minutes.**

was associated with life-threatening side effects[12] and therefore an infusion rate lower than this should be used. Infusion rates of 0.3 and 0.35 mg/kg/min required the administration of additional propofol to ensure the maintenance of an adequate depth of anaesthesia[12]. Therefore, for the maintenance of adequate anaesthesia an infusion rate in the region of 0.4 mg/kg/min is required[12]. Only minor surgical and diagnostic procedures were performed in this study without the benefit of balanced anaesthesia[12]. It is possible that a lower infusion rate would have been applicable if balanced anaesthesia was used. Watkins[29] showed that an infusion rate of 0.38 mg/kg/min was required in premedicated (acetylpromazine and atropine) patients to maintain an adequate depth of anaesthesia[35]. This is close to the value calculated by Hall and Chambers[12]. Morgan and Legge came up with similar results (premedicated (acetylpromazine and atropine) patients 0.26 mg/kg/min and unpremedicated patients 0.41 mg/kg/min)[24]. Both of these studies calculated the infusion rate from multiple bolus doses of propofol administered to maintain anaesthetic depth. Fonda used a syringe driver pump to administered propofol continuously and determined that an infusion rate of propofol between 0.33 and 0.41 mg/kg/min was required for surgical and endoscopic procedures while for non-invasive procedures a dose of 0.27 mg/kg/min was required[9]. All these animals were premedicated with acetylpromazine and atropine[9] and again the use of balanced anaesthesia may have an effect on the administration rate. Vainio showed that an infusion rate of 0.15 mg/kg/min was required to maintain

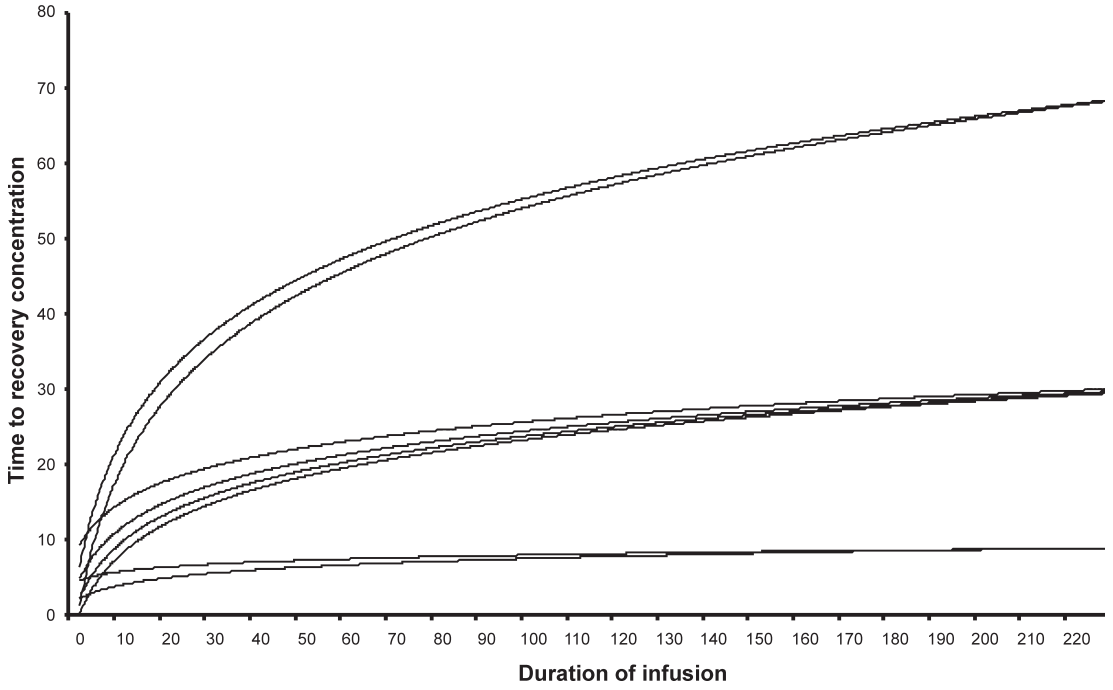

Fig. 5: **Recovery time plotted as a trend line against the duration of the infusion over 240 minutes. The predicted time to decrease in predicted plasma concentrations of either 1 or 2 µg/mℓ graphed against the duration of an infusion for various infusion rates. Recovery time increased with the duration of the infusion and starts to level off after 240 minutes.**

anaesthesia following premedication with medetomidine[33]. Thurmon showed that a similar infusion rate (0.165 mg/kg/min) was required after medetomidine premedication[32]. Medetomidine is known to cause a significant reduction in anaesthetic requirements and may not represent a fair comparison to other premedications[27,34,38]. Robertson *et al.* used an infusion rate of 0.4 mg/kg/min of propofol to maintain anaesthesia in greyhounds and non-greyhounds without life-threatening side effects[29]. Keegan and Greene found that an infusion rate of 0.44 mg/kg/min was required to maintain anaesthesia[16]. These studies indicate that an optimal infusion of approximately 0.4 mg/kg/min is required for surgical anaesthesia.

The plasma concentration falls to a trough of 5.84 μg/mℓ (after a bolus of 8 mg/kg and infusion of 0.4 mg/kg/min), which is close to the 1440 min concentration of a 0.3 mg/kg/min CRI. An infusion rate of 0.3 mg/kg/min has been associated with signs of inadequate anaesthesia[1,12]. Nolan and Reid showed that a plasma concentration of 3.77–5.52 μg/mℓ produced a light plane of anaesthesia but these patients were premedicated with acetylpromazine and papaveretum[25]. The balanced anaesthesia may have resulted in the reduced plasma concentration of propofol. Beths *et al.* showed that an infusion rate of 0.31 mg/kg/min was required and plasma concentration of between 2.5–4.7 μg/mℓ of propofol was required to maintain anaesthesia[2]. The decrease in plasma concentration after the administration of bolus dose and the immediate start of CRI is important as it may become evident as a lightening of anaesthetic plane between 15 to 30 min after the start of an infusion. Even with a high induction dose and immediate CRI, anaesthetic depth may become inadequate if not appropriately monitored especially if balanced anaesthesia is not used. With a manual CRI, an increase in infusion rate or the administration of a bolus dose may be required during this period to maintain anaesthesia. A lightened anaesthetic plane is more likely with lower infusion rates and smaller induction boluses. With targeted plasma concentrations administered by a computer-controlled infusion pump this is theoretically less likely to happen.

Plasma concentrations of propofol above 6.5 μg/mℓ have been associated with apnoea and muscle twitches[2]. From the simulation data, a CRI of 0.4 mg/kg results in a plasma concentration of propofol of 5.83 μg/mℓ after 60 min and a 1440 min plasma concentration of 7.21 μg/mℓ. Most studies have used an infusion time of 60 min or less[1,12,25,29,32,33]. The observation that an infusion of 0.4 mg/kg/min is ideal may be inappropriate if maintained for longer than an hour as dangerously high plasma concentration may be reached. The simulated data indicate that plasma concentrations are only 80 % of steady state values for 0.4 mg/kg/min CRI and close to steady state concentration (5.41 μg/mℓ) achieved by a CRI of 0.3 mg/kg/min and this infusion rate may be ideal for anaesthesia lasting more than an hour.

As constant rate infusion of propofol results in a slowly increasing plasma concentration[5,13,20,25], it is logical to target a plasma concentration rather than administer a CRI. When a plasma concentration is targeted by a computer-controlled infusion program a steady decrease in infusion rate occurs (Fig. 4). Most of the decreases occur in the 1st hour of the infusion. From the simulation data, it makes sense to decrease the infusion rate by 10 % at 10, 30 and 70 min after the start of the infusion. A further decrease of 10 % occurs during the next 24 hours and is most probably not clinically very significant. When planning a total intravenous anaesthetic protocol, it is important to realise that a higher infusion rate is initially required and that most of the changes in infusion rate are going to occur in the 1st 60 min. Monitoring of anaesthetic depth is critical during this period to ensure that the patient does not become too deeply anaesthetised. After 70 min, only smaller changes in infusion rates are required.

The recovery concentrations used in this study of 1–2 μg/mℓ were based on recovery concentrations previously reported (Table 3). The initial predicted recovery times for propofol after a bolus dose and 5 min of an infusion varied between 9 and 28 min for both recovery concentrations. This correlated well with the recovery times and concentrations reported in previous studies[9,16,24–26,28,29,33,36,39] (Table 3 and 4) and indicates that the pharmacokinetic simulation gave potentially useful and clinically relevant data. As the duration of the infusion increased it was evident that the recovery time increased. Cockshott *et al.* showed that the clearance of propofol decreased with time during a 6-hour infusion of propofol[5]. They suggested the decrease in clearance could be a result of decreased hepatic perfusion[5]. Hall *et al.* did not report any changes in the pharmacokinetic variables of propofol after an infusion of 60 min[13] indicating that the increase in recovery time may be unrelated to hepatic perfusion.

Recovery from anaesthesia generally occurs because of redistribution of an anaesthetic agent from the central nervous system to adipose and muscular tissue. With a CRI, it can be expected that these tissues becomes saturated and recovery is delayed. This is classically observed when anaesthesia is maintained with thiopentone[3]. The context-sensitive half-life has been used to describe the changes in recovery characteristics of a drug in relation to the duration of an infusion[15]. The essence of this concept is that as the peripheral compartment is filled with an anaesthetic agent, the rate of transfer into this compartment decreases as the infusion continues. When the infusion is discontinued, the large store in the peripheral compartment can be transferred back into the central compartment and hence maintain plasma concentrations for longer than expected[15]. The context was originally described as the time required to decrease a plasma concentration by 50 %[15]. The change in context-sensitive half-life would be seen as a change in clearance or elimination[15]. Cockshott *et al.* suggested a decrease in clearance of propofol during a 6-hour infusion of propofol may be the result of this and not due to a decreased liver perfusion as suggested[5]. Changes in the context-sensitive half-life can be dramatic (e.g. fentanyl). Fentanyl has a short half-life (30 min) after a single bolus but this increases to over 300 min after an 8-hour infusion[15]. Propofol has a slower increase in context-sensitive half-life over an 8-hour infusion[15].

The context chosen has been shown to influence the time to a predetermined drop in plasma concentration[31]. The larger the decreases required in plasma concentration the longer the context-sensitive half-life[31]. In this study, the context-sensitive half-life was defined as the time to achieve a plasma concentration of 1–2 μg/mℓ as this is related to the estimated recovery concentration and is more relevant than a predetermined percentage reduction in plasma concentration. The context-sensitive half-life increased by 43 min over the duration of a 240 min infusion. The large standard deviation is the result of different infusion rates and recovery concentrations used in the simulations. Higher infusion rates and lower recovery concentrations increased the time as is evident in Fig. 5. From the simulated data, it would seem prudent after a long infusion of propofol to decrease or terminate infusion well in advance of the anticipated recovery time to allow for a decline in plasma concentrations. Cockshott *et al.* have suggested that acute tolerance to propofol may develop and a higher plasma concentration is evident at recovery[5]. The simulation data indicate that this statement is valid in dogs but a slower recovery can be

expected after a long infusion.

A number of studies have used infusion pumps to administered propofol on CRI basis[9,12,16,29,33]. The use of computer-controlled infusion is poorly investigated in veterinary medicine[2,17] compared with human medicine[7,18,22,30]. Computer-controlled infusions adjusted by changes in auditory-evoked potential or burst suppression have been used to maintain anaesthetic depth[17,19]. Pharmacodynamic modelling of effector site concentration has already become available in human medicine[23,37]. Once effect site data are available for veterinary patients, computer-controlled infusion can be used to target effect sites rather than plasma concentration, resulting in potentially better control of anaesthesia. Computer simulations used in conjunction with anaesthetic depth monitors can be used to assist us in devising suitable CRI protocols with combination drugs. Refinement of these developments will provide the private practitioner with a system that is easy to use and simple to understand.

The program Stelpump appears to provide simulation data that correlate well with published data. Further clinical testing of the program is required before it can be recommended for clinical use. Stelpump is capable of using the effector site equilibrium constant to target effector site concentrations.

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