

Target-controlled infusion of propofol in dogs – evaluation of four targets for induction of anaesthesia

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Four groups of 20 dogs were anaesthetised by means of target-controlled infusions of propofol designed to achieve 2.5 µg/ml, 3.0 µg/ml, 3.5 µg/ml or 4.0 µg/ml of propofol in blood. The dogs' pulse rate and respiratory rate were recorded before premedication and induction, immediately after endotracheal intubation and three and five minutes later (times 0, 3 and 5, respectively), and their arterial blood pressure was recorded oscillometrically just before induction and at times 0, 3 and 5. The targets of 2.5, 3.0, 3.5 and 4.0 µg/ml resulted in the successful induction of anaesthesia in 13 (65 per cent), 16 (80 per cent), 20 (100 per cent) and 20 (100 per cent) of the dogs, respectively. The incidence of postinduction apnoea was 0 (0 per cent), one (5 per cent), two (10 per cent) and eight (40 per cent) at time 5 for groups 2.5, 3.0, 3.5 and 4.0 µg/ml, respectively, and its incidence at time 5 was significantly higher in the 4.0 µg/ml group ($P<0.05$) than in the other groups. In all the groups there was a significant ($P<0.05$) decrease in blood pressure between just before induction and the later measurements. Although there were no statistically significant differences between the groups in terms of inducing anaesthesia at a specific target, a target of 3.5 µg/ml appears to ensure a successful induction of anaesthesia without a significant increase in the incidence of apnoea.

TOTAL intravenous anaesthesia (TIVA) is widely used in human medicine, but is used much less in veterinary medicine, where inhalational techniques are still most commonly applied for the maintenance of anaesthesia (Reid and Nolan 1999). This is unfortunate, because TIVA has several potential advantages over the use of gaseous agents. For example, people have been shown to recover significantly more quickly after being anaesthetised with a propofol-based TIVA technique, than after having anaesthesia maintained with a volatile agent (Vallane 1992, Biro and others 1995). Moreover, both the quality and controllability of propofol TIVA have been reported to be superior to inhalational anaesthesia (Miller 1994). Another important advantage is the elimination of the occupational exposure of operating theatre personnel to inhalational agents (Engbers 1996, Smith and White 1998a).

A variety of drug administration protocols can be used to achieve TIVA. The intermittent bolus administration of a drug may result in high peak plasma concentrations, and excessive depth of anaesthesia and side effects, alternating with troughs associated with inadequate anaesthesia and the possibility of awareness (Smith and White 1998b). Better control and a more steady state can be achieved by administering short-acting drugs by continuous infusion, at either a variable or a constant rate. In the former case, the regimen involves the delivery of a bolus dose or a loading infusion to achieve an adequate blood concentration of drug for endotracheal intubation, followed by a decreasing rate of infusion to compensate for the redistribution and elimination of the drug, while maintaining an effective concentration at the drug's site of action. This procedure requires an estimate of the rate of clearance of the drug, and the plasma concentration achieved may be higher or lower than the intended concentration. A commonly used 'step-down' procedure for the use of propofol in human beings is to inject a bolus dose of 1 mg/kg, followed by an infusion, initially at a rate of 10 mg/kg/hour for 10 minutes, then 8 mg/kg/hour for the next 10 minutes, and finally a maintenance infusion rate of 6 mg/kg/hour; this is known as the 'Bristol technique' (Tackley and others 1987). In combination with nitrous oxide and fentanyl this technique achieves, on average, a plasma concentration of propofol of 3 µg/ml (Aitkenhead 2001). In the case of a constant rate

of infusion there is the potential, depending on the duration of anaesthesia and the drug's pharmacokinetics, for the drug to accumulate and for its plasma concentration to exceed the intended or required level. Either a continuous or a variable rate of infusion can produce a more stable level of anaesthesia than the use of intermittent boluses, and is more economical in terms of the total amount of drug used (Fragen 1991).

A target-controlled infusion (TCI) of anaesthetic is designed to achieve a predicted target blood concentration based on population pharmacokinetics, and although the actual concentrations may be higher or lower than the target selected, it is likely to provide the closest approximation for an individual patient. For successful induction of anaesthesia, the concentration of drug at the effector site in the brain must be sufficient to produce loss of consciousness. However, time is needed to transfer the drug from the blood to the effector site, and this time depends on the concentration gradient between the blood and the site; the steeper the gradient, the shorter the time required to induce anaesthesia. A high target blood concentration will result in the rapid induction of anaesthesia, but may be accompanied by an unacceptable degree of cardiopulmonary depression due to the high blood concentration of the drug, whereas a lower target blood concentration may minimise these effects, but unacceptably prolong the time to induce anaesthesia. The aim, therefore, is to achieve a balance between the successful induction of anaesthesia within an acceptable period, and the avoidance of cardiovascular and respiratory depression.

The technique involves the computer-controlled administration of the drug by means of an infusion pump. The pharmacokinetic profile of the drug is programmed into the computer and the rate of infusion is determined by the rate of redistribution and elimination of the drug from the body. The pharmacokinetic model determines the initial rate of infusion, in the form of a rapid zero-order infusion to achieve the predicted target concentration, and this is followed by a slower rate to maintain this concentration (Beths and others 2001). The result will approximate a stable plasma concentration of drug, which can easily be changed in response to its clinical effects (Smith and White 1998b). The disadvantages of the system are the potential variability between patients

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TABLE 1: Mean (sd) ages and weights, and the numbers of different breeds constituting the four groups of 20 dogs with target blood concentrations of 2.5, 3.0, 3.5 and 4.0 µg/ml propofol

	Group			
	2.5 µg/ml	3.0 µg/ml	3.5 µg/ml	4.0 µg/ml
Age range (years)	0.8-7.5	0.5-7.0	0.6-8.0	0.5-8.0
Mean (sd) age (years)	4.15 (2.46)	3.06 (2.13)	4.09 (2.78)	3.68 (2.84)
Weight range (kg)	8.5-56.0	4.0-68.0	3.5-71.5	7.8-54.5
Mean (sd) weight (kg)	30.91 (45.6)	22.0 (14.4)	29.6 (17.5)	29.1 (14.3)
Number of different breeds	14	14	15	14

and the expense of both the anaesthetic drug and the infusion pump (Smith and White 1998b).

The pharmacokinetics of propofol (a rapid distribution phase, rapid elimination and lack of accumulation on repeated administration) make it suitable for use either as an intravenous anaesthetic alone or for the induction of anaesthesia (Lumb and Jones 1996). These properties give it an advantage over other intravenous induction agents and make it the most suitable drug for the maintenance of anaesthesia by continuous infusion (Reid and Nolan 1999). The mean induction doses of propofol given by slow intravenous injection in unpremedicated and premedicated dogs have been reported to be 6.55 mg/kg and 4.5 mg/kg, respectively (Morgan and Legge 1989). These doses approximate to predicted peak concentrations of 8.4 µg/ml and 5.8 µg/ml propofol in the blood, according to a modelling program for intravenous drugs (PK-SIM version 3.11; Specialized Data Systems), considerably higher than the targets assessed here. A bolus induction dose may be associated with considerable cardiovascular and respiratory depression, and apnoea has been reported frequently. In dogs apnoea is reported to be the most prevalent adverse side effect after induction with propofol (Smith and others 1993) and it appears to be independent of the preanaesthetic agent given. In human studies it has been demonstrated that there is less cardiorespiratory depression when anaesthesia is induced with propofol by means of a TCI system (Taylor and Kenny 1998), most probably because the drug is administered at a relatively slower rate and the induction dose is smaller.

Propofol TCI is widely used in human anaesthesia, but it has only recently been reported in dogs (Beths and others 2001). Beths and others (2001) induced anaesthesia in 16 dogs and concluded that an induction target of 3 µg/ml consistently produced ideal conditions for intubation within three minutes, and, although slow, the induction of anaesthesia was remarkably smooth and controlled. The optimisation of an induction target was not the aim of their study, and although anaesthesia was induced at this target concentration in nine of 16 dogs, the conclusion was based only upon a clinical impression. Targets of up to 15 µg/ml were investigated, but at the higher induction targets the incidence of muscle twitching and postinduction apnoea was unacceptably high, despite a rapid induction of anaesthesia. The choice of induction target will be influenced by several factors, including the premedicant drugs, the age, physical condition and health of the dog, and the speed at which it is desired to induce anaesthesia.

In view of the many potential benefits of TCI and its relative ease of use, this study was undertaken to investigate the suitability of four different propofol target concentrations for the induction of anaesthesia in healthy dogs. The targets were chosen on the basis of the study by Beths and others (2001).

MATERIALS AND METHODS

The study was a prospective randomised study of 80 client-owned dogs aged between six months and eight years and with

TABLE 2: Numbers of dogs in each of the four groups of 20 dogs with target blood concentrations of 2.5, 3.0, 3.5 and 4.0 µg/ml propofol in which anaesthesia was not induced at the target concentration and the concentrations at which they were induced

	Group			
	2.5 µg/ml	3.0 µg/ml	3.5 µg/ml	4.0 µg/ml
Number of dogs in which anaesthesia was not induced at the designated target	7	4	0	0
Target required (µg/ml) (number of dogs)	3.0 (5) 3.5 (2)	3.5 (2) 4.0 (1) 4.5 (1)		

American Society of Anesthesiologists scores 1 or 2, which underwent minor to moderate surgical procedures at the University of Glasgow veterinary school. The dogs were randomly assigned using computer-generated numbers to four groups of 20. After a preanaesthetic clinical examination and a fasting period of 12 hours, the dogs were premedicated with a combination of 0.03 to 0.05 mg/kg acetylpromazine (ACP Injection; C-Vet), up to a maximum of 1 mg, and 0.2 mg/kg morphine (Morphine Sulphate Injection BP; Martindale Pharmaceuticals) by intramuscular injection, 20 to 30 minutes before anaesthesia was induced. A cannula was placed in a cephalic vein and 100 per cent oxygen was administered via a face mask during the induction period. Propofol (Rapinivet; Schering Plough Animal Health) was administered through a TCI system programmed for propofol in dogs. The age and weight of the dog, and the concentration of propofol, were entered as the variable parameters and one of the four target blood concentrations was selected. Three minutes after the TCI display screen indicated that the target blood concentrations of propofol had been attained, endotracheal intubation was attempted; the conditions for intubation were considered adequate if there was no swallowing or tongue withdrawal. A laryngoscope was not used and the anaesthetist was not blinded to the induction target. If the dog could not be intubated the target concentration was increased by 0.5 µg/ml and by the same increment each minute thereafter until intubation was possible; intubation was attempted one minute after each new target concentration was attained. After it had been intubated, the dog was placed in lateral recumbency and connected to a non-rebreathing anaesthetic system with 100 per cent oxygen delivered at an appropriate fresh gas flow.

Each dog's pulse rate and respiratory rate were recorded before premedication and induction, immediately after it had been intubated (time 0) and three (time 3) and five (time 5) minutes later. The pulse rate was assessed by palpation of a peripheral pulse, and the respiratory rate by observing the movements of the thoracic wall or of the reservoir bag of the breathing system. For the purposes of this study, postinduction apnoea was defined as apnoea lasting for more than 15 seconds, after endotracheal intubation. If apnoea occurred, positive manual pressure ventilation was applied at a rate of four breaths per minute. Arterial blood pressure was recorded oscillometrically (DINAMAP; Critikion) before induction, immediately after the dog had been intubated, and three and five minutes later, with an appropriately-sized cuff placed over the dorsal pedal artery. A single measurement was taken at each time point. After collection of the final data five minutes after intubation, the anaesthetic was continued according to requirements for the individual case.

No blood samples were collected to compare the actual blood concentration of propofol with the predicted target of the TCI system, because the performance of the system had been validated by Beths and others (2001).

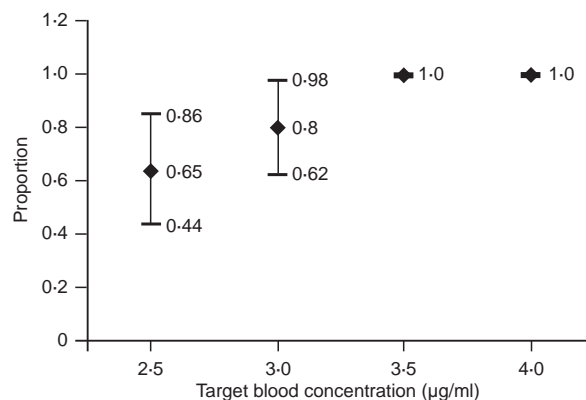


FIG 1: Proportions of the dogs (95 per cent confidence intervals) with target blood concentrations of propofol of 2.5, 3.0, 3.5 and 4.0 µg/ml in which anaesthesia was induced at the target concentration

The results were analysed by calculating 95 per cent confidence intervals for the proportions of the dogs in the four groups that were successfully anaesthetised at the assigned target, and that were apnoeic after induction. A Z test was used to compare the proportions. A general linear model, with the dog as a random factor (Tukey multiple comparison), was used to compare the changes in blood pressure and pulse rate. A one-way analysis of variance was used to compare the groups with respect to weight and age. Values of $P < 0.05$ were considered significant.

RESULTS

The 80 dogs were aged between six months and eight years, and weighed between 3.5 and 71.5 kg. There were 34 different breeds, and labrador retrievers were the most common ($n=10$), with Cavalier King Charles spaniels the second most common ($n=7$) (Table 1). There were no significant differences between the four groups with respect to their weight and age.

The targets of 2.5, 3.0, 3.5 and 4.0 µg/ml propofol resulted in the successful induction of anaesthesia in 13 (65 per cent), 16 (80 per cent), 20 (100 per cent) and 20 (100 per cent) of the dogs respectively; the differences were not statistically significant (Fig 1). The dogs that were not successfully induced at their assigned target were induced at a higher target (Table 2).

The incidence of postinduction apnoea was six (30 per cent), six (30 per cent), seven (35 per cent) and nine (45 per cent) at time 0, two (10 per cent), two (10 per cent), three (15 per cent) and eight (40 per cent) at time 3 and 0, one (5 per cent), two (10 per cent) and eight (40 per cent) at time 5 for groups 2.5, 3.0, 3.5 and 4.0 µg/ml, respectively (Fig 2). At time 3 the incidence of apnoea was significantly higher in the group with the 4.0 µg/ml target than in the groups with the 2.5 and 3.0 µg/ml targets, and at time 5 the incidence in the group with the 4.0 µg/ml target was significantly higher than in all the other groups.

In each group there was a significant decrease in arterial blood pressure between just before induction and time 3 and 5 (Fig 3). In the 2.5 µg/ml group there were significant decreases in arterial blood pressure when comparing between just before induction with times 0, 3 and 5. In the 3.0 µg/ml group the same effect was seen when comparing just before induction with times 0, 3 and 5 and also when comparing time 0 with time 3 and time 5. For the 3.5 µg/ml group the same trends were evident when comparing just before induction with time 3 and time 5, and when comparing time 0 with time 5. In the 4.0 µg/ml group there was a significant decrease

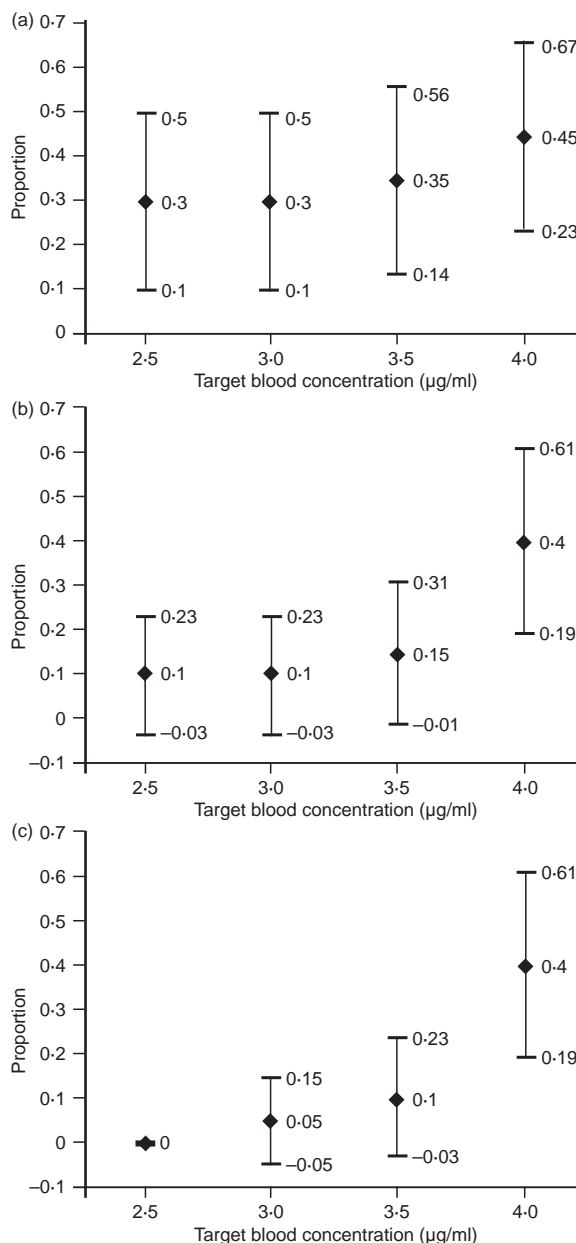


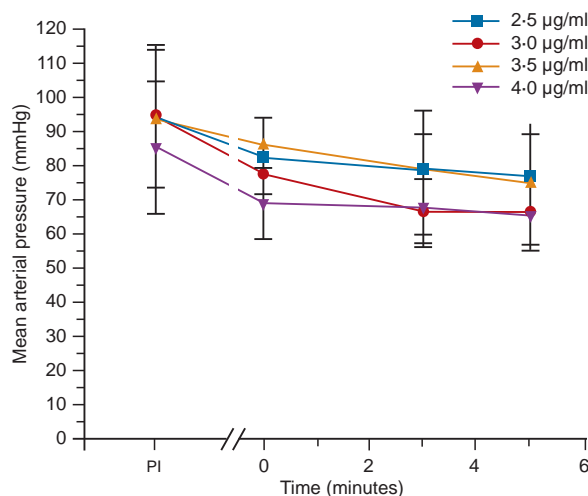
FIG 2: Proportions of the dogs (95 per cent confidence intervals) with target blood concentrations of 2.5, 3.0, 3.5 and 4.0 µg/ml propofol which were apnoeic (a) immediately after they were intubated, (b) three minutes later and (c) five minutes later

in arterial blood pressure when comparing just before induction with times 0, 3 and 5. The results show that when comparing preinduction values with measurements taken three and five minutes after induction there is a significant decrease in blood pressure in all groups. Although there was a significant decrease in blood pressure in all the groups at times 3 and 5, the incidence of hypotension (mean blood pressure < 60 mmHg) was relatively low (Table 3). A significantly higher proportion of the dogs in the 4.0 µg/ml group became hypotensive compared with the other three groups, but none of the dogs had a mean arterial blood pressure below 50 mmHg.

There was a significant drop in pulse rate in the 2.5 µg/ml group when comparing just before induction with time 5 (Fig 4). In the 3.5 µg/ml group there was a slight increase when comparing pulse rate just before induction with time 0 and a significant decrease when comparing time 0 with time 3 and time 5. In the other two groups there were no significant changes in pulse rate and overall there was no apparent trend in change in pulse rate within the groups.

Muscle twitching was observed after induction in six dogs, the signs ranging from minimal twitching of the muscles of

FIG 3: Mean (sd) arterial blood pressures of the four groups of 20 dogs with target blood concentrations of 2.5, 3.0, 3.5 and 4.0 µg/ml propofol just before induction (PI), immediately after intubation (0) and three and five minutes later



the forelimbs, neck and face to opisthotonos; two of the dogs were in the 2.5 µg/ml group, one each in the 3.0 and 3.5 µg/ml groups and two in the 4.0 µg/ml group.

In each of the groups, it was apparent that some of the dogs could have been intubated less than three minutes after the target blood concentration of propofol had been reached. However, to maintain a standard procedure, they were maintained on 100 per cent oxygen delivered via a face mask for the complete three minutes.

DISCUSSION

In human beings, blood propofol concentrations ranging from 3 µg/ml to 15 µg/ml have been used to induce anaesthesia (Chaudhri and others 1992, Taylor and Kenny 1998, Short and Bufalari 1999), and it can be concluded that there is no single blood concentration that will be correct for all patients. The dose must be titrated to obtain the required clinical effect and chosen on an individual basis. The choice of induction target will be influenced by the drugs used for premedication, age, patient status and the speed at which it is desired to induce anaesthesia. The pharmacokinetic model for TCI calculates the rate of infusion on a set of species-specific pharmacokinetic variables for propofol. On the basis of the fact that in human beings the half-life for equilibration between blood and the drug's site of action is approximately 2.6 minutes (J. B. Glen, personal communication), three minutes were allowed from the attainment of the desired target blood concentration to the first attempt at intubation. Subsequent attempts at intubation were made one minute after the attainment of the next target concentration, to allow for a second equilibration phase.

A variety of side effects have been reported with propofol (Smith and others 1993), but the only adverse effects observed

TABLE 3: Numbers of dogs in each of the four groups of 20 dogs with target concentrations of 2.5, 3.0, 3.5 and 4.0 µg/ml propofol that suffered hypotension (mean arterial blood pressure [MAP] <60 mmHg) overall, and just before induction, at intubation and three and five minutes after intubation

	Group			
	2.5 µg/ml	3.0 µg/ml	3.5 µg/ml	4.0 µg/ml
Total dogs MAP <60 mmHg	1	6	3	8
Just before induction	0	0	1	1
Intubation	0	1	0	4
Three minutes	1	6	0	5
Five minutes	0	3	2	4

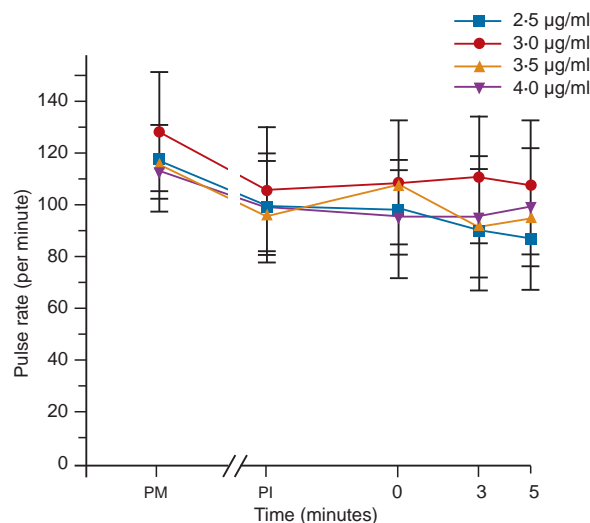


FIG 4: Mean (sd) pulse rates of the four groups of 20 dogs with target blood concentrations of 2.5, 3.0, 3.5 and 4.0 µg/ml propofol before premedication (PM), just before induction (PI), immediately after intubation (0), and three and five minutes later

in the dogs in the present study were related to excitation and respiratory depression. Excitatory effects following the administration of propofol to dogs are well recognised (Davies 1991, Smith and others 1993). Signs of central nervous system excitement, including involuntary movements, muscle tremors, twitching and coughing, may occur at all stages of induction, maintenance and recovery. The manifestations are often mild and it can be concluded that anaesthesia with propofol is generally smooth and provides satisfactory conditions for surgery. In this study, six of the 80 dogs (7.5 per cent) displayed mild twitching and opisthotonos, a proportion similar to that observed in other studies (Davies 1991, Smith and others 1993). The intravenous administration of a benzodiazepine may attenuate any movements which impede positioning or surgery (Davies 1991).

Respiratory depression is an important complication of propofol anaesthesia in people, cats and dogs (Smith and others 1993), and is a result of the direct depression of the central inspiratory drive and the ventilatory response to PaCO₂. It has been the most commonly reported adverse effect of propofol in dogs (Morgan and Legge 1989, Smith and others 1993, Quandt and others 1998). Although there were no statistically significant differences between the groups in terms of inducing anaesthesia at a specific target, the relative incidence of postinduction apnoea may influence the choice of induction target. The incidence of apnoea decreased with time in each group but was always greater with the higher target concentrations. Five minutes after the induction of anaesthesia, eight (40 per cent) of the dogs in the group with a target of 4.0 µg/ml were still apnoeic, suggesting that the incidence of apnoea was dose dependent, in agreement with the findings in other studies (Muir and Gadawski 1998). The higher target concentrations of propofol induced anaesthesia more reliably and, provided that respiration is monitored closely and intermittent positive pressure ventilation can be provided, postinduction apnoea need not be a serious problem.

Mean arterial blood pressure values were obtained oscillometrically, a reliable method for the measurement of systemic arterial blood pressure in dogs (Hamlin and others 1982, Sawyer and others 2004). In all the groups there was a statistically significant decrease in mean arterial pressure when comparing measurements taken just before induction with time 3 and time 5. There was no similar trend in respect to the dogs' pulse rate. These findings are consistent with the

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results of other studies in human beings and dogs (Claeys and others 1988, Chaudhri and others 1992, Nolan and Reid 1993, Smith and others 1993). Propofol can decrease arterial blood pressure by depressing sympathetic neural output centrally, resulting in decreased systemic vascular resistance (Claeys and others 1988). Claeys and others (1988) concluded that the major haemodynamic effect of propofol was to decrease arterial blood pressure by reducing systemic vascular resistance, rather than by reducing stroke volume or cardiac output. The effects of propofol on the baroreceptor reflex show that it resets the reflex to allow slower heart rates, despite a decrease in arterial pressure. It does not affect the sensitivity of the baroreflex (Sebel and Lowdon 1989).

When using a TCI system to induce anaesthesia in a dog, the target concentration must be titrated to achieve the required effect in that individual; the aim should be to titrate the delivery rate to achieve the desired clinical effect while minimising the side effects. The effects of propofol are closely related to its blood concentration (Short and Bufalari 1999), which can be easily altered by changing the target on the syringe driver. Although controlled ventilation may be necessary and the dog's blood pressure should be monitored, propofol TCI is a suitable technique for the induction of anaesthesia in healthy dogs. Although there were no significant differences between the four groups of dogs in terms of inducing anaesthesia at a specific target concentration, a target of 3.5 µg/ml appears to offer a greater likelihood of a successful induction of anaesthesia without a significant increase in the incidence of apnoea.

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