Total intravenous anesthesia in dogs

Totale intraveneuze anesthesie bij de hond

T. Waelbers, P. Vermoere, I. Polis

Department of Small Animal Medicine and Clinical Biology
Faculty of Veterinary Medicine
Ghent University, Salisburylaan 133, B-9820 Merelbeke

tim.waelbers@UGent.be

ABSTRACT

Inhalation anesthesia is the main method used for maintenance of anesthesia in dogs. One of the most important drawbacks of this technique, however, is that it pollutes the environment. Total intravenous anesthesia, or TIVA, can provide a valuable alternative to this method, an alternative whereby several different drugs or drug combinations and different means of administration can be used. Despite the existence of various options, a continuous rate infusion (CRI) of propofol or alfaxalone seems to be the most obvious choice in dogs.

Just as with inhalation anesthesia, endotracheal intubation and the administration of oxygen is highly recommended during TIVA. The possibility for artificial ventilation must also be taken into consideration. The main disadvantage of TIVA seems to be the higher cost, especially in large dogs and during long-lasting interventions.

SAMENVATTING

Voor het onderhoud van de anesthesie bij de hond wordt er meestal gebruik gemaakt van inhalatieanesthesie. Eén van de belangrijkste nadelen van deze techniek is echter de pollutie van de omgevingslucht. Totale intraveneuze anesthesie (TIVA) kan hiervoor een waardevol alternatief bieden. Verschillende (combinaties van) producten en verscheidene toedieningswijzen komen voor TIVA in aanmerking. Ondanks het bestaan van meerdere mogelijkheden lijkt bij de hond een "continuous rate infusion" (CRI) van propofol of alfaxalone als basis van de anesthesie de meest voor de hand liggende keuze.

Net zoals bij inhalatieanesthesie worden tijdens TIVA een endotracheale intubatie en de toediening van zuurstof aangeraden. Ook de mogelijkheid tot artificiële respiratie mag niet vergeten worden. Het grootste nadeel, namelijk de hoge kostprijs, lijkt in de praktijk vooral mee te spelen bij grote honden en langdurige ingrepen.

INTRODUCTION

Anesthesia can be classified according to the type of drug used and/or the route of drug administration. Basically there are two major ways to obtain general anesthesia in veterinary medicine: either via the parenteral injection of anesthetic drugs (subcutaneously, intramuscularly or intravenously) or via inhalation of volatile anesthetic agents. An ideal anesthetic produces sleep, amnesia, analgesia and muscle relaxation. As all these characteristics cannot be provided by a sole agent, a combination of drugs is used. This technique is referred to as "balanced anesthesia" (Thurmon and Short, 2007). Practically speaking, balanced intravenous anesthesia can be obtained by administering sedatives and analgesics in the premedication phase, as well as by using different analgesics (opioids, (dex)medetomidine, ketamine, lidocaine) as continuous rate infusions or by using CRI's during the anesthesia. The analgesic and anesthetic-sparing effects of these drugs then allow reduced infusion rates of the intravenously administered general anesthetic (Kästner, 2007).

Inhalation anesthetics owe their popularity to the predictable and rapid adjustment of anesthetic depth. Additionally, since endotracheal intubation needs to be performed, the administration of a high percentage of oxygen and artificial ventilation becomes possible. These components help minimize patient morbidity and mortality (Dodman, 1977).

Several disadvantages are inherent to inhalation anesthesia. Inhalant anesthetics require the use of a cumbersome and costly anesthetic machine, including a suitable breathing system and vaporizer (Matthews, 2007). Another of the major disadvantages when using volatile anesthetics is the exposure of operating-room personnel to the pollution in the ambient air. Replacing mask induction for induction of the anesthesia by adapted intravenous agents reduces the occupational exposure of anesthesiologists to anesthetic gases drastically (Hasei *et al.*, 2003), since the operating room air is contaminated by vaporizer filling, by leaks in the patient breathing circuit and by the spillage of liquid agent (Byhahn *et al.*, 2001; Steffey and Mama, 2007).

In recent years, intravenous anesthetics with rapid

onset, redistribution and clearance have become available, which creates the possibility of maintaining anesthesia using these intravenous agents. Even more, the use of intravenous anesthetic agents for the induction and maintenance of anesthesia does not exclude endotracheal intubation, oxygen administration or artificial ventilation. This, together with the exposure hazard when using volatile anesthetics, explains the increased interest of veterinarians in this so-called total intravenous anesthesia (TIVA).

PHARMACOKINETICS

Simple one- or multicompartmental pharmacokinetic models may be sufficient for explaining many applications in clinical pharmacology. However, understanding the pharmacokinetics of early drug distribution is necessary as well when dealing with rapidly acting intravenously administered drugs (Henthorn *et al.*, 2008). In order to provide a pharmacokinetic basis for interindividual variability in response to these rapidly acting drugs, a recirculatory pharmacokinetic model was developed (Krejcie *et al.*, 1996; Avram and Krejcie, 2003). Elimination half-life, which provides a parsimonious description of the rate of drug disposition in the one-compartment model, may be of little value in describing multicompartmental models. As a result, the time required for the central compartment drug concentration at the end of an infusion to decrease by 50% was defined as a "context-sensitive half-life" (Hughes *et al.*, 1992). Practically speaking, the use of a drug with a short context-sensitive half-life results in a fast recovery independent of the duration of infusion (Chism and Rickert, 1996).

In summary, a short context-sensitive half-life and rapid redistribution and biotransformation into inactive metabolites are favorable properties in an anesthetic used for TIVA (Morton, 1998). These properties allow infusion over prolonged periods of time at a constant rate and without accumulation. However, surgical stimulation, distribution processes over time, and individual and breed differences in terms of pharmacokinetics and sensitivity to a given drug make adjustments of the infusion rate necessary (Kästner, 2007).

ADVANTAGES AND DISADVANTAGES

Together with the advantages mentioned in the discussion of the different drugs (see below), an important advantage of TIVA is the prevention of contamination of operating room air (Monedero *et al.*, 1994).

The most important disadvantage of propofol-based TIVA still seems to be the cost. Particularly during procedures lasting longer than 60 minutes, the higher cost is considered significant (Short and Bufalari, 1999). However, comparing inhalation and total intravenous anesthesia remains difficult since the combination with other sedatives and analgesics also plays an important role (Suttner *et al.*, 1999). In humans, propofol-based anesthesia is associated with the highest intraoperative cost, but it does enable the most rapid recovery from anesthesia with the fewest postoperative side effects, and it also enables earlier discharge from the postanesthesia care unit (Suttner *et al.*, 1999).

The calculation of the total volume of anesthetics used and the cost of six different anesthetic regimes are represented in Tables 1a and 1b. As the administration of oxygen is also recommended during TIVA, the cost for oxygen has not been taken into account. This calculation shows that some combinations of sedatives and intravenous anesthetics (combination of

Table 1a. Calculation of the total volume of anesthetics used and the cost for six different anesthetic regimes.

TIVA protocols	Premedication	Induction	Maintenance
Protocol 1	Medetomidine [1] 40 µg/kg IM + Butorphanol [5] 0.1 mg/kg IM	Propofol [2] 1 mg/kg IV	Propofol 0.15 mg/kg/min
Protocol 2	Medetomidine 40 µg/kg IM + Butorphanol 0.1 mg/kg IM	Propofol 0.5 mg/kg IV + ketamine [3] 1 mg/kg IV	Propofol 0.075 mg/kg/min + ketamine 33 µg/kg/min
Protocol 3	Medetomidine 40 µg/kg IM + Butorphanol 0.1 mg/kg IM	Propofol 1 mg/kg IV	Isoflurane [4] (vaporizer setting 1%; fresh gas flow 1 l/min)
Protocol 4	Acepromazine 0.05 mg/kg IM + Butorphanol 0.1 mg/kg IM	Propofol 3 mg/kg IV	Propofol 0.4 mg/kg/min
Protocol 5	Acepromazine 0.05 mg/kg IM + Butorphanol 0.1 mg/kg IM	Propofol 3 mg/kg IV	Isoflurane [4] (vaporizer setting 2%; fresh gas flow 1 l/min)
Protocol 6	Acepromazine 0.05 mg/kg IM + Butorphanol 0.1 mg/kg IM	Alfaxalone [6] 2 mg/kg IV	Alfaxalone 0.1 mg/kg/min

[1] Sedator® (1 mg/ml) Eurovet Animal Health, Bladel, The Netherlands
[2] Propovet® (10 mg/ml) Abbott Laboratories, Queensborough, Kent, UK
[3] Anesketin® (100 mg/ml) Eurovet NV, Heusden-Zolder, Belgium
[4] Isoflo® Abbott Laboratories, Queensborough, Kent, UK
[5] Dolorex® (10 mg/ml) Intervet Belgium NV, Mechelen, Belgium
[6] Alfaxan® (10 mg/ml) Vétoquinol UK, Buckingham, UK

Table 1b. Total volume of anesthetics used in ml (e.g. 20 kg dog and 1 hour anesthesia) and corresponding cost (June 2008).

	Medetomidine + Butorphanol	Propofol	Ketamine	Isoflurane	Total cost
Protocol 1	0.8 + 0.2	20			**€ 12.66**
Protocol 2	0.8 + 0.2	11	0.6		**€ 10.02**
Protocol 3	0.8 + 0.2	2		3 [7]	**€ 8.56**
	Acepromazine + butorphanol	**Propofol**	**Alfaxalone**	**Isoflurane**	
Protocol 4	0.05 + 0.2	54			**€ 23.34**
Protocol 5	0.05 + 0.2	6		6	**€ 7.62**
Protocol 6	0.05 + 0.2		16		**€ 20.94**

[7] Calculated according to Steffey (1996)

medetomidine, butorphanol, ketamine and propofol, for example) aimed at decreasing the rate of propofol administration are economically reasonable.

ADMINISTRATION

TIVA always involves the delivery of a bolus dose or a fast loading infusion to achieve an adequate blood concentration of the anesthetic drug. Maintenance of anesthesia can be obtained by administering intermittent boluses, by continuous rate infusion or by target-controlled infusion.

The intermittent bolus administration of a drug may result in high peak plasma concentrations and excessive depth of anesthesia and side effects, alternating with periods of inadequate anesthesia and the possibility of awareness (Musk *et al.*, 2005). Both infusion techniques, on the other hand, aim at achieving a more stable plane of anesthesia which, in terms of the total amount of drug used, is also more economical.

When continuous infusion is used, the anesthetics can be administered as a continuous rate infusion (CRI), either with or without manual adjustment (variable rate infusion or VRI), or by using a volumetric infusion pump or a syringe driver (Kästner, 2007). Since drug effect is more closely related to blood concentration than to infusion rate, another and probably more accurate way of achieving TIVA is the so-called target-controlled infusion or TCI (van den Nieuwenhuyzen *et al.*, 2000). This technique involves computer-controlled administration of the anesthetic by means of an infusion pump. The pharmacokinetic profile of the drug is programmed into the computer and the rate of infusion is determined on the basis of the rate of redistribution and elimination of the drug from the body. The result will approximate a stable plasma concentration of the drug, which can easily be adjusted in response to its clinical effects, more or less like the end tidal concentration of a volatile anesthetic is adjusted (Beths *et al.*, 2001; Musk *et al.*, 2005).

Different studies in dogs have resulted in wide variation in the mean pharmacokinetic parameters of propofol (Cockshott *et al.*, 1992; Zoran *et al.*, 1993; Nolan and Reid, 1993; Nolan *et al.*, 1993; Reid and Nolan, 1993; Hall *et al.*, 1994; Mandsager *et al.*, 1995). When these parameters were used as inputs to a computer simulation to obtain predicted propofol concentration profiles for comparison with the measured profile, none of the published pharmacokinetic models provided an accurate prediction of the measured profile. The performance of the predictive model was then further improved by making empirical adjustments to the volume of distribution of the central compartment and to the rate constant for elimination from the central compartment (Beths *et al.*, 2001).

As the infusion device of such a system is controlled by a microprocessor that uses population pharmacokinetic data, variations in pharmacokinetic parameters between patients still oblige anesthetists to rely on their traditional skills to titrate and individualize TIVA techniques (Morton, 1998; Absalom and Kenny, 1999). Hence, providing a stable plasma concentration is the ultimate goal when using a TCI.

Up to now, syringe drivers controlled by a custom-built external computer and pharmacokinetic modeling software have been used to target plasma concentrations of various drugs mainly in experimental animal studies and for the evaluation of a TCI propofol protocol in dogs. Although a propofol TCI study in dogs undergoing ovariohysterectomy showed promising results using less propofol compared to CRI, the TCI idea is not yet ready for use in daily veterinary practice, because of the limited commercial availability of infusion hardware and software, as well as the limited evaluated population pharmacokinetics (Kästner, 2007; Hatschbach *et al.*, 2008).

PREMEDICATION

An appropriate selection of premedication drugs can significantly improve intraoperative cardiovascular stability, perioperative analgesia and the quality of recovery. Cardiovascular stability is mainly improved by premedication since the quantity of potentially more dangerous drugs used to produce general anesthesia can be decreased. In order to optimize the advantages of premedication, it is important to select drugs based upon the needs of the individual patient and its physical status (American Society of Anesthesiologists or ASA status) (Murrell, 2007). For procedures associated with peri- and postoperative pain, premedication should always include an analgesic

(Bednarski, 2007). The same principles are legitimate for TIVA, and they should be taken into account.

Discussing the different sedatives and analgesics used for premedication seems beyond the scope of this article, but reduction of the dose rate of the injectable anesthetic during TIVA should be considered when a patient is profoundly sedated. The use of medetomidine, a drug routinely used for the premedication of small animals, for example, decreases injectable and inhalational anesthetic requirements dramatically in dogs (Lemke, 2007).This emphasizes the need for anesthetists to closely monitor the depth of anesthesia and to carefully titrate the dose of the anesthetic agents against the needs and responses of the individual patient (Short and Bufalari, 1999).

INJECTABLE ANAESTHETICS

The ideal intravenous anesthetic agent for TIVA should be water soluble and have a long period of stability when stored at room temperature. It should be painless and non-irritant on injection, while rapidly inducing sleep with a minimum of respiratory and cardiovascular side effects. In addition, the potential for anaphylactoid and other allergic reactions should be very low (Morton, 1998).

Several different combinations used in providing TIVA are described in Table 2.

Table 2. Total intravenous anesthesia (TIVA) protocols in dogs.

Premedication	Induction (IV)	Maintenance (IV)	Reference
ACP IM Atropine IM	Propofol 3.2 mg/kg IV	Propofol 0.4 mg/kg/min	(Robertson *et al.*, 1992)[1]
-	Propofol 5 mg/kg IV	Propofol 0.44 mg/kg/min	(Keegan and Greene, 1993)[2]
Methadone 0.5 mg/kg IM Atropine 0.05 mg/kg IM	Propofol IV to effect	Propofol 0.33 mg/kg/min Remifentanil 0.6 µg/kg/min	(Murrell *et al.*, 2005)
Methadone 0.2 mg/kg IM	Propofol IV to effect Lidocaine 1 mg/kg	Propofol ≤ 0.4 mg/kg/min Alfentanil ≤ 1 µg/kg/min	(Raisis *et al.*, 2007)
ACP 0.05 mg/kg IM	Propofol 4 mg/kg	Propofol 0.2-0.4 mg/kg/min Fentanyl 2 µg/kg loading dose Atropine 0.04 mg/kg Fentanyl 0.1-0.5 µg/kg/min	(Hughes and Nolan, 1999)[1,2,3]
ACP 0.05 mg/kg IV OR Diazepam 0.3 mg/kg IV	Propofol 1.5-2 mg/kg	Propofol 0.1-0.6 mg/kg/min	(Tsai *et al.*, 2007)
-	Propofol 3 µg/ml (TCI)	Propofol 2.5-4.7 µg/ml (TCI)	(Beths *et al.*, 2001)[4]
Medetomidine 1000-1500 µg/m^2 IM [5]	Propofol 2 mg/kg OR Ketamine 3 mg/kg	Propofol 0.06 mg/kg/min ketamine 0.09 mg/kg/min	(Hellebrekers and Sap, 1997)[6]
Medetomidine 40 µg/kg IM 20 µg/kg 1 hour later	Propofol 1 mg/kg OR propofol 0.5 mg/kg AND ketamine 1 mg/kg	Propofol 0.15 mg/kg/min OR propofol 0.075 mg/kg/min AND ketamine 2 mg/kg/hour	(Seliskar *et al.*, 2007)[1]
Methotrimeprazine 1 mg/kg	Midazolam 0.2 mg/kg AND ketamine 5 mg/kg	Midazolam 0.2-0.4 mg/kg/hour AND ketamine 15 mg/kg/hour (and xylazine 1mg/kg/hour)	(Santos *et al.*, 2006)[1]
Medetomidine 15 µg/kg IM	Etomidate 0.5 mg/kg	Etomidate 50 µg/kg/min	(Ko *et al.*, 1994)[1]
Fentanyl 31.5 µg/kg AND fluanisone 1mg/kg IM AND atropine 20 µg/kg IM	Midazolam 0.3-0.6 mg/kg AND alfentanil 0-40 µg/kg	Midazolam 5 µg/kg/min AND alfentanil 4-5 µg/kg/min	(Flecknell *et al.*, 1989)
[7]	Alfaxalone 2 mg/kg	Alfaxalone 0.1-0.12 mg/kg/min	Manufacturer's guidelines [7]

[1] No surgical stimulation
[2] Experiment in greyhounds
[3] Some unsatisfactory recoveries
[4] Target Controlled Infusion resulting in a light plane of anesthesia sufficient for routine dental work
[5] m^2 body surface area
[6] Maintenance of anesthesia by incremental doses of induction agent; overall dose including induction
[7] Dosage for premedicated dogs (drugs used for premedication not specified)

Thiopental

Thiopental is a barbiturate with an ultrashort action time due to its rapid redistribution into well perfused tissues first and into body fat later on (Brodie *et al.*, 1952; Tsai *et al.*, 2007). Recovery from thiobarbiturate anesthesia in dogs occurs by redistribution of the drug from brain to muscle and fat with concomitant elimination of the drug from the body by liver metabolism (Sams and Muir, 1988).

This agent can be used in dogs for the induction of anesthesia or as a sole agent for anesthesia of very short duration. The use of thiopental without premedication is recommended when assessing laryngeal function in dogs, as this results in greater arytenoid motion than with other anesthetics (Jackson *et al.*, 2004). However, repeated dosing causes accumulation of the drug in the body fat and saturation of the tissue sites. This, together with the slow liver metabolism, leads to higher plasma levels, thus causing serious cardiorespiratory depression and prolonged recoveries. Therefore thiopental should not be used for the maintenance of anesthesia (Kästner, 2007; Branson, 2007).

Especially in Greyhounds, recovery tends to be rough and much slower. This is caused by the delayed redistribution to the body fat because of the lean conformation of these dogs and by the lower hepatic clearance of these drugs (Sams *et al.*, 1985; Robinson *et al.*, 1986; Court MH, 1999). Therefore, the (continuous) use of thiobarbiturates seems to be less indicated in Greyhounds, certainly in the presence of valuable alternatives (Kästner, 2007).

Propofol

Propofol is a newer generation injectable anesthetic agent which was introduced in veterinary medicine in the 1990's (Tsai *et al.*, 2007). It is a hypnotic alkyl phenol, it is not water soluble and it is formulated in a lipid emulsion containing extracts of soya and egg protein, which makes it an ideal culture medium for bacteria (Morton, 1998; Kästner, 2007). It is usually injected as a single bolus for the induction of general anesthesia in dogs. In general, propofol induces a rapid, smooth induction, followed by a short period of unconsciousness (Morgan and Legge, 1989). Propofol is rapidly redistributed from the brain to other tissues and is also efficiently eliminated from plasma by hydroxylation by one or more hepatic cytochrome P-450 isoforms, which explains its short action and the rapid recovery (Zoran *et al.*, 1993). Due to these pharmacokinetic properties, it is considered to be a suitable drug for the maintenance of anesthesia by continuous rate infusion (Musk *et al.*, 2005).

Whereas in humans, recovery is rapid and free of emergence excitement after constant infusion or repeated bolus administration, recovery in dogs may be slightly prolonged after a CRI of propofol exceeding 30 minutes (Robertson *et al.*, 1992; Tsai *et al.*, 2007). Others, however, found no differences in time to extubation when comparing propofol with isoflurane (Keegan and Greene, 1993). Hence, propofol can be used to maintain anesthesia in dogs either by intermittent bolus or continuous infusion (Smith *et al.*, 1993; Thurmon *et al.*, 1994; Kästner, 2007).

One important issue is that propofol has only minimal analgesic properties. This explains the need for concurrent administration of analgesics when propofol is used during painful procedures. Several studies on the concomitant use of propofol and a short acting opioid have been done. In non-Greyhound dogs undergoing craniectomy, a TIVA combining propofol and alfentanil produced a smooth and excitement-free recovery, with no association between duration of anesthesia, total amounts of drugs administered and recovery times (Raisis *et al.*, 2007). Also in dogs undergoing ovariectomy, the combination of propofol and remifentanil resulted in a smooth recovery in a large majority of the cases (Murrell *et al.*, 2005). In Greyhounds, the recovery was found to be longer compared to other breeds after the use of a propofol-based TIVA (Robertson *et al.*, 1992). This is probably the result of a defect associated with the reduced activity of a specific hepatic cytochrome P_{450} enzyme in this breed (Hay Kraus *et al.*, 2000). However, the combination of propofol and fentanyl can also be successfully used in Greyhounds, despite some unsatisfactory recoveries (Hughes and Nolan, 1999).

Even though propofol can decrease arterial blood pressure by depressing sympathetic neural output centrally, resulting in a decreased vascular resistance, hemodynamic stability seems to be one of the advantages of a propofol-based TIVA, especially when compared to an isoflurane-based balanced anesthesia protocol in humans (Claeys *et al.*, 1988; Van Aken H. *et al.*, 1990). In dogs, as well, the arterial blood pressure was well maintained during a 60-minute propofol infusion, and the hemodynamic variables were considered clinically acceptable during a propofol-remifentanil combination (Robertson *et al.*, 1992; Murrell *et al.*, 2005). Systemic arterial blood pressure was even higher during a propofol TIVA, compared to an isoflurane; anesthesia (Keegan and Greene, 1993). Hemodynamic stability was also reported during the use of a target controlled infusion (TCI) of propofol and morphine and of a propofol-alfentanil combination, both in dogs undergoing neurosurgical procedures (Joubert *et al.*, 2004; Raisis *et al.*, 2007).

The most common adverse effects observed with the use of propofol are pain on injection, respiratory depression and excitatory effects. Pain during injection is commonly reported in humans and likely occurs in small animals, as well. The prevalence in small animals, however, seems to be much less, and the pain can be minimized by premedication with an opioid or an α_2-agonist (Sano *et al.*, 2003; Branson, 2007). In humans, pretreatment with lidocaine IV seems to prevent vascular pain during propofol injection to some extent (Picard and Tramer, 2000; Rochette *et al.*, 2008). However, this has not (yet) been confirmed in dogs.

The excitatory effects (involuntary movements, muscle tremors, twitching and coughing) of propofol are well recognized and may occur at all stages of induction, maintenance and recovery. The manifestations are often mild and can be attenuated by the intravenous administration of a benzodiazepine (Davies and Hall, 1991; Musk *et al.*, 2005).

The rapid injection of propofol can result in apnea and, after repeated or continuous propofol dosing, respiratory depression with hypercapnia can occur (Kästner, 2007). However, provided that the respiration is closely monitored and intermittent positive pressure ventilation can be provided, this does not necessarily need to be a serious problem (Musk *et al.*, 2005). Moreover, an appropriate consideration of dose reduction on account of premedication and a slower rate of administration reduces the degree of respiratory depression (Short and Bufalari, 1999).

Ketamine

Ketamine is a dissociative anesthetic as it interrupts ascending transmission from those parts of the brain responsible for unconscious and conscious functions. It produces dose-related unconsciousness and, mainly somatic, analgesia. Antagonism of the N-methyl-D-aspartate (NMDA) receptor has been proposed as the most likely molecular mechanism responsible for most of its actions (Lin, 2007).

Ketamine possibly increases muscle tone and it induces spontaneous movement and, occasionally, convulsions. To reduce these undesirable effects, it is often used in conjunction with propofol, benzodiazepines, acepromazine or α_2-agonists.

Recovery from ketamine anesthesia is often associated with hyperexcitability, whereby animals are hypersensitive to noise, light and handling (Kästner, 2007). To minimize these excitatory central nervous system effects, a concurrent infusion of a benzodiazepine has to be considered (Morton, 1998). Combinations with propofol and medetomidine have also been reported in dogs (Hellebrekers and Sap, 1997; Hellebrekers *et al.*, 1998; Seliskar *et al.*, 2007). In all these studies, poor recovery quality seems to be the most significant disadvantage when using a ketamine-based TIVA, although one study in human medicine reported better recoveries after prolonged abdominal surgery with a midazolam-ketamine based TIVA compared to inhalation anesthesia with halothane and nitrous oxide (Shorrab and Atallah, 2003).

Concerning cardiovascular parameters during a ketamine-based TIVA, a significantly higher heart rate was reported in a group of dogs receiving ketamine compared to a group of dogs receiving propofol (Hellebrekers *et al.*, 1998). Other authors also reported a higher heart rate and mean arterial blood pressure in dogs anesthetized with a combination of propofol and ketamine than with propofol alone (Seliskar *et al.*, 2007). These findings are not surprising since ketamine is known to cause stimulation of the sympathetic system, which results in these cardiovascular effects which are unique, at least for an anesthetic agent (Kästner, 2007).

Although ketamine has minimal effects on the central respiratory drive, initial respiratory depression occurs after bolus administration, often followed by a so-called "apneuistic" breathing pattern, which is characterized by periodic breath holding on inspiration followed by short periods of hyperventilation (Kästner, 2007). An initial decrease of minute volume after administration of ketamine 10 mg/kg IV, returning to baseline values within 15 minutes, has been reported in dogs (Haskins *et al.*, 1985). During an infusion of the combination of propofol and ketamine in dogs, however, a progressive hypercapnia was noticed, which was more pronounced than during the administration of propofol alone (Seliskar *et al.*, 2007). In a study of thirty methotrimeprazine premedicated dogs, the end tidal CO_2 ($EtCO_2$) stayed within physiological limits during a midazolam-ketamine based TIVA (Santos *et al.*, 2006). When xylazine was added to the TIVA protocol, however, $EtCO_2$ was significantly increased.

In practice, it seems that the combination of ketamine with a benzodiazepine can be used in premedicated dogs for procedures taking less than one hour, whereas for longer procedures the combination of ketamine with propofol seems to be a better option.

Etomidate

The non-barbiturate hypnotic agent etomidate is an imidazole derivative that works in a fashion similar to that of propofol and thiopental since it enhances the action of the inhibitory neurotransmitter γ-aminobutyric-acid (GABA) (Branson, 2007). Because it causes rapid induction and recovery and little or only minimal cardiovascular changes even in hypovolemic dogs, it seems to be the ideal anesthetic for TIVA (Nagel *et al.*, 1979; Pascoe *et al.*, 1992; Kästner, 2007; Branson, 2007). Unfortunately, the intravenous injection of this agent induces excitement, myoclonus, pain on injection, vomiting and apnea during the induction of anesthesia, all of which can be attenuated or eliminated by prior administration of diazepam, acepromazine or morphine (Muir and Mason, 1989).

Etomidate provides a safe method for TIVA in cases where inhalation anesthesia is undesirable (Robertson, 1992). A continuous rate infusion of etomidate after medetomidine premedication produces anesthesia with only minimal hemodynamic changes and smooth recoveries (Ko *et al.*, 1994). In humans, as well, the use of etomidate for TIVA appears to be easily applicable (van Dijk, 1979).

The influence of etomidate on the respiratory function is somewhat uncertain, as some authors report no influence and others describe a decreased respiration rate after its administration (Ko *et al.*, 1994; Kästner, 2007; Branson, 2007).

The major problem when using etomidate seems to be that it inhibits adrenal steroidogenesis (Branson, 2007). Normally, pain induced by surgical trauma evokes characteristic responses typified by activation of

the sympathetic branch of the autonomic nervous system, resulting in the secretion of glucocorticoids (Muir, 2007). A single bolus of etomidate reduces this adrenocortical response to anesthesia and surgery for up to six hours (Kruse-Elliott *et al.*, 1987; Dodam *et al.*, 1990). The lack of this stress response seems to have no detrimental effects after a single intravenous bolus (Kästner, 2007). However, attention has been given to the development of Addisonian crisis produced by etomidate-induced blockade of corticosteroid production during prolonged infusion to maintain sedation in intensive care patients (Kruse-Elliott *et al.*, 1987; Muir and Mason, 1989).

In practice, etomidate can be used for a TIVA in dogs with a low cardiac reserve and hypovolemia (Kästner, 2007).

Neuroleptanalgesia

The concept of neuroleptanalgesia involves the combination of a neuroleptic agent (benzodiazepines, butyrophenones or phenothiazines) with a potent opioid. At high doses administered intravenously, the combination can produce sufficient depression of the central nervous system to allow endotracheal intubation and moderate surgical stimulation. Using such high doses of potent opioids, of course, may possibly lead to the necessity of using artificial ventilation. As in healthy, young animals, unduly high doses have to be used to reach a true anesthetic state. These combinations are not suitable for the routine induction of anesthesia in this group of animals.

The neuroleptanalgesic combinations containing phenothiazines or butyrophenones can lead to hypotension caused by alpha1-receptor blockade. Benzodiazepine-opioid combinations, on the other hand, can have a profound effect in high-risk patients and can be used to induce and even maintain anesthesia, thus providing a wide margin of safety (Kästner, 2007). The use of this combination is also described in depressed, exhausted parturients, for the induction and maintenance of anesthesia during a caesarean section (Raffe and Carpenter, 2008).

In healthy dogs, a combination of midazolam and sufentanil has been used for the recording of transcranial magnetic motor evoked potentials (Van Ham *et al.*, 1996). The hemodynamic stability of such combinations was demonstrated by maintaining anesthesia for 24 hours during and after unilateral pneumonectomy (Flecknell *et al.*, 1989). In that study, opioid-induced bradycardia was prevented by prior administration of atropine, and smooth and rapid inductions were reported.

It seems that the benzodiazepine-opioid combinations should be reserved for severely debilitated patients and only when artificial ventilation is possible.

Alfaxalone

Alfaxalone is a water-soluble synthetic neuroactive steroid that interacts with the GABA receptor, producing anesthesia and muscle relaxation. The molecule was used in the past in cats and dogs (Saffan®; Schering Plough Animal Health, Union, NJ, USA) in a co-formulation with the related steroid alfadolone and a surfactant (Cremophor EL, 20% W/V, BASF Fine Chemicals, Limburgerhof, Germany). One of the major advantages of this anesthetic was its wide safety margin. However, Cremophor EL caused adverse effects such as hyperemia or edema of the pinnae or forepaws in cats and anaphylactoid reactions in dogs (Child *et al.*, 1971; Dodman, 1980). Recently, a new, Cremophor-free formulation of alfaxalone, without alfadolone, has been developed for use in small animals (Alfaxan®, Vétoquinol UK Limited, Buckingham, UK).

Alfaxalone produces rapid and excitement free induction of anesthesia, uneventful maintenance, good muscle relaxation and stress-free recovery from anesthesia. Cardiac output is increased either slightly or not at all at clinically relevant dosages, apnea does not occur and only minimal changes are reported in respiratory rate (Muir *et al.*, 2008).

The average clearance of alfaxalone in the dog is high, resulting in rapid recovery from anesthesia; this average clearance is comparable to the values reported for propofol. It does not appear to accumulate and therefore it can be used for a TIVA (Nolan and Reid, 1993; Pasloske *et al.*, 2005; Ferre *et al.*, 2006). In a clinical trial in over two hundred dogs, the anesthetic quality scores were similar between alfaxalone and propofol. In addition, the safety and efficacy of alfaxalone as an induction and maintenance anesthetic agent in dogs has been confirmed (Pasloske *et al.*, 2005). As with the use of propofol, the cost seems to become the main disadvantage when using alfaxalone for a TIVA, certainly during long procedures in large dogs.

Undoubtedly, more studies will be published in the near future concerning the properties of this new formulation, both as an induction agent or for the maintenance of anesthesia.

CONCLUSION

Total intravenous anesthesia provides the veterinarian with a useful alternative for inhalation anesthesia in dogs, with a propofol- or alfaxalone-based protocol as the most evident choice. A calculation of the product costs for a 1 hour anesthesia of a 20 kg dog shows that even economically a TIVA can be a reasonable alternative to inhalation anesthesia.

Intubation and oxygen administration is inherent to the technique of inhalation anesthesia, but this should also be the case when using a TIVA. Especially in view of the respiratory depressant effects of all the intravenous agents described, the need for the possibility of artificial ventilation should be emphasized. Furthermore, premedication and the administration of analgesics should not be overlooked, and the depth of the anesthesia should be assessed, which will result in an adjustment of the infusion rate, if necessary. As in inhalation anesthesia, cardiorespiratory monitoring during anesthesia is mandatory during TIVA.

REFERENCES

Absalom A., Kenny G.N. (1999). Current and future applications of target-controlled infusions. *Drugs Today (Barc.) 35*, 823-834.

Avram M. J., Krejcie T.C. (2003). Using front-end kinetics to optimize target-controlled drug infusions. *Anesthesiology 99*, 1078-1086.

Bednarski R. M. (2007). Anesthesia, analgesia and immobilization of Dogs and Cats. In: Tranquilli, W. J., Thurmon, J. C., Grimm, K. A. (editors). *Lumb & Jones' Veterinary Anesthesia and Analgesia*. Fourth edition. Blackwell Publishing Ltd, Oxford p.705-715.

Beths T., Glen J.B., Reid J., Monteiro A.M., Nolan A.M. (2001). Evaluation and optimisation of a target-controlled infusion system for administering propofol to dogs as part of a total intravenous anaesthetic technique during dental surgery. *The Veterinary Record 148*, 198-203.

Branson K. R. (2007). Injectable and Alternative Anesthetic Techniques. In: Tranquilli, W. J., Thurmon, J. C., Grimm, K. A. (editors). *Lumb & Jones' Veterinary Anesthesia and Analgesia*. Fourth edition. Blackwell Publishing Ltd, Oxford p.273-299.

Brodie B. B., Bernstein E., Mark L.C. (1952). The role of body fat in limiting the duration of action of thiopental. *The Journal of Pharmacology and Experimental Therapeutics 105*, 421-426.

Byhahn C., Heller K., Lischke V., Westphal K. (2001). Surgeon's occupational exposure to nitrous oxide and sevoflurane during pediatric surgery. *World Journal of Surgery 25*, 1109-1112.

Child K. J., Currie J.P., Davis B., Dodds M.G., Pearce D.R., Twissell D.J. (1971). Pharmacological Properties in Animals of Ct1341 - New Steroid Anaesthetic Agent. *British Journal of Anaesthesia 43*, 2.

Chism J. P., Rickert D.E. (1996). The pharmacokinetics and extra-hepatic clearance of remifentanil, a short acting opioid agonist, in male beagle dogs during constant rate infusions. *Drug Metabolism and Disposition 24*, 34-40.

Claeys M. A., Gepts E., Camu F. (1988). Haemodynamic changes during anaesthesia induced and maintained with propofol. *British Journal of Anaesthesia 60*, 3-9.

Cockshott I. D., Douglas E.J., Plummer G.F., Simons P.J. (1992). The Pharmacokinetics of Propofol in Laboratory-Animals. *Xenobiotica 22*, 369-375.

Court MH (1999). Anesthesia of the sighthound. *Clinical Techniques in Small Animal Practice 14*, 38-43.

Davies C., Hall L.W. (1991). Propofol and excitatory sequelae in dogs. *Anaesthesia 46*, 797-798.

Dodam J. R., Kruse-Elliott K.T., Aucoin D.P., Swanson C.R. (1990). Duration of etomidate-induced adrenocortical suppression during surgery in dogs. *American Journal of Veterinary Research 51*, 786-788.

Dodman N. H. (1980). Complications of Saffan Anesthesia in Cats. *The Veterinary Record 107*, 481-483.

Dodman N. H. (1977). Feline Anesthesia Survey. *Journal of Small Animal Practice 18*, 653-658.

Ferre P. J., Pasloske K., Whittem T., Ranasinghe M.G., Li Q., Lefebvre H.P. (2006). Plasma pharmacokinetics of alfaxalone in dogs after an intravenous bolus of Alfaxan-CD RTU. *Veterinary Anaesthesia and Analgesia 33*, 229-236.

Flecknell P. A., Hooper T.L., Fetherstony G., Locke T.J., McGregor C.G. (1989). Long-term anaesthesia with alfentanil and midazolam for lung transplantation in the dog. *Laboratory Animals 23*, 278-284.

Hall L. W., Lagerweij E., Nolan A.M., Sear J.W. (1994). Effect of Medetomidine on the Pharmacokinetics of Propofol in Dogs. *American Journal of Veterinary Research 55*, 116-120.

Hasei M., Hirata T., Nishihara H., Tanigami H., Takashina M., Mori T. (2003). [Occupational exposure of operating room staff to anesthetic gases during inhaled induction - a comparison with intravenous anesthesia induction]. *Masui 52*, 394-398.

Haskins S. C., Farver T.B., Patz J.D. (1985). Ketamine in dogs. *American Journal of Veterinary Research 46*, 1855-1860.

Hatschbach E., Silva F.C., Beier S.L., Lima A.F., Massone F. (2008). Comparative study between target-controlled-infusion and continuous-infusion anesthesia in dogs treated with methotrimeprazine and treated with propofol and remifentanil. *Acta Cirurgica Brasileira 23*, 65-72.

Hay Kraus B. L., Greenblatt D.J., Venkatakrishnan K., Court MH (2000). Evidence for propofol hydroxylation by cytochrome P4502B11 in canine liver microsomes: breed and gender differences. *Xenobiotica 30*, 575-588.

Hellebrekers L. J., Sap R. (1997). Medetomidine as a premedicant for ketamine, propofol or fentanyl anaesthesia in dogs. *The Veterinary Record 140*, 545-548.

Hellebrekers L. J., van H.H., Hird J.F., Rosenhagen C.U., Sap R., Vainio O. (1998). Clinical efficacy and safety of propofol or ketamine anaesthesia in dogs premedicated with medetomidine. *The Veterinary Record 142*, 631-634.

Henthorn T. K., Krejcie T.C., Avram M.J. (2008). Early drug distribution: A generally neglected aspect of pharmacokinetics of particular relevance to intravenously administered anesthetic agents. *Clinical Pharmacology & Therapeutics 84*, 18-22.

Hughes J. M., Nolan A.M. (1999). Total intravenous anesthesia in greyhounds: pharmacokinetics of propofol and fentanyl - a preliminary study. *Veterinary Surgery 28*, 513-524.

Hughes M. A., Glass P.S.A., Jacobs J.R. (1992). Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *Anesthesiology 76*, 334-341.

Jackson A. M., Tobias K., Long C., Bartges J., Harvey R. (2004). Effects of various anesthetic agents on laryngeal motion during laryngoscopy in normal dogs. *Veterinary Surgery 33*, 102-106.

Joubert K. E., Keller N., Du Plessis C.J. (2004). A retrospective case series of computer-controlled total intravenous anaesthesia in dogs presented for neurosurgery. *Journal of the South African Veterinary Association 75*, 85-89.

Kästner S. B. R. (2007). Intravenous anaesthetics. In: Seymour C., Duke-Novakovski T. (editors). *BSAVA Manual of Canine and Feline Anaesthesia and Analgesia*. Second edition. British Small Animal Veterinary Association, Gloucester p.133-149.

Keegan R. D., Greene S.A. (1993). Cardiovascular effects of a continuous two-hour propofol infusion in dogs. Comparison with isoflurane anesthesia. *Veterinary Surgery 22*, 537-543.

Ko J. C., Thurmon J.C., Benson G.J., Tranquilli W.J., Olson W.A., Vaha-Vahe A.T. (1994). Hemodynamic and anesthetic effects of etomidate infusion in medetomidine-premedicated dogs. *American Journal of Veterinary Research 55*, 842-846.

Krejcie T. C., Henthorn T.K., Niemann C.U., Klein C., Gupta D.K., Gentry W.B., Shanks C.A., Avram M.J.

(1996). Recirculatory pharmacokinetic models of markers of blood, extracellular fluid and total body water administered concomitantly. *Journal of Pharmacology and Experimental Therapeutics 278*, 1050-1057.

Kruse-Elliott K. T., Swanson C.R., Aucoin D.P. (1987). Effects of etomidate on adrenocortical function in canine surgical patients. *American Journal of Veterinary Research 48*, 1098-1100.

Lemke, K. A. (2007). Anticholinergics and Sedatives. In: Tranquilli, W. J., Thurmon, J. C., Grimm, K. A. (editors). *Lumb & Jones' Veterinary Anesthesia and Analgesia*. Fourth edition. Blackwell Publishing Ltd, Oxford p.203-239.

Lin, H-C. (2007). Dissociative anesthetics. In: Tranquilli, W. J., Thurmon, J. C., Grimm, K. A. (editors). *Lumb & Jones' Veterinary Anesthesia and Analgesia,* fourth edition. Blackwell Publishing Ltd, Oxford p.301-353.

Mandsager R. E., Clarke C.R., Shawley R.V., Hague C.M. (1995). Effects of chloramphenicol on infusion pharmacokinetics of propofol in greyhounds. *American Journal of Veterinary Research 56*, 95-99.

Matthews, N. S. (2007). Inhalant anaesthetics. In: Seymour C., Duke-Novakovski T. (editors). *BSAVA Manual of Canine and Feline Anaesthesia and Analgesia*. Second edition. British Small Animal Veterinary Association, Gloucester p.150-155.

Monedero P., Carrascosa F., Garcia-Pedrajas F., Panadero A., Hidalgo F., Arroyo J.L. (1994). Does propofol have advantages over midazolam and isoflurane? Comparative study of 2 total intravenous anesthesia techniques using midazolam and propofol, versus balanced anesthesia with isoflurane. *Revista Espanola De Anestesiologia y Reanimacion 41*, 156-164.

Morgan D. W., Legge K. (1989). Clinical evaluation of propofol as an intravenous anaesthetic agent in cats and dogs. *The Veterinary Record 124*, 31-33.

Morton N. S. (1998). Total intravenous anaesthesia (TIVA) in paediatrics: advantages and disadvantages. *Paediatric Anaesthesia 8,* 189-194.

Muir W., Lerche P., Wiese A., Nelson L., Pasloske K., Whittem T. (2008). Cardiorespiratory and anesthetic effects of clinical and supraclinical doses of alfaxalone in dogs. *Veterinary Anaesthia and Analgesia 35, 451-462*.

Muir, W. W. (2007). Considerations for general anesthesia. In: Tranquilli, W. J., Thurmon, J. C., Grimm, K. A. (editors). *Lumb & Jones' Veterinary Anesthesia and Analgesia*. Fourth edition. Blackwell Publishing Ltd, Oxford p.7-30.

Muir W. W., Mason D.E. (1989). Side effects of etomidate in dogs. *Journal of the American Veterinary Medical Association 194*, 1430-1434.

Murrell, J. C. (2007). Premedication and sedation. In: Seymour C., Duke-Novakovski T. (editors). *BSAVA Manual of Canine and Feline Anaesthesia and Analgesia*. Second edition. British Small Animal Veterinary Association, Gloucester p.120-132.

Murrell J. C., van Notten R.W., Hellebrekers L.J. (2005). Clinical investigation of remifentanil and propofol for the total intravenous anaesthesia of dogs. *The Veterinary Record 156*, 804-808.

Musk G. C., Pang D.S., Beths T., Flaherty D.A. (2005). Target-controlled infusion of propofol in dogs evaluation of four targets for induction of anaesthesia. *The Veterinary Record 157*, 766-770.

Nagel M. L., Muir W.W., Nguyen K. (1979). Comparison of the cardiopulmonary effects of etomidate and thiamylal in dogs. *American Journal of Veterinary Research 40*, 193-196.

Nolan A., Reid J. (1993). Pharmacokinetics of propofol administered by infusion in dogs undergoing surgery. *British Journal of Anaesthesia 70*, 546-551.

Nolan A. M., Reid J., Grant S. (1993). The Effects of Halothane and Nitrous-Oxide on the Pharmacokinetics of Propofol in Dogs. *Journal of Veterinary Pharmacology and Therapeutics 16*, 335-342.

Pascoe P. J., Ilkiw J.E., Haskins S.C., Patz J.D. (1992). Cardiopulmonary effects of etomidate in hypovolemic dogs. *American Journal of Veterinary Research 53*, 2178-2182.

Pasloske K., Gazzard B., Perkins N., Dunlop C., Whittem T. (2005). A multicentre clinical trial evaluating the efficacy and safety af Alfaxan-CD RTU administered to dogs for induction and maintenance of anaesthesia. *48th Annual British Small Animal Veterinary Congress*, Birmingham, UK, 556.

Picard P., Tramer M.R. (2000). Prevention of pain on injection with propofol: A quantitative systematic review. *Anesthesia and Analgesia 90*, 963-969.

Raffe M. R., Carpenter R. E. (2008). Anesthetic management of cesarean section patients. In: Tranquilli W. J., Thurmon J. C., Grimm K. A. (editors). *Lumb & Jones' Veterinary Anesthesia and Analgesia*. Fourth edition. Blackwell Publishing Ltd, Oxford p.955-967.

Raisis A. L., Leece E.A., Platt S.R., Adams V.J., Corletto F., Brearley J. (2007). Evaluation of an anaesthetic technique used in dogs undergoing craniectomy for tumour resection. *Veterinary Anaesthesia and Analgesia 34*, 171-180.

Reid J., Nolan A.M. (1993). Pharmacokinetics of propofol in dogs premedicated with acepromazine and maintained with halothane and nitrous-oxide. *Journal of Veterinary Pharmacology and Therapeutics 16*, 501-505.

Robertson S. (1992). Advantages of etomidate use as an anesthetic agent. *The Veterinary Clinics of North America. Small Animal Practice 22*, 277-280.

Robertson S. A., Johnston S., Beemsterboer J. (1992). Cardiopulmonary, anesthetic, and postanesthetic effects of intravenous infusions of propofol in greyhounds and non-greyhounds. *American Journal of Veterinary Research* 53, 1027-1032.

Robinson E. P., Sams R.A., Muir W.W. (1986). Barbiturate anesthesia in greyhound and mixed-breed dogs: comparative cardiopulmonary effects, anesthetic effects, and recovery rates. *American Journal of Veterinary Research 47*, 2105-2112.

Rochette A., Hocquet A.F., Dadure C., Boufroukh D., Raux O., Lubrano J.F., Bringuier S., Capdevila X. (2008). Avoiding propofol injection pain in children: a prospective, randomized, double-blinded, placebo-controlled study. *British Journal of Anaesthesia 101*, 390-394.

Sams R. A., Muir W.W. (1988). Effects of phenobarbital on thiopental pharmacokinetics in greyhounds. *American Journal of Veterinary Research 49*, 245-249.

Sams R. A., Muir W.W., Detra R.L., Robinson E.P. (1985). Comparative pharmacokinetics and anesthetic effects of methohexital, pentobarbital, thiamylal, and thiopental in Greyhound dogs and non-Greyhound, mixed-breed dogs. *American Journal of Veterinary Research 46*, 1677-1683.

Sano T., Nishimura R., Mochizuki M., Hara Y., Tagawa M., Sasaki N. (2003). Clinical usefulness of propofol as an anesthetic induction agent in dogs and cats. *Journal of Veterinary Medical Science 65,* 641-643.

Santos G. J., Hatschbach E., Mattos J.E., Massone F. (2006).

Parametric evaluation of methotrimeprazine-midazolam-ketamine and methotrimeprazine-midazolam-ketamine-xylazine combination in dogs. *Acta Cirurgica Brasileira 21*, 304-309.

Seliskar A., Nemec A., Roskar T., Butinar J. (2007). Total intravenous anaesthesia with propofol or propofol/ketamine in spontaneously breathing dogs premedicated with medetomidine. *The Veterinary Record 160*, 85-91.

Shafer S. L., Varvel J.R. (1991). Pharmacokinetics, pharmacodynamics, and rational opioid selection. *Anesthesiology 74*, 53-63.

Shorrab A. A., Atallah M.M. (2003). Total intravenous anaesthesia with ketamine-midazolam versus halothane-nitrous oxide-oxygen anaesthesia for prolonged abdominal surgery. *European Journal of Anaesthesiology 20*, 925-931.

Short C. E., Bufalari A. (1999). Propofol anesthesia. *The Veterinary Clinics of North Americ: Small Animal Practice 29*, 747-778.

Smith J. A., Gaynor J.S., Bednarski R.M., Muir W.W. (1993). Adverse effects of administration of propofol with various preanesthetic regimens in dogs. *Journal of the American Veterinary Medical Association 202*, 1111-1115.

Steffey E. P. (1996). Inhalation anesthetics. In: Thurmon, J. C., Tranquilli, W. J., Benson, G. J. (editors). *Lumb & Jones' Veterinary Anesthesia.* Third edition. Williams & Wilkins, Baltimore p.297-329

Steffey E. P., Mama K. R. (2007). Inhalation anesthetics. In: Tranquilli W. J., Thurmon J. C., Grimm K. A. (editors). *Lumb & Jones' Veterinary Anesthesia and Analgesia* Blackwell Publishing Ltd, Oxford p.355-393

Suttner S., Boldt J., Schmidt C., Piper S., Kumle B. (1999). Cost analysis of target-controlled infusion-based anesthesia compared with standard anesthesia regimens. *Anesthesia and Analgesia 88*, 77-82.

Thurmon J. C., Ko J.C., Benson G.J., Tranquilli W.J., Olson W.A. (1994). Hemodynamic and analgesic effects of propofol infusion in medetomidine-premedicated dogs. *American Journal of Veterinary Research 55*, 363-367.

Thurmon, J. C., Short, C. E. (2007). History and overview of veterinary anesthesia. In: Tranquilli W. J., Thurmon J. C., Grimm K. A. (editors). *Lumb & Jones' Veterinary Anesthesia and Analgesia*. Fourth edition. Blackwell Publishing Ltd, Oxford p.3-6

Tsai Y. C., Wang L.Y., Yeh L.S. (2007). Clinical comparison of recovery from total intravenous anesthesia with propofol and inhalation anesthesia with isoflurane in dogs. *The Journal of Veterinary Medical Science / The Japanese Society of Veterinary Science 69*, 1179-1182.

Van Aken H., Van Hemelrijck J., Merckx L., Mollhoff T., Mulier J., Lubbesmeyer H.J. (1990). Total intravenous anesthesia using propofol and alfentanil in comparison with balanced anesthesia in neurosurgery. *Anasthesie, Intensivtherapie, Notfallmedizin 25*, 54-58.

van den Nieuwenhuyzen M. C., Engbers F.H., Vuyk J., Burm A.G. (2000). Target-controlled infusion systems: role in anaesthesia and analgesia. *Clinical Pharmacokinetics 38*, 181-190.

van Dijk B. (1979). Etomidate-fentanyl-air anesthesia. *Acta Anaesthesiologica Belgica 30*, Suppl, 89-100.

Van Ham L. M., Nijs J., Mattheeuws D.R., Vanderstraeten G.G. (1996). Sufentanil and nitrous oxide anaesthesia for the recording of transcranial magnetic motor evoked potentials in dogs. *The Veterinary Record 138*, 642-645.

Zoran D. L., Riedesel D.H., Dyer D.C. (1993). Pharmacokinetics of propofol in mixed-breed dogs and greyhounds. *American Journal of Veterinary Research 54*, 755-760.