The effects of a propofol/alfentanil admixture on total intravenous anaesthesia in dogs undergoing splenectomy

N. JIA, C. ZHAO, L. WANG, Y. LI, J. CUI, S. CAO, R. LI, C. WANG, Y. WU, A. WEN

Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi, China

ABSTRACT: The aim of this study was to compare the cardiovascular and respiratory effects and the bispectral scale index (BIS) as well as the recovery period characteristics in response to treatment with a propofol/alfentanil admixture of different concentrations in dogs undergoing splenectomy. We conducted a **p**rospective, randomised, blinded experimental trial. Anaesthesia was induced and maintained by continuous-infusion anaesthesia of propofol and alfentanil or a propofol/alfentanil admixture after premedication with acepromazine (0.03 mg/kg). Dogs were assigned to receive different concentrations of the admixture. Changes in BIS value, heart rate (HR), respiratory rate (f_R), non-invasive arterial blood pressure, pulse oximetry (SpO₂), end-tidal carbon dioxide concentrations (ETCO₂) and rectal temperature (RT) were recorded at predefined time points during anaesthesia. Data [mean ± standard deviation (SD)] were analysed by analysis of variance (ANOVA) for repeated measures followed by a Dunnett's test and Student's *t*-test (*P* < 0.05) and where necessary, the Mann-Whitney *U*-test. No significant differences were found between groups with respect to age, body mass, SpO₂, ETCO₂, f_R, systolic, diastolic and mean arterial blood pressure (SAP, DAP and MAP). BIS values were significantly lower in Group 2 when compared to Group 1 at T7, T8, T9. The HR of Group 2 was significantly lower at T2 to T9 when compared to Group 1. The propofol and alfentanil admixture provided satisfactory results in dogs undergoing splenectomy. Thus, an admixture of propofol/alfentanil admixture provided satisfactory results in dogs at the infusion rates determined in this study.

Keywords: propofol; alfentanil; admixture; total intravenous anaesthesia; dogs

Total intravenous anaesthesia (TIVA) has become a popular technique in humans because of its advantages compared with inhalant techniques, and the development of drugs such as propofol and short-acting opioids, as well as improved infusion systems (Cicek et al. 2005). During TIVA, combinations of intravenous anaesthetics with opioid analgesics have been used to achieve balanced anaesthesia with reduced side-effects, and their use promotes earlier recovery time and less postoperative nausea and vomiting.

Propofol is a highly lipophilic anaesthetic agent characterised by rapid onset, distribution and elimination phases after intravenous administration (Aguiar et al. 2001). Alfentanil is a derivative of fentanyl, with quicker onset and shorter duration and more intense vagomimetic properties than those of fentanyl and sufentanil. It may cause less intense respiratory depression than equianalgesic doses of fentanyl. Clinical trials indicate that alfentanil can be used effectively as an analgesic, or as an analgesic supplement in anaesthesia, and as the major component of a general anaesthetic (Vuyk et al. 1996). Alfentanil reduced the hypnotic and anaesthetic dose of propofol in humans by 20% and 73%, respectively (Short et al. 1992). In the clinic, alfentanil has been combined with propofol to achieve more effective intravenous anaesthesia.

The propofol/alfentanil admixture (PA) provides the double effects of anaesthesia and analgesia with the advantages of fast onset and convenience of use. It is especially appropriate for short-term and

Supported by the National New Drug "R&D" (Grant No. 2011ZXJ09302) and the National Nature Science Foundation of China (Grants No. 81403159 and No. 81201985).

emergency anaesthesia. In recent years, the efficacy of an admixture of propofol and alfentanil has been explored. Our earlier research suggested that the combination of alfentanil and propofol synergistically suppressed acute phasic and tonic pain in mice (Wu et al. 2014). The combined effect of these agents has been previously associated with a favourable haemodynamic profile. Each drug could partially attenuate the undesirable effects of the other (Ilkiw et al. 2003). The safety and stability of this combination have been documented (Vuyk et al. 1996; Mendes and Selmi 2003; Auckburally et al. 2008; Padilha et al. 2011). However, prior work largely evaluated the effect of continuous infusions for procedural sedation and with variable ratios of propofol and alfentanil. There is a paucity of data regarding fixed-ratio regimens of PA for the purpose of induction and maintenance of general anaesthesia. Moreover, drug combinations typically reduce the total dose of both drugs individually which may be beneficial in certain situations (Smischney et al. 2012).

Combinations of propofol and alfentanil have been shown to be pharmaceutically stable (Taylor et al. 1992). Since the pharmacokinetic profile of alfentanil is similar to propofol, the resultant mixture is suitable for induction and maintenance of short-term anaesthesia (Auckburally et al. 2008). To date, there are no published clinical studies, in which PA was used for induction and maintenance of anaesthesia in dogs undergoing surgery. The aim of this study was to assess the cardiovascular and anaesthetic effects of PA for induction and maintenance of anaesthesia in dogs undergoing splenectomy. Dosages of the admixture required to attenuate autonomic responses during surgery were also evaluated.

MATERIAL AND METHODS

This study adhered to the National Institutes of Health Guidelines for the Use of Laboratory Animals and was approved by the Fourth Military Medical University Committee on Animal Care.

Animals. The experiments were carried out on forty dogs with an average weight of 24.2 ± 7.5 kg and average age of 3.1 ± 0.5 years. All dogs were determined to be healthy as judged by physical examination and any animal considered to be overweight was excluded from the study. All dogs were fasted for 12 h prior to anaesthesia, but were allowed free

access to water. The dogs were kept under controlled environmental conditions, (temperature 20-22 °C, humidity (55 \pm 5%). All animals underwent a period of acclimation of 48 h before the study. The dogs were randomly allocated to four different groups (n = 10), using computer-generated random numbers: Group 1 – the control group: in which a variable ratio of propofol (Diprivan, AstraZeneca, London, UK) and alfentanil (Rapifen, Janssen-Cilag Ltd, High Wycombe, Bucks, UK), was administered by the anaesthetist; Group 2 - PA [10 mg (1 ml) propofol with 133.0 µg (0.266 ml) alfentanil]; Group 3 – PA [10 mg (1 ml) propofol with 66.7 μ g (0.133 ml) alfentanil]; Group 4 - PA [10 mg (1 ml) propofol with $33.3 \,\mu g \,(0.067 \,\mathrm{ml})$ alfentanil]. The infusion rate of drugs could be adjusted by the anaesthetist as needed during the surgery in all groups.

Anaesthesia, surgery and treatments. An intravenous cannula was placed in a suitable peripheral vein and preoxygenation was performed with a face mask using 100% oxygen for 5 min prior to induction of anaesthesia. Anaesthesia was induced and maintained with the PA except in the control group. The induction dose of the admixture (4 mg/kg) was given over approximately 20 s by the intravenous (*i.v.*) route, until a moderate depth of anaesthesia (eyeball rotation, absence of palpebral reflex and decreased jaw tone) was achieved and intubation with an appropriately sized, cuffed endotracheal tube could be performed. The tube was connected to a Bain-circuit system and 100% oxygen was provided. The fresh gas flow was set at 300 ml/kg/min. After induction of anaesthesia, dogs were then positioned in dorsal recumbency on a thermal blanket for instrumentation and surgery. Anaesthesia was managed by a single observer (STP) and the infusion rates of drugs were adjusted to keep the bispectral (BIS) value at 50 ± 5 in all groups (Bleijenberg et al. 2011). The anaesthesia was continued with a continuous infusion of propofol (0.4~0.6 mg/kg/min) or alfentanil (4.0~6.0 µg/kg/min) in Group 1, and an infusion of PA 0.4~0.6 mg/kg/min was administered to Groups 2 to 4, respectively.

A lactated Ringer's solution was administered at 10 ml/kg/h throughout surgery. In the case of hypotension, a fluid bolus of 15 ml/kg was administered over 15 min. The expected surgery time was less than 60 min. All surgical procedures were performed by one experienced surgeon. Using a scalpel blade, a ventral midline incision was performed over the skin, subcutaneous tissue and the *linea*

alba. A standard three-clamp technique was used. The abdominal wall and subcutaneous tissues were closed separately using a simple continuous pattern of absorbable sutures and the skin was closed in a simple interrupted pattern.

Monitoring and time points. The BIS was recorded using the BIS monitor (Bispectral monitor A-2000 XP; Aspect Medical Systems Inc, USA). Before premedication, the head was clipped and the skin was cleaned with ether. The sensors for assessing the BIS were attached in a frontal-temporal configuration. Electrode 1 was positioned on the mid-sagittal plane, at the rostral third of an imaginary line connecting the zygomatic process of the frontal bone to the more caudal portion of the front crista, while electrodes 2 (earth) and 4 (reference) were positioned at an angle of 15-30° to the transverse plane. Thus, electrodes 2 and 4 were automatically dorsal to the eyelid and caudodorsal to the lateral corner of the eye, respectively. Electrode 3 was placed in the temporal region, just above the zygomatic process. This configuration was adapted from the one recommended by the manufacturer for the human BIS (de Mattos Jr et al. 2011). Rectal temperature (RT) was monitored with a digital thermometer. Airway gas samples were continuously obtained from the proximal end of the endotracheal tube and analysed with an infrared gas analyser to monitor respiratory rate (f_{p}) and end-tidal carbon dioxide concentrations (ETCO₂). Assisted ventilation was provided to maintain eucapnia (ETCO₂ values from 32 to 37 mmHg) in all dogs. Heart rate (HR) and systolic, diastolic and mean arterial blood pressure (SAP, DAP and MAP) were monitored using Doppler pulse detection with the cuff placed around the antebrachium; cuff width was approximately 40% of the circumference of the limb. Adhesive electrodes were placed to obtain a continuous lead II ECG. Pulse oximetry (SpO₂) was estimated with a pulse oximeter with an infrared sensor attached to the dog's tongue.

All dogs underwent splenectomy. Data were collected 15 min after pre-anaesthetic administration, immediately before skin incision (T0), and then at specific time points during surgery: at the midpoint of endotracheal intubation (T1); at 1 (T2), 3 (T3) and 5 (T4) min post endotracheal intubation; T5 at 10 min after the start of anaesthesia maintenance; T6 at immediately after skin incision; T7 at excision of the spleen; T8 at muscle suturing; T9 at skin suturing and T10 at 10 min after the end of anaesthetic administration.

All infusions were discontinued at the end of the surgery. Surgery time (time elapsed from the first incision until placement of the last suture), anaesthesia time (time elapsed from injection of propofol or the PA to termination of propofol or PA infusion), and extubation time (time elapsed from termination of propofol or PA infusion until extubation) were recorded for each dog. Time to first head lift, time to attain sternal recumbency, and time to standing (defined as ability to ambulate at least 5 s without assistance) were recorded for each dog. Extubation was performed once the dog's palpebral reflexes were evident and prior to swallowing. Recovery time points were recorded as time elapsed from the end of the infusions to observation of the specified event.

Statistical analysis. Data are presented as mean ± SD unless otherwise stated. Data were analysed using commercial software (Graphpad Prism software, version 4.00, Graphpad Software, San Diego, California, USA). All data were considered nor-

Table 1. Body weight, surgery time, anaesthetic time, and specific recovery times (mean \pm SD) in dogs ($n = 10$ /group)	
undergoing splenectomy	

Variable	Group						
variable	1	2	3	4			
Body weight (kg)	11.8 ± 0.3	12.0 ± 0.2	11.7 ± 0.3	11.9 ± 0.1			
Surgery time (min)	53.3 ± 10	55.2 ± 11	49.4 ± 9	56.7 ± 12			
Anaesthetic time (min)	58.0 ± 13	63.1 ± 12	55.9 ± 10	60.8 ± 13			
Time to extubation (min)	40.4 (6-10)	67.9 (12–17)*	45.7 (9-6)	43.7 (11-24)			
Time to head lift (min)	51.6 ± 12.4	$77.3 \pm 23.0^{*}$	58.2 ± 17.5	55.8 ± 19.1			
Time to sternal recumbency (min)	54.9 ± 17.2	$81.2 \pm 20.4^{*}$	58.5 ± 11.1	54.8 ± 26.9			
Time to standing (min)	62.5 ± 19.4	90.3 ± 30.3*	67.4 ± 19.5	65.1 ± 28.6			

**P* < 0.05 from Group 1

mally distributed and passed normality tests using the Shapiro-Wilk test. Data within each treatment group were analysed for changes with time by use of one-way analysis of variance (ANOVA) for repeated measures followed by Dunnett's test, if appropriate. Variables were compared between groups using Student's *t*-test or the Mann-Whitney *U*-test, and all differences were considered to be significant at P < 0.05.

RESULTS

All groups showed a tranquil recovery without undesirable effects such as agitation, vocalisation, moans, muscle shivering, and vomiting or salivation. None of the dogs required additional propofol during the study period, which indicated that the dose of the sedative was sufficient. No significant differences (P = 0.201) were found between groups in body weight, anaesthetic duration and surgery time (Table 1). Extubation time, time to head lift, time to sternal recumbency and time to standing were longer in Group 2 than other groups (P = 0.032) (Table 1). No significant differences in RT, f_p , ETCO₂ and SpO₂ values were found in any of the groups compared to the baseline (P = 0.082), with the exception of RT, which was lower at T9 and T10 compared to T0 (P = 0.016) (Table 2). Thus, usage of PA may result in a light hypothermia during the surgery.

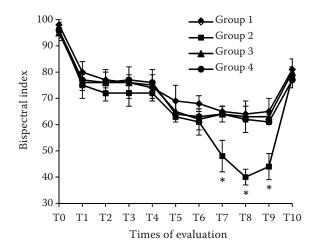


Figure 1. Mean (\pm SD) bispectral index (BIS) measurements in different groups and time points of evaluation. *Statistically significant (P < 0.05) when compared to the control group within the treatment. This variable was expressed as mean \pm standard deviation as both tests used for analysis (Student's *t*-test or Mann-Whitney *U*-test) detected a significant difference between groups

We observed a decrease in BIS from the T0 values at all-time points in all groups. In the comparative assessment, the values obtained at T0 and T1 were similar in each group. At T2, the values recorded in Group 2 were lower than the values recorded in Groups 1, 3 and 4. At T7, T8 and T9, BIS values were significantly lower in Group 2 compared to Group 1 (P = 0.0006) (Figure 1). In Group 2, HR was significantly lower at T2 to T9 compared to Group 1 (P =0.007) (Figure 2). The results revealed that the HR values were close to bradycardia in Group 2. The differences in SAP, DAP and MAP between the four groups did not achieve statistical significance (Figure 3). Arterial pressures followed the same pattern. A light hypotension was evident from T1 onwards. Notably, no dogs had undesirable symptoms during the PA anaesthesia compared with the control group.

DISCUSSION

This study shows that the PA provided satisfactory results in forty dogs undergoing splenectomy. Recovery from anaesthesia was uneventful in all four groups. To the authors' knowledge, there are as of yet no published studies on the application of a propofol and alfentanil admixture in dogs undergoing splenectomy. In addition, these doses will be useful in clinical practice as there are only a few reports re-

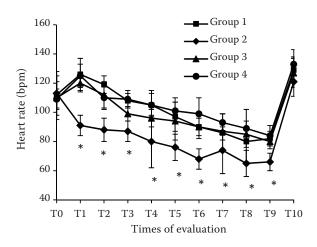
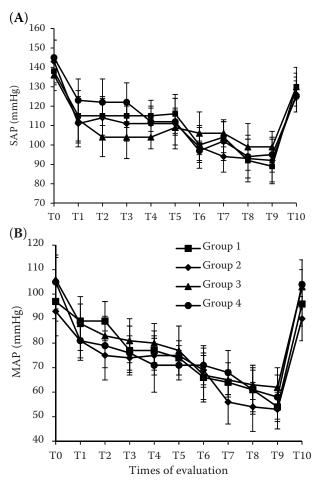


Figure 2. Comparison of mean heart rate (\pm SD) measurements in different groups and time points of evaluation. *No significant differences were found between four groups in SAP, MAP and DAP. This variable was expressed as mean \pm standard deviation as both tests used for analysis (Student's *t*-test or Mann-Whitney *U*-test) detected a significant difference between groups

Variable	Group		Time points									
variable	Group	T0	T1	T2	T3	T4	T5	T6	T7	T8	Т9	T10
	1	30 ± 2	28 ± 3	27 ± 2	27 ± 4	27 ± 7	27 ± 2	27 ± 3	25 ± 4	25 ± 2	25 ± 3	25 ± 3
f _R	2	26 ± 4	26 ± 3	26 ± 2	26 ± 2	26 ± 3	26 ± 2	26 ± 3	26 ± 1	26 ± 5	26 ± 2	26 ± 3
(bpm)	3	31 ± 2	24 ± 4	24 ± 3	24 ± 2	24 ± 5	24 ± 2	25 ± 1	25 ± 2	25 ± 3	25 ± 4	25 ± 2
	4	29 ± 5	23 ± 2	23 ± 4	23 ± 3	23 ± 2	23 ± 5	23 ± 2	23 ± 4	23 ± 2	23 ± 6	23 ± 2
	1	99.6 ± 0.3	98.2 ± 1.2	99.0 ± 0.9	99.5 ± 0.5	99.4 ± 0.2	98.4 ± 1.2	99.6 ± 0.1	98.5 ± 0.8	99.2 ± 0.3	99.1 ± 0.8	98.0 ± 1.6
5-0	2	98.3 ± 0.6	99.5 ± 0.4	97.8 ± 1.9	99.3 ± 0.6	98.3 ± 1.4	97.6 ± 1.3	99.3 ± 0.5	99.8 ± 0.1	98.2 ± 0.7	99.4 ± 0.6	99.6 ± 0.3
SpO_2	3	99.7 ± 0.1	97.4 ± 2.3	98.3 ± 1.6	98.1 ± 1.8	99.6 ± 0.3	99.4 ± 0.5	98.5 ± 0.9	99.6 ± 0.2	99.4 ± 0.5	99.2 ± 0.7	97.7 ± 2.0
	4	99.5 ± 0.3	99.8 ± 0.1	99.7 ± 0.2	97.5 ± 2.4	99.6 ± 0.2	99.7 ± 0.2	97.3 ± 2.5	98.9 ± 0.9	99.8 ± 0.1	98.2 ± 1.4	99.4 ± 0.5
	1	_	_	_	_	_	35 ± 4	35 ± 3	35 ± 5	34 ± 3	36 ± 2	36±3
FTCO	2	-	-	-	-	-	37 ± 2	36 ± 4	36 ± 4	37 ± 2	34 ± 5	35 ± 7
ETCO ₂	3	_	-	-	-	-	36 ± 2	35 ± 3	33 ± 5	33 ± 6	33 ± 2	33 ± 5
	4	_	-	-	-	-	33 ± 6	34 ± 3	34 ± 5	34 ± 2	35 ± 6	33 ± 4
	1	38.6 ± 0.2	38.4 ± 0.4	38.4 ± 0.5	38.4 ± 0.4	38.4 ± 0.1	38.2 ± 0.5	38.0 ± 0.6	37.8 ± 0.5	37.6 ± 0.2	$37.3 \pm 0.8^{*}$	$36.9 \pm 0.5^{*}$
DT(°C)	2	38.6 ± 0.3	38.4 ± 0.2	38.4 ± 0.4	38.4 ± 0.1	38.4 ± 0.5	38.2 ± 0.4	37.9 ± 0.2	37.7 ± 0.7	37.6 ± 0.7	$37.4 \pm 0.5^{*}$	$37.0\pm0.8^*$
RT(°C)	3	38.5 ± 0.4	38.3 ± 0.6	38.3 ± 0.5	38.3 ± 0.2	38.3 ± 0.2	38.1 ± 0.3	38.0 ± 0.5	37.7 ± 0.3	37.5 ± 0.3	$37.3 \pm 0.6^{*}$	$36.7\pm0.4^*$
	4	38.6 ± 0.6	38.4 ± 0.3	38.4 ± 0.3	38.4 ± 0.2	38.4 ± 0.3	38.2 ± 0.6	38.0 ± 0.5	37.8 ± 0.2	37.5 ± 0.4	37.2 ± 0.2*	36.8±0.7*

Table 2. Respiratory rate, pulse oximetry, end-tidal carbon dioxide concentration, and rectal temperature in dogs (n = 10/group) undergoing splenectomy

*P < 0.05 from Group 1



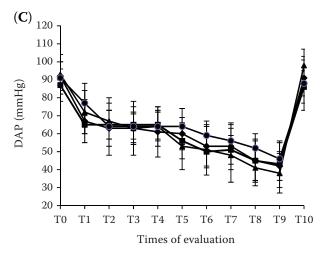


Figure 3. Physiological behaviour of SAP (**A**), MAP (**B**), DAP (**C**) in different groups and time points of evaluation. No significant differences were found between four groups in SAP, MAP and DAP. This variable was expressed as mean \pm standard deviation as both tests used for analysis of data (Student's *t*-test or Mann-Whitney *U*-test) detected a significant difference between groups.

garding the effects of ultra-short-acting opioids in dogs. In the aforementioned study by Auckburally et al. (2008), a propofol and alfentanil admixture was used to induce anaesthesia in dogs. During surgery, propofol was adjusted as needed. In the current study, we evaluated the fixed concentration ratio of propofol and alfentanil admixture in induction and maintenance of anaesthesia in dogs. Our previous study suggested that propofol and alfentanil exhibit synergetic effects. Combinations of intravenous anaesthetics with opioid analgesics have been used for achieving balanced anaesthesia with reduced sideeffects, and promote earlier recovery time and less postoperative nausea and vomiting (Wu et al. 2014).

The reported dose of propofol required to induce general anaesthesia in dogs is approximately 4 mg/kg (Auckburally et al. 2008). In comparison, the mean dose of propofol in Group 1 was 4.1 mg/kg. Alfentanil has also been used as an intravenous bolus as part of a co-induction technique in dogs (Chambers 1989). Based on previous studies and the authors' clinical experience (Chambers 1989; Freye et al. 1998; Michou et al. 2012), the mean doses of alfentanil administered in the present study were selected to be 53.3, 26.7 and 10.8 μ g/kg in Groups 2, 3 and 4, respectively. During surgery in dogs, the minimum infusion rate (MIR) for propofol was 0.3-0.35 mg/kg/min, and surgical anaesthesia was induced in all dogs at 0.4 mg/ kg/min (Hall and Chambers 1987; Ilkiw et al. 2003). We found a dosage of propofol (0.4~0.6 mg/kg/min) that provided a satisfactory depth of anaesthesia in dogs, which suggests a maintenance dose of propofol in prospective clinical studies. Pharmacodynamic interactions between propofol and alfentanil have been described in human patients; propofol reduced the dose of alfentanil required to suppress responses to a variety of clinically relevant stimuli (Pavlin et al. 1996; Vuyk et al. 1996; Hui et al. 2002). According to the infusion rate of propofol, an initial infusion rate of 0.4~0.6 mg/kg/min of the propofol/alfentanil admixture was chosen for Groups 2 to 4.

During anaesthetic procedures, BIS was found to objectively monitor the degree of sedation in humans (Ibrahim et al. 2001). Dogs and other species can also be quantified by bispectral monitoring (Greene et al. 2003; Martin-Cancho et al. 2003). In humans, BIS values above 90 indicate consciousness and values below 50 are considered to be ideal for surgical procedures (Glass et al. 1997). The values described in this study demonstrate that BIS values above 95 for dogs do not differ from those in humans, since the animals were conscious and responsive to stimuli even after sedation. The values in our study are similar to those described by Carrasco-Jimenez et al. (2004) in non-sedated dogs (mean 97). It is expected that the administration of opioids to the anaesthetic protocol does not change the values of BIS, because these drugs have no direct hypnotic action. Lysakowski et al. (2001) studied the effects of fentanyl, alfentanil, remifentanil and sufentanil on the bispectral index during anaesthesia with propofol in humans; no significant differences were observed between the fentanyl group and the placebo group. Hatschbach et al. (2008) found that the addition of remifentanil did not change the bispectral index in dogs undergoing propofol-mediated anaesthesiology. In our study, BIS values in Groups 3 and 4 were similar to the control group (Group 1) (Figure 1). The BIS values in Group 2 were lower than in Group 1 at the T7, T8 and T9 time points. This may be explained by the use of propofol in combination with a high dose of alfentanil. It is well known that co-administration reduces the dose of hypnotic required and minimises the adverse effects of each individual drug. Alfentanil can reduce the hypnotic and anaesthetic dose of propofol required in humans (Short et al. 1992; Vuyk et al. 1996; Glass et al. 1997). The same dosage of propofol was used in each group, but a combination of propofol with a high dose of alfentanil resulted in lower BIS values (Group 2), while the administration of alfentanil alone does not change BIS values (Lysakowski et al. 2001). In other words, the combination of alfentanil with propofol could reduce both the hypnotic and anaesthetic doses of propofol.

In Group 2, HR was much lower than in other groups during surgery. This may be due to the fact that the highest dose of alfentanil was used in Group 2. The HR values were close to what we would consider to be bradycardia. Bradycardia may be explained by two factors: firstly, inhibition of sympathetic activity, which leads to a smaller baroreflex sensitivity at the beginning of surgery, and which is also responsible for controlling the cardiovascular stability (Hatschbach et al. 2008); the second and main factor was the usage of alfentanil which has a high affinity to the µ receptor, and thus exerts significant effects on the cardiovascular system by reducing the CF through a parasympathetically mediated central mechanism. In Group 3 and 4, HR values were close to the control group. Surgical stimulus may have induced higher HR values at T6, T7, T8 and T9 due to autonomic nervous system activation.

Co-induction of anaesthesia with an infusion of propofol combined with a suitable opioid usually resulted in cardiovascular stability (Auckburally et al. 2008), and the administration of PA has been shown to induce minimal cardiovascular depression when used for maintenance of anaesthesia in adult human patients (Taylor et al. 1992). In our present study, SAP, DAP and MAP were determined. There was no significant difference between the control and other three groups in blood pressure. Cardiovascular and respiratory functions were well maintained, even at doses at which all somatic reflex responses were lost.

The administration of opioids and propofol is associated with respiratory depression and hypercapnia in a dose-dependent manner (Aguiar et al. 2001). For this reason, dogs were allowed to breathe spontaneously, but adjuvant ventilation was provided intermittently in order to maintain eucapnia (ETCO₂ values from 32-37 mmHg). All groups exhibited a significant decrease in respiratory rate during surgery. Both propofol (Muir and Gadawski 1998) and alfentanil (Freye et al. 1997) have been shown to cause respiratory depression or apnoea in previous studies. This effect may be dose-dependent. In this study, none of the dogs stopped breathing for any length of time with either agent. Four medicinal groups showed significantly lower body temperatures at the T6-T10 time points compared to the baseline. The normal body temperature range in dogs is 38.0–39.0 °C; therefore, the results evidenced a light hypothermia which was due to the central effects on thermoregulation inhibition, besides the peripheral vasodilatation brought about by propofol, which favoured the decrease in body temperature (Hatschbach et al. 2008). This light hypothermia was due to practices that serve to reduce heat loss during the anaesthetic procedure such as thermal mattresses, warm fluid therapy and warm air insufflators. No significant difference in anaesthetic recovery time was found between Groups 3, 4 and 1. But recovery time was dramatically prolonged in Group 2 compared to Group 1 (Table 2). Excessive alfentanil infusions may cause significantly delayed anaesthetic recovery in dogs (Hoffman et al. 1993). The prolonged recovery time was to be expected as dogs were given a propofol-opioid infusion for approximately an hour. Prolonged propofol infusions cause significantly delayed anaesthetic recoveries in cats (Padilha et al. 2011).

In summary, the administration of PA provided effective and satisfactory anaesthesia in dogs under-

going splenectomy. Side effects were not observed in this study. Nevertheless, assisted ventilation was provided and marked respiratory depression could have occurred otherwise. In the four groups, the extubation and recovery of dogs was steady and with no collateral effects; however recovery in Groups 3 and 4 was faster than in Group 2. The PA infusion led to good hypnosis, but the combinations caused bradycardia, while also maintaining stability of blood pressure and respiration.

REFERENCES

- Aguiar AJ, Luna SP, Oliva VN, Eugenio FR, Castro GB (2001): Continuous infusion of propofol in dogs premedicated with methotrimeprazine. Veterinary Anaesthesia and Analgesia 28, 220–224.
- Auckburally A, Pawson P, Flaherty D (2008): A comparison of induction of anaesthesia using a target-controlled infusion device in dogs with propofol or a propofol and alfentanil admixture. Veterinary Anaesthesia and Analgesia 35, 319–325.
- Bleijenberg EH, van Oostrom H, Akkerdaas LC, Doornenbal A, Hellebrekers LJ (2011): Bispectral index and the clinically evaluated anaesthetic depth in dogs. Veterinary Anaesthesia and Analgesia 38, 536–543.
- Carrasco-Jimenez MS, Martin Cancho MF, Lima JR, Crisostomo V, Uson Gargallo J, Ezquerra LJ (2004): Relationships between a proprietary index, bispectral index, and hemodynamic variables as a means for evaluating depth of anesthesia in dogs anesthetized with sevoflurane. American Journal of Veterinary Research 65, 1128–1135.
- Chambers J (1989): Induction of anaesthesia in dogs with alfentanil and propofol. Veterinary Anaesthesia and Analgesia 16, 14–17.
- Cicek M, Koroglu A, Demirbilek S, Teksan H, Ersoy MO (2005): Comparison of propofol-alfentanil and propofolremifentanil anaesthesia in percutaneous nephrolithotripsy. European Journal of Anaesthesiology 22, 683–688.
- de Mattos Jr E, Ito KC, Conti Patara A, de Carvalho Hda S, Reinoldes A, Caldeira Jde A, Cortopassi SR (2011): Bispectral monitoring in dogs subjected to ovariohysterectomy and anesthetized with halothane, isoflurane or sevoflurane. Veterinary Anaesthesia and Analgesia 38, 475–483.
- Freye E, Neruda B, Smith OW (1997): Studies on the abstinence-like overshoot following reversal of the potent 19-isoamyl derivative of etorphine with naloxone. A comparison with the opioids fentanyl and alfentanil. Arzneimittel-Forschung 47, 6–9.

- Freye E, Latasch L, Von Bredow G, Neruda B (1998): The opioid tramadol demonstrates excitatory properties of nonopioid character – a preclinical study using alfentanil as a comparison. Schmerz 12, 19–24.
- Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P (1997): Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. Anesthesiology 86, 836–847.
- Greene SA, Tranquilli WJ, Benson GJ, Grimm KA (2003): Effect of medetomidine administration on bispectral index measurements in dogs during anesthesia with isoflurane. American Journal of Veterinary Research 64, 316–320.
- Hall L, Chambers J (1987): A clinical trial of propofol infusion anaesthesia in dogs. Journal of Small Animal Practice 28, 623–637.
- Hatschbach E, Silva Fdo C, Beier SL, Lima AF, 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.
- Hoffman WE, Cunningham F, James MK, Baughman VL, Albrecht RF (1993): Effects of remifentanil, a new short-acting opioid, on cerebral blood flow, brain electrical activity, and intracranial pressure in dogs anesthetized with isoflurane and nitrous oxide. Anesthesiology 79, 107–113.
- Hui JK, Critchley LA, Karmakar MK, Lam PK (2002): Coadministration of alfentanil-propofol improves laryngeal mask airway insertion compared to fentanyl-propofol. Canadian Journal of Anaesthesia 49, 508–512.
- Ibrahim AE, Taraday JK, Kharasch ED (2001): Bispectral index monitoring during sedation with sevoflurane, midazolam, and propofol. Anesthesiology 95, 1151–1159.
- Ilkiw JE, Pascoe PJ, Tripp LD (2003): Effect of variable-dose propofol alone and in combination with two fixed doses of ketamine for total intravenous anesthesia in cats. American Journal of Veterinary Research 64, 907–912.
- Lysakowski C, Dumont L, Pellegrini M, Clergue F, Tassonyi E (2001): Effects of fentanyl, alfentanil, remifentanil and sufentanil on loss of consciousness and bispectral index during propofol induction of anaesthesia. British Journal of Anaesthesia 86, 523–527.
- Martin Cancho MF, Lima JR, Luis L, Crisostomo V, Ezquerra LJ, Carrasco MS, Uson Gargallo J (2003): Bispectral index, spectral edge frequency 95%, and median frequency recorded for various concentrations of isoflurane and sevo-

flurane in pigs. American Journal of Veterinary Research 64, 866–873.

- Mendes GM, Selmi AL (2003): Use of a combination of propofol and fentanyl, alfentanil, or sufentanil for total intravenous anesthesia in cats. Journal of the American Veterinary Medical Association 223, 1608–1613.
- Michou JN, Leece EA, Brearley JC (2012): Comparison of pain on injection during induction of anaesthesia with alfaxalone and two formulations of propofol in dogs. Veterinary Anaesthesia and Analgesia 39, 275–281.
- Muir WW, Gadawski JE (1998): Respiratory depression and apnea induced by propofol in dogs. American Journal of Veterinary Research 59, 157–161.
- Padilha ST, Steagall PV, Monteiro BP, Kahvegian MA, Ubukata R, Rodrigues EO, Rosa AL, Aguiar AJ (2011): A clinical comparison of remifentanil or alfentanil in propofol-anesthetized cats undergoing ovariohysterectomy. Journal of Feline Medicine and Surgery 13, 738–743.
- Pavlin DJ, Coda B, Shen DD, Tschanz J, Nguyen Q, Schaffer R, Donaldson G, Jacobson RC, Chapman CR (1996): Effects of combining propofol and alfentanil on ventilation, analgesia, sedation, and emesis in human volunteers. Anesthesiology 84, 23–37.
- Short TG, Plummer JL, Chui PT (1992): Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil. British Journal of Anaesthesia 69, 162–167.
- Smischney NJ, Beach ML, Loftus RW, Dodds TM, Koff MD (2012): Ketamine/propofol admixture (ketofol) is associated with improved hemodynamics as an induction agent: a randomized, controlled trial. Journal of Trauma and Acute Care Surgery 73, 94–101.
- Taylor IN, Kenny GN, Glen JB (1992): Pharmacodynamic stability of a mixture of propofol and alfentanil. British Journal of Anaesthesia 69, 168–171.
- Vuyk J, Engbers FH, Burm AG, Vletter AA, Griever GE, Olofsen E, Bovill JG (1996): Pharmacodynamic interaction between propofol and alfentanil when given for induction of anesthesia. Anesthesiology 84, 288–299.
- Wu Y, Jia N, Zhao C, Li Y, Shi XP, Li YW, Wang C, Li RL, Wang JW, Wen AD (2014): Synergistic antinociception of propofol-alfentanil combination in mice. Pharmacology, Biochemistry and Behavior 116, 25–29.

Received: 2014–04–16 Accepted after corrections: 2015–03–17

Corresponding Authors:

Aidong Wen and Yin Wu, Fourth Military Medical University, Xijing Hospital, Department of Pharmacy, Changle West Street 127, Xi'an, Shaanxi, China E-mail: adwen2014@outlook.com: wuwin_2005@126.com

E-mail: adwen2014@outlook.com; wuyin_2005@126.com