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Original article

COMPARISON OF CARDIORESPIRATORY AND ANAESTHETIC EFFECT OF ALFAXALONE OR PROPOFOL IN DOGS PREMEDICATED WITH ACEPROMAZINE-BUPRENORPHINE

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Summary

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The study compared the cardiorespiratory and anaesthetic effects of alfaxalone or propofol for total intravenous anaesthesia (TIVA) in dogs premedicated with acepromazine-buprenorphine. Six adult Nigerian dogs with mean±S.D. body weight of 11.5±1.6 kg were studied. Acepromazine hydrochloride (0.03 mg/kg) and buprenorphine (0.02 mg/kg) were mixed in the same syringe and administered intramuscularly as premedicants. Following obvious sedation, anaesthesia was induced with bolus intravenous (IV) injection of either 2.0 mg/kg alfaxalone or 4.0 mg/kg propofol over a period of about 30 s. Repeated IV bolus injection of either 1.0 mg/kg alfaxalone or 2.0 mg/kg propofol was administered at 10 minute interval for maintenance of anaesthesia over 90 minutes. Physiological variables were measured and recorded at 15 minute intervals over 90 minutes using a multi-parameter monitor. Onset and duration of analgesia with alfaxalone protocol (2.2±0.4 min and 106.2±4.0 min) were significantly ($P<0.05$) shorter than those with propofol protocol (4.5±1.4 min and 124.5±3.4 min) respectively. Duration of recumbency with alfaxalone (159.5±18.9 min) and propofol (150.8±5.7 min) were not significantly different. Time to standing and recovery time with alfaxalone (38.2±10.8 min and 76.8±28.4 min) were significantly ($P<0.05$) longer than those with propofol (14.0±3.8 min and 23.5±6.4 min respectively). There were no significant differences between mean heart rate (HR), mean arterial pressure (MAP), respiratory rate (RR), haemoglobin oxygen saturation (SpO_2) and rectal temperature (RT) between both protocols. In conclusion, either alfaxalone or propofol appeared to be equally efficacious and safe for induction and maintenance of anaesthesia in healthy dogs premedicated with acepromazine-buprenorphine.

Key words: acepromazine, alfaxalone, buprenorphine, dogs, propofol, total intravenous anaesthesia (TIVA)

INTRODUCTION

Total intravenous anaesthesia (TIVA) is a technique of general anaesthesia that is achieved by using agents given solely through intravenous (IV) route (McGrenaghan & Wilson, 2019). The use of TIVA is gaining popularity in small ani-

mal anaesthesia although inhalant agents are still commonly favoured for anaesthesia maintenance (Brodbelt *et al.*, 2008). Drugs such as propofol and alfaxalone are used for induction to allow endotracheal intubation or for maintenance of the anaesthesia (Muir *et al*., 2008). Drugs used for maintenance of anaesthesia should have a pharmacokinetic profile that allows adjustment of anaesthetic depth by changing the infusion rate over prolonged periods of time without significant accumulation and prolonged recovery. This means rapid onset of action, short duration of action, rapid metabolism to inactivate substances and high clearance rate (McGrenaghan & Wilson, 2019).

Propofol, a chemically inert phenolic compound with anaesthetic properties has become the standard anaesthetic agent used in TIVA techniques due to its rapid clearance from the body, resulting in little accumulation even after prolonged infusion or repeated bolus injection of the drug. The drug is a poor reflex suppressant, and for major surgical procedures must be combined with potent analgesic agents, such as opioids and alpha 2-agonists (Redondo *et al.*, 1999).

Alfaxalone, a synthetic neuroactive steroid with general anaesthetic and muscle relaxant properties, is another drug used for TIVA in the dog (Ferré *et al.*, 2006). The average clearance of alfaxalone in the dog is high, resulting in rapid recovery from anaesthesia; this average clearance is comparable to the values reported for propofol (Nolan & Reid, 1993; Muqattash & Krunz, 2003; Ziser *et al*., 2003; Ferré *et al.*, 2006). The benefits of alfaxalone in dogs include rapid and excitement free induction of anaesthesia, uneventful maintenance, good muscle relaxation and stress-free recovery from anaesthesia (Maddern *et al.*, 2010). The safety and efficacy of alfaxalone as an induction and maintenance anaesthetic agent in dogs have been confirmed (Metcalfe *et al.*, 2014).

Premedication refers to a sedative-analgesic drug given to a patient before anaesthetic induction. Its aims are to calm the patient, reduce total dose of anaesthetics, reduce autonomic side effects, relieve pain, smoothen the recovery period and reduce other side effects of anaesthesia. Acepromazine, a phenothiazine derivative, is a potent neuroleptic agent with relatively low toxicity. It induces mild to moderate tranquilisation, muscle relaxation and a decrease in spontaneous activity attributable principally to central dopaminergic antagonism. Acepromazine possesses antiemetic, anticonvulsant, antispasmodic, hypotensive and hypothermic properties (Yohannes, 2018). Buprenorphine is a synthetic partial opioid agonist which produces dose-related analgesia, is licensed for use in dogs by intramuscular injection, but is also widely used both subcutaneously and intravenously (Pathan & Williams, 2012). The drug has a slow association with, and dissociation from, opioid receptors, and this accounts for the slow onset of action and the prolonged duration of effect.

Buprenorphine has been used in combination with acepromazine, the most commonly used phenothiazine tranquilizer (Jacobson *et al.*, 1994). To produce neuroleptanalgesia in dogs, 0.03 mg/kg of acepromazine can be combined with 0.01–0.02 mg/kg of buprenorphine (Bradbury, 2011). Acepromazine-buprenorphine combination produces profound sedation with a long duration of action. Smooth and uncomplicated recovery was reported with the use of acepromazine-buprenorphine combination as premedi-

cant prior to TIVA with alfaxalone in dogs (Herbert *et al.*, 2013).

Intravenous administration of either alfaxalone or propofol in dogs produces rapid onset of action, rapid clearance from the body, short duration of action and rapid, complete recovery (Morgan & Legge, 1989; Ferré *et al*., 2006; Jiménez *et al.*, 2012; Suarez *et al.*, 2012). In addition, the drugs are non-irritant when injected extravascularly and non-histamine releasing. However, both drugs lack analgesia, produce dose-dependent hypotension and respiratory depression. Excitement and myoclonus (sudden spasm of the muscle) may occur during recovery from alfaxalone anaesthesia in unpremedicated dogs (Ferré *et al.*, 2006). The use of acepromazine-buprenorphine premedication with either alfaxalone or propofol anaesthesia should be expected to produce profound sedation and analgesia, marked dose-sparing of the anaesthetics, potentiation of anaesthetics effects of the drugs and smooth recovery from the anaesthesia (Herbert *et al*., 2013). So far, cardiorespiratory and anaesthetic effects of alfaxalone and propofol in dogs premedicated with acepromazine-buprenorphine have not been compared.

The aim of the study was to compare the efficacy and safety of alfaxalone and propofol anaesthesia when used for TIVA following premedication with acepromazine-buprenorphine in healthy dogs not undergoing surgical intervention.

MATERIALS AND METHODS

Experimental animals

A total of six Nigerian indigenous dogs of either sex (3 males, 3 females) with mean±S.D. body weight of 11.5±1.6 kg were studied. Dogs were apparently healthy and purchased from a local market in Ibadan. They were housed in a standard kennel at the Faculty of Veterinary Medicine, University of Ibadan and fed balanced diet with fresh water freely available in the kennel. The dogs were conditioned for 4 weeks. Just before the experiments, they were judged to be in good general health based on findings at complete physical and clinical examination. Ethical approval (UI-ACUREC/App/ 2015/003) was obtained for inclusion of the dogs in the study.

Study design

The experimental design was a prospective, randomised study in which dogs premedicated with 0.03 mg/kg acepromazine hydrochloride (VEDCO, Vedco Inc. Saint Joseph Missouri) and 0.02 mg/kg buprenorphine (Temgesic®, Schering-Plough, South Africa) received either 2.0 mg/kg alfaxalone (Alfaxan® CD-RTU, Kyron, Benrose, South Africa) or 4.0 mg/kg propofol (Propofol – Lipuro, Fresenius kabi, Halfway House, South Africa) for anaesthetic induction and 1.0 mg/kg alfaxalone or 2.0 mg/kg propofol respectively for anaesthetic maintenance at one week interval (7 days wash-out period).

Experimental procedure

Dogs were fasted overnight and water was available till one hour before premedication. Acepromazine hydrochloride solution (0.03 mg/kg) and buprenorphine hydrochloride solution (0.02 mg/kg) were mixed in the same syringe and administered intramuscularly as premedicant. Following obvious sedation, venous access was secured at the right cephalic vein using a 21-gauge winged needle (Agary® pharmaceutical Ltd, Nigeria). Induction of anaesthesia was achieved with bolus in-

travenous (IV) injection of either 2.0 mg/kg alfaxalone or 4.0 mg/kg propofol over a period of about 30 seconds. Following loss of jaw tone and pharyngeal reflex, endotracheal intubation was performed using a cuffed endotracheal tube (ET) with 6 mm internal diameter and dogs were allowed to breathe room air spontaneously. Ringer's lactate solution (UNIHART®, Unique pharmaceutical Ltd, Nigeria) was intravenously administered to all dogs at an infusion rate of 5.0 mL/kg/h during the anaesthesia period. Respective repeated IV bolus injection of either 1.0 mg/kg alfaxalone or 2.0 mg/kg propofol was administered at 10 minute interval for maintenance of anaesthesia over 90 minutes. Pedal withdrawal reflex was assessed for analgesia by application of pressure with the use of forceps on the interdigital skin web between the toes at 2 minutes interval.

Measurements

A multiparameter veterinary patient monitor (Cardell® 9500 HD) was connected to the dogs for measurement of physiological variables. Heart rate (HR), respiratory rate (RR), mean arterial blood pressure (MAP), haemoglobin oxygen saturation (SpO_2) and rectal temperature (RT) were measured for safety immediately after induction of anaesthesia and during maintenance of anaesthesia at 15 minute intervals over a period of 90 minutes.

Quality of anaesthesia evaluation

The efficacy of alfaxalone and propofol anaesthesia was assessed as followed: 1) Onset of analgesia: time interval (in minutes) between the initial bolus injection of alfaxalone or propofol to disappearance of the pedal reflex. Pedal withdrawal reflex was assessed by response to pressure applied to the toe web with a forceps closed to the first ratchet; 2) Duration of analgesia: time interval (in minutes) between the disappearance and return of the pedal reflex; 3) Duration of recumbency: time interval (in minutes) between acepromazine-buprenorphine induced recumbency and the dog's assumption of sternal posture; 4) Time to standing: time interval (in minutes) between assumption of sternal posture and the dog's ability to stand; 5) Recovery time: time interval (in minutes) between the last bolus injection of either alfaxalone or propofol and the dog's ability to stand.

Statistical analysis

Data were presented as mean±standard deviation (SD) of six dogs. Anaesthetic indices (onset of analgesia, duration of analgesia, duration of recumbency, standing time and recovery time) for both anaesthetic protocols were compared using Student's *t*-test for paired data. Mean heart rate, mean arterial pressure, haemoglobin oxygen saturation, respiratory rate and rectal temperature values for both protocols were analysed using analysis of variance (ANOVA) for repeated measures. A value of $P<0.05$ was accepted as significant in all cases.

RESULTS

Anaesthetic indices

Onset of analgesia with alfaxalone protocol (2.2±0.4 min) was significantly ($P<0.05$) shorter than that with propofol protocol (4.5±1.4 min). Duration of analgesia with alfaxalone (106.2±4.0 min) was significantly ($P<0.05$) shorter than that with propofol (124.5±3.4 min) (Table 1). Duration of recumbency did not differ significantly ($P>0.05$) between alfaxalone and propofol protocols (159.5±18.9 min

vs 150.8±5.7 min, respectively). Time to standing with alfaxalone protocol (38.2±10.8 min) exceeded significantly (P<0.05) that with propofol protocol (14.0±3.8 min). Similarly, recovery time with alfaxalone (76.8±28.4 min) was significantly (P<0.05) longer than that with propofol (23.5±6.4 min) (Table 1).

Cardiopulmonary parameters

The cardiopulmonary parameters of acepromazine-buprenorphine premedicated dogs given either alfaxalone or propofola anaesthesia are presented in Table 2. There was no significant difference between mean HR, MAP with alfaxalone and propofol. The mean HR was within the normal range of 60 to 180 beats/min.

Table 1. Anaesthetic indices during anaesthesia with either alfaxalone or propofol following premedication with acepromazine-buprenorphine. Values are presented as mean± SD, n=6

Anaesthetic index	Alfaxalone	Propofol
Onset of analgesia (min)	2.2±0.4*	4.5±1.4
Duration of analgesia (min)	106.2±4.0*	124.5±3.4
Duration of recumbency (min)	159.5±18.9	150.8±5.7
Time to standing (min)	38.2±10.8*	14.0±3.8
Recovery time (min)	76.8±28.4**	23.5±6.4

Table 2. Cardiopulmonary parameters of dogs anaesthetised with either alfaxalone or propofol following premedication with acepromazine-buprenorphine. Values are presented as mean± SD, n=6

Variable	Time interval (mins) following anaesthetic induction					
	15	30	45	60	75	90
Heart rate (beats/minute)						
Alfaxalone	150.0±26.3	139.2± 6.8	138.7± 6.1	137.3± 9.6	126.8± 6.5	118.8±25.0
Propofol	141.2±21.5	138.3± 8.9	139.7± 5.5	126.3± 1.9	123.3± 7.7	123.5± 24.5
Respiratory rate (breath/minute)						
Alfaxalone	14.7±5.4	19.0±9.9	12.3±3.3	14.7±8.6	12.7±4.8	12.7±4.9
Propofol	23.5±5.1	19.5±3.1	19.5±3.6	18.8±5.0	17.0±4.9	18.0±6.2
Mean arterial blood pressure (mmHg)						
Alfaxalone	61.2±18.1	63.2±16.5	71.2±18.8	63.2±14.5	64.2±10.7	64.2±9.7
Propofol	65.8±11.4	67.7±12.9	70.0±15.8	71.0±15.5	74.5±12.9	70.8±15.3
Haemoglobin-oxygen saturation (%)						
Alfaxalone	93.2±5.2	90.7±7.1	91.0±2.1	93.8±2.0	92.8±1.7	93.8±1.5
Propofol	92.7±5.2	93.2±3.5	94.5±3.0	94.5±2.3	94.3±1.9	92.3±3.6
Rectal temperature (°C)						
Alfaxalone	36.6±0.9	36.6±1.1	36.5±1.1	36.3±1.0	36.2±1.0	36.0±1.0
Propofol	37.4±0.7	37.1±0.7	37.0±0.7	36.7±0.7	36.7±0.6	36.6±0.7

0.03 mg kg^{-1} acepromazine + 0.02 mg kg^{-1} buprenorphine intramuscularly for premedication; 2.0 mg kg^{-1} alfaxalone or 4.0 mg kg^{-1} propofol intravenously for anaesthetic induction; 1.0 mg kg^{-1} alfaxalone or 2.0 mg kg^{-1} propofol intravenously 10 $mins^{-1}$ for anaesthetic maintenance.

The MAP was lower than the normal values (MAP; 80–120 mmHg) in both anaesthetic protocols, but these changes were not significantly pronounced during anaesthesia in either group.

No significant difference was observed in mean RR, SpO_2 and RT values between both protocols. The mean respiratory rate was within normal range (10–30 breaths/min) in both groups (alfaxalone group; 12.3±3.3 to 19.0±9.9 breaths/min; propofol group; 17.0±4.9 to 23.5±5.1 breaths/min). The mean haemoglobin oxygen saturation using pulse oximetry (SpO_2) was normal (≥ 90%) for both alfaxalone (90.7±7.1 to 93.2±5.2 %) and propofol (92.3±3.6 to 94.5±3.0 %) groups. There was a slight drop in body temperature from the normal range of 37 to 40 ºC. The mean RT range obtained for alfaxalone group was 36.0±1.0 to 36.6±1.1 ºC and for propofol group: 36.6±0.7 to 37.4±0.7 ºC (Table 2).

DISCUSSION

Drugs used in TIVA technique should have desirable pharmacokinetic profile which includes rapid onset of action, short duration of action and high clearance rate from the body so that there are no cumulative effects (Shelley & Sutcliffe, 2010). Alfaxalone and propofol were selected as anaesthetic agents of choice for this study because both drugs possess this desirable pharmacokinetic profile.

Administration of alfaxalone to unpremedicated dogs has been reported to cause excitement and myoclonus during recovery (Ferré *et al.*, 2006; Cruz-Benedetti *et al.*, 2018). The use of premedicants is aimed at relieving anxiety in order to smoothen anaesthetic induction, maintenance and recovery phase especially if the premedicant has a long duration of action. Its use also decreases the required doses of induction and maintenance agent, thereby reducing their side effects. Premedicants also provide preemptive analgesia and this necessitates its use with alfaxalone and propofol anaesthetics as both drugs lack analgesic property.

Recommended dosage of intravenous alfaxalone for induction in premedicated dogs is 2.0 mg/kg and for propofol – 4.0 mg/kg but these drugs can be titrated to effect depending on the patient's need (Short & Bufalari, 1999; Ferré *et al.*, 2006; Keates & Whittem, 2012). Whereas anaesthetic dose is normally tailored to patient's need in clinical practice, fixed doses of alfaxalone and propofol at regular intervals were used in this study to facilitate comparison of the efficacy and safety of both anaesthetic agents.

Airway management is important in anaesthesia because an anaesthetised patient is not able to protect its airway from occlusion or aspiration of secretions. Therefore, it is an accepted norm in clinical practice to intubate animals under general anaesthesia in order to ensure a patent airway, decrease dead space and facilitate trachea suction if required (Murrell, 2013). For this reason, the dogs used for this study were intubated.

The dogs recovered in a quiet and warm environment without receiving any stimulus until complete recovery was attained and it was smooth for both protocols. Recent and previous studies have demonstrated signs of excitement, myoclonus, and prolonged recoveries with alfaxalone in dogs (Ferré *et al.*, 2006; Conde Ruiz *et al*., 2016; Dehuisser *et al.*, 2017; White & Yates, 2017). In a study in which clinical and supra-clinical doses of alfaxalone were used for anaesthetic induction in unpremedicated dogs, agitation

and noise hypersensitivity in a small number of animals were reported (Ferré *et al*., 2006). Excitement and increased motor activity with head movements, paddling and some myoclonus were observed during induction of alfaxalone anaesthesia in dogs (Zapata *et al.*, 2018). In the present study, no signs of excitement or agitation were observed and the use of acepromazine-buprenorphine premedication could explain the difference in recovery quality from the previous studies. Propofol protocol had longer duration of analgesia suggesting it as a better choice for moderately long surgical procedures. It may also be more suitable than alfaxalone for use in out-patient surgical procedures due to its shorter recovery time.

One of the haemodynamic effects of propofol is the decrease in arterial blood pressure with accompanying decrease in systemic vascular resistance (Fairfield *et al*., 1991; Lowe *et al.,* 1996; de Wit *et al.*, 2016; Cattai *et al.*, 2018). The haemodynamic effects of alfaxalone were studied by others who reported mild to moderate decreases in arterial blood pressure after induction in dogs using therapeutic doses (Muir *et al*., 2008; Okushima *et al.*, 2015; Zapata *et al.,* 2018). Acepromazine blocks alpha-1-adrenergic receptor thereby causing vasodilation and hypotension (Grasso *et al*., 2015; Murphy *et al.,* 2017).

The hypotension observed in this study therefore, is most likely induced by drugs (alfaxalone, propofol, acepromazine). However, it is not clinically significant because MAP value was not below minimum requirement (60 mm Hg) for glomerular filteration, adequate cerebral and coronary perfusion (Hall *et al.*, 2001). The standard fluid administration rate for anaesthetised animals ranges from 5 to 10 mL/kg/h (Hall *et al.*, 2001). Intravenous fluid flow rate used for this study was 5.0 mL/kg/h because no surgery was performed. It is therefore suggested that TIVA with alfaxalone or propofol used in conjunction with premedication agents (acepromazine 0.03 mg/kg and buprenorphine 0.02 mg/kg) in dogs may require tremendous increase in intravenous fluid flow rate in order to avert hypotension.

Respiratory depression in dogs after alfaxalone or propofol induction has been previously described (Smith *et al*., 1993; Muir & Gadawski, 1998; Grimm *et al.*, 2001; Muir *et al*., 2008; Maddern *et al*., 2010; Maney *et al*., 2013; Zapata *et al.*, 2018). Respiratory depression was observed when 20 mg/kg dose of alfaxalone was administered to unpremedicated dogs but respiratory data were within normal limits when 2.0 and 6.0 mg/kg doses of alfaxalone were administered (Muir *et al*., 2008). Depression in respiratory rate following anaesthetic induction with 6.0 mg/kg propofol was reported (Smith *et al.*, 1993). Therefore, the difference in the result obtained for the present study may be due to reduced dose of alfaxalone (2.0 mg/kg) and propofol (4.0 mg/kg) used as anaesthetics with 0.03 mg/kg acepromazine and 0.02 mg/kg buprenorphine used as premedicant. Respiration is rarely affected by acepromazine at therapeutic doses (Bigby *et al*., 2017). Though opioids are known to cause respiratory depression, buprenorphine, being a partial mu-opioid agonist, may have a wider safety profile compared to full mu agonists, especially with regard to respiratory depression (Pergolizzi *et al.*, 2010). One of the earliest assessments of buprenorphine when given parenterally at dosage between 0.3 to 0.6 mg/kg for postoperative pain found that it generally provided good and adequate pain relief with an incidence of less than 1% of drug-associated respiratory depression (Harcus *et al.*, 1980).

Pulse oximetry (SpO_2) is a noninvasive, readily available diagnostic monitoring tool that can be used to evaluate oxygenation, and is often considered the first objective method for assessing severity of hypoxaemia in a patient. It provides an estimate of the percent haemoglobin saturated with oxygen (SpO_2). SpO_2 is an indirect measurement of SaO_2 which is an invasive method requiring arterial blood sample to determine haemoglobin saturation, so monitoring the SpO_2 is an excellent alternative that provides early warning of desaturation (Pachtinger, 2013). SpO_2 obtained in the present study (>90%) suggests that the available haemoglobin in the blood were adequately saturated with oxygen throughout the period of measurement. This was supported by the result obtained for respiratory rate.

There was a progressive drop in rectal temperature for both drug protocols. This is expected as propofol and alfaxalone like other anaesthetic agents, cause hypothermia directly through depression of the thermoregulatory centres in the hypothalamus or indirectly through peripheral vasodilation. The hypothermia observed in the present study was not significant as clinical hypothermia occurs below 35 ºC. However, placing the dogs on warm blanket and/or infusion of warm intravenous fluid during the clinical trial might have prevented occurrence of the mild hypothermia.

CONCLUSIONS

Alfaxalone and propofol appeared to be equally efficacious and safe for induction and maintenance of anaesthesia in dogs premedicated with acepromazine-buprenorphine. Both produced smooth and rapid induction without complications with similar cardiopulmonary effects. Hypotension was the most prominent adverse effect from both anaesthetic agents suggesting a need to increase circulatory support during prolonged periods of TIVA with either anaesthetic agent. However, both alfaxalone and propofol produced satisfactory anaesthetic induction and maintenance in healthy dogs premedicated with acepromazine-buprenorphine and not undergoing any surgical procedure. Both drugs produced rapid induction, minimal blood pressure depression, good muscle relaxation and smooth recovery.

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