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Multicentre, randomised clinical trial evaluating the efficacy and safety of alfaxalone administered to bitches for induction of anaesthesia prior to caesarean section

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Objective To determine the clinical safety and efficacy of alfaxalone in bitches undergoing caesarean section (CS) and their puppies when it is administered for induction of anaesthesia followed by maintenance with isoflurane and oxygen and in conjunction with perioperative pharmaceuticals.

Design A multicentre, randomised, positive-controlled clinical study.

Methods A total of 74 bitches were enrolled in the study with 48/74 (65%) and 26/74 (35%) receiving alfaxalone and propofol, respectively, for induction of anaesthesia. Bitches were examined prior to induction and monitored during induction, surgery and recovery. Assessments were made for quality of induction, maintenance and recovery from anaesthesia. Assessments were made on pup viability for suction, dorsal flexion, withdrawal and anogenital reflexes.

Results Of the 48 bitches receiving alfaxalone, 47 (98%) and 39 (81%) scored a top score of excellent for induction and anaesthesia effectiveness, respectively. For the same parameters with propofol in 26 bitches, 23 (88%) and 17 (65%) scored excellent. Average scores for recovery were not different between the two treatment groups with alfaxalone 46/48 (96%) and 25/26 (96%) of propofol induced bitches scoring a good or excellent rating. Bitches tolerated a number of concurrent medications throughout the perioperative period. No bitch fatalities were observed in this study. There were no statistically significant differences between treatment groups for the puppy variables. Live puppies born by CS to bitches having been administered alfaxalone or propofol had similar survival rates 24 h after birth (i.e. 205/213 (96%) and 124/131 (95%), respectively).

Conclusion This study confirms the safety and efficacy of alfaxalone for the purpose of anaesthetic induction for CS in the bitch. In addition, alfaxalone had a negligible effect on the neonate with >95% of puppies alive 24 h after the bitch had recovered from anaesthesia with alfaxalone induction.

Keywords alfaxalone; anaesthesia; caesarean section; dogs

Abbreviation CS, caesarean section

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Published reports describe the use of propofol, thiopental, ketamine, thiamylal, xylazine and alfaxalone as injectable induction agents, followed by halothane, methoxyflurane and isoflurane with and without nitrous oxide as inhalational induction agents for caesarean section (CS) in bitches.[1–7] No bitch deaths were recorded in a study of 141 bitches undergoing CS following propofol induction and isoflurane but one brachycephalic bitch developed respiratory distress during recovery, which required a temporary tracheostomy.[2] The use of thiopental, ketamine, xylazine and methoxyflurane has been associated with puppies being delivered dead.[4,5] Others[3–5] have shown that cumulative neonatal survival percentages at time of delivery, at 2 h of age and at 7 days of age were 92% (3127 of 3410), 87% (2951 of 3392) and 80% (2641 of 3301) for all CS protocols in a retrospective study, but with propofol induction and isoflurane maintenance being associated with a positive effect on neonatal survival at 7 days. In a study of 412 pups delivered from 141 bitches undergoing CS using propofol induction and isoflurane in oxygen with nitrous oxide, Funkquist et al. observed a live pup delivery proportion of 293/412 (71%), a live but died within 20 min proportion of 13/412 (3%) and a stillborn rate of 126/412 (26%).[2] Their protocol included a 20-min delay from induction to delivery to allow redistribution of propofol from the undelivered fetuses back to the bitch.

A recently published study compared a number of outcomes for bitches and puppies when CS was performed after either propofol or alfaxalone induction and isoflurane maintenance.[7] That study showed similar survival rates for both groups of puppies, but higher Apgar scores in puppies delivered after alfaxalone induction.

Epidural anaesthesia and analgesia have been used successfully to allow CS to be performed in bitches but have the drawbacks of technical difficulty, undesirable prolonged paralysis, hypotension and restlessness requiring subsequent general anaesthesia.[2]

Alfaxan® (Jurox Pty Ltd, Rutherford, NSW, Australia) is an injectable formulation of the neuro-active steroid anaesthetic drug, alfaxalone, which has been formulated for use in small animal anaesthesia. Alfaxalone has been evaluated in dogs for dose-dependent safety and drug interactions,[8–10] safety in juvenile dogs[11] and for its pharmacokinetics.[12,13] The primary mechanism of the anaesthetic action of alfaxalone is modulation of neuronal cell membrane chloride ion transport, induced by binding of alfaxalone to gamma-amino butyric acid A cell surface receptors. In non-pregnant beagle bitches, mean terminal half-life of a 2 mg/kg bolus of alfaxalone for induction of general anaesthesia has been recorded as 24.0 ± 1.9 min.[12] In unpremedicated and premedicated Greyhounds, mean terminal half-lives for a 2 mg/kg bolus of alfaxalone were documented as 34.3 min and 42.1 min, respectively.[9] In six dogs (including four females of which three were Labradors) given a 6.5 mg/kg bolus of propofol, mean terminal half-life was recorded as 90.9 min.[14,15]

This investigation was a special population study designed to evaluate the clinical efficacy and safety of alfaxalone use by veterinary clinicians for bitches undergoing CS under practical, clinical conditions.

Materials and methods

This was a prospective, multiple-site, positive-controlled, randomised, clinical study involving two parallel groups: group A received alfaxalone (Alfaxan®, Jurox Pty Ltd) and the positive control group P dogs were dosed with propofol (Rapinovet®-X; Schering-Plough Animal Health Corporation). The study was conducted according to the Principles of Good Clinical Practice[16] and with Animal Ethics Committee approval. All cases were enrolled over an 8-month period during 2006 in Western Australia, Victoria and Queensland.

Bitches presenting for CS involving anaesthesia and surgery were enrolled consecutively. The cases were randomised in blocks of three, such that two cases in three would receive alfaxalone and one in three would receive propofol. Bitches were enrolled after obtaining informed owner consent. No exclusions were made for breed, parity, urgency – emergency, expedient or elective CS – or whether any pups had been born naturally prior to presentation. Individualised anaesthetic plans were designed by each investigator in accordance with the protocol based on the patient's signalment and the investigator's experience.

The wellbeing and clinical status of each patient were determined by physical examination. Ultrasonographic examination of the bitch was performed at the discretion of the investigator. Venous blood samples for haematology and biochemistry were collected immediately prior to induction. Industry-accepted anaesthetic procedures were used, including anaesthetic induction by intravenous administration through a pre-placed intravenous catheter of either propofol or alfaxalone and maintenance of anaesthesia with isoflurane inhalation anaesthetic. Surgery was performed by ventral midline coeliotomy with the bitch in dorsal recumbency in all cases.

Premedication was not permitted in this study to prevent confounding of premedicant effects on the variables being measured. The induction volume dispensed for each individual case was that equalling 2 mg/kg body weight (i.e. 0.2 mL/kg) of alfaxalone or 7 mg/kg body weight (i.e. 0.7 mL/kg) of propofol. The rate of intravenous injection was sufficient that the total dose, if required, was administered evenly over 60 s. Administration continued until the investigator determined that the depth of anaesthesia was sufficient for endotracheal intubation, or until the entire dose had been administered. If intubation was still not possible 60 s after delivery of the induction dose, one further induction dose could be administered to effect. Bitches were judged to have experienced post-induction apnoea if the time interval from induction to the first involuntary breath was greater than 30 s. The quality of induction, maintenance and recovery was assessed according to the criteria in Table 1. Following intubation, general anaesthesia was maintained in all bitches using inhalational isoflurane and oxygen. Anaesthetic maintenance apnoea was recorded if more than 30 s occurred between inspirations.

Respiratory rate, pulse rate and oxygen saturation of haemoglobin were measured at multiple intervals during the procedure. The time of each measurement was recorded and assigned to one of three time categories: 1 after induction, 2 during the anaesthesia and 3 during the recovery phase. Measurements during time category 1 were recorded once per animal. During the anaesthesia and recovery (time categories 2 and 3), measurements were generally taken every several minutes, with multiple measurements observed in any one animal during time class 2 and time class 3.

Table 1. Induction, maintenance and recovery scoring criteria for bitches undergoing anaesthesia for caesarean section

Induction	
Excellent	Smooth; bitch readily intubated after administration of no more than the calculated induction dose
Good	Required induction agent in excess of maximum calculated dose; difficult to intubate and/or large amount of jaw tone
Unacceptable	Intubation not possible even with additional induction agent
Maintenance	
Excellent	Minimal tongue flicking and head shaking; bitch maintained in lateral, ventral or dorsal recumbency and immobilisation; minimal muscle tremors or twitching; no response to noise
Acceptable	Frequent tongue flicking and head shaking; frequent movement; short duration of lateral, ventral or dorsal recumbency and numerous attempts to rise immediately after assuming lateral, ventral or dorsal recumbency; some muscle tremors and twitching
Unacceptable	Constant tongue flicking and head shaking; does not become laterally, dorsally or ventrally recumbent or assumes lateral, dorsal or ventral recumbency briefly; muscle rigidity accompanied with twitching, vocalisation, defecation and response to noise
Recovery	
Excellent	Completely smooth recovery
Good	Smooth recovery with minor paddling or tremors
Fair	Paddling or thrashing when moving
Poor	Rough recovery, vocalisation, opisthotonus and/or clonic–tonic seizures

After induction and delivery of the pups, local anaesthetic, analgesic, anti-emetic, antibiotic, procoagulant and tocomimetic drugs were administered as indicated by the needs of the bitch and the preference of each investigator. As soon as possible after delivery each pup was assessed for live/dead status. Each live pup was extricated from the fetal membranes, if necessary, and then scored positive or negative for the reflexes listed in Table 2. At 24 h after delivery, each pup was reassessed for live/dead status.

All statistical procedures were performed in Microsoft Excel or SAS for Windows, version 8.02 (SAS Institute Inc, Cary, NC, USA). Variability is expressed as standard deviations unless otherwise stated. Logistic regression was used to compare proportions between the two treatment groups. Linear regression was performed to evaluate

Table 2. Puppy response reflexes after caesarean section

Withdrawal reflex	Firm pressure applied to a limb of the pup: rapid withdrawal of the limb considered a positive response
Sucking reflex	Finger gently placed in the pup's mouth and assessed for a sucking reflex
Anogenital response	Anogenital region gently wiped with a sterile surgical swab: urination and/or defecation in response to stimulation considered a positive response
Flexion reflex	Pup gently scruffed using the loose skin on the neck: vocalisation, arching of the spine and/or exaggerated limb movement in response to the stimulation considered a positive response

Table 3. Demographics of study population of bitches undergoing anaesthesia for caesarean section

	Group A	Group P
No. of bitches	48	26
Mean weight (kg)	28.4 ± 18.9	32.2 ± 14.4
Mean age (months)	48.9 ± 21.4	58.3 ± 18.1
No. of Greyhounds	10 (21%)	9 (35%)
No. of brachycephalic bitches	9 (19%)	12 (25%)
Mean induction dose (mg/kg)	1.87 ± 0.39	5.46 ± 1.05

A, alfaxalone; P, propofol.

potential associations between continuous variables. Student's t-tests were used to compare means of group A and group P outcomes.

Results

In total, 74 bitches (48 in group A, 26 in group P) were enrolled in the study from four sites. Seven veterinarians managed the cases (sites 1, 2 and 3 – 1 veterinarian each; site 4 – 4 veterinarians).

The demographics of the population are shown in Table 3. The most common breed was Greyhound. Brachycephalic bitches accounted for 19% in group A and 15% in group P. No record was made of previous CS and no bitch was enrolled more than once. The delivery of one or more pups prior to presentation was recorded in 12/48 (25%) bitches from group A and in 5/26 (19%) bitches from group P. No bitch fatalities were recorded in this study and all enrolled bitches completed the study.

Induction apnoea was recorded in 7/47 (15%) in group A and 6/24 (25%) bitches in group P. During anaesthetic maintenance, two bitches from group A and four from group P were judged to have apnoea, but only on one occasion was the apnoea duration recorded.

Duration of anaesthesia from intubation to extubation was 48.6 ± 19.1 min for group A and 51.7 ± 19.5 min for group P. Cardiovascular and respiratory parameters were well maintained during induction, maintenance and recovery periods for both treatment groups (Table 4).

Table 4. Summary statistics for respiratory rate, pulse rate, oxygen saturation and rectal temperature measurements by time category for bitches by time category and treatment group

	Group A Time class[a]				Group P Time class			
	Pre-enrol	1	2	3	Pre-enrol	1	2	3
Respiratory rate (/min)								
n[b]	44	46	468	104	20	21	281	54
mean	57.2	41.1	31.7	35.7	58.4	30.6	31.7	33.8
SD	28.8	26.3	19.6	18.5	30.5	19.7	17.9	17.3
Pulse rate (/min)								
n	48	48	481	46	25	24	292	25
mean	129.8	148.9	126.8	124.1	123.0	125.4	120.8	116.2
SD	24.0	18.8	21.6	19.8	26.4	29.7	20.1	15.3
Oxygen saturation (%)								
n		46	483	21		25	290	11
mean		95.3	95.8	96.2		93.9	95.8	96.6
SD		3.4	3.0	3.1		3.62	2.3	2.5
Temperature (°C)								
n	47			44	26			26
mean	37.87			36.63	37.88			36.86
SD	0.45			0.84	0.41			0.62

[a]Time class: 1, after induction; 2, during anaesthesia; 3, during recovery phase.
[b]No. of measurements made.
A, alfaxalone; P, propofol.

Table 5. Summary of subjective scores of anaesthetic induction, maintenance and recovery quality (percentages represent counts as a percentage of all animals for that group) for 74 bitches presented for caesarean section

Score	Group A		Group P	
	n	(%)	n	(%)
Induction score[a]				
1	0	(0)	1	(4)
2	1	(2)	1	(4)
3	47	(98)	23	(88)
Missing	0		1	(4)
Anaesthetic effectiveness score[b]				
1	2	(4)	0	(0)
2	7	(15)	9	(35)
3	39	(81)	17	(65)
Recovery score[c]				
1	2	(4)	0	(0)
2	0	(0)	1	(4)
3	11	(23)	7	(27)
4	35	(73)	18	(69)

Scoring system as described by Ko et al.[17]
[a]1, unacceptable; 2, intermediate; 3, acceptable.
[b]1, unacceptable; 2, acceptable; 3, excellent.
[c]1, poor; 2, fair; 3, good; 4, excellent.
A, alfaxalone; P, propofol.

Induction, maintenance and recovery scores are presented in Table 5. Perioperative (after the last pup was extracted from the uterus) opiate analgesics (buprenorphine, butorphanol or methadone) were administered after delivery in 39/48 (81%) and 19/26 (73%) of bitches in groups A and P, respectively. Non-steroidal anti-inflammatory drugs (carprofen or meloxicam) were administered subsequent to delivery in 38/48 (79%) and 21/26 (81%) of bitches in groups A and P, respectively.

A greater percentage of group A pups were positive for all four health vigour assessments compared with group P: (1) withdrawal reflex (95.8% vs 93.1%), (2) suction reflex (93.9% vs 84.0%), (3) anogenital reflex (82.7% vs 80.9%) and (4) flexion reflex (90.1% vs 83.2%); however, these numerical differences did not reach statistical significance. The mean number of pups per litter with normal withdrawal reflex, suction reflex, anogenital reflex and flexion reflex did not differ between treatment groups (P = 0.5, 0.9, 0.6 and 0.8 respectively; Table 6).

The group A puppy survival percentages 24 h after birth did not differ from those in group P (96.2% vs 94.7%, respectively; P = 0.7). The proportion of pups that were alive at 24 h (expressed as a proportion of the number of pups alive at birth) did not differ between the two treatment groups (P = 0.9; Table 7). There was no significant relationship detected between litter size at birth and total number of deaths as measured at 24 h post birth (P = 0.76). There was no effect detected of treatment group on the total number of deaths (P = 0.7).

Table 6. Summary of normal reflex parameters measured on live-born puppies immediately after delivery by caesarean section

	Group A	Group P	P value
Total live-born			
Litters (n)	48	26	
Pups (n)	213	131	
Mean ± SD live pups per litter	4.44 ± 2.9	5.04 ± 3.17	0.41
Withdrawal reflex			
Litters showing normal pain reflex (n)	46	24	
Pups showing normal pain reflex (n)	204	122	
Mean ± SD pups with a normal pain reflex per litter	4.25 ± 2.94	4.69 ± 3.16	0.5
Suction reflex			
Litters showing normal suction reflex (n)	46	24	
Pups showing normal suction reflex (n)	200	110	
Mean ± SD pups with a normal suction reflex per litter	4.17 ± 2.93	4.23 ± 3.29	0.9
Anogenital reflex			
Litters showing normal anogenital reflex (n)	46	24	
Pups showing normal anogenital reflex (n)	176	106	
Mean ± SD pups with a normal anogenital reflex per litter	3.67 ± 3.04	4.08 ± 3.26	0.6
Flexion reflex			
Litters showing normal flexion reflex (n)	46	24	
Pups showing normal flexion reflex (n)	192	109	
Mean ± SD pups with a normal flexion reflex per litter	4 ± 2.89	4.19 ± 3.35	0.8

A, alfaxalone; P, propofol.

Table 7. Litter parameters for 74 bitches presented for caesarean section

	Group A (n = 48)		Group P (n = 26)	
Total no. of pups	229		139	
Mean ± SD pups per litter[a]	4.77	± 2.82	5.35	± 2.98
Live at birth (% of group)[b]	213	(93%)	131	(94%)
Live at 24 h (% of group)[c]	205	(89%)	124	(89%)

[a]Comparison of the mean number of pups born between each group (A vs P) was done using a t-test (P = 0.41).
[b]Comparison of the proportion of pups live at birth was done using logistic regression (P = 0.7).
[c]Comparison of the proportion of pups live at 24 h between each group (A vs P) was done using logistic regression (P = 0.9).
A, alfaxalone; P, propofol.

Discussion

This study showed that induction of anaesthesia for bitches undergoing CS using alfaxalone gave equivalent results for the bitch and pups when compared with propofol as an induction agent. The doses chosen for induction of each agent were suitable.

No bitch deaths were recorded in this study and as such, no inferences can be made of lack of safety regardless of bitch breed, parity or urgency (emergency, expedient or elective CS) for either drug.

In a similar recently published study, alfaxalone induction of the bitch was associated with superior Apgar scores for delivered puppies at 5, 15 and 60 min post delivery, compared with those of pups delivered after propofol induction of the bitch.[7] In that study, the investigators allocating Apgar scores were blinded to the treatment group, potentially offering greater relevance to these differences. In our study, it was not possible to blind investigators scoring puppy vigour to treatment groups and we failed to show statistical difference in puppy vigour parameters measured 2–5 min after removal from the uterus. It is likely that our puppy vigour scoring system lacked the sensitivity to detect subtle differences in physiology that the Apgar score offered.

The use of perioperative medications was purposely withheld until after delivery of the last pup to avoid interference with assessment of all variables. However, the use or withholding of opiate analgesics and local anaesthetics may have affected the quality scores for maintenance and recovery. The potential for poorer results exists when the clearance of the induction drug from circulation is more rapid than the duration of the anaesthetic event. Concurrent analgesia could be provided to ensure better quality of maintenance and recovery. The non-steroidal anti-inflammatory drugs used in this study may not have had any effect on the bitch parameters measured in this study because of the short time interval between administration after the last pup and recovery to extubation.

All premedicants may potentially circulate via the attached placenta to unborn pups. Unlike the study by Funkquist etal,[2] no deliberate 20-min delay after induction and prior to surgery to deliver the first pup was implemented. Although phase II metabolism by in utero pups occurs, the results in this study show that based on the proportion of live pups born, there does not appear to be any detriment to commencing surgery as soon as a surgical plane of anaesthesia is reached. The need to delay the removal of a pup from the uterus 20 min after anaesthetic induction assumes that no pups are compromised and/or have undergone placental detachment. In a clinical situation, this can be difficult and time consuming to assess prior to CS and result in unnecessary delays in delivering the pups.

Because of the clinical situation of performing a CS in the bitch, the urgency of some cases and the variable availability of staff, some observations were not recorded or recorded incorrectly and these data were not included in the final analyses.

Conclusion

This study confirms the safety and efficacy of alfaxalone for the purpose of anaesthetic induction for CS in the bitch. In addition, alfaxalone had a negligible effect on the neonate with > 95% of puppies alive 24 h after the bitch had recovered from anaesthesia with alfaxalone induction.

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OBITUARY

Professor Kenneth Jubb

1928–2013

Ken Jubb was a distinguished veterinary pathologist, a quiet, deep thinker with a remarkable intellect and an extraordinary record of contribution to veterinary education.

One of nine children, Ken was born in Victoria. The family farmed in Hexham and wartime events in 1942 caused him to remain at home to help on the farm. He then decided to become a veterinarian so that he could travel the Western District and talk to farmers about their sheep.

Assisted by a Victorian Department of Agriculture cadetship, Ken graduated as a veterinarian from the University of Sydney in 1952. He accepted a position as Instructor in Pathology at the New York State Veterinary College in the USA where he began his research and writing on the pathology of animal disease.

In 1957, Ken was appointed Professor of Pathology at the Ontario Veterinary College, Canada. There he began gathering knowledge of veterinary pathology into his *Pathology of Domestic Animals*, written with Peter Kennedy, and first published in 1963. Successive editions have remained the standard international reference on the subject. Ken also contributed to the 6th edition, including co-authoring the chapter on diseases of the pancreas.

In 2002, Ken received the Peter Olafson Award from the American College of Veterinary Pathologists. Dr Bruce Car accepted on Ken's behalf and commented, 'Through creating this monumental text and his own acute observations during years of research and practice of pathology, Professor Jubb achieved a breadth and depth of understanding of animal diseases and veterinary science hitherto and unlikely in the future to be surpassed.'

During the late 1950s, the Australian Veterinary Association and the Victorian Graziers Association successfully lobbied for a veterinary school in Victoria. In 1963, at the age of 35, Ken returned to the University of Melbourne as Professor of Veterinary Pathology with the task of founding a School of Veterinary Science under the leadership of Professor Doug Blood. Ken was made Dean in 1969 and occupied that position for the next 21 years until retiring in 1990.

Ken's work in veterinary education also included assisting in advanced training for veterinary scientists in Malaysia, Indonesia, China and the Philippines. He also advised on the establishment of universities and veterinary schools at the Universiti Pertanian Malaysia, and Murdoch University, Western Australia.

Ken was a Foundation Fellow of the Australian College of Veterinary Scientists, a Fellow of the Australian Academy of Technological Sciences and a governor of the Ian Clunies Ross Memorial Foundation, and Chairman of its Executive. He served on the Zoological Parks and Gardens Board of Victoria from 1969 to 1990, including 2-year stints as Vice-Chairman and then Chairman. He was a member of a small committee assisting the Australian Government on its bilateral programs for science and technology and convened a small expert committee to oversee the establishment of the Werribee Technology Precinct.

In 1989, Ken was awarded Honorary Membership, a rare distinction, by the American College of Veterinary Pathologists and the Gilruth Prize by the Australian Veterinary Association. In 2011, he was awarded an OAM.

After retiring in 1990, for the next 22 years, until two months before his death at age 84, Ken took great pleasure in being a full-on professor emeritus of the University of Melbourne, active in mentoring of graduate veterinarians in microscopy sessions, supervising autopsies of animals, advising on interpretation of pathology tests and providing informal leadership in pathology journal clubs.

Ken is survived by his wife of 57 years, Trudi, their son Tristan, eight grandchildren and one great-grand daughter. Their eldest son, also named Ken and a veterinarian, died in 2008.

Professor Kenneth Hinchcliff

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