Alfaxalone induction dose following administration of medetomidine and butorphanol in the dog

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Abstract

Objective To determine in dogs the effects of medetomidine and butorphanol, alone and in combination, on the induction dose of alfaxalone and to describe the induction and intubation conditions.

Study design Prospective, randomized, blinded clinical trial.

Animals Eighty-five client-owned dogs (ASA 1 or 2).

Methods Subjects were block randomized to treatment group according to temperament. The treatment groups were: medetomidine 4 μg kg⁻¹ (M), butorphanol 0.1 mg kg⁻¹ (B), or a combination of both (MB), all administered intramuscularly. After 30 minutes, a sedation score was assigned, and alfaxalone 0.5 mg kg⁻¹ was administered intravenously over 60 seconds by an observer who was unaware of treatment group. Tracheal intubation conditions were assessed and, if tracheal intubation was not possible after 20 seconds, further boluses of 0.2 mg kg⁻¹ were given every 20 seconds until intubation was achieved. Induction dose and adverse events (sneezing, twitching, paddling, excitement, apnoea and cyanosis) were recorded; induction quality and intubation conditions were scored and recorded.

Results The mean dose of alfaxalone required for induction was similar for groups M and B: 1.2 ± 0.4 mg kg⁻¹. The mean dose requirement for group MB (0.8 ± 0.3 mg kg⁻¹) was lower than groups M and B (p < 0.0001). Induction dose was not influenced by temperament or level of sedation. Induction and intubation scores did not differ between treatment groups. Adverse events were noted in 16 dogs; there was no association with treatment group, temperament or level of sedation.

Conclusions and clinical relevance Medetomidine and butorphanol administered in combination reduce the anaesthetic induction dose of alfaxalone compared to either agent alone. This difference should be taken into account when using this combination of drugs in a clinical setting.

Keywords alfaxalone, anaesthesia, butorphanol, medetomidine.

Introduction

Using a combination of anaesthetic drugs to provide hypnosis, analgesia and muscle relaxation is referred to as balanced anaesthesia. Balanced anaesthesia utilizes the theory that drugs used in combination may act in an additive or synergistic manner which can minimize the adverse effects of individual drugs. Pre-anaesthetic
medication plays an important role in balanced anaesthesia.

Medetomidine is a potent and specific alpha-2-adrenoceptor agonist which provides sedation, analgesia and muscle relaxation. Butorphanol is an opioid which is thought to be a partial agonist at the KOP (κ) (Remmers et al. 1999) and MOP (μ) (Emmerson et al. 1996) opioid receptors. Butorphanol provides sedation, and limited, short duration analgesia for minimally painful procedures. Both frequently are used as pre-anaesthetic medications, either alone or in combination (Bartram et al. 1994; Muir et al. 1999). Both agents have been reported to reduce the dose required for anaesthetic induction of a variety of commonly used intravenous agents including propofol and thiopental (Bufalari et al. 1996; Kojima et al. 2002; Sano et al. 2003; Ko et al. 2006).

Alfaxalone is a steroid anaesthetic agent. It is highly insoluble in water and historically was formulated in combination with alphadalone and cremaphor EL, a solubilizing agent. Cremaphor has been associated with a high incidence of histamine release in the dog (Child et al. 1971), making it unsuitable for use in this species. Recently alfaxalone has been solubilized with 2-hydroxypropyl-beta-cyclodextrin. This formulation has been used clinically to induce general anaesthesia in a variety of species including the dog (Ferre et al. 2006; Muir et al. 2008). Alfaxalone has been marketed in Australia, New Zealand and South Africa for a number of years and has been released for use in the United Kingdom and Europe more recently. Alfaxalone has been used successfully with a variety of pre-anaesthetic medications including butorphanol and medetomidine (Muir et al. 2004; Pasloske et al. 2005) but its use with both medetomidine and butorphanol in combination has, to our knowledge, not yet been documented.

Earlier studies have determined the dose of alfaxalone required to induce anaesthesia in unpremedicated dogs to range from 1.7 mg kg\(^{-1}\) (Muir et al. 1999) to 2.2 mg kg\(^{-1}\) (Pasloske et al. 2005). Pre-medication with medetomidine 4 μg kg\(^{-1}\) or butorphanol 0.2 mg kg\(^{-1}\) in one experimental investigation (Muir et al. 1999) reduced the induction dose from 1.7 to 1.6 and 1.4 mg kg\(^{-1}\) respectively. When the dose of medetomidine was increased to 40 μg kg\(^{-1}\), the induction dose decreased further to 1.0 mg kg\(^{-1}\).

The aim of this study was to establish whether medetomidine and butorphanol in combination would cause a reduction in the dose of alfaxalone required to induce anaesthesia when compared with either agent used alone.

Materials and methods

Local ethical committee approval was obtained prior to commencement of the investigation. A prospective randomized and blinded clinical trial using client-owned dogs was designed. A pilot study was conducted and a sample size calculation performed. The pilot group contained 28 animals spread across the three treatment groups. The standard deviation of the induction dose was 0.3 mg kg\(^{-1}\). From this it was estimated that if each treatment group contained 30 animals a difference of 0.28 mg kg\(^{-1}\) could be detected in the required alfaxalone dose with a study power of 80% and an alpha level of 0.05. The pilot study also identified a wide range of temperaments among dogs. It was noted that dogs with more excitable temperaments appeared to require a higher dose of alfaxalone. For this reason stratification according to temperament was employed to ensure that each treatment group contained dogs of similar temperament.

Dogs undergoing anaesthesia were included if they were over 12 weeks of age, fitted American Association of Anesthesiologists (ASA) physical status classification 1 or 2 and were not in pain or undergoing a painful procedure. Dogs were excluded if they showed evidence of cardiopulmonary or airway dysfunction on clinical examination or were receiving phenobarbital, benzodiazepines, opioids or any other drugs with known sedative effects.

In order to achieve approximately balanced groups based on temperament, dogs were randomly assigned to treatment group after stratifying by temperament score. A score of 1 was awarded to a calm friendly dog; 2 if mildly excited and/or nervous; 3 if moderately excited and/or nervous; and 4 if very excitable or nervous. A temperament score was assigned to each animal by one observer (N.H.). Dogs that were aggressive or required heavy sedation for placement of an intravenous catheter were excluded from the study. Dogs were then divided into two groups. The first temperament group contained dogs with a temperament score of 1 or 2; these dogs were deemed to be ‘not excitable’. The second temperament group contained dogs with a temperament score of 3 or 4; these dogs were deemed to be ‘excitable’. Within these two groups...
the dogs were randomly allocated to one of the three treatment groups. A body condition score (BCS) was assigned to each animal by the first observer using the 9-point system (Laflamme et al. 1994).

All animals received the randomly assigned pre-anaesthetic medication 30 minutes prior to induction of anaesthesia. Treatment group M received medetomidine 4 μg kg⁻¹, treatment group B received butorphanol 0.1 mg kg⁻¹ and treatment group MB received medetomidine 4 μg kg⁻¹ and butorphanol 0.1 mg kg⁻¹. Pre-anaesthetic medications were administered intramuscularly into the quadriceps muscle. An intravenous over the needle catheter 20 or 22 gauge was placed aseptically into the cephalic vein. Immediately prior to induction of anaesthesia, sedation was assessed and a sedation score (Table 3) was assigned to each animal by a second observer (K.M.) who was unaware of the treatment group.

Oxygen at 3 L minute⁻¹ was administered to the patient through either a circle or Bain anaesthetic breathing system: the patient end of the anaesthetic breathing system was held near the dog’s nose. This was done for 1 minute prior to the commencement of and during the anaesthetic induction process. Alfaxalone was administered by the second observer until loss of jaw tone and pharyngeal reflexes occurred and tracheal intubation was possible. In order to achieve accurate dosing, alfaxalone was diluted with sterile water for injection (Zaki et al. 2009) to a concentration of 2.5 mg mL⁻¹ for dogs weighing over 10 kg and 1 mg mL⁻¹ for dogs weighing less than 10 kg. All dilutions were made immediately prior to injection. Induction was carried out in an incremental manner. An initial dose of 0.5 mg kg⁻¹ was administered over a 60-second period. If tracheal intubation was not possible 20 seconds after the end of the initial dose further doses of 0.2 mg kg⁻¹ were given over 20 seconds and intubation conditions continuously assessed by the second observer until tracheal intubation was possible.

Following tracheal intubation, anaesthetic induction and tracheal intubation scores (Table 3) were assigned by the second observer. The total dose of alfaxalone administered was recorded and adverse events including apnoea, cyanosis, excitement, paddling and muscle twitching noted. Excitement was defined as the absence of a smooth transition from consciousness to the anaesthetized state which included but was not limited to rigidity, vocalization and apparent distress. Cyanosis was determined by visual inspection of the mucous membranes and apnoea was defined as the absence of spontaneous ventilation >30 seconds. If apnoea or cyanosis were noted alfaxalone was administered more rapidly, in order to achieve tracheal intubation and enable the lungs to be ventilated with 100% oxygen. Data from any dogs receiving a more rapid rate of administration of alfaxalone were excluded from the analysis of alfaxalone dose requirements.

One-way analysis of variance (ANOVA) with Scheffe’s test for post-hoc multiple comparisons was used to examine the effect of treatment group on the induction dose of alfaxalone, time from sedation to start of induction, time taken to induce anaesthesia, sedation score, intubation score and induction score. The effect of temperament score on the induction dose of alfaxalone was also examined using one-way ANOVA. The effect of more than one potential predictor on induction dose was assessed using general ANOVA. Cross-tabulations and Fishers exact tests were used to examine the effect of treatment group on the occurrence of adverse effects and the effect of temperament score on sedation score, intubation score, induction score and the occurrence of adverse effects. The level of significance was set at p < 0.05 and results are reported as mean ± standard deviation and mean difference with 95% confidence intervals (CI) where appropriate.

**Results**

A total of 85 dogs were included in the study: 29 in group M, 29 in group B and 27 in group MB. The groups were similar for average age, sex, weight and BCS (Table 1).

There was a significant treatment effect (p < 0.0001) with a lower mean alfaxalone dose for anaesthetic induction in group MB compared to group M and also compared to group B (Table 2). Mean alfaxalone dose in group M was not significantly different from group B (p = 0.9). Sedation scores (Table 3) were also affected by treatment group (p = 0.01) with a higher sedation score in group MB compared to group M (p = 0.02) and also compared to group B (p = 0.001). Mean sedation score in group M was not significantly different from group B (p = 0.6). There was no effect of temperament on induction dose of alfaxalone, sedation score, induction score or intubation score (p > 0.3). The mean time from sedation to induction of
anaesthesia was 37.53 ± 8.17 minutes and did not vary by treatment group (\(p = 0.6\)). The mean induction time was 184 ± 57 seconds.

Median anaesthetic induction scores were similar for all treatment groups (\(p = 0.7\)) (Table 3) with the most frequent induction score being a score of I which equated with a smooth uneventful induction. Median intubation scores were also similar for all treatment groups (\(p = 0.3\)) (Table 2) with the most frequent score being a score of II and this equated with the occurrence of some mild coughing on intubation.

Adverse events were noted in 16 dogs. Excitation was noted in seven dogs, paddling in five, twitching in ten, one dog was apnoeic for 32 seconds, one dog was observed to be cyanotic on completion of tracheal intubation and no dogs sneezed. No dogs required an increased rate of delivery of alfaxalone for completion of anaesthetic induction. There was no association between treatment group and the occurrence of any individual adverse event or when all adverse events were combined (\(p > 0.4\)). There was also no association between induction dose of alfaxalone and the occurrence of any individual adverse event or when all adverse events were combined (\(p > 0.1\)).

### Discussion

The present study found anaesthetic induction doses of alfaxalone to be 1.2 ± 0.4 mg kg\(^{-1}\) when either medetomidine 4 μg kg\(^{-1}\); B: butorphanol 0.1 mg kg\(^{-1}\); MB: medetomidine 4 μg kg\(^{-1}\) and butorphanol 0.1 mg kg\(^{-1}\). Other investigations reported higher dose requirements even with larger

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**Table 1** Descriptive statistics for age, weight, body condition score (BCS) and gender according to intramuscular premedication treatment group

<table>
<thead>
<tr>
<th></th>
<th>M</th>
<th>B</th>
<th>MB</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>29</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>Age (years)</td>
<td>5.93 (3.2)</td>
<td>6.50 (2.88)</td>
<td>5.03 (2.96)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>25.0 (12.4)</td>
<td>26.1 (15.0)</td>
<td>25.1 (13.2)</td>
</tr>
<tr>
<td>BCS (1–9)</td>
<td>6 (1)</td>
<td>6 (1)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

Values expressed as mean (SD) or number of cases. M: medetomidine 4 μg kg\(^{-1}\); B: butorphanol 0.1 mg kg\(^{-1}\); MB: medetomidine 4 μg kg\(^{-1}\) and butorphanol 0.1 mg kg\(^{-1}\).

**Table 2** Mean anaesthetic induction dose of alfaxalone required in 85 dogs premedicated with intramuscular medetomidine 4 μg kg\(^{-1}\) (M), butorphanol 0.1 mg kg\(^{-1}\) (B), or medetomidine 4 μg kg\(^{-1}\)and butorphanol 0.1 mg kg\(^{-1}\) (MB) according to treatment group

<table>
<thead>
<tr>
<th>Treatment group ((n))</th>
<th>Anaesthetic induction dose of alfaxalone (mg kg(^{-1}))</th>
<th>Mean (mg kg(^{-1})) (SD)</th>
<th>Mean difference compared to MB (95% CI)</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M (29)</td>
<td>1.2 (0.4)*</td>
<td>0.4 (0.20, 0.66)</td>
<td>0.00009</td>
<td></td>
</tr>
<tr>
<td>B (29)</td>
<td>1.2 (0.4)*</td>
<td>0.4 (0.21, 0.67)</td>
<td>0.00006</td>
<td></td>
</tr>
<tr>
<td>MB (27)</td>
<td>0.8 (0.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values expressed as mean (SD). *Mean values are significantly different from group MB.

**Table 3** Sedation, anaesthetic induction and tracheal intubation scores according to treatment group

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Sedation score</th>
<th>Anaesthetic induction score</th>
<th>Tracheal intubation score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>M</td>
<td>10</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>15</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>MB</td>
<td>4</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>29</td>
<td>8</td>
</tr>
</tbody>
</table>

M: medetomidine 4 μg kg\(^{-1}\); B: butorphanol 0.1 mg kg\(^{-1}\); MB: medetomidine 4 μg kg\(^{-1}\) and butorphanol 0.1 mg kg\(^{-1}\); NR: not recorded. Sedation scores – I: no discernable effect; II: mild sedation – appears sleepy; III: moderate sedation – very sleepy may be recumbent but could be roused; IV: heavy sedation – recumbent difficulty rousing; V: profound sedation – lateral recumbency, not rousable; NR: not recorded. Anaesthetic induction scores I: smooth uneventful induction; II: some mild paddling/twitching/excitement; III: poor induction, pronounced paddling/twitching/excitement. Tracheal intubation scores – I: smooth intubation; II: some mild coughing; III: pronounced coughing; IV: swallowing, coughing gagging – failed attempt.
doses of pre-anaesthetic medication (Muir et al. 2004; Pasloske et al. 2005). These differences may have occurred as a result of the longer induction process in the current study. Stokes & Hutton (1991) investigated propofol administered via infusion for anaesthetic induction in humans and found that when the infusion rate was slower the induction dose was lower. Mean overall induction time in the current investigation was 184 ± 57 seconds compared to an average induction time of 53 seconds in a previous clinical study (Pasloske et al. 2005). The longer time to intubation may have allowed greater drug concentrations at the effect site to be achieved (Jacobs & Reves 1993).

The effect of dilution of a drug on the required dose for induction of anaesthesia has been evaluated in both humans and veterinary species. Zaki et al. (2009) found that dilution of alfaxalone to 5 mg mL⁻¹ reduced the required induction dose of alfaxalone in cats. This is possibly due to the effect of the operator administering the drug at a slower rate when diluted. Kazama et al. (2000) reported a reduction in induction dose with diluted versus undiluted propofol administered to humans as an intravenous infusion. The current investigation did not compare diluted to undiluted alfaxalone, but the fact that alfaxalone was diluted may have contributed to the lower dose requirement.

Another possible explanation for the lower doses of alfaxalone reported in this study may be that tracheal intubation was attempted at a light plane of anaesthesia. In other studies intubation was carried out by a variety of observers (Pasloske et al. 2005) or not at all (Muir et al. 2004). In the absence of tracheal intubation the end point of anaesthetic induction was not clearly identified. This may account further for differences between the studies in dose administered. When used in combination, medetomidine and butorphanol reduced the dose of alfaxalone required to 0.77 ± 0.33 mg kg⁻¹. This is equivalent to a dose reduction of 36% when compared with the required dose for either agent alone. This dose is much lower than in any other reports documenting induction dose of alfaxalone, regardless of the pre-anaesthetic agent used (Muir et al. 2004; Pasloske et al. 2005). The magnitude of dose reduction is similar to previous findings of a 33.9% reduction in requirements for dogs receiving thiopentone as the induction agent when administered butorphanol 0.2 mg kg⁻¹ and medetomidine 10 μg kg⁻¹ in combination compared with medetomidine 10 μg kg⁻¹ alone (Muir et al. 1999). Based on the findings of this study, when medetomidine and butorphanol are used in combination with alfaxalone for anaesthetic induction, the total cost of pre-anaesthetic medication and induction is approximately 35% less than when either agent is used alone.

Sedation was greater in the treatment group that received both medetomidine and butorphanol. When alpha-2-agonists and opioids are used together certain effects including analgesia (Grimm et al. 2000) and sedation (Becker & Schmidt-Oechtering 1993) may be enhanced. The mechanism that accounts for increased sedation or reduction in anaesthetic requirements has not been determined, though the analgesic effects of these two classes of drug are thought to be synergistic (Drasner & Fields 1988).

The recorded incidence of adverse events that occurred during induction was greater than might be expected compared with other investigations of anaesthetic induction with alfaxalone (Muir et al. 2004, 2008; Pasloske et al. 2005, 2007). This may be attributed to the relatively long induction time that resulted from the incremental method of induction used. However, Stokes & Hutton (1991) reported a reduction in the incidence of excitement in humans receiving propofol when it was administered over a longer time, although it may not be appropriate to extrapolate between species and different drugs. The incidence of adverse events may not be clinically relevant if it does relate to induction time as the recommended time over which alfaxalone is administered is 60 seconds. The mean time taken for induction in this study was three times longer than suggested by the manufacturer; however, the optimum speed of injection for administration of alfaxalone has not been determined.

Cyanosis of the oral mucous membranes was noted in one dog on completion of endotracheal intubation. This occurred despite the dog spontaneously ventilating and receiving supplemental oxygen. No information was obtained with regard to the tidal volume or end-tidal carbon dioxide tensions to assess the adequacy of ventilation; it is possible that this dog was hypoventilating. Although oxygen was administered, the inspired oxygen fraction (FiO₂) was not measured and it is possible that the FiO₂ was not increased by the technique used. There were no other extraneous reasons found for the cyanosis. The incidence of apnoea, 1 of 85 animals (1.2%), was markedly less than that reported by Pasloske et al. (2005) with
apnoea occurring in 56 animals (31%). In Muir et al.’s (2004) investigation no dogs experienced apnoea. However, in the current investigation the one case of apnoea was of 32 seconds duration, only 2 seconds over the threshold for apnoea. Muir et al. (2008) showed a mean duration of apnoea of 30 seconds in dogs administered 2 mg kg⁻¹ alfaxalone without any pre-medication. Duration of apnoea caused by alfaxalone is thought to be dose related (Pearson et al. 2003).

There was no effect of a reduced induction dose of alfaxalone on quality of anaesthetic induction, ease of tracheal intubation or the incidence of adverse events. Cardiovascular effects were not assessed. Muir et al. (2008) found a dose-dependent decrease in arterial blood pressure and increases in heart rate in unpremedicated dogs receiving alfaxalone. Although these reductions were minimal at a dose of 2 mg kg⁻¹ Muir’s (2008) investigation was conducted in healthy patients and the results may not reflect changes that occur in dogs with co-existing disease. Evaluation of the effects of medetomidine and butorphanol on cardiovascular function during anaesthetic induction with alfaxalone may be beneficial. Other possible benefits of a reduction in alfaxalone dose may include reduced recovery times and improved recovery quality and this may also warrant further investigation.

In conclusion, medetomidine and butorphanol used in combination reduced the induction dose of alfaxalone compared with either agent used alone. This difference should be taken into account when using this combination of drugs in a clinical setting.

References


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