Anesthetic and Cardiopulmonary Effects of Propofol in Dogs Premedicated with Atropine, Butorphanol, and Medetomidine

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ABSTRACT

This study evaluated the anesthetic and cardiorespiratory effects of a combination of intravenous propofol (2.2 mg/kg), intramuscular medetomidine (22.0 μg/kg), intravenous butorphanol (0.22 mg/kg), and intravenous atropine (0.022 mg/kg) in healthy dogs. Anesthesia was characterized by muscle relaxation and analgesia. Heart rate decreased after medetomidine and propofol administration (131 to 113 beats/min) but returned to baseline after intravenous atipamezole (110 μg/kg). Mild acidemia, hypercapnia, hypoxemia, and decreased SaO_2 developed after premedication. PaO_2 and SaO_2 were further decreased by propofol injection. In conclusion, this combination proved to be an effective anesthetic protocol for healthy dogs and should be adequate for minor surgical procedures.

INTRODUCTION

Balanced anesthesia is characterized by muscle relaxation, unconsciousness, and analgesia induced by a combination of drugs, each having a different predominant mechanism of action. The combination of complementary drugs permits use of a decreased dose of each drug to achieve anesthesia and decreases their commensurate side effects. The use of an opioid in combination with an α_2-adrenergic agonist by intrathecal, epidural, and intramuscular routes of administration has been shown to enhance the intensity of opioid analgesia in several species.[1–4] Medetomidine (an α_2-adrenergic agonist) also prolongs the duration of effect and consistency of response to butorphanol (an opioid agonist–antagonist) when administered intramuscularly to dogs receiving a subanesthetic dose of isoflurane.[5]

Propofol is an intravenous hypnotic agent approved for induction and maintenance of anesthesia by bolus or continuous infusion in dogs. Propofol infused intravenously at high dose rates can decrease arterial pressure, cardiac index, and left ventricular systolic and diastolic function in unpremedicated dogs.[6] Propofol has also been observed to induce apnea and respiratory depression after large dose administration in dogs.[7] Propofol in combination with α_2-adrenergic agonists (e.g., xylazine or medetomidine) has been shown to be suitable for short periods of anesthesia.[8–11] Medetomidine decreases the amount of propofol required and enhances analgesia during propofol anesthesia, likely resulting from a combined pharmacokinetic/pharmacodynamic interaction between the two drugs.[8,9,12]

The combination of medetomidine, butorphanol, atropine, and thiopental (a barbiturate hypnotic) induces hypnosis, analgesia, and muscle relaxation sufficient to perform surgical castration in dogs.[13] With this combination, the recovery characteristics after atipamezole administration were more variable and longer than would be expected after use of a very low dose of intravenous thiopental (2.2 mg/kg). Other authors have reported recovery after atipamezole administration to be prolonged in animals receiving a barbiturate.[14] The present study was designed to evaluate the anesthetic effects of butorphanol, medetomidine, and propofol as an injectable combination for routine short surgical procedures in healthy dogs. The speed and consistency of arousal after atipamezole administration approximately 1 hour after propofol administration was also recorded.

MATERIALS AND METHODS

This study was approved by the Office of Laboratory Animal Resources at the University of Illinois and was in compliance with local and federal guidelines governing laboratory animal care and housing.

Eight intact male (n = 3) and female (n = 5) English Pointer dogs (17 to 24 kg), all free of apparent disease based on history and physical examination, received intravenous butorphanol (Torbugesic®**;** Fort Dodge Laboratories, Fort Dodge, IA; 0.22 mg/kg body weight) and intravenous atropine (Atropine sulfate; Elkins-Sinn, Inc, Cherry Hill, NJ; 0.022 mg/kg body weight). After 5 minutes they also received intramuscular medetomidine (Domitor®; Meiji Seika Kaisha Ltd, Tokyo, Japan; 22.0 µg/kg body weight), and 5 minutes later intravenous propofol (Diprivan®; Zeneca Pharmaceuticals, Wilmington, DE; 2.2 mg/kg body weight). Propofol was administered within 60 seconds; the dogs were then orotracheally intubated and allowed to spontaneously breathe room air. All dogs received intravenous atipamezole (Antisedan®; Pfizer Animal Health, Exton, PA; 110 µg/kg body weight) 60 minutes after propofol administration or immediately after gross purposeful movement.

Before drug administration, a venous catheter (20 gauge, 2.5 inches; Angiocath™, Becton Dickinson, Sandy, UT) was placed in the right cephalic vein. The skin over the dorsal pedal artery was then aseptically prepared for arterial catheter placement. Lidocaine, 0.25 mL of a 2% solution, was injected subcutaneously to desensitize the skin. Through this desensitized area, a catheter (20 gauge, 2.5 inches) was percutaneously placed into the artery for measurement of blood pressure (BP) and collection of arterial blood samples. Catheter placement was confirmed by characteristic pulsatile waveforms on the oscilloscope (Datascope® 3000A; Datascope Corp, Paramus, NJ). Arterial BP measurements were performed with dogs in right lateral recumbency. The transducer (TruWave Pressure Transducer™; Baxter Healthcare Corp-Edwards Critical Care, Irvine, CA) was zeroed at the level of the

right atrium. Heart rate and rhythm were monitored continuously on an oscilloscope using a standard base apex electrocardiogram. Response to a supramaximal stimulus was used to assess the adequacy of anesthesia. The stimulus was produced by applying Foerster sponge forceps at a point where the circumference of the tail was 10 cm. The clamp was closed to full ratchet and left in place for 60 seconds or until the animal responded with gross purposeful movement. Response to the tail clamp was assessed at 10, 20, 30, 40, 50, and 60 minutes after administering propofol.

Systolic BP, diastolic BP, and mean arterial pressure (MAP) were recorded before administering butorphanol; 4.5 minutes after atropine; 4.5 minutes after medetomidine; 1, 2, 3, 4, 5, 20, 40, and 60 minutes after propofol; immediately before atipamezole administration; and again after the dogs became sternal. Heart rate was recorded at the same times except for the 1-, 2-, 3-, and 4-minute readings after propofol administration. One-mL arterial blood samples were collected with heparinized syringes from the dorsal pedal arterial catheter before treatment; 4.5 minutes after administering atropine-butorphanol; 4.5 minutes after administering medetomidine; 1, 5, 10, 15, 20, 25, 35, 45, and 55 minutes after administering propofol; and again when the dogs became sternal. Samples were analyzed immediately (Ciba-Corning 288 Blood Gas System; Ciba Corning Diagnostic Corp, East Walpole, MA), and values for PaO_2, $PaCO_2$, pH, and oxyhemoglobin saturation (SaO_2) were recorded.

STATISTICAL ANALYSIS

The data for heart rate, systolic BP, diastolic BP, MAP, pH, PaO_2, $PaCO_2$, and SaO_2 were analyzed using a one-way analysis of variance for repeated measures. When the F value was significant, a Bonferroni t-test was used to analyze multiple comparisons versus the baseline val-

ues. A P value of ≤.05 was considered significant. Descriptive statistical analyses were performed for time after atipamezole administration until sternal recumbency and standing. All values are reported as mean ± SEM. Data analysis was performed on a personal computer using a statistical analysis program (Statgraphics Plus for Windows® 3.0; Manugistics, Rockville, MD).

RESULTS

After administering atropine and butorphanol, all dogs developed a transient second-degree atrioventricular blockade lasting 2.06 ± 0.58 minutes. After the dysrhythmia, heart rhythm became regular and mean heart rate increased from a baseline of 108 ± 9 to 131 ± 10 beats/min (Figure 1). Administering atropine and butorphanol did not result in a significant change in systolic BP, diastolic BP, or MAP (Figure 2). Administering medetomidine reduced heart rate from 131 ± 10 to 123 ± 6 beats/min, and increased systolic BP from 176 ± 13 to 253 ± 17 mm Hg, diastolic BP from 103 ± 9 to 175 ± 12 mm Hg, and MAP from 127 ± 10 to 201 ± 13 mm Hg. One minute after propofol injection, systolic BP, diastolic BP, and MAP decreased to 238 ± 16 mm Hg, 166 ± 12 mm Hg, and 190 ± 14 mm Hg, respectively. Heart rate decreased from 123 ± 6 to 113 ± 6 beats/min 5 minutes after propofol injection; however, the decrease was not statistically significant. Systolic BP, diastolic BP, MAP, and heart rate gradually decreased from the time of propofol injection until atipamezole administration (Figure 2).

Arterial blood pH decreased significantly from a baseline pH of 7.401 ± .011 at all times after administering a combination of atropine and butorphanol. The lowest pH value of 7.323 ± .010 occurred 15 minutes after propofol administration (Figure 3). This decrease in arterial blood pH coincides with an increase in
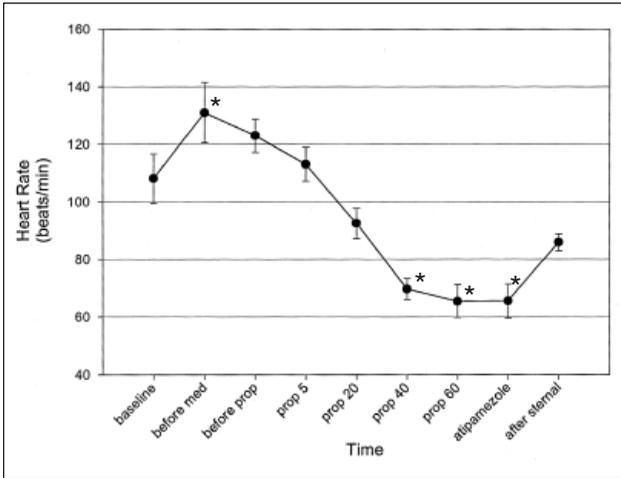
Figure 1. *Mean heart rate after administering atropine, butorphanol, medetomidine, propofol, and atipamezole to dogs. Time points labeled* after *were measured 5 minutes after drug administration; the time point labeled* before *was immediately before administering atipamezole. Other measurements were taken at the times indicated.*
*Values significantly different from baseline (one-way analysis of variance for repeated measures with a Bonferroni t-test when indicated; $P \leq .05$ was considered significant). Error bars are SEM.

$PaCO_2$ and is representative of a respiratory acidosis. $PaCO_2$ increased from a baseline value of 36.5 ± 0.9 mm Hg to a maximum of 46.7 ± 0.9 mm Hg at 5 minutes after propofol administration (Figure 4). The increase in $PaCO_2$ was significant at all times after administering the combination of atropine and butorphanol. PaO_2 decreased from a baseline value of 90.9 ± 2.2 to 71.2 ± 2.4 mm Hg immediately after administering the combination of atropine and butorphanol (Figure 4). Medetomidine administration caused no further reduction in PaO_2 immediately after injection. Propofol administration was followed by a rapid decrease in PaO_2 (56.9 ± 5.1 mm Hg) and SaO_2 (81.6% ± 3.6%) within 1 minute of injection. Within 10 minutes of administering propofol, PaO_2 values returned to levels similar to those immediately after administering the combination of atropine and butorphanol; however, they re-

mained below baseline until after atipamezole administration.

Quality of anesthesia was characterized by excellent muscle relaxation, narcosis, and analgesia. None of the dogs in this study responded with gross purposeful movement to a 60-second application of the supramaximal stimulus. Recovery after atipamezole administration was smooth and rapid in all dogs. The average times to reach sternal recumbency and stand after atipamezole administration were 4.7 ± 0.87 and 8.2 ± 1.16 minutes, respectively. Atipamezole administration decreased systolic BP, diastolic BP, and MAP; only systolic BP was significantly less than baseline values (Figure 2). Heart rate increased from 65 ± 6 to 85 ± 3 beats/min, which was not statistically different from the baseline heart rate value. Atipamezole administration had less of an effect on arterial blood gas values; statistically insignificant increases occurred in $PaCO_2$, PaO_2, and SaO_2 (Figure 4).

DISCUSSION

Combined use of medetomidine and butorphanol has reportedly provided excellent sedation and analgesia for minor procedures not requiring deep surgical anesthesia.[15,16] One proposed mechanism for enhancement of the antinociceptive action of the opioid agonist–antagonist butorphanol by medetomidine is through interaction of opioid and α_2-adrenoceptors at the level of the spinal cord.[2] Opioid and α_2-adrenoceptors share a common second messenger mechanism, and activating both receptors hyperpolarizes neurons by altering potassium–ion channel conductance by means of a G-protein–coupled receptor mechanism
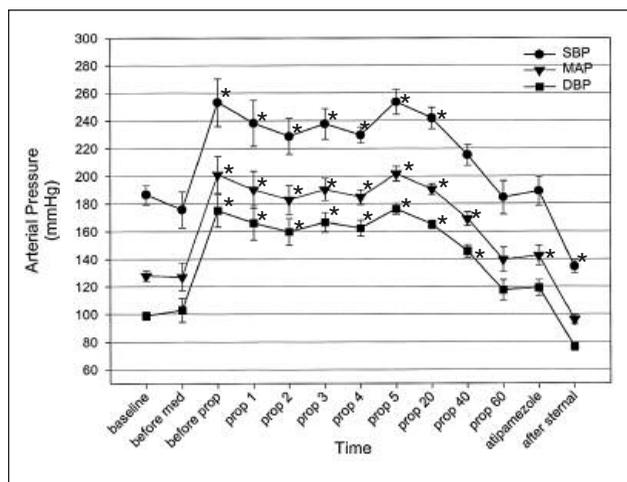
Figure 2. *Mean systolic, diastolic, and arterial blood pressure after administering atropine, butorphanol, medetomidine, propofol, and atipamezole to dogs. Time points labeled* after *were measured 5 minutes after drug administration; the time point labeled* before *was immediately before administering atipamezole. Other measurements were taken at the times indicated.*

*Values significantly different from baseline (one-way analysis of variance for repeated measures with a Bonferroni t-test when indicated; P ≤ .05 was considered significant). Error bars are SEM.

and inhibiting neurotransmitter release.[17] Opioid and α_2-adrenergic receptors are present in the same superficial layers of the dorsal horn of the spinal cord, and both inhibit C-fiber activity.[18] Activating both α_2-adrenergic and opioid receptors can enhance the effect by independently altering intracellular mechanisms coupled to G-protein activity, yielding a net effect greater than that of the sum of each individual drug's effect (synergism).[2]

Alpha$_2$-adrenergic agonists have an anesthetic-sparing action. Anesthetic-sparing effects have been documented in several species, including dogs.[19–26] A decrease in propofol dose requirement after medetomidine administration could presumably be the result of a pharmacokinetic and/or a pharmacodynamic interaction. Hall et al demonstrated a pharmacodynamic interaction (decrease in the minimum effective

concentration) but showed no pharmacokinetic interaction (total body clearance was unchanged) in dogs.[27] However, propofol can be described by a three-compartment model, and administering a peripheral vasoconstrictor likely changes blood-flow distribution to peripheral tissue. The net effect would be less initial distribution of the drug to peripheral compartments with more drug remaining in the central compartment. With such a highly lipophilic drug as propofol, the apparent volume of distribution would logically be decreased. The effects of medetomidine on thiopental pharmacokinetics have been previously described.[28] Confinement of drugs to the central compartment is likely to occur with medetomidine-induced decreased cardiac output and peripheral α_2-mediated vasoconstriction. Conversely, administering atipamezole reestablishes normal cardiac output and blood flow to peripheral compartments, hastening arousal.[29] Arousal after atipamezole administration may not be similar in thiopental- and propofol-anesthetized dogs; however, the time required for complete arousal in dogs given low doses of propofol in this study was shorter than that in dogs receiving the same premedication and low doses of thiopental.[13] Five minutes between administering medetomidine and propofol were allowed so that the hemodynamic effects of medetomidine would be present when propofol was administered, yet the analgesic actions of both butorphanol and medetomidine, in addition to the central depressant effects of propofol, paralleled the most intense surgical stimulation.

The present study demonstrated that a relatively low dose of propofol (2.2 mg/kg) was ca-
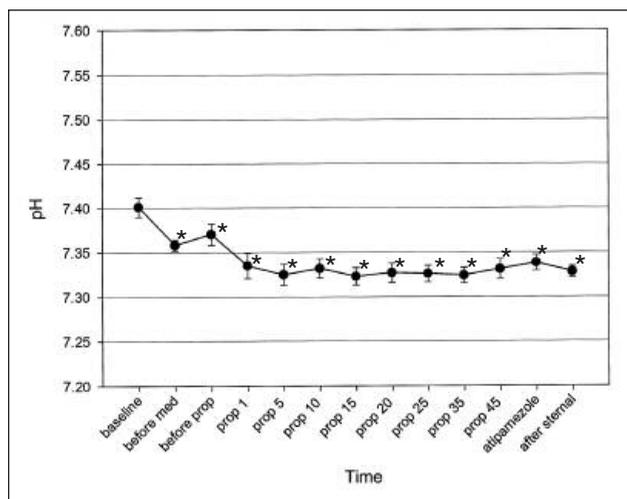
Figure 3. *Mean arterial blood pH after administering atropine, butorphanol, medetomidine, propofol, and atipamezole to dogs. Time points labeled* after *were measured 5 minutes after drug administration; the time point labeled* before *was immediately before administering atipamezole. Other measurements were taken at the times indicated.*
Values significantly different from baseline (one-way analysis of variance for repeated measures with a Bonferroni t-test when indicated; P ≤ .05 was considered significant). Error bars are SEM.

pable of producing over 60 minutes of anesthesia in dogs premedicated with atropine, butorphanol, and medetomidine. Use of medetomidine allowed for the use of a subanesthetic dose of propofol while providing the potential for reversal of the anesthetic state by administering atipamezole. Bradycardia typically induced by α₂-adrenergic–agonist administration was avoided in these trials by previously administering atropine (Figure 1). Use of intravenous atropine prevented bradycardia but did not result in tachycardia. Heart rate was significantly decreased from baseline 40 minutes after propofol injection until immediately before atipamezole administration. Heart rate was likely decreased by the combined effects of increased BP, a medetomidine-induced decrease in the central sympathetic nervous system tone, and waning effects of atropine. In contrast, atipamezole administration decreased BP and likely restored normal sympathetic activity, returning heart rate to baseline values (Figures 1 and 2).

Use of medetomidine typically induces hemodynamic alterations. Thus its use in dogs afflicted with many forms of cardiovascular disease is questionable. Investigators in this study hoped that the high initial BP reported in other studies could be decreased by decreasing the dose of medetomidine to 22.0 μg/kg from the manufacturer's recommended dose of 30.0 to 35.0 μg/kg.[30,31] However, this dose of medetomidine (in combination with atropine and butorphanol) still induced intense vasoconstriction, increasing BP, and afterload.[16]

Although significant hypertension was caused by administering this drug combination, clinical experience suggests that transient BP changes of this magnitude are tolerated in healthy animals. Hypertension caused by administering atropine and an α₂-agonist is usually temporary and typically wanes with the decreasing effects of atropine on the heart or the initiation of inhalant anesthetic delivery. Hypertension resulting from short-term drug effects is etiologically different from hypertension associated with disease. However, use of this drug combination, even at the dose used in this study, should be reserved for healthy dogs. Hypotension did not occur in any dog during the 1-hour observation.

Arterial blood gas values after drug administration in dogs that breathed room air are an indication that supplementation with oxygen can be beneficial. Most published reports suggest butorphanol has minimal cardiovascular
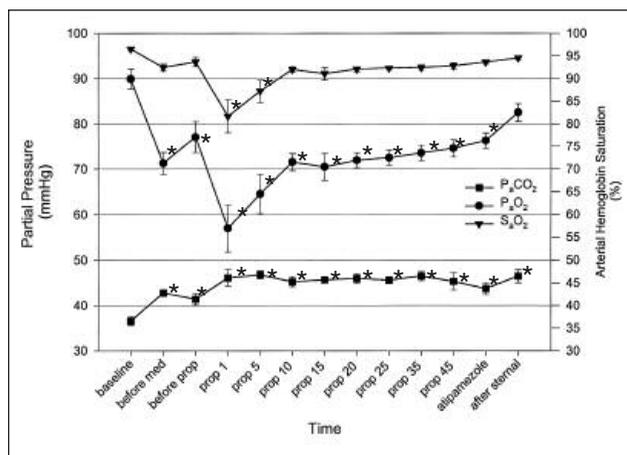
Figure 4. *Mean SaO_2, PaO_2, and $PaCO_2$ after administering atropine, butorphanol, medetomidine, propofol, and atipamezole to dogs. Time points labeled* after *were measured 5 minutes after drug administration; the time point labeled* before *was immediately before administering atipamezole. Other measurements were taken at the times indicated.*
*Values significantly different from baseline (one-way analysis of variance for repeated measures with a Bonferroni t-test when indicated; P ≤ .05 was considered significant). Error bars are SEM.

and respiratory effects, but results of the study reported here demonstrate that the combination of atropine and butorphanol may produce transient second-degree heart block and mild respiratory depression.[32,33] The cause of the second-degree atrioventricular blockade could not be determined; however, administering atropine at the low end of the therapeutic dose range can cause atrioventricular blockade that is usually transient or abolished by further atropine administration.[34] The block reportedly can be caused by transient stimulation of vagal nuclei of the medulla oblongata or a peripheral block of presynaptic muscarinic receptors, resulting in transient enhancement of acetylcholine release at the sinoatrial node. The vagal stimulating properties of opioids, and presumably butorphanol, can be additive or synergistic with the transient effects of atropine, resulting in atrioventricular blockade.

Other studies suggest that use of medetomidine only can be associated with mild respiratory depression and its combination with butorphanol enhances this effect.[35] In this study, these changes were further enhanced by concurrently administering medetomidine and propofol (Figure 4) but gradually returned toward baseline values during the observation period, presumably as a function of waning drug effects. Although no dog experienced prolonged hypoxemia, the low values for PaO_2 and SaO_2 while breathing room air could conceivably lead to tissue hypoxia in dogs with increased metabolic demands. PaO_2 rapidly decreased in all dogs after propofol administration, but the mechanism responsible for this was not clear. A relatively small increase in $PaCO_2$ persisted for most of the study, indicating mild hypoventilation had occurred after both butorphanol and propofol injection. The most abrupt decrease in PaO_2 coincided with administering propofol and appears to be greater than the percentage change in $PaCO_2$ or ventilation. Propofol-induced decreases in cardiac output and ventilation, coupled with medetomidine-induced alterations in pulmonary blood flow distribution, possibly increased overall pulmonary shunting and/or ventilation–perfusion mismatch and resulted in the observed changes in both PaO_2 and SaO_2. Throughout the study, changes in PaO_2 and SaO_2 were parallel (Figure 4), indicating that changes in SaO_2 were a function of decreased PaO_2. Atipamezole administration hastened the return to baseline PaO_2 and heart rate values. Whether the effect on heart rate and PaO_2 was caused by direct antagonism of the cardiopulmonary effects of medetomidine or simply

arousal cannot be determined from this study design.

Administration of supplemental oxygen might have reduced the degree of hypoxia observed after propofol administration during this study, and therefore could be recommended. One concern with administering additional oxygen is depression of hypoxic ventilatory drive. However, hypoxic ventilatory drive generally predominates only when PaO_2 values decrease below 55 to 60 mm Hg.[36] In this study, the mean PaO_2 was below 60 mm Hg for only a few minutes immediately after propofol injection. When PaO_2 returned to levels above those capable of inducing hypoxic ventilatory drive, administering oxygen would not be expected to significantly effect ventilatory drive and thus $PaCO_2$.[36] Even if administering oxygen transiently increases $PaCO_2$, arterial hypoxemia is a more serious complication and should be treated. However, the mean $PaCO_2$ values observed during the period of lowest PaO_2 was 48 mm Hg which is only a slight elevation above normal. Any further increases caused by inhibiting hypoxic drive with oxygen therapy would likely be of minor clinical significance.

CONCLUSION

An anesthetic regimen of premedication with intravenous butorphanol (0.22 mg/kg) and atropine (0.022 mg/kg) followed by intramuscular medetomidine (22.0 μg/kg) and intravenous propofol (2.2 mg/kg) rendered all dogs unresponsive to a supramaximal stimulus for 60 minutes. Analgesia, narcosis, and muscle relaxation were assessed to be adequate for minor surgical procedures. The transient decrease in BP after propofol injection did not significantly obtund the increase induced by intramuscular medetomidine. Intense vasoconstriction after a 22.0-μg/kg dose of medetomidine contraindicates its use in dogs with cardiac disease. Oxygen supplementation may be beneficial in maintaining baseline PaO_2 and SaO_2 values.

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