Considerable advances have been made in the diagnosis and treatment of various causes of glaucoma in veterinary and human patients. Animal-based models that mimic primate physiology are fundamental for evaluating disease pathophysiology and for the development of treatment options. Sheep-based models for glaucoma have been validated by multiple studies and used to assess the efficacy of various therapeutic agents. However, such animal-based models have a requirement for anesthesia. Therefore, to create optimal designs for studies involving animal-based models, it is imperative to understand how various commonly used anesthetic agents affect IOP in the experimental species.

During anesthesia, IOP is influenced by several pharmacological and physiologic factors. Pharmacological agents may alter IOP by changing aqueous humor production or drainage, tone of the extraocular muscles, or intraocular choroidal blood volume or by modifying central diencephalic control centers. However, secondary effects of anesthetic agents such as hemodynamic changes and alterations in ventilation can also influence IOP. Knowledge of how various pharmacological agents impact IOP in a given species can help optimize anesthetic conditions to avoid unnecessary changes in IOP.

ABBREVIATIONS

- IOP: Intraocular pressure
- PETCO2: End-tidal partial pressure of carbon dioxide
- SRB: Sustained-release buprenorphine hydrochloride

OBJECTIVE

To determine the effects of diazepam combined with ketamine hydrochloride or propofol for induction of anesthesia (IOA) following premedication with sustained-release buprenorphine hydrochloride (SRB) on intraocular pressure (IOP) in sheep.

ANIMALS

20 healthy adult sheep.

PROCEDURES

Diazepam with ketamine or propofol was given IV to each of 10 sheep after premedication with SRB (0.01 mg/kg, SC); after > 4 weeks, each sheep received the other induction combination with no premedication. For both eyes, IOPs were measured before premedication (if given), 10 minutes prior to (baseline) and immediately following administration of ketamine or propofol (time of IOA), after endotracheal intubation, and 5 minutes after IOA. Peak end-tidal P\textsubscript{ETCO2}, globe position, and pupillary diameter were also analyzed.

RESULTS

Data were not available for all sheep for all anesthetic episodes. Propofol-diazepam administration alone had no significant effect on IOP, whereas there was a significant decrease in IOP immediately following ketamine-diazepam administration alone. At 5 minutes after ketamine-diazepam administration, SRB-premedicated sheep had significantly higher IOP than unpremedicated sheep. Intraocular pressure was significantly higher at baseline, at intubation, and 5 minutes after IOA in SRB-premedicated sheep receiving propofol-diazepam, compared with unpremedicated sheep. Peak end-tidal P\textsubscript{ETCO2} at intubation was significantly higher in SRB-premedicated sheep. For sheep receiving either anesthetic treatment, IOPs did not differ significantly with or without SRB premedication. Globe position or pupillary diameter and IOP were not significantly related at any time point.

CONCLUSIONS AND CLINICAL RELEVANCE

Results suggested that both ketamine-diazepam and propofol-diazepam combinations were suitable for IOA without increasing IOP in sheep. The use of SRB should be avoided in sheep when increases in IOP are undesirable. (Am J Vet Res 2015;76:771–779)
Propofol is a short-acting, phenol-derived hypnotic agent commonly used for induction of anesthesia in veterinary and human patients. Although propofol consistently reduces IOP in humans,8–10 its effect on IOP varies in other species.11–17 Propofol is known to cause transient systemic hypotension,18 apnea,19 and generalized CNS depression, all of which can potentially impact IOP. The variable influence of each of these factors may explain the species differences in IOP following propofol administration. A recent study17 in sheep revealed that induction of anesthesia with propofol did not significantly alter IOP.

Ketamine hydrochloride is a phencyclidine-derived dissociative anesthetic agent, which causes changes in IOP that vary both among and within species. When administered alone, ketamine reportedly causes significant increases in IOP in both cats20 and dogs,21,22 however, when combined with additional anesthetic agents such as benzodiazepines, opioids, α2-adrenoreceptor agonists, and phenothiazines, ketamine appears to cause either no changes or mild increases in IOP in dogs.23–25 The effect of ketamine on IOP in horses is also controversial, given that induction of anesthesia with ketamine has resulted in no change26 to moderate increases16 in IOP. To the authors’ knowledge, the effect of ketamine on IOP in sheep has never been investigated.

The use of sustained-release analgesics that provide prolonged therapeutic plasma concentrations has become increasingly popular in veterinary medicine. Sustained-release buprenorphine provides effective analgesia for up to 72 hours in cats.27 However, the effect of this opioid formulation on IOP in veterinary species has not been described, to the authors’ knowledge.

The objective of the study reported here was to determine the effects of induction of anesthesia with diazepam in combination with ketamine hydrochloride or propofol on IOP in sheep as well as the effect of premedication with SRB before induction of anesthesia. We hypothesized that induction of anesthesia with ketamine-diazepam would increase IOP, compared with pretreatment values, whereas induction of anesthesia with propofol-diazepam would not cause a significant change in IOP. We also hypothesized that premedication with SRB would not significantly alter IOP, compared with findings in sheep that were not premedicated.

Materials and Methods

Animals

Twenty university-owned sexually intact female adult sheep scheduled to undergo cervical stabilization surgery followed by CT 4 weeks later were used for this study. Results of physical examination, CBC, and biochemical analyses were within reference limits for all sheep included in the study. No abnormalities were detected in any of the sheep during ophthalmologic examination, including indirect ophthalmoscopy, fundic examination, and applanation tonometry, by an experienced veterinarian (BJG). Sheep had a mean ± SD body weight of 67.2 ± 7.7 kg; age could not be definitively determined. Food was withheld from sheep for 24 hours, and access to water ceased 8 hours prior to anesthesia. The protocol was approved by the Institutional Animal Care and Use Committee at the University of Florida.

Experimental procedures

The sheep were enrolled in an additional study in which they received premedication with SRB (0.01 mg/kg, SC) 12 hours prior to surgery. A trained individual (BJG) measured IOP in both eyes by means of applanation tonometry prior to administration of the premedication. Sheep were removed from the study if they received any additional medications other than the experimental drugs within 12 hours prior to anesthesia.

On the day of anesthesia, each sheep was transported to an anesthetic induction stall, where an 18-gauge, 2-inch catheter was aseptically inserted into a cephalic vein. Following IV catheterization, each sheep was allowed to acclimate to the environment for a minimum of 10 minutes. Each sheep was assigned by a random number generator to receive ketamine hydrochloride or propofol (in combination with diazepam) for induction of anesthesia (10 sheep/group). One minute after each sheep received diazepam (0.25 mg/kg, IV), ketamine (up to 5 mg/kg, IV) or propofol (up to 4 mg/kg, IV) was administered slowly over 60 seconds until a loss of laryngeal reflexes allowed orotracheal intubation with the aid of a laryngoscope. Sheep were removed from the study if they required additional doses of the anesthetic drug to maintain an adequate anesthetic plane prior to the end of the study or if orotracheal intubation was not successful within the experimental period. After a minimum of 4 weeks, sheep were anesthetized a second time with the other drug combination. The same study protocol was used, but SRB premedication was not administered prior to the second anesthetic period and IOP was not measured at a corresponding time point (ie, 12 hours prior to induction of anesthesia).

After IOP data were collected prior to the time of premedication (if given), measurements were obtained at 4 additional time points: 10 minutes prior to (baseline) and immediately following administration of ketamine or propofol (considered time of induction of anesthesia), after orotracheal intubation, and 5 minutes after induction of anesthesia. Data recorded for each sheep at each of these time points included IOP, globe position, and pupillary diameter of each eye; heart rate; and respiratory rate. Heart rate and respiratory rate were determined by counting heartbeats and thoracic excursions during a timed period of thoracic auscultation. The pupillary diameter of each eye was subjectively assessed in comparison to the baseline pupillary diameter observed in ambient light during the acclimation period and was determined to be larg-
er, smaller, or unchanged. Globe position was noted to be either central or ventral prior to each measurement of IOP. A sidestream infrared capnometry was attached to the end of the endotracheal tube immediately following intubation, and PETCO₂ was recorded. All measurements and subjective observations were obtained by the same individual (BJG), who was unaware of treatment group assignments.

All IOP measurements were obtained with an applanation tonometer, with each sheep in a standing, sitting, or sternally recumbent position; the head was held in a natural head position, with care taken to avoid flexion or extension of the neck. Occlusion of the jugular veins was avoided during restraint for IOP measurements. Prior to IOP measurement, a single drop of 0.5% tetracaine hydrochloride ophthalmic solution was applied to the surface of each eye. The tonometer used was factory calibrated prior to the study and was manually calibrated each day in accordance with manufacturer guidelines. The applanation tonometer provided an estimate of error of 5%, 10%, or 20%, depending on the consistency of repeated measurements. Only IOP readings with a 5% error estimate were recorded.

**Statistical analysis**

A retrospective power estimate determined that 8 sheep/group would be required to detect a clinically relevant difference in IOP of 2.5 mm Hg with a power of 0.8 and α = 0.05. Normality of data was tested by means of a Shapiro-Wilk test. Parametric data were expressed as mean ± SD. A paired 2-tailed t test showed no significant difference in IOP between right and left eyes at each time point within each treatment group. Therefore, data for the right and left eyes were combined for further analyses. Repeated-measures 2-way ANOVA with a post hoc Tukey-Kramer test was used to evaluate within-group changes in IOP over time and to analyze changes in heart rate, respiratory rate, and PETCO₂ over time within and between treatment groups. A paired 2-tailed t test was used to compare body weights between groups, doses of anesthetic induction agents between groups, and IOP between treatment groups for each time point. Multiple linear regression modeling was applied to compare globe position and pupillary diameter with IOP as the dependent variable at each time point. Values of P ≤ 0.05 were considered significant. Statistical analysis was performed with commercial software.

**Results**

Body weight was not significantly (P = 0.78) different between sheep that received ketamine-diazepam and those that received propofol-diazepam. Of the 20 sheep, 10 met the exclusion criteria during one of the anesthetic episodes; thus, 6 sheep received ketamine-diazepam after SRB premedication, 8 received ketamine-diazepam without premedication, 7 received propofol-diazepam after SRB premedication, and 9 received propofol-diazepam without premedication. For all sheep that received SRB premedication, mean ± SD IOP was not significantly (P = 0.11) different at baseline (14.9 ± 5.8 mm Hg), compared with prior to premedication (18.3 ± 5.6 mm Hg).

**IOP during induction of anesthesia without premedication**

For the 8 sheep receiving ketamine-diazepam without premedication, IOP significantly decreased immediately following induction of anesthesia (9.7 ± 2.0 mm Hg), compared with baseline values (12.4 ± 3.5 mm Hg; Figure 1). However, IOP returned close to baseline after intubation and 5 minutes following after anesthetic drug administration. In the 9 sheep that received propofol-diazepam without premedication, there was no significant change in IOP, compared with baseline values, at any time point.

**IOP during induction of anesthesia with premedication**

In SRB-premedicated sheep, changes in IOP following induction of anesthesia with ketamine-diazepam or...
propofol-diazepam, compared with baseline IOP were evident (Figure 2). For the 6 sheep receiving ketamine-diazepam for induction of anesthesia following premedication with SRB, IOP was decreased immediately after anesthetic drug administration (10.5 ± 2.0 mm Hg), compared with baseline (13.3 ± 4.0 mm Hg), although this difference was not significant. However, compared with IOP immediately after anesthetic drug administration, IOP was significantly (P = 0.01) increased after intubation (15.6 ± 6.0 mm Hg) and 5 minutes after anesthetic drug administration (16.1 ± 3.4 mm Hg).

For the 7 sheep receiving propofol-diazepam for induction of anesthesia following premedication with SRB, IOP was decreased immediately after anesthetic drug administration (12.1 ± 3.9 mm Hg), compared with baseline (15.6 ± 5.4 mm Hg), although this difference was not significant. However, compared with IOP immediately after induction of anesthesia, IOP was significantly increased 5 minutes after induction of anesthesia (19.4 ± 5.5 mm Hg).

Among sheep receiving either anesthetic induction agent combination, there was no significant difference in IOP at any time point between those that did or did not receive SRB premedication. However, for sheep receiving ketamine-diazepam, premedication with SRB resulted in significantly greater IOP 5 minutes after anesthetic drug administration, compared with that in sheep that did not receive premedication (Figure 3). Likewise, for sheep receiving propofol-diazepam, premedication with SRB resulted in significantly greater IOP at baseline, at intubation, and 5 minutes after induction of anesthesia, compared with findings in sheep that did not receive premedication (Figure 4).

**Cardiovascular, respiratory, and ocular variables**

Differences in cardiorespiratory variables were summarized (Table 1). For sheep receiving ketamine-diazepam for induction of anesthesia with or without premedication and for sheep receiving propofol-diazepam for induction of anesthesia without premedication, heart rate was significantly lower at baseline than at all other time points. However, in sheep that were premedicated with SRB followed by induction of anesthesia with propofol-diazepam, there was no significant difference in heart rate over time. For sheep receiving either drug combination without premedication, respiratory rate was significantly higher at baseline than at all other time points. Baseline respiratory rates were significantly greater in sheep that were not premedicated than in sheep premedicated with SRB. Also, in sheep that received SRB premedication and propofol-diazepam, respiratory rate was significantly lower at intubation and 5 minutes following induction of anesthesia, compared with findings in sheep that received propofol-diazepam without premedication.

In sheep in which anesthesia was induced with ketamine-diazepam, \( P_{\text{ETCO}_2} \) was significantly (P = 0.045) higher following intubation in those that were premedicated with SRB (43.8 ± 4.0 mm Hg), compared with those that were not premedicated (35.9 ± 6.0 mm Hg). This pattern in \( P_{\text{ETCO}_2} \) was also observed in sheep after induction of anesthesia with propofol-diazepam with or without SRB premedication, although the difference was not significant. There was no significant relationship between globe position or pupillary diameter and IOP at any time point for sheep receiving any of the treatment protocols.
Adverse events

Apnea (lack of spontaneous ventilation for at least 30 seconds) occurred in 4 sheep receiving propofol-diazepam for induction of anesthesia, one of which also received SRB premedication. For these sheep, a single manually ventilated breath was delivered to confirm intubation by capnography, but manual ventilation was not further provided because all sheep began spontaneous ventilation without further assistance after a maximum interval of 60 seconds. No other adverse events were noted during the study.

Anesthetic induction agent dosages

Mean ketamine dose used in this study for all sheep was 5.1 mg/kg (range, 4.9 to 5.7 mg/kg), and mean propofol dose was 3.0 mg/kg (range, 1.8 to 4.0 mg/kg). There was no significant ($P = 0.49$) difference in ketamine dose when sheep did not receive premedication (5.3 ± 0.6 mg/kg) and when sheep did receive SRB premedication (4.99 ± 0.3 mg/kg). Likewise, there was no significant ($P = 0.11$) difference in propofol dose when sheep did not receive premedication (3.2 ± 0.5 mg/kg) and when sheep did receive SRB premedication (2.8 ± 0.4 mg/kg).

Discussion

In the present study, in unpremedicated sheep, IOP significantly decreased immediately following administration of ketamine-diazepam for induction of anesthesia, compared with baseline IOP (ie, measured 10 minutes prior to anesthetic drug administration). Although a reduction in IOP was

Table 1 — Cardiorespiratory variables over time in healthy adult sheep undergoing induction of anesthesia by IV administration of diazepam (0.25 mg/kg, IV) and ketamine (up to 5 mg/kg, IV) or propofol (up to 4 mg/kg, IV) after premedication with SRB (0.01 mg/kg, SC) or without premedication.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Drugs administered</th>
<th>Baseline (induction of anesthesia)</th>
<th>Intubation (induction of anesthesia)</th>
<th>5 min after induction of anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>Ketamine-diazepam</td>
<td>86.3 ± 15.7a</td>
<td>116 ± 21.8a</td>
<td>133.5 ± 7.6a</td>
</tr>
<tr>
<td></td>
<td>SRB premedication and ketamine-diazepam</td>
<td>87 ± 20.4a</td>
<td>124 ± 21a</td>
<td>129.2 ± 24.8a</td>
</tr>
<tr>
<td></td>
<td>Propofol-diazepam and ketamine-diazepam</td>
<td>78 ± 10a</td>
<td>116.7 ± 29.6b</td>
<td>127 ± 31.5b</td>
</tr>
<tr>
<td></td>
<td>SRB premedication</td>
<td>101.4 ± 31.7b</td>
<td>109.1 ± 27.9b</td>
<td>128.4 ± 31.7b</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>Ketamine-diazepam</td>
<td>104.3 ± 36.1b**</td>
<td>35.3 ± 16.8b</td>
<td>35.2 ± 18.9b**</td>
</tr>
<tr>
<td></td>
<td>SRB premedication and ketamine-diazepam</td>
<td>30 ± 12b</td>
<td>35 ± 15.4b</td>
<td>22.5 ± 9.9b**</td>
</tr>
<tr>
<td></td>
<td>Propofol-diazepam and ketamine-diazepam</td>
<td>103.3 ± 64.2b**</td>
<td>18.7 ± 16.6b</td>
<td>32.1 ± 48.5b**</td>
</tr>
<tr>
<td></td>
<td>SRB premedication</td>
<td>30.7 ± 21.8b</td>
<td>24.4 ± 12.8b</td>
<td>12.7 ± 8.8b**</td>
</tr>
<tr>
<td>Petco2 (mm Hg)</td>
<td>Ketamine-diazepam</td>
<td>—</td>
<td>—</td>
<td>35.9 ± 6b</td>
</tr>
<tr>
<td></td>
<td>SRB premedication and ketamine-diazepam</td>
<td>—</td>
<td>—</td>
<td>43.8 ± 4.4†</td>
</tr>
<tr>
<td></td>
<td>Propofol-diazepam</td>
<td>—</td>
<td>—</td>
<td>39.5 ± 6.7†</td>
</tr>
<tr>
<td></td>
<td>SRB premedication and propofol-diazepam</td>
<td>—</td>
<td>—</td>
<td>44.5 ± 5.3†</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

* †Within a column for a given variable, values with different symbols are significantly ($P \leq 0.05$) different.

** ‡Within a row, values with different superscript letters are significantly ($P \leq 0.05$) different.

Sheep received ketamine-diazepam or propofol-diazepam after premedication and, after a > 4-week interval, received the other treatment without premedication. Ten sheep were initially assigned to each treatment group; however, sheep were removed from the study if they required additional doses of the anesthetic induction agent to maintain an adequate anesthetic plane prior to the end of the study or if orotracheal intubation was not successful within the experimental period. Heart rate and respiratory rate were determined by counting heartbeats and thoracic excursions during a timed period of thoracic auscultation. A sidestream infrared capnometer was attached to the end of the endotracheal tube immediately following intubation, and $\text{PetCO}_2$ was recorded. Heart rate and respiratory rate data were collected 10 minutes prior to administration of ketamine or propofol (baseline), immediately following anesthetic drug administration (ie, induction of anesthesia), after orotracheal intubation, and 5 minutes after induction of anesthesia.
also observed in unpremedicated sheep following administration of propofol-diazepam for induction of anesthesia, this change was not significant. The decrease in IOP following ketamine-diazepam administration contrasts with results of studies in other species where administration of ketamine (without diazepam) resulted in an increase in IOP in dogs, horses, and cats, whereas IOP was not markedly affected following ketamine administration in children. To the authors’ knowledge, this is the first report of the effects of ketamine-diazepam on IOP in sheep.

Following intubation, in unpremedicated sheep that received ketamine-diazepam, IOP returned close to baseline. In humans, intubation is known to incite increases in IOP due to coughing, increased extraocular muscle tone, extreme flexion of the head augmenting jugular venous pressure, or heightened sympathetic tone. To facilitate endotracheal intubation of the sheep, the head was positioned in extreme extension, but care was taken to return the head to a natural resting position prior to IOP measurement. Although coughing occasionally occurred during endotracheal intubation, IOP measurements were avoided when the sheep were actively coughing. Ketamine is well documented to cause muscle rigidity and enhance sympathetic tone. Despite increases in heart rate observed following administration of ketamine-diazepam for induction of anesthesia, IOP decreased prior the return of heart rate to baseline, suggesting that any increase in sympathetic tone had a marginal effect on IOP.

Although the mechanism of action by which propofol influences IOP remains a matter of speculation, it has been suggested that propofol alters CNS control of aqueous humor production and drainage in humans. The lack of change in IOP observed in sheep of the present study during the period following administration of propofol-diazepam for induction of anesthesia without premedication contrasts with findings of studies performed in other veterinary species. In dogs administered propofol for induction of anesthesia, IOP markedly increased immediately following drug administration but before intubation. In horses, IOP modestly increased 2 minutes following propofol administration. The findings of the present study are similar to those of a recent investigation in sheep comparing the effects of propofol and alfaxalone on IOP, in which propofol administration did not result in any significant changes in IOP at 2 and 5 minutes after injection. It is important to note that in that study, unlike in the study of this report, sheep received a larger dose of propofol (6 mg/kg) that was administered more slowly without additional anesthetic induction agents and were also not intubated.

In the present study, IOP was not influenced by intubation following propofol-diazepam induction of anesthesia without SRB premedication. The effect that propofol has on IOP specifically during intubation appears to be species dependent. In people, propofol blunts intubation-associated IOP increases, whereas in dogs, this effect is not as apparent, although it appears to be dose dependent.

Mean baseline IOP in sheep in the present study ranged from 12.4 to 15.6 mm Hg among the treatment protocols. These values are within the range in other studies evaluating IOP in clinically normal sheep (10.6 to 16.2 mm Hg). In the present study, all IOP measurements were performed with an applanation tonometer, which has good correlation to direct anterior chamber manometry in sheep and therefore can be used to provide reproducible and accurate estimates of IOP in this species.

Benzodiazepine administration to small ruminants provides anxiolysis, muscle relaxation, and sedation. In dogs, the inclusion of diazepam as part of an anesthetic induction protocol blunts increases in IOP caused by ketamine alone. Also, induction of anesthesia with ketamine and midazolam results in a clinically negligible change in IOP. Likewise, the addition of either diazepam or midazolam significantly decreases changes in IOP after intubation in dogs, compared with those following administration of propofol alone. Muscle relaxation and CNS depression provided by diazepam may have either decreased IOP or attenuated any possible increase in IOP caused by ketamine or propofol in the sheep of the present study. Although it would have been ideal to administer ketamine and propofol alone to elucidate their individual effect, sheep did not receive premedication in 1 treatment protocol, which would likely have resulted in anesthetic induction of less than acceptable quality with ketamine alone. Future studies are needed to evaluate the effect of diazepam on IOP of sheep.

The sheep included in the present study were enrolled in a separate study evaluating the postoperative analgesic efficacy of SRB administered 12 hours prior to surgery. In the present study, administration of SRB significantly altered IOP in sheep at certain time points, compared with sheep that did not receive a premedication. Systemic administration of µ-opioid receptor agonists can result in species-dependent pupillary diameter changes, which can alter IOP by changing aqueous humor flow. Short-acting opioid receptor agonists have also been shown to prevent increases in IOP classically associated with intubation in humans. Buprenorphine administration is also associated with variable degrees of respiratory depression and species-dependent behavioral changes, which in turn can affect sympathetic tone and alter IOP. To the authors’ knowledge, there are no studies evaluating the effect of sustained-release formulations of µ-opioid receptor agonists on IOP, although an IV bolus of buprenorphine caused no significant changes in IOP in anesthetized humans.

Intraocular pressure is influenced by a variety of physiologic factors, such as extraocular muscle tone, scleral rigidity, lens position, choroidal blood volume, and aqueous humor production and drainage.
esthetic agents can alter IOP directly or indirectly by an array of mechanisms that cause variations in one or more of these factors. The mechanism of action by which ketamine may temporarily decrease IOP is unknown. Although sheep in the present study underwent a period of acclimation, anxiety and stress may have resulted in greater baseline IOP than typically found in calm sheep. It is possible that the combination of ketamine with diazepam, and to a lesser extent propofol with diazepam, lead to greater sedation and anxiolysis, resulting in relaxation of extraocular muscles and subsequently decreasing IOP.

The degree of sedation caused by buprenorphine depends on the dose and route of administration as well as the species. In dogs and cats, buprenorphine causes mild sedation at lower doses when administered by a variety of routes. However, buprenorphine administration in horses with no signs of pain results in excitatory behaviors such as restlessness, head nodding, shaking, and vocalization. Goats also have excitatory behavior following IV or IM administration of buprenorphine, which causes agitation, decreases rumination, and increases plasma cortisol and vasopressin concentrations. Although sedation scores were not evaluated in the present study, it is possible that sheep receiving SRB premedication had greater signs of agitation and anxiety (similar to other small ruminants), resulting in greater baseline IOP, compared with sheep that did not receive premedication. This may be the reason for the higher baseline heart rate and baseline IOP in the sheep receiving propofol-diazepam after SRB premedication, compared with findings in sheep receiving propofol-diazepam without premedication.

Apnea developed infrequently in the sheep of the present study following administration of propofol-diazepam. Respiratory depression is a common adverse effect of propofol, and prolonged apnea can lead to hypercapnia and eventual hypoxemia. Buprenorphine also causes prolonged respiratory depression in humans because of its high affinity for μ-opioid receptors and its slow receptor dissociation, which results in sustained adverse reactions. Increases in PaCO2 lead to increased choroidal blood volume and aqueous humor production as well as decreased aqueous drainage, thereby resulting in increases in IOP. Likewise, hypoxemia can cause vasodilation of choroidal blood vessels, leading to increases in IOP. Sheep that received SRB premedication in the present study had a lower respiratory rate at baseline and after intubation than did sheep that were not premedicated. Also, the lowest respiratory rate observed at intubation was evident in sheep that received SRB premedication followed by diazepam and propofol for induction of anesthesia. This reduction in respiratory frequency may have resulted in hypoventilation, as reflected by the PETCO2 measured following intubation, which was greater in sheep premedicated with SRB and was the highest in the sheep receiving the propofol-diazepam combination. Likely, in sheep undergoing induction of anesthesia with propofol-diazepam, an elevation in PaCO2 resulted in a greater IOP during intubation in those premedicated with SRB, compared with findings in unpremedicated sheep.

The higher PETCO2 in sheep administered SRB in the present study contrasted with results of a previous study in sheep in which there were no changes in PaCO2 following IV administration of buprenorphine. However, the sheep in that study were not anesthetized. It is possible that induction of anesthesia may have augmented any respiratory depression caused by SRB in the present study. In pregnant sheep, PaCO2 is approximately 6 mm Hg greater than PETCO2. However, the PaCO2-PETCO2 gradient is not necessarily fixed and can change throughout the course of anesthesia. Therefore, measurement of PaCO2 through arterial blood gas analysis would have been ideal to assess the effect of ventilation on IOP in the experimental period.

Anesthetic agents have variable effects on pupillary diameter, which is known to influence IOP. In mammals, pupillary diameter is under adrenergic receptor control, where fluctuating sympathetic and parasympathetic tone alters pupil size. Direct adrenergic receptor stimulation causes excitatory input to dilator muscles with concurrent inhibitory effects on the sphincter muscles, resulting in mydriasis, whereas miosis is associated with increasing parasympathetic tone. Miosis widens the drainage apparatus, causing an increase in either iridocorneal or uveoscleral aqueous humor outflow and subsequently lowering IOP whereas mydriasis results in the opposite effect on IOP. Ketamine, a sympathetic stimulant, has been shown to increase pupillary diameter in dogs 5 minutes following administration, which may contribute to increases in IOP observed with this anesthetic induction agent. Propofol administration causes miosis in both dogs and sheep, although an association between IOP and pupillary diameter has yet to be determined in those species. In the present study, changes in pupillary diameter and globe position did not correlate with alterations in IOP and therefore any possible variations in pupil size caused by SRB, ketamine, or propofol likely did not influence IOP. To eliminate any possible IOP changes caused by variations in pupillary diameter and to ensure accurate applanation tonometry readings by measuring IOP on a centrally positioned globe, a neuromuscular blocking agent could have been administered during induction of anesthesia. However, inclusion of a neuromuscular blocking agent during induction of anesthesia in sheep is not routine and the study was designed to mimic typical clinical scenarios.

A limitation of the present study was the lack of direct arterial blood pressure monitoring. The study sheep were participating in another study that precluded the placement of an arterial catheter prior to induction of anesthesia. Although changes in arterial blood pressure may cause alterations in choroidal blood flow, the eyes are capable of autoregulating...
blood flow over a wide range of systemic pressures.\textsuperscript{6,7} Therefore, arterial blood pressures in a physiologic range have a minor role in IOP regulation. Several studies\textsuperscript{12,15,31} in other veterinary species in which linear regression modeling was used to compare changes in arterial blood pressure with changes in IOP found that variations in IOP occur independently of alterations in arterial blood pressure. Although these study findings suggest that changes in IOP cannot be attributed to changes in arterial blood pressure, the possibility that the variations in IOP observed in this study were due to alternations in arterial blood pressure rather than the effects of the drugs themselves cannot be excluded.

Another possible limitation of the study of this report was that the anesthetic induction agent doses were titrated to allow orotracheal intubation; therefore, a fixed dose of each anesthetic induction agent was not administered. Results of a study\textsuperscript{52} in children suggest that ketamine has a dose-dependent effect on IOP. Given the limited range of ketamine doses used in this study, any effect that the dose of ketamine may have had on IOP of sheep was likely minimal. Also, the experimental design was chosen to simulate typical clinical scenarios; thus, a fixed dose of ketamine and propofol was not administered.

In the present study, IV administration of diazepam and ketamine in sheep caused a clinically relevant decrease in IOP immediately following induction of anesthesia, and no changes in IOP were observed following induction of anesthesia with diazepam and propofol. Premedication with SRB resulted in significant increases in IOP at various time points in the period prior to and up to 5 minutes after induction of anesthesia, regardless of the anesthetic induction agent combination administered. For sheep with conditions in which moderate increases in IOP may be harmful, induction of anesthesia with diazepam and ketamine or propofol appears suitable; however, administration of SRB should be avoided and other analgesic techniques should be used. Further studies are needed to evaluate the use of diazepam with ketamine or propofol in sheep with ocular diseases.

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Footnotes
\textsuperscript{a} Tono-Pen XL.\textsuperscript{b} ZooPharm, Laramie, Wyo.\textsuperscript{c} Keised, Boehringer Ingelheim Vetmedica Inc, St Joseph, Mo.\textsuperscript{d} PropoFlo, Abbott Laboratories, North Chicago, Ill.\textsuperscript{e} Hospira Inc, Lake Forest, Ill.\textsuperscript{f} Surgivet Advisor Vital Signs Monitor V9204, Smiths Medical, Dublin, Ohio.\textsuperscript{g} Bausch & Lomb Inc, Tampa, Fla.\textsuperscript{h} MedCalc; version 15.2.1, MedCalc Software bvba, Ostend, Belgium.

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22. Hofmeister EH, Mosunic CB, Torres BT, et al. Effects of ketamine,