Effects of ketamine, diazepam, and their combination on intraocular pressures in clinically normal dogs

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Objective—To evaluate the effects of ketamine, diazepam, and the combination of ketamine and diazepam on intraocular pressures (IOPs) in clinically normal dogs in which premedication was not administered.

Animals—50 dogs.

Procedures—Dogs were randomly allocated to 1 of 5 groups. Dogs received ketamine alone (5 mg/kg [KET5] or 10 mg/kg [KET10], IV), ketamine (10 mg/kg) with diazepam (0.5 mg/kg, IV; KETVAL), diazepam alone (0.5 mg/kg, IV; VAL), or saline (0.9% NaCl) solution (0.1 mL/kg, IV; SAL). Intraocular pressures were measured immediately before and after injection and at 5, 10, 15, and 20 minutes after injection.

Results—IOP was increased over baseline values immediately after injection and at 5 and 10 minutes in the KET5 group and immediately after injection in the KETVAL group. Compared with the SAL group, the mean change in IOP was greater immediately after injection and at 5 and 10 minutes in the KET5 group. The mean IOP increased to 5.7, 3.2, 3.1, 0.8, and 0.8 mm Hg over mean baseline values in the KET5, KET10, KETVAL, SAL, and VAL groups, respectively. All dogs in the KET5 and most dogs in the KETVAL and KET10 groups had an overall increase in IOP over baseline values.

Conclusions and Clinical Relevance—Compared with baseline values and values obtained from dogs in the SAL group, ketamine administered at a dose of 5 mg/kg, IV, caused a significant and clinically important increase in IOP in dogs in which premedication was not administered. Ketamine should not be used in dogs with corneal trauma or glaucoma or in those undergoing intraocular surgery. (*Am J Vet Res* 2006;67:1136–1139)

Abbreviation

IOP Intraocular pressure

Intraocular pressure is maintained within a specific range by the CNS with a balance between aqueous humor production and outflow.[1,2] The IOP can be affected by 3 principal factors: external pressure, scleral rigidity, and intraocular changes.[2] Various medications, including anesthetic premedication, induction, and maintenance drugs, can alter IOP by increasing extraocular muscle tone or by changing the rate of aqueous production or outflow.[3]

Maintaining an IOP within or below reference range throughout sedation or general anesthesia is essential for certain ocular diseases. For example, corneal lesions that approach full thickness require delicate handling and control of IOP to avoid inadvertent perforation prior to and during surgery. Corneal perforations, particularly those that result in iris prolapse, have a notably worse prognosis for preservation of vision postoperatively.[4] In the authors' experience, elective surgeries such as cataract extraction are more easily performed if the IOP is within or below reference range. In patients with glaucoma, maintaining a low IOP is important. Results of 1 study[5] indicate that even minimal increases in IOP > 25 mm Hg significantly lower axoplasmic flow within the optic nerve.

The purpose of the study reported here was to evaluate the effects of ketamine, diazepam, and the combination of ketamine and diazepam on IOP in clinically normal dogs in which premedication was not administered.

Materials and Methods

Dogs—Random-source (obtained from municipal animal shelters) dogs anesthetized for a junior surgical exercises laboratory were used in the study. The protocol was approved by the University of Georgia Animal Care and Use Committee, and husbandry was provided according to established institutional guidelines. Age was not recorded because a definitive age could not be established for most dogs. Body condition score was assessed by use of a previously published system.[6] A complete ophthalmologic examination was performed by an experienced veterinarian (CBM or PAM) who was unaware of treatment group allocations. Dogs determined to be unhealthy on the basis of physical examination findings or that had abnormal PCV, total protein concentration, Schirmer's test, IOP, or ophthalmologic examination results were prospectively excluded from the study. Data were collected until 10 dogs for each group satisfied the criteria for inclusion in the study.

Dogs were randomly allocated to 1 of 5 treatment groups. Dogs received ketamine administered at a dose of 5 mg/kg (KET5 group) or 10 mg/kg (KET10 group), IV; ketamine

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administered at a dose of 10 mg/kg with diazepam administered at a dose of 0.5 mg/kg, IV (KETVAL group); diazepam administered at a dose of 0.5 mg/kg, IV (VAL group); and saline (0.9% NaCl) solution administered at a dose of 0.1 mL/kg, IV (SAL group). For the KETVAL group, ketamine and diazepam were mixed in the same syringe immediately prior to administration. All dogs were medicated between 5 PM and 7 PM, and the time of administration and any adverse reactions were recorded for each dog. Schirmer's tests were performed prior to administration of medication.

The applanation tonometer[a] was factory-calibrated prior to initiation of the study and was hand-calibrated each day prior to data collection. The IOP measurements were obtained immediately before and after administration of medications and at 5, 10, 15, and 20 minutes after administration of medications. Prior to each IOP measurement, 1 drop (approx 0.03 mL) of proparacaine HCl 0.5% was applied topically to the eye. All IOP measurements were performed with the dog standing, sitting, or in sternal recumbency with the head raised and care taken not to occlude the jugular veins or place pressure on the globe while retracting the eyelids.

Intraocular pressure was measured in both eyes of all dogs by a trained individual who was unaware of treatment group allocations. The applanation tonometer provides a value with an internally estimated error of 5%, 10%, or 20% for each reading obtained. Only IOP readings with a 5% error were recorded. Three readings were recorded for each eye at each measurement.

Dogs were classified as having an overall increase in IOP if a positive change in IOP from baseline was recorded for 3 or more measurements. Dogs were classified as having an overall decrease in IOP if a negative change in IOP from baseline was recorded for 3 or more measurements.

Statistical analysis—A prospective power estimate was performed to determine the sample size required to detect a change of 3 mm Hg with an α of 0.05 and $\beta < 0.2$. Results of the power study indicated that 9 dogs would be required in each group.

A 1-way ANOVA was performed to compare the IOP (6 replicate values, 3 from each eye, pooled) of each group at each measurement, the 3 IOP readings, the time of administration of medication, Schirmer's test results, weight, and body condition scores. An ANOVA with repeated measures was used to evaluate within-group changes in IOP with time. Post hoc analysis was performed by use of the Tukey multiple comparison test. To determine whether a change in the user's technique influenced IOP during the study, baseline IOP measurements from the first 25 dogs were compared with baseline IOP measurements from the last 25 dogs by use of a 2-tailed unpaired *t* test. A 2-tailed unpaired *t* test was used to compare the mean change in IOP from baseline, the first IOP reading with the mean of all 3 IOP readings, and IOPs in the right and left eye. The number of dogs that had an increase in IOP and the sex and breeds of dogs were compared by use of the χ^2 test. A value of $P < 0.05$ was considered significant.

Results

There were no significant differences among groups with regard to weight ($P = 0.52$), body condition scores ($P = 0.83$), time of administration of medication ($P = 0.43$), Schirmer's test results ($P = 0.14$), sex ($P = 0.22$), or breed ($P = 0.26$). The mean baseline IOP for all dogs was 16.5 mm Hg (95% confidence interval, 15.7 to 17.4 mm Hg) in the right eye and 15.8 mm Hg (95% confidence interval, 15.0 to 16.7 mm Hg) in the left eye. There was no significant difference between eyes; therefore, data from both eyes were pooled (treated as replicates) for subsequent analysis. There was no significant difference between the first reading and the mean of the 3 readings (right eye, $P = 0.61$; left eye, $P = 0.26$) or among the 3 readings obtained for each eye (right eye, $P = 0.70$; left eye, $P = 0.14$). The range for the first reading was consistently broader than the range for the mean of the 3 readings.

Dogs in the KET5 group had significantly ($P < 0.05$) higher IOP values immediately after injection and at 5 and 10 minutes, compared with baseline (**Table 1**; **Figure 1**). Dogs in the KET5 group had significantly ($P < 0.05$) higher IOP values at 5 minutes than dogs in the SAL or VAL groups. Dogs in the KETVAL group had significantly ($P < 0.05$) higher IOP values immediately after injection, compared with baseline. Dogs in the KET5 group had a significantly ($P < 0.05$) greater increase in IOP than dogs in the SAL or VAL groups immediately after injection and at 5 and 10 minutes (**Table 2**). Dogs in the KET5 group had a significantly ($P < 0.05$) greater increase in IOP than dogs in any other group at 5 minutes. One hundred percent, 70%, 70%, 40%, and 60% of dogs had an overall increase in IOP in the KET5, KET10, KETVAL, SAL, and VAL groups, respectively. There was no significant difference in the number of dogs that had an increase or decrease in IOP from baseline among groups. There was no significant ($P = 0.11$) difference in baseline IOP among the first 25 dogs and the last 25 dogs.

Table 1—Mean ± SD IOP (mm Hg) measured in dogs (n = 10/group) immediately before (0; baseline) and immediately after and at 5, 10, 15, and 20 minutes after administration of ketamine at a dose of 5 mg/kg (KET5) or 10 mg/kg (KET10), IV; ketamine at a dose of 10 mg/kg combined with diazepam at a dose of 0.5 mg/kg, IV (KETVAL); diazepam at a dose of 0.5 mg/kg, IV (VAL); or saline (0.9% NaCl) solution at a dose of 0.1 mL/kg, IV (SAL).

	Group				
Time	**KET5**	**KET10**	**KETVAL**	**VAL**	**SAL**
0	14.9 ± 2.5	17.7 ± 3.9	17.0 ± 2.6	15.6 ± 2.0	15.7 ± 2.8
After	20.0 ± 4.2†‡	20.8 ± 5.4	20.1 ± 4.4†	16.4 ± 3.5	16.5 ± 3.1
5	20.6 ± 3.8*†‡	19.4 ± 4.7	18.8 ± 3.3	15.2 ± 2.7	15.1 ± 3.0
10	19.4 ± 4.3†	19.1 ± 3.0	17.9 ± 2.5	15.8 ± 2.2	15.9 ± 3.3
15	17.5 ± 3.6	18.9 ± 3.4	18.0 ± 2.3	16.3 ± 3.9	15.9 ± 3.4
20	16.6 ± 4.0	18.8 ± 2.5	19.2 ± 2.7	15.9 ± 2.9	15.6 ± 3.3

*Within a measurement time, significantly ($P < 0.05$) different from mean values for SAL and VAL groups. †Within a group, significantly ($P < 0.05$) different from baseline value. ‡Within a group, significantly ($P < 0.05$) different from the mean value measured at 15 and 20 minutes.

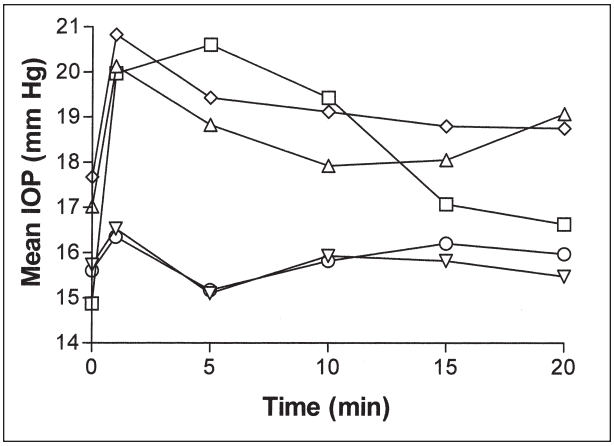

Figure 1—Mean IOP (mm Hg) measured in dogs (n = 10/group) immediately before (0; baseline) and immediately after and at 5, 10, 15, and 20 minutes after administration of ketamine at a dose of 5 mg/kg (squares) or 10 mg/kg (diamonds), IV; ketamine at a dose of 10 mg/kg combined with diazepam at a dose of 0.5 mg/kg, IV (triangles); diazepam at a dose of 0.5 mg/kg, IV (circles); or saline (0.9% NaCl) solution at a dose of 0.1 mL/kg, IV (inverted triangles).

Table 2—Mean change in IOP (mm Hg) measured in dogs immediately after and at 5, 10, 15, and 20 minutes after administration of ketamine alone, ketamine combined with diazepam, diazepam alone, or saline solution, compared with baseline value.

	Group				
Time	KET5	KET10	KETVAL	SAL	VAL
After	5.1*	3.2	3.1	0.8	0.8
5	5.7†	1.8	1.8	–0.6	–0.4
10	4.6*	1.5	0.9	0.2	0.2
15	2.2	1.1	1.0	0.1	0.6
20	1.8	1.1	2.1	–0.3	0.4

†Within a measurement time, significantly ($P < 0.05$) different from all other groups.
See Table 1 for remainder of key.

Discussion

Results of the study reported here indicated that administration of a low dose of ketamine alone and administration of diazepam at a dose of 0.5 mg/kg combined with ketamine at a dose of 10 mg/kg increased IOP in clinically normal dogs in which premedication was not administered. Dogs receiving ketamine alone at a dose of 10 mg/kg had a nonsignificant increase in IOP, compared with saline solution (control) or baseline values. The baseline IOP (mean ± SD, 16.2 ± 2.8 mm Hg) was within the reported reference range.[7]

Ketamine is cited as causing an increase in IOP in animals.[8] In rabbits[9] and cats[10] in which premedication was not administered, ketamine causes a small but significant increase in IOP. Following premedication with xylazine (0.5 or 1.1 mg/kg, IV), ketamine (1.0 or 2.2 mg/kg, IV) reportedly does not cause a change in IOP in ponies and horses, respectively.[11,12]

Two studies have investigated the effects of ketamine on IOP in dogs. In dogs premedicated with acepromazine (0.5 mg/kg, IV) or xylazine (1 mg/kg, IV), ketamine administered at a dose of 10 mg/kg, IV, caused no change or a nonsignificant increase, respectively, in IOP.[13] In dogs premedicated with acepromazine (0.1 mg/kg, IM) and meperidine (2 mg/kg, IM) or butorphanol (0.4 mg/kg, IM) and induced with midazolam (0.5 mg/kg, IV) and ketamine (3 mg/kg, IV), there was a mild, nonsignificant increase in IOP 10 minutes after induction.[14]

Benzodiazepines maintain or decrease IOP in humans and dogs and may serve to blunt the increase in IOP induced by ketamine.[15,16] Furthermore, premedication with diazepam blunts the increase in intracranial pressure induced by ketamine.[8,17] However, results of our study indicated that administration of diazepam concurrently with ketamine did not prevent the increase in IOP caused by ketamine. It is possible that premedication with diazepam may have blunted the increase in IOP caused by ketamine. However, in our study, we administered ketamine and diazepam together because this is how the authors administer these drugs for induction of anesthesia in clinical practice.

It is common practice to obtain 3 readings when performing IOP measurements. It has been postulated that repeat readings result in increased aqueous outflow, decreasing IOP.[18] This effect was not observed in our study. There was no significant difference between the first IOP reading obtained and the mean of 3 readings or among the 3 readings. However, the range of IOP for the mean of the readings was less than the range for the first reading obtained. This suggests that obtaining the mean of 3 readings provides a less variable IOP measurement than obtaining only 1 reading.

It is difficult to explain why dogs in the KET5 group had a change in mean IOP, whereas dogs in the KET10 group had no change and dogs in the KETVAL group had only a transient change. It is possible that the higher dose of ketamine (10 mg/kg, IV) used in the KET10 and KETVAL groups induced greater sedation, compared with the low dose of ketamine (5 mg/kg, IV) used in the KET5 group. With greater sedation, extraocular muscle tone may have been less, thus causing a less marked increase in IOP.

In the study reported here, IOPs were compared with baseline and negative control (SAL group) values. The negative control group was included to allow for the effect of time as a variable on IOP measurements. Measurements obtained 5 minutes after administration of medications in only the KET5 group were significantly different from measurements obtained in the SAL group. This result was consistent with findings indicating that measurements obtained from dogs in the KET5 group changed most dramatically from baseline. It is possible that there were no significant differences between other data points and data obtained from the SAL group because of the vagaries of the statistical analysis and the wide SDs encountered, relative to our pilot research.

On the basis of a retrospective analysis of our data, for an α of 0.05 and a β of < 0.2, there was insufficient power to detect a small treatment effect (approx 3 mm Hg); however, there was sufficient power to detect a moderate treatment effect (approx 5 mm Hg). This indicates that there may have been no significant difference found among the groups when there may, in fact, be a small (20% treatment effect) difference.

In the study reported here, dogs were followed for 20 minutes after drug administration. This duration

was chosen on the basis of the clinical observation that dogs begin to recover from the effects of ketamine within 20 minutes. After the last measurement time, almost all dogs were able to stand without assistance. The mean IOP for each group was not significantly different from baseline by 15 minutes, confirming that changes in IOP induced by ketamine alone and ketamine combined with diazepam paralleled the clinical duration of the drugs.

Changes in IOP can be expected with fluctuations in jugular venous pressure, arterial blood pressure, posture, and arterial carbon dioxide concentration. These parameters were not measured in our study because the study was designed to simulate a clinical setting and evaluate the overall effect of the drug protocol on IOP measurements. Changes in posture were minimized by performing all measurements with dogs in sternal recumbency, sitting, or standing, with care taken not to apply pressure on the jugular veins. Effects of ketamine alone and ketamine combined with diazepam on jugular venous pressure, arterial blood pressure, ocular position, and arterial carbon dioxide concentration and the contribution of these variables to changes in IOP were beyond the scope of our study.

In the study reported here, ketamine administered at a dose of 5 mg/kg, IV, caused a clinically important and significant increase in IOP in clinically normal dogs that did not receive premedication. Diazepam alone caused no change in IOP. Ketamine should not be used as an anesthetic agent in dogs with corneal trauma or glaucoma or in those dogs undergoing intraocular surgical procedures.

a. Tonopen XL, Medtronic Solan Inc, Jacksonville, Fla.

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