Effects of diurnal variation and anesthetic agents on intraocular pressure in Syrian hamsters (Mesocricetus auratus)

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OBJECTIVE
To determine effects of diurnal variation and anesthetic agents on intraocular pressure (IOP) in Syrian hamsters (Mesocricetus auratus).

ANIMALS
90 healthy adult Syrian hamsters (45 males and 45 females).

PROCEDURES
IOP was measured with a rebound tonometer. In phase 1, IOP was measured in all hamsters 3 times during a 24-hour period (7 am, 3 pm, and 11 pm). In phase 2, hamsters were assigned to 5 groups (18 animals [9 males and 9 females] /group). Each group received an anesthetic agent or combination of anesthetic agents (ketamine hydrochloride, xylazine hydrochloride, diazepam, ketamine-diazepam [KD], or ketamine-xylazine [KX] groups) administered via the IP route. The IOP was measured before (time 0 [baseline]) and 10, 30, 60, 90, 120, and 150 minutes after administration of drugs.

RESULTS
Mean ± SD IOP values were 2.58 ± 0.87 mm Hg, 4.46 ± 1.58 mm Hg, and 5.96 ± 1.23 mm Hg at 7 am, 3 pm, and 11 pm, respectively. Mean baseline IOP was 6.25 ± 0.28 mm Hg, 6.12 ± 0.23 mm Hg, 5.75 ± 0.64 mm Hg, 5.12 ± 1.40 mm Hg, and 4.50 ± 1.30 mm Hg for the ketamine, xylazine, diazepam, KD, and KX groups, respectively. A significant decrease in IOP, compared with baseline IOP, was detected in only the KX group at 30, 60, and 90 minutes after drug administration.

CONCLUSIONS AND CLINICAL RELEVANCE
Maximum IOP in Syrian hamsters was detected at night. The ketamine-xylazine anesthetic combination significantly decreased IOP in Syrian hamsters. (Am J Vet Res 2017;78:85–89)

The order Rodentia is the largest order of mammals. It contains 2,020 living species placed in 28 families, which is approximately half of all mammalian species. Despite the large number of rodent species, few are owned as pets. Rodents commonly kept as pets are rats, mice, hamsters, gerbils, guinea pigs, and chinchillas.

Hamsters are one of the most popular pet species among rodents. Approximately 1.1 million hamsters are maintained as pets in approximately 0.87 million homes in the United States.

Ophthalmic examination is a necessary part of a complete routine health assessment for all domestic animals. Systemic diseases can be associated with ocular lesions in all animal species. Recognition of these ocular signs is useful in the diagnosis and treatment of systemic diseases. The assessment of IOP is a crucial component of a complete ophthalmic examination because assessment of IOP can contribute to the diagnosis of severe ocular diseases (eg, glaucoma or uveitis). Assessment of IOP could help clinicians to more accurately diagnose ocular and systemic diseases and to more effectively make treatment decisions.

The IOP can be affected by the tone of extraocular muscles, closure of the eyelids, retraction of the retractor bulbi muscle, external pressure, intraocular changes, drugs, curvature and thickness of the cornea, corneal and scleral rigidity, time of day, head and body position, and tear film viscosity. It is known that IOP is not constant and varies considerably throughout the day. However, the physiologic role of and mechanisms for daily variation are poorly understood.

The use of certain drugs, such as anesthetics, may cause alterations in IOP. Ketamine is a dissociative drug that can be used as a sole agent for inducing anesthesia or in combination with other agents for inducing and maintaining anesthesia. In clinical practice, ketamine-diazepam and ketamine-xylazine combinations have been used for the induction of anesthesia in hamsters.

In a previous study conducted by our research group, reference values for ophthalmic diagnostic

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tests (including IOP) in clinically normal Syrian hamsters (*Mesocricetus auratus*) were reported. The purpose of the study reported here was to assess circadian variation in IOP throughout the day in Syrian hamsters, a nocturnal species. We also assessed effects of anesthetic agents on IOP in clinically normal Syrian hamsters.

**Materials and Methods**

**Animals**

Ninety healthy adult (1-year-old) Syrian hamsters (45 males and 45 females) were included in the study. All hamsters were examined prior to entrance into the study. Two hamsters had conjunctivitis and were replaced. Hamsters weighed between 50.2 and 120 g (mean ± SD, 85.5 ± 22.8 g).

Hamsters were judged to be free of disease on the basis of results for physical and ocular examinations, including slit-lamp biomicroscopy, indirect ophthalmoscopy, fluorescein staining, and a phenol red thread test. Animals were housed individually in labeled cages in an air-conditioned room with constant temperature (20° to 22°C) and relative humidity (50% to 55%) for a period of 7 days before onset of the study. They were exposed to a constant 24-hour lighting cycle (12 hours of light and 12 hours of darkness) and fed a commercial diet formulated for hamsters; water was available ad libitum. Experiments were conducted under the supervision of the Iran Society for the Prevention of Cruelty to Animals in accordance with the Iranian ethics for studies on laboratory animals.

**Experimental procedures**

The study was conducted in 2 phases. In both phases, IOP was measured with a rebound tonometer. Calibration of the device was achieved with the setting p.

In phase 1, IOP was measured in all hamsters 3 times during a 24-hour period (7 am, 3 pm, and 11 pm). The tonometer made 6 consecutive measurements and displayed the mean IOP for those 6 measurements. The series of measurements was repeated until the tonometer indicated that an acceptable SD was obtained for the 6 measurements. The procedure was repeated for each eye.

Phase 2 was conducted 2 days after phase 1. The hamsters were randomly assigned (simple random sampling) to 5 groups (18 males and 9 females/group). Each group received an anesthetic agent or anesthetic combination. Ketamine hydrochloride (100 mg/kg), xylazine hydrochloride (5 mg/kg), diazepam (10 mg/kg), ketamine-diazepam (KD group; 40 mg/kg and 2 mg/kg for ketamine and diazepam, respectively), and ketamine-xylazine (KX group; 50 mg/kg and 5 mg/kg for ketamine and xylazine, respectively) were administered via the IP route (ketamine, xylazine, diazepam, KD, and KX groups, respectively). After anesthetic agents were injected, oxygen was administered via a face mask (flow rate, 0.5 L/min) to each hamster. The IOP was measured before (time 0 [baseline]) and 10, 30, 60, 90, 120, and 150 minutes after drug administration. All measurements were obtained between 3 pm and 7 pm by 1 investigator (SMR). Hamsters were placed in sternal recumbency with their head horizontal to the ground, and the eyelids were not manipulated during IOP measurements.

**Statistical analysis**

Data were analyzed by use of a statistical software program. Normality was tested by use of a 1-sample Kolmogorov-Smirnov test; all continuous data obtained for the study population were normally distributed (P > 0.3). A paired-sample t test was used to compare the IOP between the right and left eyes. Mean and SD were calculated for the right and left eyes separately and for both eyes combined. Mean IOP values were not compared among groups. A repeated-measures ANOVA was used to analyze the data within each group. An independent-samples t test was used to compare mean IOP for sex and body weight within each group. Values of P < 0.05 were considered significant.

**Results**

**Phase 1**

Mean ± SD IOPs were 2.58 ± 0.87 mm Hg, 4.46 ± 1.58 mm Hg, and 5.96 ± 1.23 mm Hg at 7 am, 3 pm, and 11 pm, respectively (Table 1). The IOP differed significantly (P < 0.001) between 7 am and 3 pm and between 7 am and 11 pm. There was no significant (P = 0.063) difference in IOP between 3 pm and 11 pm.

**Phase 2**

Mean ± SD baseline IOP values were 6.25 ± 0.28 mm Hg, 6.12 ± 0.23 mm Hg, 5.75 ± 0.64 mm Hg, 5.12 ± 1.40 mm Hg, and 4.50 ± 1.30 mm Hg for the ketamine, xylazine, diazepam, KD, and KX groups, respectively. For the ketamine, diazepam, xylazine, and KD groups, there were no significant changes in IOP after drug administration, compared with the baseline value. For the KX group, there was a significant decrease in IOP at 30 (P = 0.001), 60 (P = 0.007), and 90 (P = 0.001) minutes after drug administration, compared with the baseline value (Figure 1).

No significant difference was found between the right and left eyes or between males and females for all groups. There was no association between the measured IOP and body weight of the hamsters.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 am</td>
<td>2.58 ± 0.87</td>
<td>1–4</td>
<td>2.03–3.14</td>
</tr>
<tr>
<td>3 pm</td>
<td>4.46 ± 1.58</td>
<td>2–7</td>
<td>3.45–5.47</td>
</tr>
<tr>
<td>11 pm</td>
<td>5.96 ± 1.23</td>
<td>3–10</td>
<td>5.18–6.47</td>
</tr>
</tbody>
</table>

*Value differs significantly (P < 0.001) from the values at 3 pm and 11 pm.*
Discussion

Intraocular pressure is dynamic and fluctuates from minute to minute as the physiologic state changes. Fluctuations in IOP associated with the time of day could affect diagnostic interpretations and therapeutic decisions. Measurements of IOP at various times of day have been obtained for rats, rabbits, llamas, cats, rhesus monkeys (Macaca mulatta), and dogs. For the hamsters of the study reported here, maximum IOP was detected at night and minimum IOP was detected in the morning of the study. In rabbits and rats, measurements have consistently revealed that IOP increases during the night. In rhesus monkeys, an increase in IOP was detected early in the morning. In dogs, maximum IOP was detected in the morning and minimum IOP was detected early in the evening. In nocturnal species such as rats and rabbits, IOP is higher at night. Results for the present study were consistent with the fact that hamsters are nocturnal animals.

Eyes of all rodents have similar anatomic and developmental characteristics. Despite this fact, the IOP of Syrian hamsters was slightly lower than the IOP of mice and other small rodents. Handling and restraint, type of tonometer, housing environment, and anatomic differences can influence IOP; however, the exact cause of the low IOP in hamsters of the present study is unknown. Further studies should be conducted to evaluate anatomic features and outflow facility of hamster eyes to determine the cause of the difference in IOP between hamsters and other small rodents.

Ketamine hydrochloride is used in combination with other anesthetic drugs and is a strong dissociative analgesic agent. Ketamine induces signifi-
cant increases in cerebral blood flow, intracranial fluid pressure, and CSF pressure as a result of cerebral vasodilatation, and it may cause an increase in systemic blood pressure with increased IOP as a possible adverse effect. Ketamine reportedly increases IOP through constriction of extraocular muscles in several species.29

Diazepam is often used as a general anesthetic owing to its sedative, tranquilizing, muscle relaxant, and anticonvulsant effects. Diazepam decreases systemic blood pressure, cerebral blood pressure, and cerebral pressure and also concurrently decreases IOP.24

In the present study, injection of the anesthetic agents alone (ketamine, diazepam, or xylazine) did not cause significant changes in IOP. Administration of xylazine resulted in a decrease in IOP, compared with baseline IOP, at 10 and 30 minutes after injection; however, these changes were not significantly different or clinically relevant.

The ketamine-diazepam combination decreased IOP 10 minutes after drug administration, but not significantly so. The IOP then increased gradually. At 150 minutes, IOP was higher than the baseline value, but not significantly so. It appeared that the effect of ketamine on IOP was dominant during anesthesia 30 minutes after the drug was administered to Syrian hamsters.

For the ketamine-xylazine combination, IOP was decreased, compared with the baseline value, at all times after administration. The IOP was 0 mm Hg in a small number of hamsters, especially at 30 minutes. It appeared that the effect of xylazine was predominant at 120 minutes after administration to the hamsters. However, all the hamsters were able to walk and had no abnormalities in righting and pinch reflexes by 150 minutes.

Intramuscular administration of a ketamine-xylazine combination to New Zealand White rabbits significantly decreased IOP by 10 minutes after administration, and this effect was maintained for at least 45 minutes after administration.23 In the hamsters of the present study, a decrease in IOP was detected at 30 minutes and was maintained until at least 90 minutes after injection of the ketamine-xylazine combination.

An effect of a ketamine-diazepam combination was detected in New Zealand White rabbits of another study,26 whereby IM administration of a ketamine-diazepam combination moderately increased IOP at 5 minutes after administration, and this increase was maintained for at least 25 minutes. In dogs, IV administration of a xylazine-ketamine combination significantly reduced IOP.27 However, in another study,28 administration of a low dose of ketamine (10 mg/kg) and a combination of diazepam (0.5 mg/kg) and ketamine (10 mg/kg) increased IOP in clinically normal dogs. Xylazine is a potent α2-adrenergic receptor agonist and has been found to decrease IOP in several species, including dogs,27,28 horses,29,30 monkeys,31 and cats.32 In the study reported here, IOP was not increased after administration of ketamine (100 mg/kg) to clinically normal hamsters. The anatomic difference between the eyes of hamsters and dogs could be responsible for this difference. The eyes of hamsters are somewhat proptotic, even in clinically normal animals, and we suggest that this reduces the compressive effects of extraocular muscle spasm, which is the reason for increased IOP in human patients.32

For the KX group, the dose of ketamine was 50 mg/kg, whereas for the KD group, it was 40 mg/kg. Effects of ketamine on IOP are inconsistent. Some studies have indicated that ketamine decreases IOP in humans33 and mice,34 whereas others have indicated that ketamine increases IOP in humans35 and rabbits.26 In dogs, an increase in the ketamine dose caused deeper sedation; therefore, an IOP increase was not detected at a higher ketamine dose.28 In contrast to results for dogs, IM injection of ketamine to anesthetized children caused a dose-dependent effect on IOP, with 6 mg/kg causing a small increase in IOP (1 to 2 mm Hg at 5 to 10 minutes after injection) and 3 mg/kg not inducing changes in IOP.35

In the present study, there were differences in IOP measured in Syrian hamsters at 3 times within a 24-hour period. In addition, administration of a ketamine-xylazine combination to Syrian hamsters caused a significant decrease in IOP. Results of this study indicated that none of the anesthetic drugs administered alone (ketamine, xylazine, and diazepam) had detrimental effects on IOP in Syrian hamsters.

Footnotes

References