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Effect of Sedation with Xylazine and Ketamine on Intraocular Pressure in New Zealand White Rabbits

Dana L Holve,[1,*] Glenwood G Gum,[2] and Stacy L Pritt[2]

To determine the effects of intravenous and intramuscular xylazine–ketamine on intraocular pressure (IOP) in laboratory rabbits, 10 New Zealand white rabbits received xylazine (0.46 mg/kg) and ketamine (1.5 mg/kg) intravenously whereas another 10 rabbits received intramuscular xylazine (10 mg/kg) and ketamine (50 mg/kg). IOP was measured at baseline and 5, 10, 20, and 25 min after administration in rabbits that were injected intravenously and at baseline and 10, 20, 30, and 45 min in rabbits injected intramuscularly. Baseline IOP (mean ± 1 SD; intravenous group, 20.15 ± 2.24 mm Hg; intramuscular group, 19.03 ± 1.77 mm Hg) did not differ between groups. Compared with baseline values, IOP decreased significantly after intravenous administration at 10, 20, and 25 min (decreases of 2.73, 4.10, and 4.55 mm Hg, respectively) but not at 5 min (decrease of 1.40 mm Hg). IOP in intramuscularly dosed rabbits showed significant differences from baseline at 10, 20, 30, and 45 min (decreases of 2.88, 3.30, 3.95, and 4.60 mm Hg, respectively). In the intravenous group, IOP differed at 10 min compared with 25 min (1.83 mm Hg, $P = 0.0143$) but not at 20 min compared with 25 min (0.450 mm Hg). In the intramuscular group, differences in IOP at 10 min compared with 20 min, 20 min compared with 30 min, and 30 min compared with 45 min were nonsignificant. Intravenous and intramuscular xylazine–ketamine decreased IOP in laboratory rabbits and may be used safely during ocular procedures for which increased IOP is a concern.

Abbreviation: IOP, intraocular pressure.

Xylazine hydrochloride, an α2 adrenergic agonist, and ketamine hydrochloride, an N-methyl D-aspartate receptor antagonist, are often used in combination for sedation in rabbits.[6] Studies have shown that xylazine causes a decrease in intraocular pressure (IOP) in rabbits after topical and intraarterial administration,[3] whereas ketamine results in increased IOP when administered intramuscularly.[1,2,11] IOP showed no significant change in rabbits when intramuscular xylazine–ketamine was used in combination with a retrobulbar nerve block.[5] IOP is commonly used as a biomarker for efficacy or adverse effect of an investigational drug or device. When IOP is assessed in a sedated animal, it is important to be aware how the combination of sedation might affect the animal's baseline IOP. In addition, increases in intraocular pressure could result in negative consequences, such as retinal detachment or vitreal hemorrhage. Therefore, it is important to choose sedation that minimizes increases in IOP when performing procedures on patients for which increased IOP is a concern. The purpose of the current study was to evaluate the effects of intravenous and intramuscular xylazine–ketamine on IOP in clinically normal laboratory New Zealand white rabbits. A specific dose was chosen for each route.

Materials and Methods

Study design. Female SPF New Zealand White rabbits (*Oryctolagus cuniculi*; $n = 20$; age, 15 wk) were obtained from a commercial vendor (Western Oregon Rabbitry, Philomath, OR). Rabbits were separated into 2 groups of 10 each (weight, 2.42 to 2.89 kg). Rabbits were housed individually in stainless steel cages with no bedding material. Rabbits received a certified pelleted diet and water ad libitum. A temperature of 19 ± 3 °C, 12:12-h light:dark cycle, and at least 10 air changes hourly were maintained. Environmental enrichment devices (plastic dumbbells and balls) were provided on a rotational basis for nonnutritive environmental enrichment. Rabbits were housed in an AAALAC-accredited facility in compliance with the *Guide for the Care and Use of Laboratory Animals*.[8]

All rabbits underwent a complete ophthalmic examination, including slit lamp biomicroscopy (model SL15, Kowa, Tokyo, Japan) and indirect ophthalmoscopy (Vantage Plus Wireless Binocular Indirect, Keeler, Windsor, UK; model 20D, Volk Optical, Mentor, OH) prior to enrollment in the study. All rabbits had clinically normal eyes. Animals were acclimated prior to start of the study for 2 wk to their environment and were handled as they would be during IOP measurements. Animals were conditioned, without the use of sedation, to having their IOP measured by using the applanation tonometer (Model 30 Classic Pneumatonometer with Tonography, Reichert Technology, Depew, NY) on 3 occasions before the start of the study. Prior to IOP measurement, 1 drop of proparacaine hydrochloride ophthalmic solution (0.5%; Falcon Pharmaceuticals, Fort Worth, TX) was delivered to each eye.[9] All experimental and animal care procedures were performed in compliance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research and approved by the IACUC of Absorption Systems (San Diego, CA).

Rabbits were assigned to 2 groups ($n = 10$ each) based on the route administered one injection of combined xylazine hydrochloride (Akorn, Decatur, IL) and ketamine hydrochloride

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[1]Eye Care for Animals, Tustin, California and [2]Absorptions Systems, San Diego, California.
[*]Corresponding author. Email: danaholve@yahoo.com

(Bioniche Teoranta, Galway, Ireland). Rabbits injected intravenously received 0.46 mg/kg xylazine and 1.5 mg/kg ketamine in the marginal ear vein; IOP measurements were obtained at baseline (prior to sedation) and at 5, 10, 20, and 25 min after administration. Rabbits injected intramuscularly received 10 mg/kg xylazine and 50 mg/kg ketamine in the quadriceps muscle; IOP measurements were obtained at baseline (prior to sedation) and at 10, 20, 30, and 45 min after administration. Different time points were chosen in light of time to effect and duration of the sedation regimen administered by different routes.

IOP measurements. Pressure readings were measured bilaterally by using an applanation tonometer on the central cornea. At each time point, 1 drop of proparacaine hydrochloride 0.5% ophthalmic solution (Falcon Pharmaceuticals) was delivered to each eye prior to IOP measurement. All measurements were obtained by the same examiner and performed within a 4-h time period. The left eye was measured first, followed by the right eye, for each rabbit at each time point.

Data analysis. Statistical analysis was performed by using Prism (version 4, Graphpad Software, San Diego, CA).The Student *t* test was used to compare differences in IOP within groups between time points and between groups at baseline, 10 min, and 20 min. Values were considered to be significantly different when the *P* value was less than 0.05.

Results

Regardless of whether rabbits were sedated intravenously or intramuscularly, no adverse reactions were noted at any site of injection.

Applanation tonometry values for intravenously sedated rabbits. Among rabbits injected intravenously with xylazine and ketamine, IOP (mean ± 1 SD) was 20.15 ± 2.24 mm Hg at baseline and 18.75 ± 2.51 mm Hg at 5 min, 17.43 ± 2.45 mm Hg at 10 min, 16.05 ± 2.70 mm Hg at 20 min, and 15.60 ± 2.04 mm Hg at 25 min after injection, with mean decreases from baseline of 1.40, 2.73, 4.10, and 4.55 mm Hg, respectively. According to the Student *t* test, IOP measurements were decreased significantly at 10, 20, and 25 min ($P = 0.0008$, 0.0001, 0.0001, respectively) but not at 5 min ($P = 0.0705$) after injection compared with baseline values. The difference between IOP at 5 min and 20 min (2.70 mm Hg), 5 min and 25 min (3.15 mm Hg), and 10 min and 25 min (1.83 mm Hg) was significant ($P = 0.0023$, 0.0001, and 0.0143, respectively), but the differences between IOP at 5 min and 10 min, 10 min and 20 min, and 20 min and 25 min (1.32, 1.38, and 0.450 mm Hg; $P = 0.1006$, 0.0987, and 0.5556, respectively) were not.

Applanation tonometry values for intramuscularly sedated rabbits. Among rabbits injected intramuscularly with xylazine and ketamine, IOP (mean ± 1 SD) was 19.03 ± 1.77 mm Hg at baseline and 16.15 ± 2.19 mm Hg at 10 min, 15.73 ± 1.65 mm Hg at 20 min, 15.08 ± 2.09 mm Hg at 30 min, and 14.43 ± 1.76 mm Hg at 45 min after injection, with mean decreases from baseline of 2.88, 3.30, 3.95, and 4.60 mm Hg, respectively. IOP measurements at all 4 time points were decreased significantly ($P = 0.0001$) compared with baseline values. In addition, only the differences in IOP between 10 min and 30 min (1.07 mm Hg) and 10 min and 45 min (1.72 mm Hg) were significant ($P = 0.1222$ and 0.0094, respectively).

Comparison of IOP measurements between treatment groups. Baseline IOP measurements did not differ between groups ($P = 0.0860$) nor did differences in IOP between baseline and 10 min or baseline and 20 min after injection ($P = 0.094$ and 0.648, respectively).

Discussion

Xylazine has been demonstrated to decrease IOP in several species, including monkeys, cats and horses,[3,12,13] and ketamine has been shown to increase IOP in dogs, cats, and horses.[4,7,10,12] In rabbits, the effect of xylazine alone on IOP has only been evaluated topically and intraarterially,[3] whereas ketamine alone has only been evaluated after intramuscular administration.[1,2,11] In one study, intramuscular xylazine–ketamine used with a retrobulbar block was assessed.[5] The current study is the first in rabbits to evaluate IOP during combination sedation with xylazine and ketamine without the addition of a retrobulbar nerve block. It is important to evaluate the combined effect of xylazine–ketamine, because these 2 drugs often are used together in rabbits on ocular and nonocular studies and, as sole agents, have opposing effects on IOP.

Intravenous xylazine combined with ketamine significantly reduced IOP from baseline at 10, 20, and 25 min after administration but not at the initial 5 min measurement. Given that ketamine has been shown to cause a peak increase in IOP at 3 to 5 min after intramuscular administration,[11] it may have blunted the IOP-lowering effect of xylazine at the initial 5-min measurement; direct comparison was not possible due to the different routes of administration. In addition, stress is known to elevate IOP. Although we minimized potential stressors as much as possible, the process of administering the drug intravenously might have affected this initial time point. In our experience, intramuscular administration is less stressful to rabbits than is intravenous dosing, therefore minimizing any stress-associated increase in IOP. Intramuscular administration led to significant decreases in IOP from baseline at all time points; however, the first measurement of IOP did not occur until 10 min after administration. By this time (and later), the ketamine-associated effect likely had dissipated and therefore did not counteract the IOP-lowering effect of xylazine at any experimental time point; however, this assumption warrants additional studies. Because intravenous or intramuscular administration of xylazine alone has not been evaluated thoroughly in rabbits, we cannot say what effect this dosage would have at the 5-min time point. Additional evaluation is needed to determine the magnitude of the change in IOP, time to peak effect of xylazine alone compared with ketamine and the xylazine–ketamine combination, and the relationship between pharmacodynamics and pharmacokinetics.

Independent administration of xylazine (topical and intraarterial) has been demonstrated to decrease IOP,[3] whereas ketamine has been shown to increase IOP.[1,2,11] The doses and routes of xylazine and ketamine that we used in the current study are those used in standard sedation protocols at our facility. This difference in doses between groups is one limitation to our study and made direct comparison difficult. However, comparing the 2 groups at common time points revealed no significant difference in the magnitude of the decrease in IOP from baseline at 10 or 20 min ($P = 0.094$ and 0.648, respectively). This finding is important, because our results show that IOP never decreased to a point of causing any clinical significance for a healthy eye, such as globe deflation, corneal decompensation, or accelerated cataract formation. In addition, xylazine–ketamine sedation likely can be used safely when an elevation in IOP is a concern. Although we did not observe a statistically significant decrease in IOP in our rabbits, the effects of xylazine and ketamine on IOP is likely dose-dependent, a variable not addressed in the current study. In addition, changing the ratio of xylazine to ketamine may further affect the IOP and is a worthy topic for future study.

The time points chosen for each group were based on the time to effect and duration of sedation associated with the different administration routes. At the given concentrations, intravenous administration had a much faster onset of action and a much shorter duration than did intramuscular administration. The approximate maximal duration of effect for the xylazine–ketamine dosage we used was 25 min for intravenous administration and 45 min for intramuscular administration; therefore IOP was not measured beyond these time points. In addition, IOP was not measured at the 5-min time point after intramuscular administration of xylazine–ketamine, because the rabbits animals often were not yet sedated deeply enough for this procedure. As described earlier, a limitation to the current study is having only the 2 common time points to compare.

Intravenous and intramuscular xylazine–ketamine significantly decreased IOP in laboratory New Zealand White rabbits with clinically normal eyes by 10 min after administration. This effect was maintained for at least 25 min after intravenous administration and for at least 45 min after intramuscular administration. At time points shared between the 2 groups (that is, 10 and 20 min), decreases in IOP from baseline did not differ between the groups, even though the doses and route of administration of xylazine–ketamine differed. When IOP is a biomarker of efficacy or adverse effect of an investigative drug or device, it is important to be aware that the combination of systemic xylazine and ketamine reduces baseline IOP. In addition, xylazine–ketamine sedation is a good choice when it is desirable to avoid increases in IOP in investigative studies or clinical situations in rabbits, particularly during procedures for which increases in IOP could result in negative consequences. Additional studies are needed to investigate possible dose-dependence, the effect of varying the ratio of the 2 agents, and the maximal duration of effect.

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