



# Ocular tolerance in rabbits after intracameral administration of a fixed combination of tropicamide, phenylephrine, and lidocaine with and without rinsing

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**Purpose:** To evaluate the safety and tolerability of a single intracameral administration of a combined mydriatic (tropicamide and phenylephrine) and anesthetic (lidocaine) formulation (Mydrane) with or without rinsing.

**Setting:** Iris Pharma, La Gaude, France.

**Design:** Experimental study.

**Methods:** Sixty pigmented rabbits received 100  $\mu$ L or 200  $\mu$ L of the combination product or a placebo (sodium chloride 0.9%) by intracameral injection. For the combination product, separate groups were included with and without rinsing after administration. From day 1 day to day 7, assessments included general clinical and ocular observations, pupil diameter measurements, corneal assessments, confocal microscopy, and electroretinography (ERG). Necropsy examinations were performed at study completion at day 8.

**Results:** Rapid mydriasis, stable 24 minutes after injection and returning to baseline levels by day 1, was induced in all groups that received the combination mydriatic and anesthetic drug. Rinsing had no effect. The combination product induced no adverse effects on the anterior or posterior segment of the eye (ie, no increased corneal thickness and endothelial cell loss, no abnormalities in ERG). Slitlamp examination showed slightly increased anterior chamber inflammation with rinsing in both the study group and placebo group. This observation was not confirmed by aqueous flare examination. No toxic effects of the products were found on histological evaluation.

**Conclusion:** The combination mydriatic and anesthetic drug administered to pigmented rabbits as a single intracameral injection at volumes of 100  $\mu$ L and 200  $\mu$ L was well tolerated with no ocular adverse effects and no effect on the corneal endothelium.

*J Cataract Refract Surg* 2017; 43:673–679 © 2017 ASCRS and ESCRS

Pharmacologically induced mydriasis and the administration of ocular local anesthetic are prerequisites for cataract surgery. Poor mydriasis increases the risk for procedural complications such as posterior capsule rupture.<sup>1</sup> Historically, tropicamide (a muscarinic receptor antagonist) and phenylephrine (an  $\alpha$ -adrenergic agonist) have been shown in mice to result in stable mydriasis,<sup>2</sup> and the combined use of a muscarinic receptor antagonist and  $\alpha$ -adrenergic agonist are now routinely used before cataract surgery in clinical practice.

Topical administration of eyedrops containing a combination of anticholinergic agents has been used commonly

to achieve preoperative mydriasis; however, administration up to 1 hour before surgery is necessary.<sup>3–6</sup> This results in a waiting time for the patient that can be several-fold longer than the surgical procedure itself as well as the associated increases in nursing time. Other limitations of this approach include the risk for cardiovascular side effects associated with the use of sympathetic agents and poor maintenance of mydriasis throughout the surgery that can require repeated administration.<sup>7–10</sup> Typically, a topical anesthetic (lidocaine 1.0% or tetracaine 1.0%, or oxybuprocaine) is used for cataract surgery; however, repeated instillation can induce epithelial corneal toxicity, especially if the

Submitted: October 6, 2016 | Final revision submitted: February 21, 2017 | Accepted: March 6, 2017

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Supported by Laboratoires Théa, Clermont-Ferrand, France, in the preparation and development of the manuscript in accordance with the European Medical Writers Association guidelines and Good Publication Practice. Andrew Lane, PhD, Lane Medical Writing, provided professional medical writing assistance.

Presented at the European Association for Vision and Eye Research, Nice, France, October 2016.

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formulation used contains a preservative, and can lead to visualization problems when surgery time is prolonged.

The use of a single intracameral mydriatic injection overcomes the lengthy preoperative waiting time associated with topical administration; in general, 95% mydriasis is achieved within 20 to 30 seconds. There is also less risk for intraoperative pupil contraction.<sup>11,12</sup> In addition, lidocaine anesthesia administered by the intracameral route<sup>13–18</sup> reduces corneal irritation during surgery and provides better delivery to the anterior chamber<sup>19</sup> to improve patient comfort. Combining the mydriatic and anesthetic agents in a single intracameral injection therefore has several advantages, including time savings for the patient and healthcare professionals,<sup>20</sup> reduced subjective pain for the patient,<sup>21</sup> and better surgeon satisfaction with the anesthesia.<sup>21</sup> For these reasons, a combined intracameral mydriatic and anesthetic injection is used increasingly for cataract surgery.

Some studies have questioned the effect of intracameral drugs on the integrity of the corneal endothelium. Thus, the objective of this study was to evaluate the safety and tolerability of a single intracameral administration of a combined mydriatic (tropicamide and phenylephrine) and anesthetic (lidocaine) formulation (Mydrane) given at 2 different injection volumes and compared with a placebo in pigmented rabbits. The effect of postinjection rinsing was also assessed to determine whether there is a variation in toxicity between brief exposure and prolonged exposure.

## MATERIALS AND METHODS

### Study Design and Animals

All animals were treated according to the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research.<sup>A</sup> Sixty (30 male, 30 female) pigmented (Fauve de Bourgogne) rabbits aged approximately 2 to 4 months at baseline (randomization) with a mean weight 1.9 to 3.2 kg were supplied by CEGAV SSC, Saint Mars d'Egrenne, France. All were in good health with no signs of ocular irritation. Animals were housed in individual standard cages at 20.8°C ± 0.5°C (SD) and relative humidity of 73.4% ± 3.3%. Rooms were continuously ventilated (15 times per hour) with an automatically controlled 12-hour light cycle. All animals had free access to food (a standard dry pellet that was distributed every other day) and tap water.

Figure 1 shows the study design. On day 1, animals were randomly assigned to receive 100 µL or 200 µL of the combined mydriatic-anesthetic formulation (test product) or a placebo (sodium chloride 0.9% [NaCl] for injection) by intracameral injection into the right eye; the left eye was untreated. Animals were anesthetized by intramuscular injection of 7.5 mg/kg xylazine (Rompun) and 32 mg/kg ketamine (Imalgene) followed by topical anesthesia of 1 drop oxybuprocaine 0.4% (Cebesine) into the right eye. Under a microscope, the peripheral cornea in the right eye was then perforated at 1 o'clock using a 26-gauge needle. After the aqueous humor flow, the test product or placebo was administered using the same needle over a 10-second period. One minute after the end of the injection, the anterior chamber was rinsed using 1 mL NaCl 0.9% solution in one half of the animals that received the test product and in all animals that received the placebo. Six groups were defined as follows: M100R (100 µL test product + rinse), M100WR (100 µL test product without rinse), M200R (200 µL test product + rinse), M200WR (200 µL test

product without rinse), P100R (100 µL placebo + rinse), and P200WR (200 µL placebo + rinse).

Animals were assessed from day 1 to day 7 for general clinical and ocular observations, measurements of pupil diameter, corneal assessments, confocal microscopy, aqueous flare, and electroretinography (ERG). They were humanely killed on day 8 by intravenous injection of pentobarbital.<sup>22</sup>

### Test Product and Placebo

The test product (Mydrane) is a salt-balanced and pH-balanced solution for injection containing tropicamide 0.02%, phenylephrine 0.31%, and lidocaine hydrochloride 1.0%. The placebo was an isotonic commercially available NaCl 0.9% solution (Laboratoires Aguettant). Both the test product and placebo were packaged and supplied as single 0.5 mL injections and stored at room temperature. One injection was used per animal.

### Assessments

**General Observations** All animals were observed daily for general appearance and mortality. Body weight was recorded at baseline (preinjection on day 1) and on the day the animal was humanely killed (day 8).

**Pupil Diameter** Photographs were taken under controlled illumination for the room, slitlamp, and microscope in both eyes for the measurement of pupil diameter before injection and 1, 6, 12, and 24 minutes after injection on day 1 in all groups and also on day 2 for animals that received the test product but no rinse (Group 2 and Group 4). All photographs included a standard graduated in millimeters so each measurement would be performed consistently.

**Ocular Observations** The conjunctiva, iris, and cornea of both eyes were examined using slitlamp biomicroscopy before injection and after injection on day 1 and days 2, 3, 4, 5, 6, and 7. Corneal assessments were performed at the end of the examination so as not to alter the potential vessel hyperemia scoring of the conjunctiva and iris. The observations were reported using the McDonald-Shadduck scale.<sup>23</sup> The corneal staining test consisted of observing the cornea with a blue-filtered light after instillation of fluorescein to detect potential corneal lesions. An examination of the lens and simple funduscopy were also performed using an ophthalmoscope.

**Aqueous Flare** Anterior chamber flare was measured using a laser flare meter in both eyes before injection and before each slitlamp examination on days 1, 3, 5, and 7.

**Confocal Microscopy** Before confocal microscopy assessment (Heidelberg Retinal Tomograph II), which was performed after the aqueous flare and slitlamp examinations, animals were anesthetized using intramuscular injections of xylazine (7.5 mg/kg) and ketamine (32 mg/kg). Confocal microscopy was then used to measure the thickness of the cornea; 3 images of the central endothelium were captured at each timepoint. Endothelial cell density (ECD) was determined using the standard corner method.<sup>24</sup> To reduce sampling error, image analysis was performed by the same certified masked technician at each site who manually defined the borders of 50 endothelial cells in the center of each image. The final ECD at each visit was the average of 3 central counts. If these parameters were homogenous throughout the cornea, measurement in a single site was performed in both eyes before injection and after injection on day 1 and days 3 and 7. If these parameters were heterogeneous throughout the cornea, measurements were performed at different corneal sites.

**Electroretinography** Electroretinographic responses were recorded using a high-volume manufacturing (HVM) ERG apparatus (Metrovision) consisting of a 2-head stimulator and a 2-way bioelectric amplifier piloted by a computerized control unit using PVM-EL software. Scleral-shaped monopolar recording

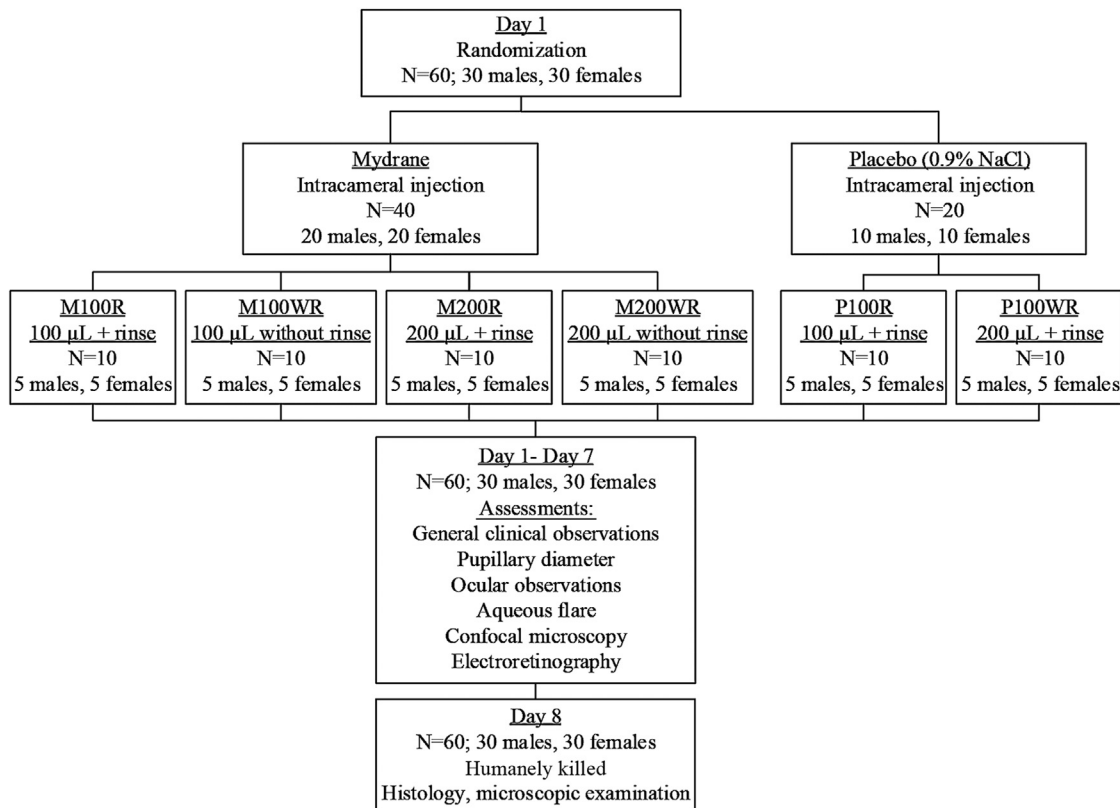


Figure 1. Study design (NaCl = sodium chloride).

electrodes were in contact with the cornea via a drop of hydroxyethylcellulose 1.3% (Goniosol). Measurements were performed in both eyes before injection and on day 8 after dark-adaptation for 3 hours of each animal. Before assessment, animals were anesthetized using intramuscular injections of xylazine (7.5 mg/kg) and ketamine (32 mg/kg) and the pupils were dilated using 1 drop of tropicamide 0.5% (Mydriaticum) and 1 drop of phenylephrine 10.0% (Neo-Synephrine). The settings for the standard parameters were flash: color = white maximum, distance eye-flash = 10 cm, maximum intensity = 2.6 candelas/m<sup>2</sup>; 2-way recording: filter 50 Hz, impedance threshold = 90 kΩ; response of mixed rods and cones (scotopic); flash: intensity =

maximum (0 dB), duration = 0.4 millisecond, number = 6, period = 10 seconds; recording: scale = 50 µV (amplitude/230 milliseconds [course]), gain = 3125, low frequency = 1 Hz, high frequency = 104 Hz. For results, the settings were a-wave amplitude and implicit time; b-wave amplitude and implicit time.

**Histology and Microscopic Examination** After the rabbits were humanely killed, both globes (ie, from the treated right eye and the untreated left eye), including the optic nerve and extraocular muscles, were removed and fixed in Bouin-Hollande solution, dehydrated, and embedded in paraffin wax. They were then each cut into 4 sections measuring 5 to 7 µm and stained using Masson

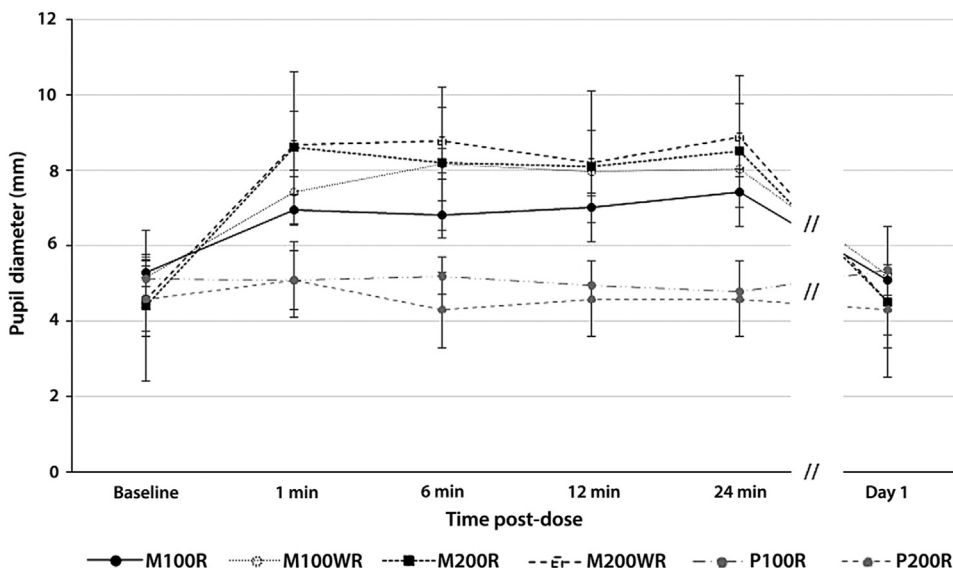


Figure 2. Mean ± SD pupil diameter (right eye; males and females combined).

**Table 1. Finding of day 1 to day 7 slitlamp examinations (McDonald-Shadduck scale) (right eye; males and females combined).**

Group	Conjunctiva			Cornea			Other			
	Congestion	Swelling	Discharge	Opacity	Vascularization	Staining	AC Inflammation	Iris Hyperemia	Lens	Fundus
M100R	0/210	0/280	0/210	0/280	0/140	61/280	91/210	0/280	0/70	0/70
M100WR	0/210	0/280	0/210	0/280	0/140	19/280	7/210	0/280	6/70	0/70
M200R	5/192	3/256	0/192	0/256	0/128	38/256	26/192	0/256	3/64	0/64
M200WR	3/210	1/280	1/210	0/280	0/140	21/280	7/210	0/280	0/70	0/70
P100R	0/210	0/280	0/210	17/280	0/140	20/280	32/210	0/280	0/70	0/70
P200R	3/210	1/280	0/210	0/280	2/140	22/280	10/210	0/280	2/70	0/70

AC = anterior chamber

trichrome. The lenses were removed 24 to 48 hours after fixation and processed separately. They were frozen in optimum cutting temperature compound and then cut into 7 to 10  $\mu\text{m}$  sections and stained with hematoxylin–eosin. All sections were examined microscopically at the end of the study.

### Statistical Analysis

Statistical analysis was performed for body weight using a multivariate analysis of variance test; pupil diameter, confocal microscopy, aqueous flare, and ERG data were analyzed using a Mann-Whitney *U* test. Statistical analyses were independent of sex.

## RESULTS

### General

All animals remained in good health throughout the study with the exception of 1 animal that was found dead on the morning of day 2 (probably a result of anesthesia given the previous day) and 1 animal that was humanely killed on day 4 because of a broken paw. Neither of these findings was considered to be treatment related, and the health of all remaining animals was good throughout the study, with no particular clinical signs observed and no clinically important changes in body weight in any group.

There was no difference in any parameter between males and females. Thus, pooled data for each parameter are presented for males and females combined.

### Pupil Diameter

The test product induced a statistically significant mydriatic effect in all treated animals (M100R, M100WR, M200R, and M200WR groups) compared with the effect of the placebo (P100R and P200R groups) ( $P = .002$ ). The effect was rapid, peaking at 24 minutes in the M100R group (7.44 mm), 6 minutes in M100WR group (8.18 mm), 1 minute in the M200R group (8.60 mm),

and 24 minutes in the M200WR group (8.90 mm). The mydriasis was stable 24 minutes after injection and returned to preinjection levels by day 1. The effect was similar with or without rinsing and was slightly greater in animals that received 200  $\mu\text{L}$  of the test product (M200R and M200WR groups) than in those that received 100  $\mu\text{L}$  of the test product (M100R and M100WR groups). Figure 2 shows the mean data.

### Ocular Observations

Slight conjunctival effects were observed in the M200R, M200WR, and P200R groups (200  $\mu\text{L}$  test product or placebo) (Table 1); there were no other differences based on the injection volume. There were no ocular clinically important differences in any observation between the test product–treated animals and the placebo-treated animals. Furthermore, with the exception of anterior chamber inflammation, which was slightly increased by rinsing in the test product group and the placebo group, there were no differences resulting from the rinsing (Table 1).

### Aqueous Flare

Postinjection aqueous flare measurements were performed only in animals that received 200  $\mu\text{L}$  of the test product or the placebo (M200R, M200WR, and P200R groups).

In the M200R and M200WR groups, aqueous flare increased after injection on day 1; however, no statistically significant difference was observed. Measurements returned to preinjection levels by day 3. The same effect was observed in animals that received the placebo (P200R), showing the product had no effect (Table 2).

**Table 2. Mean aqueous flare (right eye, males and females combined).**

Group	Mean Aqueous Flare (Ph/Ms) $\pm$ SD				
	Baseline	After Injection			
		Day 1*	Day 3	Day 5	Day 7
M200R (n = 10)	16.0 $\pm$ 10.0	60.6 $\pm$ 39.1	17.8 $\pm$ 10.3	14.6 $\pm$ 8.6	15.0 $\pm$ 7.8
M200WR (n = 10)	13.8 $\pm$ 5.6	51.5 $\pm$ 59.2	14.2 $\pm$ 5.3	15.0 $\pm$ 7.7	13.3 $\pm$ 7.8
P200R (n = 10)	13.7 $\pm$ 6.0	119.9 $\pm$ 94.4	16.6 $\pm$ 8.4	12.2 $\pm$ 7.1	14.7 $\pm$ 6.7

\*Procedure not performed in M100R and M100WR groups because of equipment failure

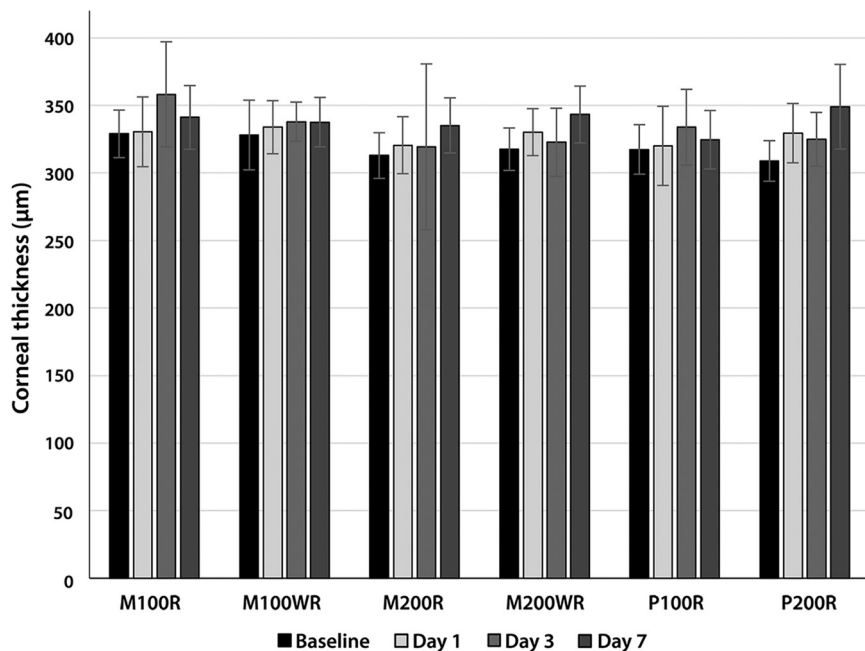


Figure 3. Mean  $\pm$  SD corneal thickness (right eye; males and females combined).

### Corneal Observations

Confocal microscopy showed no change in corneal thickness after injection in any group and no clinically significant difference between groups (Figure 3).

The ECD was similar from baseline to day 7 in all groups, and there was no clinically significant change after the injection in any group and no clinically significant difference between groups (Figure 4).

### Electroretinography

There were no changes in ERG findings (0 dB waves a and b) after injection in any group. There were no clinically significant differences between the test product or placebo, no

differences between 100  $\mu$ L and 200  $\mu$ L injections, and no effect of rinsing.

### Histological and Microscopic Analysis

No ocular clinical anomalies were found at necropsy in any group. On histological and microscopic analysis, the only findings were subepithelial extravasated lymphocytes or subepithelial follicles in the conjunctiva of the treated eye of 9 animals (1 in M100R group, 1 in M100WR group, 2 in P100R group, 2 in M200WR group, 3 in P200R group) and untreated eye of 2 animals, epithelial scratching in the treated eye of 1 animal in the P100R group and untreated eye of 2 animals, deepithelialized cornea/traumatic area of

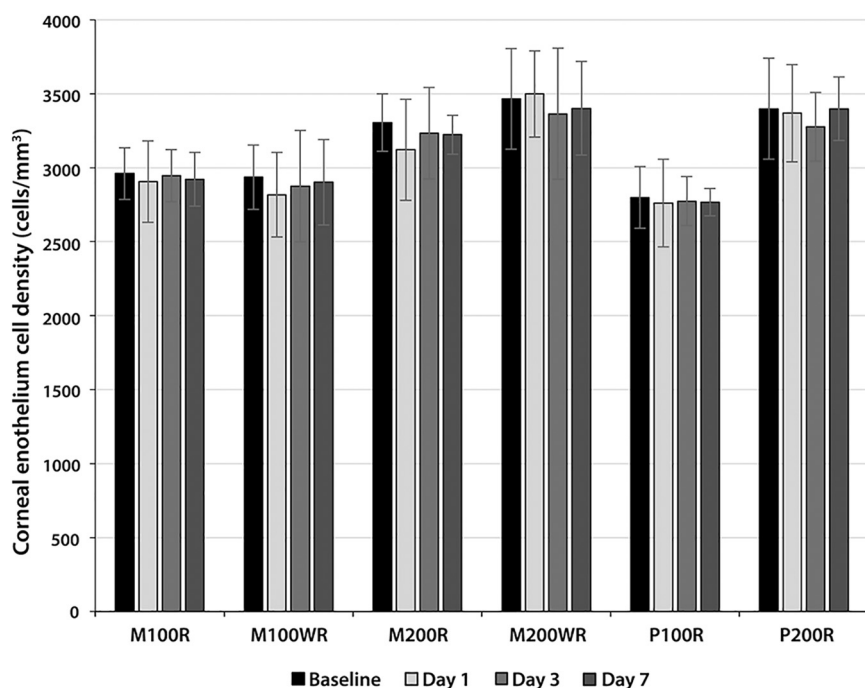


Figure 4. Mean  $\pm$  SD corneal ECD (right eye; males and females combined).

cornea in the treated eye of 1 animal in the P100R group and the untreated eyes of 2 animals, subepithelial fibrosis in the corneal stroma with connected iris in the treated eye of 1 animal in the P100R group, and extravasated erythrocytes in the untreated eye of 1 animal. These findings are common and were not treatment related, and there were no clinically significant differences between the groups.

## DISCUSSION

The intracameral injection volume of 200  $\mu\text{L}$  used in this study was based on the anterior chamber volume in the rabbit, which is 200  $\mu\text{L}$ , which compares to approximately 300  $\mu\text{L}$  in the human. This volume was chosen to completely fill the anterior chamber and exert a maximum toxicological effect. In addition, in a clinical setting some dose volume could unintentionally be washed out of the back of the eye through the paracentesis or other entry site; thus, the 200  $\mu\text{L}$  group more closely approximates the clinical situation and essentially provides a test of washout.

When used before cataract surgery in humans, the intracameral injection is followed by rinsing approximately 1 minute later as standard surgical procedure, and in clinical studies the Mydrane, the test product in our study, was found to be safe and well tolerated when used in this way and at a volume of 200  $\mu\text{L}$ .<sup>25</sup> In the present study, groups were included with and without rinsing after administration the test product or the placebo. Rinsing was meant to mimic the clinical procedure and the without rinsing was meant to provide information regarding prolonged contact time of the test product with the anterior intraocular structures. Other aspects that differentiate the present study from clinical studies of the same product are the inclusion of both 100 and 200  $\mu\text{L}$  injection volumes and an assessment of ocular histology after the animals were humanely killed.

A main finding in the present study was that no endothelial damage (no change in corneal thickness or loss of corneal ECD) was observed, even with prolonged contact of the test product with the endothelium (ie, with no rinsing). The rapid pupil dilation after intracameral injection of the test product confirms the advantage of this route over longer latency and response durations of topically administered mydriatic agents.<sup>26</sup>

In the 7 days after administration, the only toxicological finding in the pigmented rabbits was increased anterior chamber inflammation observed after slitlamp examination; however, this also occurred in eyes receiving the placebo and was an expected result of the rinsing. These differences were not confirmed by aqueous flare examination. Other than this anticipated effect, there was no observed toxicity of the test product in this study.

Limitations of this study relate mainly to the missing aqueous flare data; aqueous flare was not measured after injection in any animal in the 100  $\mu\text{L}$  injection groups (M100R, M100WR, and P100R); however, aqueous flare data were available for the higher

injection of 200  $\mu\text{L}$  (M200R, M200WR, and P200R groups) and showed no toxicity of the test product compared with the placebo. Another limitation is that the study did not evaluate the chronic effects on the corneal endothelium.

Overall, there were no clinically important differences between the study product and placebo, between the 2 administration volumes, or between male animals and female animals. In conclusion, Mydrane administered to pigmented rabbits as a single intracameral injection at volumes of 100  $\mu\text{L}$  and 200  $\mu\text{L}$ , with and without rinsing after administration, was well tolerated with no clinically significant adverse ocular effects, including no effect on the corneal endothelium.

## WHAT WAS KNOWN

- Topical administration of cholinergic agents and an anesthetic is the preferred practice before cataract surgery to achieve mydriasis and anesthesia.
- To achieve sufficient mydriasis, such administration is required up to 1 hour before surgery. In addition, topical anesthesia can be toxic to the corneal epithelium.

## WHAT THIS PAPER ADDS

- A single intracameral injection of a combined mydriatic and anesthetic formulation was well tolerated in pigmented rabbits at dose volumes of 100  $\mu\text{L}$  and 200  $\mu\text{L}$  with and without rinsing. The intracameral route can save time and seems to reduce the risk for corneal epithelial toxicity.

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- Disclosures:** Ms. Viaud-Quentric and Dr. Elena are employees of Iris Pharma. Dr. Olmière is an employee of Laboratoires Théa. Dr. Nuijts is a consultant for Alcon Laboratories, Inc. and Théa Pharma GmbH; he has received study grants from Ophtec BV, Humanoptics AG, Gebauer Co., and Alcon Laboratories, Inc. He has also received lecture fees from Alcon Laboratories, Inc. None of the other authors has a financial or proprietary interest in any material or method mentioned.