CORNEAL EFFECT OF TOPICAL DICLOFENAC CO-ADMINISTRATION WITH AMINOSIDE AND STEROID IN RABBITS.
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PURPOSE
The aim of this study was to compare the corneal tolerance of three topical ocular treatments (Dicloced® (Diclobaak®), Tobradex® and Dicloced® + Tobradex®) in both eyes of albino rabbits, after multiple (five) daily ocular instillations for 28 consecutive days.

MATERIALS AND METHODS
Twelve albino rabbits (White New Zealand) were involved in this study. Animals were allocated in four groups of three animals corresponding to four treatments. Treatments were instilled five times daily (50 µl each) spread over 8 hours for 28 consecutive days in both eyes.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Administration</th>
<th>Number of animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dicloced®</td>
<td>50 µl in both eyes.</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Tobradex®</td>
<td>5 times a day (spread over 8 hours)</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Dicloced® + Tobradex®</td>
<td>for 28 consecutive days.</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Unilarm®</td>
<td>10 min interval between instillations for group 3.</td>
<td>3</td>
</tr>
</tbody>
</table>

Dicloced® is preservative-free 0.1% diclofenac. Tobradex® contains 0.3% tobramycin + 0.1% dexamethasone, respectively. Unilarm® is preservative-free 0.9% NaCl and was used as negative control.

Ocular examinations (conjunctiva, cornea, anterior chamber and iris) were investigated with a slit-lamp using the McDonald-Shadduck’s scale before the first administration then weekly before the first daily instillation (Days 7, 14, 21 and 28). Pachymetry and cellular morphology were recorded using a confocal microscope (HRT-II) seven days before the first administration then weekly before the first daily instillation (Days 8, 15, 22 and 29).

At the end of the study (Day 29), animals were euthanised and corneas were sampled and fixed for histology analysis.

All animals were treated according to the European Convention and to the Association for Research in Vision and Ophthalmology (ARVO) Statement for the Use of Animals in Ophthalmic and Vision Research.

RESULTS
Each eye of each animal was examined weekly over a 28 day period with a slit-lamp using the McDonald-Shadduck’s scale. The following ocular structures were evaluated:
- Conjunctiva: congestion, swelling and discharge,
- Cornea: opacity (degree and area), vascularization and staining (intensity and area),
- Anterior Chamber inflammation,
- Iris hyperemia.

No ocular effect was observed for all animals except very slight and transient corneal staining for some animals of each group at all time-points. Corneal staining is commonly observed for this species and was not related to treatments.

In addition, the corneal thickness of each eye of each animal was recorded weekly over a 28 day period using a confocal microscope (HRT-II).

No modification of corneal thickness was recorded for the animals administered with Dicloced® (NS p>0.05 versus Unilarm®, n=6). A significant decrease was recorded on Day 29 for the animals administered with Tobradex® (-13%, p<0.02 versus Unilarm®, n=6) and with Dicloced® + Tobradex® (-15%, p<0.004 versus Unilarm®, n=6).

Histopathological examinations confirmed the good tolerance of each treatment.

CONCLUSION
In these experimental conditions, the corneal tolerance of these three treatments (Dicloced® (Diclobaak®), Tobradex® and Dicloced® + Tobradex®) seemed macroscopically and microscopically very well tolerated. However a significant decrease of the thickness of whole cornea was recorded after Tobradex® and Dicloced® + Tobradex® treatments. Corneal complications in patients thought to be linked with the use of NSAIDs may most likely be linked with risk factors such as high doses, misuse, co-morbidity and co-administration with other ocular surface toxic products such as certain antibiotics especially aminosides possibly combined with steroids.