Prevention and Reversal of Galactose Cataract in Rats with Topical Sorbinil

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Rats fed a 50% galactose diet were treated topically in one eye with 1% Sorbinil. The eye treated with Sorbinil remained clear during the following 4-week period. Unexpectedly, the lens of the untreated eye also maintained transparency. Histologically both lenses remained normal. Moreover, the reduced dulcitol levels in the lenses of both eyes were identical. These findings suggest that the effect of topically administered Sorbinil in galactosemic rats was mainly systemic rather than local. Confirmation of this came from the observations that the extent of inhibition of polyol synthesis in these rats was found to be similar in the sciatic nerve, blood, and lens. A reversal of the galactose cataracts also was affected by Sorbinil eye drop treatment. Invest Ophthalmol Vis Sci 25:603–605, 1984

We have shown previously that oral administration of Sorbinil is effective in preventing the development of diabetic and galactose cataracts1,2 as well as reversing the process even after cataract development has been initiated in galactosemic rats.3 The effective treatment of an ocular disease with topical application is of clinical interest, since this may reduce any possible side-effects of the drug. For this reason, we have studied the effectiveness of topically applied Sorbinil in the development of cataract in galactosemic rats. This report will demonstrate that the topical use of Sorbinil drops can halt and reverse the cataractous process in galactosemic rats.

Materials and Methods. A dozen, 3-week-old, Sprague Dawley rats weighing about 50 g were pretreated with 1% Sorbinil drops on the right eye, four times daily for 3 days, while the left eye was on placebo. At day 4, the rats were placed on a 50% galactose diet (United Stages Biochemical Corporation; Cleveland, OH) while topical Sorbinil and placebo drops were continued. Rats fed with galactose without treatment served as control. Each ml of Sorbinil drops contained: Polyvinylpyrrodone (M.W 10,000) 10 mg; Sodium phosphate dibasic heptohydrate 0.47 mg; Benzaalkonium chloride 0.1 mg; Sodium chloride 9 mg; Sorbinil 10 mg. (This preparation was suggested by Pfizer; Groton, CT). The overflowing Sorbinil drops was blotted with tissue paper in order to prevent oral contamination of Sorbinil.

The pupils of the rats were dilated with 1% cyclogyl and the lenses were examined by retroillumination with an ophthalmoscope at different periods. Rats were killed after 5, 15, and 21 days of the galactose diet. Lens dulcitol levels were measured by gas liquid chromatography.3 Simultaneously, heparinized blood was collected by heart puncture and the sciatic nerve was dissected. Both samples of blood and nerve were prepared for dulcitol measurement.4

After 5 days of galactose feeding, another group of nine galactosemic rats were treated with Sorbinil drops four times daily on both eyes for up to 2 months. Ophthalmoscopy and photography of the lenses of these rats were performed at various intervals up to 2 months. For histopathologic studies of these rat lenses, the eyes were enucleated and the lenses were prepared as described previously.2

Results. Clinical feature: In rats pretreated with eye drops containing Sorbinil for 3 days and placed on the galactose diet at day 4, the lenses of both eyes remained grossly clear as judged ophthalmoscopically up to 4 weeks, even though continuation of Sorbinil drops was applied to only one eye. As expected, the rats fed the galactose diet without Sorbinil treatment developed complete rings of equatorial opacities by day 5, a dense nuclear cataract around 2 weeks, and a mature cataract by 3 weeks.2-3 Reversal of cataracts in galactosemic rats was observed when both eyes were treated with Sorbinil drops after the sixth day of galactose feeding. In these animals lens, opacities decreased with time up to the following 2-month period. Although partial clarification of the cortex did occur, application of Sorbinil drops after 6 days on galactose did not prevent the lens changes from proceeding to the nuclear cataract stage. These results on reversal of galactose cataracts are similar to those observed in the oral Sorbinil treatment.3

Biochemical changes of the rats: The lenticular dulcitol levels of galactosemic rats were found to be con-
Table 1. Dulcitol level of blood, sciatic nerve, and lens in galactosemic rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Blood (umole/dl)</th>
<th>Sciatic nerve (umole/gm)</th>
<th>Lens (umole/gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>59.8 ± 15.8 (8)</td>
<td>6.6 ± 2.2 (8)</td>
<td>74.7 ± 8.0 (9)</td>
</tr>
<tr>
<td>Sorbinil</td>
<td>10.3 ± 2.5 (8)</td>
<td>0.16 ± 0.14 (8)</td>
<td>19.0 ± 4.0 (16)</td>
</tr>
</tbody>
</table>

Degree of inhibition: 82.8% 75.8% 74.6%

Rats fed a 5% galactose diet and killed after 5 days. Those rats receiving 1% Sorbinil eye drops were given the drops in the right eye. The results are given as averages with standard deviations.

Consistent with previous findings, in that by day 5 the level reached about 75 μmoles/g (Table 1). Lenticular dulcitol levels in the eyes treated with Sorbinil were lowered to 20 μmoles/g. The lens of the untreated eye was found to have the same level of dulcitol as the fellow treated eye, suggesting that this was due to a crossover effect through rapid entry of the topically applied Sorbinil into the systemic circulation. To examine this possibility, the dulcitol levels in the blood and sciatic nerve also were determined. The results confirmed this speculation. In the rats treated with eye drops, the dulcitol levels in the blood and sciatic nerve were substantially lower than in the tissues of untreated galactosemic rats (Table 1). The degree of inhibition in all three tissues ranged from 75–83%. Although a complete inhibition of dulcitol synthesis was observed with oral administration of Sorbinil, a complete block of dulcitol synthesis was not observed upon topical Sorbinil treatment.

Histopathologic changes of the lens: The histopathologic lens changes of galactosemic rats were the same as those described previously.2,3 Vacuolar formation was observed in the lens of a rat fed galactose for 5 days (Fig. 1A). When sorbinil was administered to one eye, both lenses remained free of vacuoles even after 24 days on the galactose diet (Fig. 1B). Such lenses could not be distinguished from the normal control lenses. Topical treatment of well-established cataracts of galactosemic rats at initial vacuolar stage (Fig. 1A) with Sorbinil drops resulted in clarification of lens opacities; histopathologic studies revealed that the pathologic process had been reversed at the end of 2-month treatment. These lenses appeared to be histologically normal and were indistinguishable from the normal control lenses (Fig. 2).

Discussion. It is well established that aldose reductase (A.R.) is implicated as a factor initiating the pathogenesis of sugar cataracts in experimental animals.5,6 Datiles et al have summarized the effect of various

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Fig. 1. A, Cross-section of a lens of a rat fed galactose for 5 days showing vacuoles formed in the equatorial and pre-equatorial cortex. B, Cross-section a lens of a rat fed galactose for 24 days treated with 1% Sorbinil eye drops showing no histopathologic changes.
Fig. 2. Cataract reversal study of rats fed galactose for 5 days, then treated with topical Sorbinil. Lens cross-section showing cataractous process was reversed with no pathologic changes 2 months after Sorbinil treatment.

A.R. inhibitors on sugar cataract formation.\(^2\) If an inhibitor is potent enough, it not only can delay but actually prevent the development of cataracts.

Under the conditions employed, Sorbinil drops applied to one eye in the rat appears to have systemic rather than local effects. In these eye drop experiments, we were careful to avoid Sorbinil contamination via the oral route. Any overflow of administered eye drops was blotted dry with tissue paper. Therefore, we suspect that the adsorption of Sorbinil to the general circulation was through conjunctival vessels and the tear duct.

Topically applied Sorbinil was not as effective as that administered orally. When Sorbinil was administered in the diet, essentially a complete block of aldose reductase activity could be observed while Sorbinil eye drops produced only 75% inhibition. It must be kept in mind that a 50% galactose diet places a tremendous stress on the lens, which quickly leads to lens changes. Therefore, a much lower level of galactose should be given to approach clinically comparable results. However, the present observations indicate that topical use of Sorbinil is effective in preventing opacities under conditions in which cataract production is highly favored.

Key words: aldose reductase, galactose cataract prevention, Sorbinil

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References