Tetrahydrotriamcinolone and triamcinolone
I. Ocular penetration

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Triamcinolone (TA) and tetrahydrotriamcinolone (THTA) are very similar in structure, but only one, TA, consistently raises intraocular pressure in susceptible individuals. It has been postulated that these differences are due to differing penetration qualities. In the present study, using anterior chamber paracentesis in human eyes, these drugs were very similar in ocular penetration.

Key words: triamcinolone, tetrahydrotriamcinolone, drug penetration, corticosteroid-induced glaucoma, anterior chamber paracentesis.

The effects of corticosteroids in raising intraocular pressure and acting to reduce inflammation are well known.[1, 2] The search continues for substances which differentially alter these features both for their clinical value and as a possible key to the mechanism of corticosteroid-induced glaucoma. It has been shown that tetrahydrotriamcinolone (THTA) does not raise intraocular pressure under the circumstances in which triamcinolone (TA) does.[3] This has been attributed to possible poor ocular penetration of THTA.[4] The present study investigates this hypothesis.

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Supported in part by Grants EY-00004 and EY-00336 from the National Eye Institute, Bethesda, Md., and the National Society for the Prevention of Blindness, New York, N. Y.

Manuscript submitted June 29, 1972; manuscript accepted Aug. 30, 1972.

Materials and methods

Thirty-six preoperative patients with senile cataracts were given three drops (0.05 ml. each) topically of a 1 per cent solution of C^{14}-labelled triamcinolone acetonide dipotassium phosphate (90.8 μCi per milliliter) or tetrahydrotriamcinolone acetonide dipotassium phosphate (101.4 μCi per milliliter). (Both drugs were prepared by the Squibb Institute for Medical Research). The time of instillation of the first drop was recorded as time zero, and subsequent drops were administered at times 8 and 15 minutes. Following a minimum of 5 minutes after the administration of the last drop the patients then underwent preparation for cataract surgery with van-Lint akinesia of the lids, topical tetracaine, scrubbing of the lids with hexachlorophene soap, and copious irrigation of the cul-de-sacs with saline. The operative field was then draped and retrobulbar anesthesia given, followed as soon as possible by anterior chamber paracentesis at the limbus with a 27 gauge needle attached to a tuberculin syringe. Aqueous (0.1 ml.) was withdrawn and the time determined from the first application of drug to the paracentesis. The anterior chamber paracenteses were performed from 30 to 130 minutes after the first application of drug. Pretreatment and postoperative plasma samples were also obtained.

The first 28 aqueous samples were diluted in scintillation solution and counted on the Packard

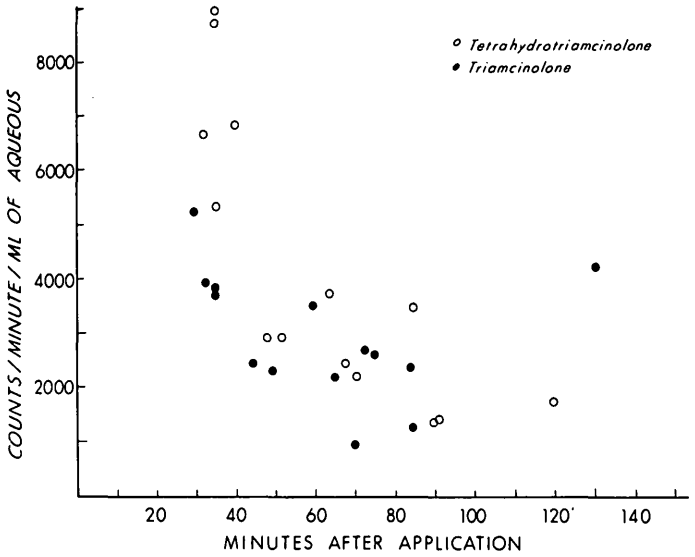

Fig. 1. Counts of radioactivity in aqueous corrected for activity in the applied drug.

3375 scintillation counter. For characterization of the labelled compound in aqueous, eight additional samples, obtained at 1 to 2.5 hours after initial instillation of drug, were pooled in two groups, one for each drug used, and made to 5 ml. with distilled water. Portions (0.05 ml.) of these samples were mixed with scintillation solution[5] and counted in the scintillation counter. Remaining portions were extracted three times with ethyl acetate. Aliquots were counted and the solvent evaporated. Residue was applied to thin-layer silica gel plates and chromatographed in methanol: chloroform (8:92 v/v). Radioautography of the plates was done on Kodak PR-54 film. Plasma samples were handled in the same manner except that the plates were divided into zones and each zone scraped, eluted with methanol, and counted.

Results

Counts of radioactivity in aqueous, corrected for activity in the applied drug and converted to counts per milliliter, are shown in Fig. 1. Ocular penetration of THTA appeared to exceed that of TA. The mean counts for samples taken within one hour of drug application were 6,035 for THTA and 3,550 for TA. The mean counts per minute per milliliter for samples obtained later than one hour after drug administration was 2,315 for THTA and 2,119 for TA. Comparison by T test shows these differences to be significant ($p < 0.05$) in the first hour and not significant ($p > 0.45$) in the second.

A total of 98 per cent of the radioactivity present in the pooled aqueous humor obtained after administration of THTA and 94 per cent of that after administration of TA was extractable with ethyl acetate. Radioautography after thin-layer chromatography of the extract of the samples from THTA-treated patients showed one band corresponding to THTA, standards were dephosphorylated THTA, while the samples from TA-treated patients showed two radioactive bands with motility greater than and one equal to that of TA (Fig. 2).

A total of 35 per cent of the radioactivity present in the pooled plasma samples obtained after administration of THTA and 29 per cent of that after administration of TA was extractable with ethyl acetate. Measurement of radioactivity in various zones after thin-layer chromatography of the extract showed counts in three zones from the samples from THTA-treated patients, none of which corresponded to the zone of a THTA standard. With the samples from the TA-treated patients counts from four zones were obtained, one corresponding to a TA standard.

Discussion

TA and THTA differ structurally only in the degree of saturation of the first ring

of the steroid nucleus (Fig. 3). Galin[6] has shown that triamcinolone acetonide hemisuccinate raises intraocular pressure in corticosteroid-responsive patients while Becker and Kolker[4] and subsequently Podos and co-workers[3] have shown that THTA does not raise intraocular pressure except in rare patients. Becker and Kolker[4] postulate that these results are due to differences in penetration between the two drugs. The present study shows that THTA penetrates the eye at least as well as, if not better than, TA and the chromatographic studies show that it does so without being metabolized except for hydrolysis of phosphate. It is interesting that the plasma samples show no intact THTA while intact TA is recoverable by this method.

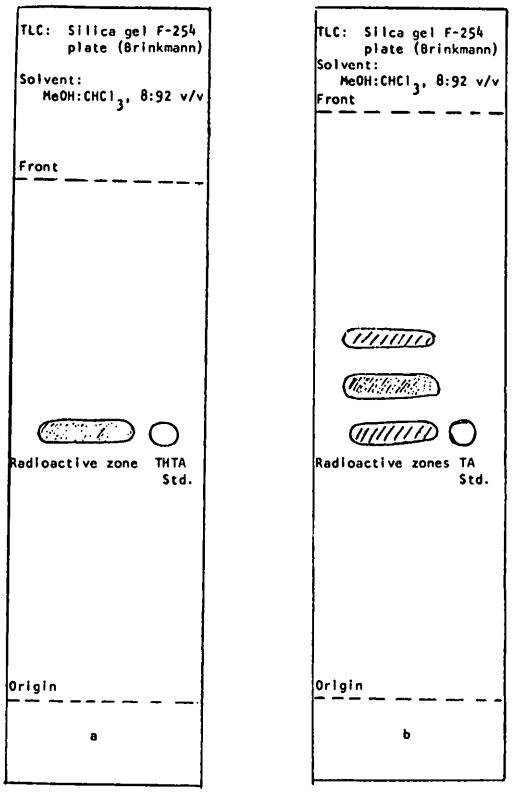

Fig. 2. Thin-layer chromatographs of pooled aqueous samples and drug standards from (a) THTA-treated patients and (b) TA-treated patients.

Differences in penetration can thus not explain the ability of TA but not THTA to cause pressure elevation in known responders to topical dexamethasone. Although aqueous levels were similar it is possible that these may not reflect tissue levels, which were not measured in this study. Since the site of steroid action is unknown it is not clear in what way aqueous levels are correlated with receptor site activity. The fact that TA and its partially metabolized form raise pressure whereas THTA in its intact form does not raise pressure suggests that possibly a metabolite of the corticosteroid molecule is responsible for this phenomenon, though the intact TA alone may account for the effect.

A comparison of the anti-inflammatory effects of TA and THTA, which may give other clues to the differences between these drugs, will be presented in another publication.

The authors wish to thank Carol Fritz and Nels Holmberg of the Department of Ophthalmology,

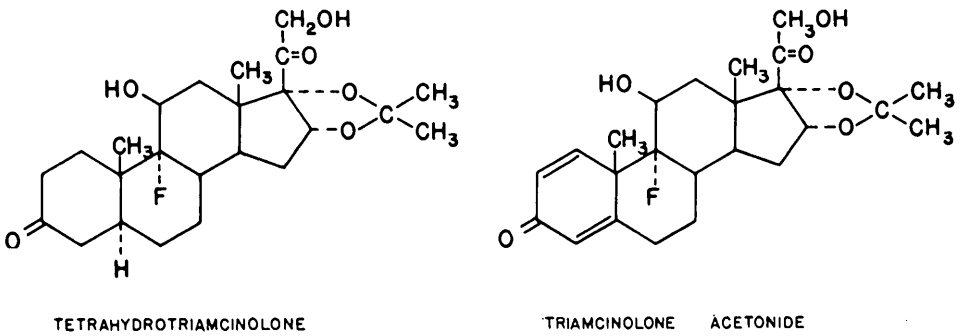

Fig. 3. Structures of TA and THTA.

Washington University School of Medicine, and F. S. Meeker, Jr. of the Squibb Institute for Medical Research for their laboratory assistance.

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