Effect of Ticrynafen on Aqueous Humor Dynamics in Monkeys

Mary Ann Croft, MS; Rong Fang Wang, MD; Steven M. Podos, MD; Arthur H. Neufeld, PhD; Paul L. Kaufman, MD

**Objective:** To determine the effect of ticrynafen, a non–sulfhydryl-reactive compound similar to ethacrynic acid, on outflow facility in normotensive monkey eyes and on intraocular pressure (IOP) in monkey eyes with laser-induced glaucoma.

**Methods:** In normotensive eyes, facility (perfusion) was measured shortly before and after bolus or exchange intracameral infusion of ticrynafen or vehicle in opposite eyes, and 3.5 to 4.5 hours after 5 days of twice-daily 2% ticrynafen or vehicle ointment. In glaucomatous eyes, baseline and vehicle diurnal IOP curves were established, 2% ticrynafen ointment was given twice daily for 5 days, and IOP was measured immediately before and 0.5 to 6 hours after each morning treatment.

**Results:** In normotensive eyes, exchange 2-mL infusion of 0.2-, 1-, or 4-mmol/L ticrynafen increased facility by 33% ± 6% (mean ± SEM), 73% ± 18%, and 60% ± 11%, respectively. Day 5 posttreatment facility was higher in the ticrynafen group than in controls by 28% ± 9%. In glaucomatous eyes, maximum IOP decline, from approximately 35 mm Hg, was 7.5 ± 2.0 mm Hg on day 4 and 9.8 ± 2.4 mm Hg on day 5 of twice-daily ticrynafen treatment.

**Conclusion:** The facility-increasing, IOP-lowering action of ticrynafen, ethacrynic acid, and derivatives may not depend entirely on sulfhydryl reactivity.

**Clinical Relevance:** Whether such drugs as ethacrynic acid and ticrynafen prove valuable for glaucoma therapy, at the least they are useful probes to study aqueous outflow mechanisms.


**ETHACRYNIC ACID** increases outflow facility in living monkey eyes,1,2 enucleated calf eyes,1,3 and organ-cultured, perfused human anterior ocular segments4 and decreases intraocular pressure (IOP) in living normotensive and glaucomatous monkey5-7 and glaucomatous human8 eyes. Ethacrynic acid is an alkylating agent, giving it sulfhydryl reactivity.9,10 This property may be responsible for both its facility-increasing and toxic corneal effects.3,11 Ticrynafen is a nonalkylating compound,9 structurally similar to ethacrynic acid (Figure 1) but putatively devoid of sulfhydryl reactivity.12 We have determined the effect of ticrynafen on IOP, outflow facility, and anterior segment biomicroscopic appearance in cynomolgus monkey eyes with normal IOP and with laser-induced glaucoma.

**RESULTS**

**MONKEYS WITH BILATERALLY NORMOTENSIVE EYES**

Pretreatment baseline facilities in the ticrynafen and contralateral control eyes were similar in all intracameral drug protocols.

**Protocol 1**

One hour after unilateral bolus intracameral infusion of 10 µL of 2.5-mmol/L ticrynafen (group A, Table), the mean postdrug-baseline facility ratio averaged 1.15 ± 0.05 (n = 6) in the ticrynafen-infused eye and 1.27 ± 0.09 in the vehicle-injected eye. These 15% and 27% increases were both statistically significant (P = .03), were of the magnitude expected for perfusion-induced resistance washout in this system,20 and did not differ significantly (treated-control postdrug facility ratio, 1.03 ± 0.10; treated-control, postdrug-baseline facility ratio, 0.92 ± 0.06; neither differing significantly from 1.0). Thus, there was no apparent ticrynafen-induced facility change. Similar results were seen with the 10-fold higher dose (10 µL of 25-mmol/L ticrynafen; group B, Table); the treated-control, postdrug-baseline facility ratio averaged 1.12 ± 0.11 (n = 6).

**Protocol 2**

Facility did not increase after 0.04-mmol/L ticrynafen exchange (Table). However, after AC exchange with 0.2-, 1-, and 4-mmol/L ticrynafen, facility relative

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MATERIALS AND METHODS

Cynomolgus Monkeys

Thirty-nine juvenile and adult cynomolgus monkeys (Macaca fascicularis) of both sexes were studied; 35 were bilaterally ocular normotensive with no biomicroscopically visible anterior chamber cells or flare or other ocular abnormalities, while 4 had stable unilateral ocular hypertension induced by repeated argon laser photoagulation of the trabecular meshwork. All experiments were conducted in accordance with National Institutes of Health (Bethesda, Md) and institutional guidelines, and with the Association for Research in Vision and Ophthalmology Statement on the Use of Animals in Ophthalmic and Vision Research.

Anesthesia

For applanation tonometry and administration of ticrynafen ointment, intramuscular ketamine hydrochloride, 10 to 12 mg/kg, supplemented at approximately 45-minute intervals by 3 mg/kg, was used, supplemented in glaucomatous monkeys by topical 0.5% proparacaine hydrochloride. For anterior chamber perfusion, intramuscular ketamine hydrochloride, 10 mg/kg, was followed by intramuscular pentobarbital sodium, 35 mg/kg.

Outflow Facility Measurement and Intracameral Drug Delivery

Total outflow facility was measured by 2-level constant-pressure (approximately 3 and 12 mm Hg above spontaneous IOP) perfusion of the anterior chamber (AC) with Bärañy mock aqueous humor. Two variations of the basic method were used. With a 1-needle technique (bolus intracameral infusion of drug and no drug in the reservoir), a second cannulation is avoided; however, the AC contents are not completely mixed or replaced, and drug concentration declines with a half-life of approximately 30 minutes (varying somewhat with the facility of the individual eye). The AC and reservoir exchange with drug solution requires 2 needles rather than 1, but allows rapid administration, more complete mixing, and closer approximation of a specific intracameral drug concentration during the posttreatment facility measurements, since the perfusand contains the desired drug concentration.

IOP Measurement

The IOP was determined with a minified Goldmann applanation tonometer in monkeys with normotensive eyes, and with a calibrated pneumatic applanation tonometer (Pneumatonometer model 30, Digilab Inc, Cambridge, Mass) in animals with laser-induced glaucoma.

Ticrynafen

Ticrynafen powder and 2% ticrynafen ointment (2% ticrynafen in mineral oil petrolatum base) were obtained (Telor Ophthalmic Pharmaceuticals, Woburn, Mass). The same 2% ticrynafen ointment preparation was used for both the bilaterally normotensive and the unilaterally glaucomatous monkeys. The manufacturer also prepared ethacrynic acid ointment with the use of a similar mineral oil petrolatum base for other studies cited herein. We chose the concentration of ticrynafen based on an IOP-effective concentration of ethacrynic acid.

Monkeys with Bilaterally Nortensive Eyes

Protocol 1

Experimental Design. After baseline slitlamp examination, facility was measured simultaneously in both eyes of 11 monkeys for approximately 45 minutes, immediately before and beginning 1 hour after a 10-µL bolus intracameral infusion of 2.5-mmol/L (group A, n = 6) or 25-mmol/L (group B, n = 6) ticrynafen in one eye and vehicle alone in the other (1 monkey was used in both protocols). These doses achieved initial concentrations of 0.25-mmol/L (group A) and 2.5-mmol/L (group B) ticrynafen in the 100-µL cynomolgus anterior chamber, and ticrynafen or vehicle was injected into the inflow tubing of the perfusion apparatus (via a T-piece) of opposite eyes and allowed to wash into the anterior chambers for 5 minutes. The eyes were then exposed to cold air for 3 minutes to enhance convection mixing. The perfusion apparatus was closed to inflow during the interval between baseline and postdrug facility measurements.

Drug Preparation. For 6 animals in group A, the phosphate buffer was adjusted to pH 6.8 with 1.0N hydrochloric acid and filtered through a 0.2-µm acetate filter. Then, 41 µg of ticrynafen was dissolved in 40 mL of phosphate buffer by ultrasonication and further diluted with buffer to 50.0 mL to achieve a final ticrynafen concentration of 41 µg/mL.

Protocol 3

Average pretreatment IOP was 13.8 mm Hg in both eyes (Figure 2). The IOP in the control eyes 18 and 19 hours after the afternoon day 4 treatment (ie, immediately before and 1 hour after the day 5 morning treatment) was essentially identical to day 1 pretreatment baseline, but decreased by approximately 3 mm Hg at 3 hours on treatment day 5. The IOP in the ticrynafen-treated eyes averaged 1 to 1.5 mm Hg less than control eyes.
than in the control eyes at the day 3 pretreatment and the 1- and 3-hour posttreatment measurements, but these differences were not statistically significant. On day 5, 3-hour posttreatment IOP was significantly lower than day 1 pretreatment baseline in both ticrynafen-treated (−3.3 ± 0.8 mm Hg; n = 6; P = .004) and control (−3.0 ± 0.9 mm Hg; P = .02) eyes. Slitlamp examination disclosed only mild superficial punctate keratopathy associated with repeated tomometry, with no differences in frequency or severity between ticrynafen- and vehicle-treated eyes.

After 5 days of twice-daily unilateral topical administration of 2% ticrynafen ointment, facility in the ticrynafen-treated eyes averaged 28% ± 9% higher than in the contralateral vehicle-treated controls (Table; n = 6; P = .03). There was no significant correlation between treated vs vehicle eye IOP differences and treated/vehicle eye facility response, with or without adjustment for baseline IOP.

MONKEYS WITH UNILATERAL LASER-INDUCED GLAUCOMA

Six-hour baseline diurnal IOP (day −4) averaged between 34.0 ± 3.1 and 37.5 ± 4.0 mm Hg (Figure 3A). The IOP immediately before and for 6 hours after
vehicle treatment the next day (day −3) averaged be-
 tween 34.0 ± 2.6 and 37.3 ± 3.3 mm Hg (Figure 3, B).
Since there was no apparent effect of the vehicle
(Figure 3, H), the vehicle-treated IOP diurnal curve
was used for comparison with ticrynafen treatment at
the same time of the day in the same eye. The onset of
IOP reduction after ticrynafen treatment did not occur
until after the seventh dose beginning on day 4. The
maximum IOP decline on day 4 averaged 7.5 ± 2.0 mm
Hg (P,.05; n = 4) at hour 4, and on day 5 averaged
9.8 ± 2.4 mm Hg (P,.05; n = 4) at hour 2. The IOP in
the untreated contralateral normotensive eyes dis-
played normal diurnal fluctuation during the course of
the experiment, averaging between 15.8 ± 1.2 and
18.5 ± 0.7 mm Hg (Figure 4).
Slitlamp examination showed no abnormalities in
any vehicle-treated eye or in 3 of 4 ticrynafen-treated eyes.
Corneal epithelial edema was noted in 1 ticrynafen-
treated eye 2 hours after dosing on days 1 and 4; the edema
lesioned by 4 hours and disappeared by 6 hours after dos-
ing. However, a confluent epithelial defect occurred in
the same eye on day 5 of treatment.

**COMMENT**

In normotensive cynomolgus monkeys, ticrynafen pro-
duced an increase in outflow facility when given by AC
and reservoir exchange, but not at similar doses given
by intracameral bolus injection. Anterior chamber and
reservoir exchange, as performed here, allows more rapid
administration of drug, more complete mixing of the AC,
and better maintenance of the drug concentration dur-
ing posttreatment facility measurements (as the perfus-
te in the reservoir contains the desired drug concentra-
tion). These pharmacodynamic differences may explain
ticrynafen's greater efficacy when given by AC-reservoir
exchange.

### Total Outflow Facility After Intracameral or Topical Ticrynafen or Vehicle in Cynomolgus Monkeys*

<table>
<thead>
<tr>
<th>Ticrynafen Concentration and Route</th>
<th>No.</th>
<th>Ticrynafen</th>
<th>Vehicle</th>
<th>Ratio, Ticrynafen/Vehicle</th>
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<tr>
<td>10 µL of 2.5-mmol/L AC bolus</td>
<td></td>
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<tr>
<td>Preinfusion</td>
<td>6</td>
<td>0.42 ± 0.70</td>
<td>0.37 ± 0.06</td>
<td>1.13 ± 0.11</td>
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<td>1 h postinfusion</td>
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<td>0.49 ± 0.09</td>
<td>0.48 ± 0.08</td>
<td>1.03 ± 0.10</td>
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<tr>
<td>Postinfusion/preinfusion</td>
<td>6</td>
<td>1.15 ± 0.05†</td>
<td>1.27 ± 0.09†</td>
<td>0.92 ± 0.06</td>
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<tr>
<td>10 µL of 25-mmol/L AC bolus</td>
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</tr>
<tr>
<td>Preinfusion</td>
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<td>0.32 ± 0.03</td>
<td>0.31 ± 0.04</td>
<td>1.15 ± 0.18</td>
</tr>
<tr>
<td>1 h postinfusion</td>
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<td>0.38 ± 0.07</td>
<td>0.31 ± 0.05</td>
<td>1.26 ± 0.18</td>
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<tr>
<td>Postinfusion/preinfusion</td>
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<td>1.13 ± 0.12</td>
<td>1.01 ± 0.06</td>
<td>1.12 ± 0.11</td>
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<td>0.04-mmol/L AC exchange</td>
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<td>0.26 ± 0.06</td>
<td>0.23 ± 0.07</td>
<td>1.45 ± 0.48</td>
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<td>0.5 h postinfusion</td>
<td>4</td>
<td>0.28 ± 0.08</td>
<td>0.23 ± 0.06</td>
<td>1.25 ± 0.32</td>
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<tr>
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<td>1.13 ± 0.12</td>
<td>1.21 ± 0.34</td>
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<td>0.35 ± 0.06</td>
<td>0.33 ± 0.04</td>
<td>1.12 ± 0.20</td>
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<tr>
<td>0.5 h postinfusion</td>
<td>5</td>
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<td>0.36 ± 0.09</td>
<td>1.29 ± 0.38</td>
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<td>1.46 ± 0.14†</td>
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<td>0.27 ± 0.03</td>
<td>1.17 ± 0.07§</td>
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<td>0.5 h postinfusion</td>
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<td>0.75 ± 0.20</td>
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<td>1.97 ± 0.29‡</td>
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<td>2.37 ± 0.27</td>
<td>-- 1.40 ± 0.15§</td>
<td>1.73 ± 0.18¶</td>
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<td>4.0-mmol/L AC exchange#</td>
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<tr>
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<td>0.29 ± 0.04</td>
<td>0.32 ± 0.04</td>
<td>0.93 ± 0.08</td>
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<tr>
<td>0.5 h postinfusion</td>
<td>9</td>
<td>0.31 ± 0.05</td>
<td>0.40 ± 0.05</td>
<td>1.36 ± 0.14§</td>
</tr>
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<td>1.84 ± 0.10</td>
<td>1.30 ± 0.13</td>
<td>1.48 ± 0.11‡</td>
</tr>
<tr>
<td>0.2-mmol/L AC exchange**</td>
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<td></td>
</tr>
<tr>
<td>Preinfusion</td>
<td>7</td>
<td>0.30 ± 0.05</td>
<td>0.33 ± 0.05</td>
<td>0.93 ± 0.10</td>
</tr>
<tr>
<td>0.5 h postinfusion</td>
<td>7</td>
<td>0.52 ± 0.07</td>
<td>0.38 ± 0.06</td>
<td>1.47 ± 0.15‡</td>
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<tr>
<td>Postinfusion/preinfusion</td>
<td>7</td>
<td>1.80 ± 0.12</td>
<td>1.14 ± 0.08§</td>
<td>1.60 ± 0.11‡</td>
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<tr>
<td>5 d 2% topical ointment</td>
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<tr>
<td>Posttreatment</td>
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<td>0.43 ± 0.03</td>
<td>0.35 ± 0.04</td>
<td>1.28 ± 0.09†</td>
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</tbody>
</table>

*Facility data are mean ± SEM microliters per minute per millimeter of mercury for the number of monkeys indicated, each contributing 1 ticrynafen-treated and
1 vehicle-treated eye. Differences between or ratios of ticrynafen-treated and vehicle-treated eyes were tested against 0 or 1, respectively, by the 2-tailed paired t
test. AC indicates anterior chamber.
†P<.05.
‡P<.005.
§P<.10.
¶P<.001.
#Results here are the same as for the section marked with double asterisks, but include 2 animals with high posttreatment facility in the control eye.
**Results here are the same as for the section marked with the number sign, but exclude 2 animals with high posttreatment facility in the control eye.
normalities in 2 of 4 eyes. In monkeys with bilaterally
ompared with contralateral control eyes.5

1.5% ethacrynic acid: 8.5 mm Hg, corneal abnormalities in 3
1.5% ointment, given once daily for 5 days, significantly
m 2.5% ethacrynic acid: 8.5 mm Hg, corneal abnormalities in 3
1.5% ethacrynic acid: 6.5 mm Hg, corneal abnormalities in 2 of 4 eyes). In monkeys with bilaterally
1.5% ethacrynic acid: 8.5 mm Hg, corneal abnormalities in 1 of 4 eyes; 2.5%
Ticrynafen, 1 mmol/L, appears maximal and increased fa-
the Goldmann equation, even a 52% facility increase to 0.50
p, episcleral venous pressure of 10 mm Hg, and uveoscleral
veins of 10 mm Hg, and episcleral venous pressure, aqueous
ES to baseline; ethacrynic acid, 0.25 mmol/L, which is also
Kruskall–Wallis analysis with Tukey test (P < .05).

Topical 2% ticrynafen ointment, administered twice daily for 5 days, produced a 28% ± 9% facility increase and no ocular abnormalities, while 1.5% ethacrynic acid ointment, administered once daily for 5 days, produced a 40% ± 15% increase in facility and ocular abnormalities in all eyes (12 of 12 eyes).3 In glaucomatous monkey eyes, topical 2% ticrynafen ointment, administered twice-daily for 5 days, produced an IOP drop similar in magnitude and with fewer corneal abnormalities than once-daily 2.5% or 1.5% ethacrynic acid ointment in a similar base of mineral oil and petrolatum (ticrynafen: 9.8 mm Hg, corneal abnormalities in 1 of 4 eyes; 2.5% ethacrynic acid: 8.5 mm Hg, corneal abnormalities in 3 of 4 eyes; 1.5% ethacrynic acid: 6.5 mm Hg, corneal abnormalities in 2 of 4 eyes). In monkeys with unilaterally normotensive eyes, IOP after unilateral 2% ticrynafen ointment, administered twice daily for 5 days, averaged 1 to 1.5 mm Hg less in the ticrynafen-treated eyes than in the control eyes at the day 3 pretreatment and the 1- and 3-hour posttreatment measurements, but these differences were not statistically significant. Ethacrynic acid, 1.5% ointment, given once daily for 5 days, significantly lowered IOP by 2.8, 1.7, and 3.7 mm Hg before and 1 and 3 hours, respectively, after treatment on day 5 compared with contralateral control eyes.3

The small IOP reduction induced by topical ticrynafen in normotensive monkeys is not surprising given the low baseline IOP. When IOP is low, even a substantial effect on inflow or outflow may have little effect on IOP; this is evident from the Goldmann equation.21 In our experiments, IOP of the control eye on day 5, 3 hours after the morning treatment (immediately before facility measurements) was 10.3 mm Hg. Assuming an episcleral venous pressure of 10 mm Hg, and episcleral venous pressure, aqueous formation, and uveoscleral outflow to be the same in both eyes, a 28% higher trabecular facility in the ticrynafen-treated eyes would predict an IOP of 10.2 mm Hg by the Goldmann equation, ie, essentially the same as in the control eyes. In fact, IOP of the ticrynafen-treated eyes on day 5, 3 hours after the morning treatment (immediately before facility measurements) averaged 9.3 mm Hg. As an even more striking example, assume an aqueous formation rate of 1.5 µL/min, IOP of 13 mm Hg, trabecular facility of 0.33 µL·min⁻¹·mmHg⁻¹, episcleral venous pressure of 10 mm Hg, and uveoscleral outflow of 0.5 µL/min. By the Goldmann equation, even a 52% facility increase to 0.50 µL·min⁻¹·mmHg⁻¹ would only yield a 1-µm Hg decrease in IOP.

Monkeys with normotensive eyes under ketamine anesthesia and receiving no other drug exhibit a time-dependent decrease in IOP during 6 to 8 hours, perhaps related to ketamine itself, to depth of anesthesia, or to the normal diurnal rhythm for IOP.22 This may partly or completely account for the small but significant contralateral IOP reduction in our ticrynafen-treated animals, rather than a contralateral effect of ticrynafen itself. As we did not measure baseline facility, we cannot say whether facility increased in the control eye. The contralateral (nonglaucomatous) eye in the unilaterally glaucomatous monkeys demonstrated only the normal diurnal IOP decline, with IOP returning to the morning baseline each day, ie, no contralateral effect was evident.

The glaucomatous monkeys had received laser treatment in the midtrabecular meshwork of all 4 quadrants, and we did not measure their perfusion or tonographic

Figure 1. Chemical structures of ethacrynic acid and ticrynafen. Although the righthand portions of the molecules are identical, ethacrynic acid has substantial sulfhydryl reactivity, whereas ticrynafen does not.

Figure 2. Intracocular pressure (IOP) in 6 cynomolgus monkeys under ketamine hydrochloride anesthesia during twice-daily topical application of ticrynafen in one eye and vehicle in the opposite eye. Data are mean ± SEM IOP (A) in ticrynafen-treated and control eyes, or IOP difference (B) between eyes. BL indicates baseline. Time 0 hours on both days is at 9 AM. Time 0 hours on day 5 is 18 hours after the afternoon treatment on day 4 and immediately precedes the morning treatment on day 5. Asterisk indicates significantly different from ipsilateral pretreatment BL by the 2-tailed paired t test (P < .05).
outflow facility after they received ticrynafen. However, pilocarpine\(^23\) does produce a substantial IOP decrease and an outflow facility increase in this model, indicating that the meshwork can still respond functionally to mechanical distortion\(^24\) or a direct drug effect.\(^25\) Epinephrine also lowers IOP in the glaucomatous monkey model,\(^23,28\) but it is not known whether this effect is caused by enhanced trabecular or uveoscleral outflow.\(^29\) Some trabecular meshwork between the burns may have been unaffected by the laser treatment or subsequent scarring and remained responsive to the drug, or even damaged trabecular meshwork could be affected functionally by ticrynafen.

Ethacrynic acid produced a small but significant transient IOP rise after the day 5 treatment compared with day 5 baseline values in cynomolgus monkeys with normotensive eyes.\(^5\) A similar trend was seen with ticrynafen in our normotensive monkeys, but the magnitude was even smaller and not statistically significant.

Some intracameral doses of some sulfhydryl-reactive compounds may produce an acute facility decrease in enucleated calf and primate eyes,\(^34\) perhaps because of trabecular cell swelling. No postticrynafen IOP rise was seen on any day in the glaucomatous monkey eyes. In 4 other glaucomatous monkeys, IOP was measured hourly for 6 hours on the third day before, and then daily for 5 days during, once-daily treatment with normal saline. The IOP tended to decline over 5 days, but the change from baseline was not statistically significant at any time point (R.F.W., unpublished data).

Four- or 5-fold excess concentrations of cysteine block the ethacrynic acid–induced facility increase in enucleated calf eyes\(^1\) and living cynomolgus monkeys (M.A.C., P.L.K., unpublished data, 1997) and the ethacrynic acid–induced shape change in cultured human trabecular meshwork cells.\(^35\) This suggests that the ethacrynic acid effects might result from sulfhydryl reactivity. However, ticrynafen, which is structurally similar to

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**Figure 3.** Intraocular pressure (IOP) in 4 monkey eyes with laser-induced glaucoma at baseline (BL) before (A) and after topical application of vehicle (B) or 2% ticrynafen ointment (C-G). All data are mean ± SEM. H, Vehicle-treated minus ipsilateral BL IOP at the corresponding time point. I through M, Ticrynafen-treated minus ipsilateral vehicle-treated IOP at the corresponding time point. Time 0 (always 9:30 AM) on vehicle and all ticrynafen days immediately precedes topical treatment; on treatment days 2 through 5, time is 18 hours after the afternoon ticrynafen treatment on the previous day. Significantly different from 0.0 by the 2-tailed paired t test: asterisk indicates \(P < .10\); dagger, \(P < .02\); double dagger, \(P < .05\).
ethacrynic acid but putatively lacks sulfhydryl reactivity,
significantly lowers IOP in glaucomatous and increases outflow facility in normotensive monkey eyes. In addition, a recently published study reported that, in excised bovine eyes, 0.125-mmol/L ticrynafen increases facility by 102% relative to baseline, significantly more than the 50% washout-induced facility increase in control eyes, and that, in contrast to ethacrynic acid, the effect is maintained in the presence of a 5-fold excess concentration of cysteine. Cytoskeletal drugs such as cytochalasins, latrunculins, and certain protein kinase inhibitors such as H-7 and staurosporine may exert their facility-increasing effect by altering the shape and adhesion of endothelial cells in the meshwork and along the inner canal wall. Ethacrynic acid and ticrynafen both induced shape changes in cultured calf pulmonary artery endothelial cells and human trabecular meshwork cells, but ethacrynic acid had a greater effect at comparable doses. This might explain why, in our present study, a 4-fold higher concentration of ticrynafen delivered via AC exchange (ticrynafen maintained during facility measurements) was required to produce a facility increase similar to that with ethacrynic acid given via bolus injection. Nonetheless, given that ticrynafen and ethacrynic acid are of reasonably comparable potency and efficacy, and that the drugs likely lower IOP and increase outflow facility by similar mechanisms (eg, cell shape change; ethacrynic acid, ticrynafen), these data suggest that the facility-increasing, IOP-lowering action of ethacrynic acid and derivatives may not depend entirely, if at all, on sulfhydryl reactivity.

Despite evidence of changes in cell shape, volume regulation, and adhesion consequent to drug effects on cytoskeletal proteins such as actin and tubulin or sodium-potassium-chloride ion cotransport, the cellular biophysical mechanism by which ethacrynic acid and related compounds such as ticrynafen lower IOP and increase outflow facility remains elusive. Whatever the mechanism, it is intriguing to note that ticrynafen increases facility and lowers IOP, apparently in conjunction with a change in cell shape, as does ethacrynic acid, but apparently without microtubule disruption, and does so in the absence of sulfhydryl reactivity. Whether drugs such as ethacrynic acid and ticrynafen prove valuable for glaucoma therapy, they are useful probes for studying aqueous outflow mechanisms.

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Reprints: Paul L. Kaufman, MD, Department of Ophthalmology and Visual Sciences, University of Wisconsin,
A look at the past . . .

Galezowski has had made an ophthalmolmo-thermometer for measuring the temperature of the eye in the living. The bulb is arranged to fit the lower cul-de-sac, where is is allowed to remain three minutes. The normal temperature of the lower cul-de-sac varies from 33.7 to 36.2.


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