References


The Effect of Vanadate on Aqueous Humor Dynamics in Cynomolgus Monkeys

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Topical administration of 1% vanadate in a formulation designed to enhance penetration lowered intraocular pressure in monkeys' eyes. The decrease in intraocular pressure was associated with significant decreases in aqueous humor flow. Tonographic outflow facility was unaltered by topical vanadate. Invest Ophthalmol Vis Sci 25:359–361, 1984

Vanadate, given either as sodium metavanadate (NaVO₃) or sodium orthovanadate (Na₃VO₄), lowers intraocular pressure equally in rabbits.¹ The fall in intraocular pressure is not associated with significant changes in outflow facility or episcleral venous pressure. A reduction in the rate of aqueous humor secretion, resulting from the inhibition of ciliary epithelium (Na⁺K⁺)ATPase by vanadate, could explain these findings.² On the basis of the results of tonographic studies, the calculated aqueous humor flow decreases approximately 30% in rabbits 2 hours after topical administration of 1% vanadate.¹,³ Direct measurements of the effect of vanadate on aqueous flow have not been reported.

The topical application of 0.5% Na₃VO₄ was also reported to lower intraocular pressure in rhesus monkeys.¹ In initial trials, we found inconsistent effects of NaVO₃ at the maximum soluble concentration of 1% on the intraocular pressure of cynomolgus monkeys and poor penetration of NaVO₃ into rabbit eyes.

We now report the effects of NaVO₃ prepared with agents to enhance penetration, dimethylsulfoxide (DMSO) and Tween 80 on intraocular pressure, outflow facility measured by tonography, and aqueous humor flow directly measured by fluorophotometry⁴ in cynomolgus monkeys.

Materials and Methods. Eight adult cynomolgus monkeys, 4–5 kg, were studied. The monkeys were kept in primate chairs throughout each experiment. A drop of a local anesthetic (0.5% proparacaine hydrochloride) was applied to the eye before all measurements. The intraocular pressure was measured in awake animals, and the outflow facility and aqueous humor flow were measured in animals anesthetized with ketamine hydrochloride, 5–10 mg/kg given intramuscularly.

Vanadate, as sodium metavanadate (NaVO₃) (E. Merck, Darmstadt, Germany), was prepared in distilled water with 10% DMSO and 5% Tween 80 just prior to topical ocular delivery. Solutions were adjusted to a pH between 7.0 and 8.0 with 1 N hydrochloric acid. For all experiments, two 50-μl drops of 1% vanadate, 3–5 min apart, were applied to either the right or left eye, chosen at random. An equal volume of the same diluent containing DMSO and Tween 80 was administered to the fellow control eye. Baseline intraocular pressure was measured with a calibrated pneumotonometer twice prior to administration of the drops. Repeat intraocular pressure measurements were made at 30, 60, 120, 240, and 360 min after administration of 1% vanadate.

Tonography was performed with an Alcon EDT-103 tonography unit. Baseline outflow facility was determined from 9 AM to 10 AM. The tonography results were obtained at 2 hours after administration of 1% vanadate.
Table 1. The effect of 1% vanadate on intraocular pressure in eight awake monkeys

<table>
<thead>
<tr>
<th></th>
<th>Mean intraocular pressure ± SE (mmHg)</th>
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<tbody>
<tr>
<td></td>
<td>0 min</td>
</tr>
<tr>
<td>Vanadate</td>
<td>19.5 ± 0.4</td>
</tr>
<tr>
<td>Diluent</td>
<td>19.6 ± 0.4</td>
</tr>
</tbody>
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* Significant difference between eyes treated with vanadate and fellow control eyes, paired t test, *P < 0.05.

Table 2. The effect of 1% vanadate on aqueous humor dynamics in eight monkeys under ketamine anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Intraocular pressure (mmHg)</th>
<th>Outflow facility (µl/min/mmHg)</th>
<th>Aqueous flow (µl/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanadate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>22.4 ± 1.0</td>
<td>0.51 ± 0.05</td>
<td>1.95 ± 0.17</td>
</tr>
<tr>
<td>Treated</td>
<td>18.1 ± 0.6†</td>
<td>0.52 ± 0.04</td>
<td>1.36 ± 0.13%</td>
</tr>
<tr>
<td>Diluent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>22.9 ± 1.3</td>
<td>0.55 ± 0.06</td>
<td>1.91 ± 0.17</td>
</tr>
<tr>
<td>Treated</td>
<td>21.5 ± 0.7</td>
<td>0.58 ± 0.08</td>
<td>1.89 ± 0.18</td>
</tr>
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</table>

* Values shown are means ± SE before and 120 min after treatment.
† Significantly different as compared with baseline (*P < 0.02) and to control eyes (*P < 0.003), paired t test.
‡ Significantly different compared with baseline and with control eyes, paired t test. *P < 0.005.
increase in posterior chamber aqueous humor ascorbate, indicative of decreased entry of water into the posterior chamber. Thus, the effect of vanadate may be presumed to be largely due to an effect on aqueous humor production.

(Na$^+$K$^+$)ATPase activity is present in ciliary epithelium. Inhibitors of this enzyme, such as ouabain given systemically, lower the rate of aqueous humor formation in cats and humans. Vanadate is also a potent inhibitor of (Na$^+$K$^+$)ATPase, which acts in a fashion different from the cardiac glycosides. Although vanadate appears to have little or no effect on human intraocular pressure when administered topically in aqueous solutions, formulations to enhance penetration, as in the current monkey study, may produce positive results. Ocular penetration and (Na$^+$K$^+$)ATPase studies currently are being performed to elucidate the vanadate mode of action.

Vanadate also is noted to stimulate adenylate cyclase activity in isolated membrane preparations. Preliminary experiments indicate that vanadate also stimulates monkey ciliary body-iris adenylate cyclase in vitro (unpublished data, T. Mittag). Cyclic AMP and its analogs are reported to increase outflow facility. The absence of increased outflow facility and the elevation of aqueous humor cyclic AMP in rabbits after topical administration of vanadate implies that in rabbits the ocular effect of vanadate is not related to adenylate cyclase stimulation. However, the recent report that forskolin, an agent that stimulates adenylate cyclase directly without affecting the cell membrane receptors that are coupled to the cyclase enzyme, lowers intraocular pressure in rabbits, monkeys, and humans and reduces aqueous flow in rabbits suggests that reduction of aqueous humor formation may be another mechanism whereby stimulation of this enzyme could affect intraocular pressure.

Key words: vanadate, intraocular pressure, monkey, aqueous humor flow, outflow facility

References


Neovascularization of the Iris: An Experimental Model in Cats

Einar Stefansson, Maurice B. Landers III, Myron L. Wolbarsht, and Gordon K. Klintworth

Neovascularization of the iris was induced in cats by removing the vitreous and lens and creating a rhegmatogenous retinal detachment. The presence of new blood vessels on the anterior surface of the iris was verified from the second month onward by slit lamp examination, as well as by light microscopy six to twelve months after the operation. Control eyes undergoing vitrectomy and lensectomy, but without retinal detachment, did not develop rubeosis iridis. This model may allow investigation into causes and therapy of rubeosis iridis. Invest Ophthalmol Vis Sci 25:361–364, 1984.

The introduction of vitrectomy for the treatment of vitreal and retinal complications of diabetes mellitus and other conditions has rekindled interest in iris neovascularization, since vitrectomy apparently predis-