Intraocular Pressure Measurement in Cynomolgus Monkeys

Tono-Pen Versus Manometry

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Purpose. In living cynomolgus monkey eyes, the authors compared manometrically set and measured intraocular pressure (IOP) with simultaneous IOP readings obtained with the Tono-Pen (TP), a handheld application tonometer based on the Mackay-Marg principle.

Methods. In three pentobarbital-anesthetized cynomolgus monkeys, IOP was set and measured manometrically after anterior chamber cannulation through the peripheral cornea with a 26-gauge needle connected to a vertically adjustable reservoir and a pressure transducer. Intraocular pressure was raised in ~5 mm Hg steps from 5 mm Hg to 60 mm Hg and then lowered in 5 mm Hg steps to 5 mm Hg, with TP measurements taken at each increment and decrement in open and stopcock modes.

Results. Linear regression analysis of TP on manometric readings for grouped data from six eyes, with each data point representing the average of all the TP readings from one eye at each manometric pressure setting, showed a slope 0.692 ± 0.016 and 0.683 ± 0.023 (both significantly different from 1; P < 0.001), intercept 1.21 ± 0.60 and 1.64 ± 0.82 mm Hg (both significantly different from 0.0, P < 0.05), and correlation coefficient 0.981 and 0.96 in open stopcock and closed stopcock mode, respectively. There were no striking differences when the data were analyzed for individual eyes or animals, for open versus closed stopcock manometry, or for increasing versus decreasing manometric IOP.


The Tono-Pen (TP; Mentor O & O, Nowell, MA) is a handheld, self-contained instrument that operates on the same principle as the Mackay-Marg tonometer and that provides ease in handling, portability, and quickness. It consists of a 1.2-mm central plunger attached to a microstrain gauge transducer, surrounded by a stationary, nearly flush 3.2-mm annulus. The force exerted on the plunger is transmitted as a voltage wave that is analyzed by a microprocessor for acceptability. Three to six accepted samples are averaged. The mean pressure reading (in mm Hg) is displayed on a liquid crystal display along with the coefficient of variance (5%, 10%, 20%, or >20%). A short click is heard for each accepted single reading. When a measurement series is completed, a tone sounds and the average is shown on the liquid crystal display. A disposable latex membrane is placed over the transducer tip for each patient.

Studies have compared the TP to the standard Goldmann application tonometer or to manometry in humans1-9 and rats,10 but no data are available for the monkey. In the current study, we compared manometrically set and measured intraocular pressure (IOP) with simultaneous IOP readings obtained with the TP in living cynomolgus monkeys.

METHODS. Three cynomolgus monkeys (Macaca fascicularis) were anesthetized with intramuscular injection of ketamine (10 mg/kg) followed by intramuscular injection of pentobarbital sodium (35 mg/kg), and they were placed in a prone position in a head-holder. Each eye was cannulated using a branched 26-gauge needle. One arm of the needle was connected to a vertically adjustable reservoir of degassed mock aqueous humor (Bárány's solution) by polyethylene tubing. The other arm was connected by polyethylene tubing to a pressure transducer, amplifier, voltmeter, and pen recorder. Intraocular pressure could be read directly from the voltmeter. It was raised

FIGURE 1. Manometric (x) versus Tono-Pen (TP) (y) readings. Each data point is the average of all the TP readings from one eye at each manometric pressure setting (six eyes, 12 manometric pressure settings). (broken line) x = y; (solid line) least square regression of TP measurements on manometric intraocular pressure. Slopes and intercepts are estimates ± SEM. P values indicate probability that slope = 1, intercept = 0; r = correlation coefficient.

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by 5-mm Hg increments from 5 mm Hg to 60 mm Hg, and then it was lowered by 5-mm Hg decrements from 60 to 5 mm Hg (by raising and lowering the reservoir). The pressure drop across the needle was calculated to be 0.17 mm Hg at 24 mm Hg. The TP was used to take one to three measurements at each level with the stopcock open and closed to the eye. We accepted measurements with a coefficient of variation of ≤5%.

This study was conducted in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

RESULTS. Linear regression analysis comparing TP and manometric readings, with each data point in Figure 1 representing the average of the TP readings taken from one eye at each manometric pressure setting (i.e., 6 eyes, 12 manometric pressure settings), showed slope 0.692 ± 0.016 (±SEM) and 0.683 ± 0.023 (both significantly different from 1, \( P < 0.001 \)), intercept 1.21 ± 0.60 mm Hg and 1.64 ± 0.82 mm Hg (both significantly different from 0, \( P < 0.05 \)), and correlation coefficient 0.981 and 0.960, in open and closed stopcock mode, respectively.

The data also were separated and regrouped in several other ways. Figure 2A shows, for open (\( A_o \)) and closed (\( A_c \)) stopcock modes separately, all TP readings collected from all six eyes whether the manometric pressure settings were in increasing or decreasing sequence. Figure 2B shows, for open (\( B_o \)) and closed (\( B_c \)) stopcock modes separately, all TP readings collected from all six eyes when the manometric pressure settings were increased sequentially, whereas Figures 2C, and 2C show the analogous data for sequentially decreasing manometric pressure settings.

There was excellent agreement between data obtained in the open versus closed stopcock modes, in right versus left eyes of an individual animal (not shown), in different animals (not shown), and in sequentially increasing versus decreasing manometric IOP.

DISCUSSION. In cynomolgus monkeys, the TP underreads IOP when compared to manometry except at IOP ≤ ~5 mm Hg, for reasons that are unclear. In six of nine previous studies in postmortem or living human eyes, the TP tended to overestimate IOP < ~17 mm Hg and to underestimate IOP > ~25 mm Hg. One study reported significant overestimation of IOP by the TP compared to the Goldmann applanation tonometer over the entire IOP range of 0 to 45 mm Hg in normal and postpenetrating keratoplasty living human eyes; the overestimate was more pronounced in the latter. Another study analogously reported significant overestimation of manometrically set and measured IOP by the TP over the entire IOP range of 0 to 65 mm Hg immediately after same-size or 0.5 mm-oversized penetrating keratoplasty in postmortem human eyes. Only one postmortem study reported accurate measurements throughout the IOP range, based on a mean of five separate measurements at five manometric pressures between 10 and 50 mm Hg. One study in Norway rats reported that the TP overestimated manometric IOP < 20 mm Hg while underestimating IOP > 25 mm Hg. However, in our animals, the correlation was strong and the variance low, meaning that the TP can be used in this and presumably other monkey species if the raw data are corrected with the appropriate calibration curve or equation. Before making...
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this generalization, however, at least one and preferably several other units of this instrument should be tested to determine how much inter-unit variability exists. Presumably, there will be little. The exercise is worthwhile because the TP is such a convenient instrument to use.

Key Words
cynomolgus monkey, glaucoma, intraocular pressure, tonometry, Tono-Pen.

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References

Dexamethasone–Cyclodextrin–Polymer Co-complexes in Aqueous Eye Drops

Aqueous Humor Pharmacokinetics in Humans

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Purpose. To test an aqueous eye drop solution containing a high concentration of dexamethasone in a cyclodextrin-based drug delivery system. This system increases both drug solubility in aqueous eye drops and drug permeability into the eye, through drug-cyclodextrin-polymer co-complexes. Methods. 2-hydroxypropyl-β-cyclodextrin is a water-soluble oligosaccharide that can be used to dissolve lipophilic drugs, such as dexamethasone, in aqueous solutions. Co-complexation with a polymer further increases the solubility and increases drug permeability through biologic membranes. Eye drops containing dexamethasone (0.32% and 0.67%), 2-hydroxypropyl-β-cyclodextrin, and polymer were given to patients before cataract surgery, and the resultant dexamethasone concentration was measured from aqueous humor samples.

Results. The dexamethasone–cyclodextrin drops give a significantly higher concentration of dexamethasone in aqueous humor than dexamethasone alcohol 0.1% (Maxidex). Heating of the dexamethasone-cyclodextrin-polymer co-complexes appears to enhance the permeability of the drug into the eye.