An improved model of experimentally induced ocular hypertension in the rabbit.

Luciano Bonomi, Laura Tomazzoli, and Demetrio Jarra.

A model of experimentally induced ocular hypertension for the evaluation of antiglaucoma drugs in the unanesthetized rabbit is described. It is based on the intravenous infusion of suitable amounts of 5 per cent glucose solution, and advantageously substitutes the oral water load. The method is sensitive to drugs acting both on the outflow facility (2 per cent pilocarpine) and on aqueous humor formation (10 per cent gwarenthidine).

In the search for improved medical therapy for glaucoma, new drugs must be tested experimentally in animals before any clinical trials in human beings are made. For practical and economical reasons the animal species most commonly used is the rabbit.

Unfortunately, the effect of many drugs on normal intraocular pressure is slight, so that their pressure-lowering properties may be missed or underestimated.

In the hope of obtaining more reliable results, many models of experimental ocular hypertension have been developed in the past, but most of them turned out to have important drawbacks and have been abandoned.

The requirements for a satisfactory experimental model of ocular hypertension are that it should (1) leave intact the ocular structures that respond to the action of the drug—for the study of drugs active on the outflow, the integrity of the outflow pathways is essential; (2) allow unanesthetized animals (therefore normally responsive to drugs and stimuli) to be used; (3) avoid trauma or excessive stimulation of the eye; and (4) be simple and easily reproducible.

It has been shown that it is possible to raise the intraocular pressure of normal rabbits by water load and that the ocular hypertension so produced is sensitive to drug action.

Recently a good experimental model based on water loading and Mackay-Marg tonometry in awake rabbits has been advocated by Seidenhamel and Dungan. The model was demonstrated to be sensitive to epinephrine and suitable for testing the effect of antiglaucoma drugs. Nevertheless it requires the rather troublesome procedure of administering large amounts of water to the animals via orogastric gavage.

Betti has demonstrated that in human beings the conventional water load can be advantageously replaced by the intravenous infusion of suitable amounts of 3 per cent glucose solution. The glucose is quickly removed from the circulation, and a lowering of the serum osmolarity ensues, which in turn produces a rise of intraocular pressure. This method has the advantage of being simpler and more reproducible than the water-drinking test, and individual variations due to differences of water absorption from the intestinal tract are avoided.

Since for reliable tonometry in awake rabbits, it is advisable to keep the animals as quiet and unfrightened as possible, avoiding excessive manipulation and stimulation, we thought of adapting this method to the rabbit with the aim of using it as a model of experimentally induced ocular hypertension for the evaluation of antiglaucoma drugs.

Methods. The experiments were performed on albino rabbits of both sexes, weighing 2 to 3 kilograms. The intraocular pressure (IOP) was measured with a Mackay-Marg electronic tonometer, after surface anesthesia (0.4 per cent benzylate [Novesine]). The tip of the tonometer was moistened with mineral oil to avoid corneal abrasion.

IOP elevation was obtained by rapid infusion of 5 per cent glucose solution through a 20-gauge needle in the marginal vein of the ear. The amounts injected were 5, 10, and 15 ml. per kilogram of body weight and the infusion was accomplished in all animals within 20 seconds.

Results and discussion. Immediately after the end of the infusion the eye pressure increased in all animals, reaching its maximum level between 5 and 10 minutes and returning to pretreatment levels within 40 minutes. The values of IOP increase were dependent on the amount of solution infused: the administration of 15 ml. per kilogram produced an increase of about 12 mm. Hg, whereas with 10 and 5 ml. per kilogram, a still
Fig. 1. Mean intraocular pressure in 18 rabbits after the intravenous infusion of different amounts of 5 per cent glucose solution.

Fig. 2. Mean intraocular pressure in the two eyes of six otherwise untreated rabbits after the intravenous infusion of 15 ml. per kilogram of 5 per cent glucose solution.
clear but quantitatively less important effect was reached (Fig. 1). The values and the course of the ocular pressure elevation were similar in the two eyes (Fig. 2).

The pupil was unaffected, the animals were not disturbed, and no evident side effects were produced by the treatment.

To ascertain whether the method is suitable for testing drugs active on the ocular pressure, two groups of six rabbits were treated, respectively, with 2 per cent pilocarpine and 10 per cent guanethidine. In each group of rabbits the drug was instilled twice in one eye, at 2 hours and at 30 minutes before the infusion of the glucose solution, and the other eye was left untreated as a control.

The results are shown in Figs. 3 and 4. It is quite evident that the ocular hypertension produced by our method is sensitive to the administration of the drug in both cases.

It is noteworthy that the pressure difference between the treated eye and the fellow eye used as a control is much more evident during the course of the experimentally induced hypertension when it reaches values of about 7 mm. Hg than in baseline conditions when it does not exceed 3 mm. Hg.

Our model of experimentally induced ocular hypertension in rabbits that we present therefore seems suitable for demonstrating the effect of drugs active both on outflow facility, like pilocarpine, and on aqueous humor formation, like guanethidine.

Our model has the advantage of being simple to perform; moreover, it is inexpensive and easily reproducible and permits the use of the intact eyes of unanesthetized, quiet, and unfrightened animals.

The procedure may also be repeated several times in the same batch of animals, giving comparable results.

From the 2nd Eye Clinic of the University of Padova, Verona, Italy. Submitted for publication March 3, 1976. Reprint requests: Prof. L. Bonomi, Direttore Clinica Oculistica Universitaria, Policlinico di Borgo Roma, 37100 Verona, Italy.

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Fig. 4. Mean intraocular pressure in six rabbits after intravenous infusion of 15 ml. per kilogram of 5 per cent glucose solution. The right eye was treated with 10 per cent guanethidine; the left eye was untreated.

REFERENCES


Effect of pilocarpine drops on the diurnal intraocular pressure variation in patients with glaucoma. DAVID M. WORTHEN.

The diurnal intraocular pressure was measured in 14 eyes of patients with glaucoma while they were using no medication and compared to the diurnal pressures while they were using pilocarpine drops. During the 48 hour control period, the pressures measured every 3 hours by the non-contact tonometer had a mean value of 26 mm. Hg and a mean maximum diurnal variation of 18.5 mm. Hg. During the pilocarpine treatment period, the mean pressure and maximum diurnal variation dropped to 17 and 8.5 mm. Hg, respectively. The greatest pressure-lowering effect occurred between 9 A.M. and 6 P.M.

This study was conducted to measure the effect of pilocarpine drops on the diurnal pressure variation in a group of patients with glaucoma. Kitazawa and Horie recently reported on the diurnal pressure variation in a group of 27 eyes with glaucoma. They found the peak pressure to occur between 8 and 14 hours (on a 24 hour clock) when the pressure was 37.6 ± 4.78 mm. Hg and the lowest pressure to occur around 1 hour when the pressure was 21.8 ± 2.43 mm. Hg. They measured the pressure every hour with a Goldmann applanation tonometer.

Henkind, Leitman, and Weitzman studied the diurnal curve in 11 subjects, six of whom had glaucoma. Pressures were measured hourly for 24 hours with a MacKay-Marg tonometer. The lowest pressures were measured between 2 and 4 a.m. in all subjects and the highest pressures between 10 and 16 hours for the 10 eyes with glaucoma.