ACTION OF DRUGS ON MOVEMENT OF OCULAR FLUIDS[1]

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This review gives attention principally to movement of aqueous humor, because little is known concerning actions of drugs on movement of other ocular fluids, and because in the eye disease glaucoma the actions of drugs on movement of aqueous humor have great practical significance.

It would certainly be valuable to have more knowledge of the actions of drugs on other ocular fluids. Edema of the cornea, cataracts, edema of the retina, detachment of the retina, and detachment of the choroid are among the important clinical problems involving movement of ocular fluids, with little known about the action of drugs. Vitreous humor causes serious problems when it pushes the lens and iris forward or when it comes forward to the cornea. No drug is yet known to affect the movement of vitreous humor selectively, but important observations have been made by Bleeker (*20*, *21*) that reducing the rate of flow of aqueous humor causes the lens to move appreciably posteriorly in some eyes, and that the volume of the vitreous humor can be increased or decreased osmotically.

The aqueous humor governs intraocular pressure according to the rate at which it is secreted into the eye and the resistance that it encounters in escaping to the veins on the surface of the eye. Formation of aqueous humor has been described in detail by Kinsey & Reddy (42), and methods for evaluation of its movement have been described by Grant (38), Bárány (4, 11), Oppelt (51), Becker (12), and Maurice (50). Much of the subject of movement of aqueous humor has to do with glaucoma, concerning which there are books (13, 28) and review articles (2, 52).

Caution is needed in comparing observations on different species. Most investigational work has been done on rabbits, but increasing use is being made of monkeys for closer comparison with human beings. Cats seem to present greater differences, with constriction of the iris artery in response to many drugs reported by Macri (49). Most important is the fact that the types of glaucoma which are common in human beings are rarely if ever encountered in animals.

Earlier reviews of physiological and pharmacological influences on in-

[1] The survey of literature pertaining to this review was concluded in September 1968.

traocular pressure by Grant (38, 40) provide the principal background for the present review, which is intended to bring the subject up to date, rather than to be comprehensive.

Cholinergic drugs.—Cholinesterase inhibitors and direct-acting cholinergic drugs have long been thought to reduce ocular pressure by reducing resistance to outflow of aqueous humor, accomplishing this in angle-closure glaucoma by constricting the pupil and opening the angle, and, in eyes with the angle open, by contracting portions of the ciliary muscle that mechanically pull upon the trabecular meshwork and cause outflow channels in this tissue to widen and to allow aqueous humor to escape more easily. For reviews of this aspect see Leopold (47) and Shaffer (69). Measurements by aqueous perfusion and anatomical studies in monkeys by Bárány (5–7, 10), Rohen (64), and Van Alphen (73) provide good support for this belief. Pilocarpine, whether injected into the blood stream or into the anterior chamber, has caused an equally prompt increase in facility of outflow, consistent with direct action on ciliary muscle rather than on trabecular meshwork, which is avascular and presumably not readily accessible from the blood stream. Significant differences in responsiveness to pilocarpine in different varieties of monkeys appear to relate to anatomical variations in their ciliary muscles (64). The structural features of the aqueous outflow channels that determine resistance to aqueous outflow, probably mainly the size of pores in the trabecular meshwork, have a considerable range of variation in normal human and monkey eyes; in eyes with open-angle glaucoma the resistance is abnormally high (39). In general, eyes with higher resistance, which probably have smaller, more critical pores, are more responsive to action of cholinergic drugs than eyes with low resistance, but among open-angle glaucomatous eyes are some exceptional ones that are peculiarly unresponsive (28).

Reduction of resistance to outflow is not the only action of cholinergic drugs. Bárány (7) and Bill (19) have shown in monkeys that while pilocarpine reduces resistance in the main channels for outflow, it impedes escape of aqueous humor by a minor route through the ciliary muscle itself, contraction of the muscle causing it to become more compact and presumably less permeable. Berggren (16) has reported that pilocarpine and physostigmine at 10^{-9} and 10^{-7} M can interfere with secretion of aqueous humor by rabbit ciliary processes.

Clinically it has long been evident that action of cholinergic drugs on the pupil is prevented by paralysis of the sphincter muscle when the intraocular pressure has become too high. Tornqvist (72) now has shown in monkeys that also the ciliary muscle, which is important for improving outflow of aqueous humor in open-angle glaucoma, is prevented from acting when ocular pressure is too high relative to the blood pressure. This has provided a new reason for taking recourse to other types of antiglaucoma agents when the ocular pressure becomes very high in either open-angle or angle-closure glaucoma.

Anticholinergic drugs.—Agents that dilate the pupil can precipitate acute angle-closure glaucoma in a small proportion of human beings who have eyes that are peculiarly anatomically predisposed by having an unusually small anterior segment, relatively large lens, and consequently very narrow anterior chamber angle. This is a potential adverse side effect of a large number of drugs that have anticholinergic properties. For clinical review see Grant (40).

In normal human eyes, anticholinergic drugs applied in sufficient concentration to cause paralysis of the ciliary muscle (i.e., cycloplegia) generally cause little or no disturbance of pressure, but in eyes with open-angle glaucoma these drugs can significantly increase resistance to aqueous humor outflow and elevate ocular pressure, with the anterior chamber angle remaining grossly open. This action is opposite to that of the cholinergic drugs and may be attributable to blocking of parasympathetic tone in the ciliary muscle. Bárány (9) has shown that, in association with cycloplegia in normal human and vervet monkey eyes, resistance to aqueous humor outflow increases more in eyes with spontaneously high resistance than in eyes with spontaneously low resistance, as though the intrinsic resistance to outflow were determined by the size of channels or pores in the trabecular meshwork, and the smaller the radius of the pore the greater the effect produced by a given change in tension of the ciliary muscle. In open-angle glaucoma, in which the resistance to outflow characteristically is higher than normal, anticholinergic drugs tend to cause a proportionally greater increase in resistance to outflow and elevation of pressure, but not necessarily uniformly for a given resistance or effective pore size. The range of possible change must be affected by additional factors including differences in amount of parasympathetic tone.

When anticholinergic drugs are administered systemically a very small fraction reaches the eye. If the amount is enough to dilate the pupil, there is the risk of precipitating angle-closure glaucoma in the peculiarly disposed people already mentioned, but there seems to be no reason to fear aggravation of open-angle glaucoma unless the amount reaching the eye is sufficient to cause cycloplegia (40). Lazenby & Reed (46) have shown that open-angle glaucomatous patients who develop mydriasis, cycloplegia, and significant rise of ocular pressure after cyclopentolate drops have been applied to the eye have had no appreciable alteration of pressure after two doses of atropine sulfate (0.6 mg each) by mouth—a quantity which does not produce significant cycloplegia. More documentation is needed of the effect of repeated administration (40).

Berggren (16) has reported inhibition of secretion of aqueous humor by 10^{-7} *M* atropine in rabbit ciliary processes, but in cynomolgus monkeys Bill (19) has found evidence of an increase in the rate of aqueous humor formation in response to atropine with relationship to human eyes uncertain.

Adrenergic drugs.—Mydriasis can produce angle-closure glaucoma in people with anatomically predisposed eyes, and, in some people with grossly

open anterior chamber angles, mydriasis has been shown by Kristensen (43) to cause transitory elevation of ocular pressure by causing dispersal of pigment from the iris; apparently pigment can temporarily obstruct outflow channels for aqueous humor.

More commonly, adrenergic drugs reduce pressure in the eye. Most adrenergic drugs can be divided into two categories according to their effects on the eye: the first, exemplified by epinephrine and norepinephrine, causes vasoconstriction and mydriasis; the second, exemplified by isoprenaline, causes vasodilation and has little or no effect on the pupil. Several drugs in both categories have been tested on normal human eyes by Weekers et al. (74–76) and have been found to reduce the pressure without particular relation to effect on pupil or vessels.

Only epinephrine has been widely used clinically (in eyedrops) in treatment of glaucoma. Isoprenaline and ethylnorphenylephrine (Russian Phetanol) have been used on a much smaller scale. All three have the disadvantage of frequently inducing contact sensitivity and consequent ocular irritation, and isoprenaline occasionally causes unpleasant sensations from cardiac side effects. Pharmacologically, only epinephrine, norepinephrine, and isoprenaline have been examined in detail, and the mechanism by which these drugs reduce the ocular pressure is still far from clear. Epinephrine applied to the eye can reduce ocular pressure for many hours, much longer than the grossly evident effects on the superficial vessels of the eye. Epinephrine has been shown to reduce resistance to outflow (66), but sometimes it has reduced ocular pressure disproportionately more, suggesting that epinephrine can also reduce the rate of formation of aqueous humor (14, 34, 76). In vervet monkeys aqueous perfusion experiments by Bárány (11) indicate that epinephrine increases both true facility of aqueous outflow and so-called pseudo-facility, which may represent a disturbance of the formation mechanism for aqueous humor. In excised ciliary processes from rabbits, Berggren (17) has observed that movement of fluid resembling aqueous secretion is inhibited by 10^{-4} *M* epinephrine.

Eakins & Ryan (34) have found reduction of ocular pressure by norepinephrine to be largely explainable by measured reduction of resistance to aqueous outflow in animals, but in human eyes the reduction of resistance seems insufficient to account for the degree of reduction of pressure, and some reduction in aqueous formation has been postulated by Weekers (74) and Bonomi (25).

In rabbits attempts have been made to evaluate the effect of vasoconstriction alone. One vasoconstrictor, angiotensin, in tests by Eakins (33) appeared to cause a small decrease in aqueous humor formation but not to affect facility of outflow, while vasopressin, tested in the anterior chamber by Sears (66), raised facility of outflow; this leaves the role of vasoconstriction still an open question.

Isoprenaline, though a vasodilator, also reduces ocular pressure, with evidence for both reducing resistance to outflow and for reducing aqueous

humor formation (34, 74). Gnädinger & Bárány (35) have provided evidence that at least in rabbit eyes reduction of resistance to outflow by this drug is attributable to β-adrenergic action.

Much has been done in trying to define the action of natural mediators of the sympathetic innervation of the eye by seeking correlation with the action of adrenergic drugs. Bárány (3), Sears (67, 68), and Langham (45) have studied the effect of cervical ganglionectomy in rabbits, consisting of increase in facility of outflow and decrease in ocular pressure developing during 24 hours in association with degeneration of nerve endings in iris and other tissues. Norepinephrine which is released appears to act directly in some as yet unknown manner upon the outflow channels for aqueous humor. Eakins (34) has shown that the eye becomes supersensitive to norepinephrine. Drugs that deplete catecholamine stores, such as reserpine and guanethidine, and α-blocking agents such as phenoxybenzamine and phentolamine interfere with the effect. Study of sympathectomy and of α- and β-adrenergic and antiadrenergic drugs has led to a belief that receptors for increase in facility of outflow are of both α and β types (8, 35).

Antiadrenergic drugs.—Predominantly α-blocking drugs, with the exception of dibenamine, have had no clinically useful action on ocular pressure. Phentolamine was found by Constant & Becker (29) to reduce aqueous humor formation transiently in rabbits, and dihydroergotoxine given as eyedrops according to Diotallevi & Auricchio (32) has reduced ocular pressure in normal and glaucomatous patients by reducing aqueous humor formation, but for less than a week, despite repeated administration.

Predominantly β-blocking drugs have also so far shown no great influence on ocular pressure (24). Propanolol given intravenously to glaucomatous patients was found by Phillips (60) to produce slight lowering of ocular pressure, but whether repeated oral administration can maintain any worthwhile effect remains to be seen. Dichloroisoprenaline was shown by Bárány (3) to improve facility of outflow and reduce ocular pressure in rabbits, but rather than due to β-blocking this appears to be an α-adrenergic action of the drug which can be blocked by the α-blocker dibenamine.

The antiadrenergic drugs betanidine, bretylium, and guanethidine administered as eyedrops, and dibenamine given intravenously, reduce ocular pressure in the eyes of animals and glaucomatous patients principally by interfering with formation of aqueous humor (23, 31, 68), but clinical usefulness is limited by various undesirable side effects. Moxisylyte (53), reserpine (22), and methyldopa (56) have reduced ocular pressure slightly in rabbits but have not proved efficacious in glaucomatous patients.

Digitalis and related glycosides.—Most attention has been given to ouabain in animal and *in vitro* experiments (16, 26, 27, 44). Ouabain has been shown by Bonting (26, 27) and Berggren (16) to reduce Na-K-ATPase activity in the ciliary processes and to reduce aqueous formation, most effectively when administered directly into contact with the ciliary body, less effectively when given intravenously.

Most testing in patients has been not on ouabain but on digitalis, digitoxin, digoxin, lanatoside-C, and strophanthin-K, administered systemically. Large intravenous doses have been most clearly effective in reducing ocular pressure in patients, but toxic side effects have limited the dosage and interfered with continuing use (30, 61). With oral administration some clinical investigators have reported significant pressure reduction (30, 62) and others little or none (54, 61). Generally the digitalis glycosides are too injurious to the cornea to use as eyedrops, but Bellone & Faraldi (15a) found that an Italian proprietary eyedrop containing 1 per cent "digitalina" was not injurious, and reduced ocular pressure about 15 per cent, interfering with intraocular Na-K-ATPase and formation of aqueous humor.

Psychotropic drugs.—The major tranquillizers, including phenothiazine derivatives and butyrophenone derivatives, given systemically, commonly reduce ocular pressure in rabbits (29, 63) and in normal and glaucomatous patients (37, 65), usually by 2 to 5 mm Hg initially; none of these drugs has proved to have a sustained lowering action on intraocular pressure when repeatedly administered. In rabbits, Constant (29) has found the initial pressure drop to be due to reduction of aqueous humor formation.

The antianxiety agents or minor tranquillizers, also barbiturates and narcotics, have shown similar patterns, commonly inducing a transitory reduction of a few mm Hg when first given in large doses to patients or rabbits, but seldom maintaining pressure reduction during repeated administration in ordinary dosage.

Anticonvulsant drugs (diphenylhydantoin, mephenytoin, primidone) that have been tested by Peczon in a few glaucomatous patients have had no appreciable effect on the ocular pressure (55).

Direct-acting central stimulating drugs that have adrenergic properties according to a recent review (40) have received little adequately controlled study regarding action on ocular pressure. Failures to obtain elevations of ocular pressure in open-angle glaucomatous patients or in monkeys have been reported after systemic administration of amphetamine and dexamphetamine, while on the other hand it has been claimed that elevation of pressure can be provoked in glaucomatous eyes by oral or subcutaneous administration of methamphetamine and methylphenidate (40). Evaluation, with proper controls and attention to spontaneous diurnal variations of pressure, is needed.

Caffeine and coffee have received much attention because of a long-standing suspicion that stimulation of the central nervous system has something to do with raising intraocular pressure. Graeber (36) has confirmed that 0.3 g of caffeine or an equivalent amount of coffee can raise the ocular pressure 5 to 6 mm Hg within an hour in a small proportion of patients with open-angle glaucoma. Whether this action has any relation to action on the central nervous system has not been established. It would be very interesting to know the mechanism.

Antidepressant monoamine oxidase inhibitors have been tested in rabbits

for effect on ocular pressure. Those effects that have been observed appear to be explained by peripheral actions on the eye or on blood pressure rather than on the central nervous system. Iproniazid has been ineffectual. Nialamide administered systemically has been shown to inhibit the monoamine oxidase in the epithelium of the ciliary processes, and, with doses that also caused a rapid fall of blood pressure, Tarkkanen (70) has found a slow and irregular lowering of the ocular pressure. Pargyline applied as eyedrops has caused a slow reduction of ocular pressure which Zeller et al. (78) have found to be sustained during continued administration.

Vasodilator drugs.—A recent review of this subject (40) indicates that there has been no conclusive evidence of significant sustained adverse action of systemically administered vasodilator drugs on ocular pressure in normal or open-angle glaucomatous human eyes, and so far no demonstration of induction of glaucoma in eyes anatomically predisposed to angle-closure. The following transient effects are observed. Inhalation of amyl nitrite occasionally causes a momentary rise of 2 to 3 mm Hg in ocular pressure, and Peczon (58) has found that inhalation of a mixture of 10 per cent carbon dioxide and 90 per cent oxygen causes a rise of 3 to 4 mm Hg in pressure in human eyes during the first 2 min, with gradual return to the original level in 5 to 6 min, regardless of whether the eye is normal or glaucomatous. Oral administration of single customary doses of nicotinic acid and cyclandelate caused no significant change in pressure in a large majority of open-angle glaucomatous human eyes, nor any appreciable change in depth of the anterior chamber (58).

Diuretic drugs.—According to a brief review and clinical appraisal by Peczon & Grant (59) only the potent carbonic anhydrase inhibitors, ethyl alcohol, and osmotic diuretics influence ocular pressure enough to be therapeutically useful in glaucomatous human beings. Furosemide reduces ocular pressure slightly. Ethyl alcohol has proved of interest as a special case. Peczon (57) and Houle (41) have shown that when given orally or intravenously to patients it reduces ocular pressure, more in glaucomatous than in normal eyes. This action is antagonized by administration of 0.5 unit of vasopressin, yet pressure reduction has been demonstrable in a glaucomatous patient with diabetes insipidus in the absence of the antidiuretic hormone.

Reduction of the rate of aqueous humor formation by acetazolamide has been reported by Linner (48) to be accompanied by a partially compensatory decrease of facility of outflow tending to limit pressure decrease in normal human eyes, but in glaucomatous eyes there is less of this seeming homeostatic response and pressure is reduced more effectively.

Little recent work has been done to elucidate the action of acetazolamide in reducing the rate of aqueous humor formation. Most investigators have agreed that the carbonic anhydrase of the ciliary processes is involved in formation of aqueous humor and that inhibition of the enzyme by acetazolamide is responsible for the reduced rate of formation, but the fact that locally applied acetazolamide has proven ineffectual except by intra-arterial

administration has remained something of an enigma. On the basis of experiments in rabbits and dogs, Thomas & Riley (71) have advanced the hypothesis that acetazolamide may suppress aqueous humor formation through a mediator from the adrenal medulla having α-adrenergic properties.

Corticosteroids.—A recent review (40) concludes that corticosteroids administered systemically appear rarely to have induced glaucoma in patients who have not had eye disease, but that they can aggravate pre-existing primary open-angle glaucoma and glaucoma secondary to uveitis.

The action of corticosteroids applied directly to the eyes has been reviewed by Armaly (1), and Becker (15), recounting that repeated application induces a rise of pressure varying in degree for different individuals; apparently the effect is genetically determined. In many instances glaucoma has been induced, seriously damaging vision in some patients. Most investigators find the rise of ocular pressure to be due mainly to increase in resistance to aqueous humor outflow (1, 15, 50), which generally is reversible.

The nature of the obstruction is unknown, but Armaly (1) and others have suggested that a mucopolysaccharide may accumulate in the trabecular meshwork. Claims of relief of corticosteroid glaucoma by trabeculotomy and by injection of hyaluronidase into the anterior chamber [Bietti & Quaranta (18)] lend some support to this hypothesis, but there has been no proof so far.

Attempts to induce glaucoma by topical administration to rabbits and monkeys were generally unsuccessful until Wood et al. (77) reported inducing elevation of ocular pressure in young rabbits.

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