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SYSTEMIC ATROPINE AND GLAUCOMA

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ATROPINE and other anticholinergic drugs are reputed dangerous for patients with glaucoma. For this reason, many psychopharmacologic agents, antihistamines, antispasmodics, and antiparkinsonian medications have been labeled with warnings against their use in the presence of glaucoma. This paper reviews the pathophysiology of the glaucomas and the effects of topical and systemic anticholinergics on intraocular pressure. Important questions to be asked urological patients who are to receive systemic anticholinergics and the consequences of the administration of these drugs will be emphasized.

The glaucomas are a series of diverse clinical conditions characterized by three main elements: increased ocular pressure, increased cupping and pallor of the optic disc, and loss of visual field. Obstruction to the outflow of aqueous humor appears to be the main basis for the increase of

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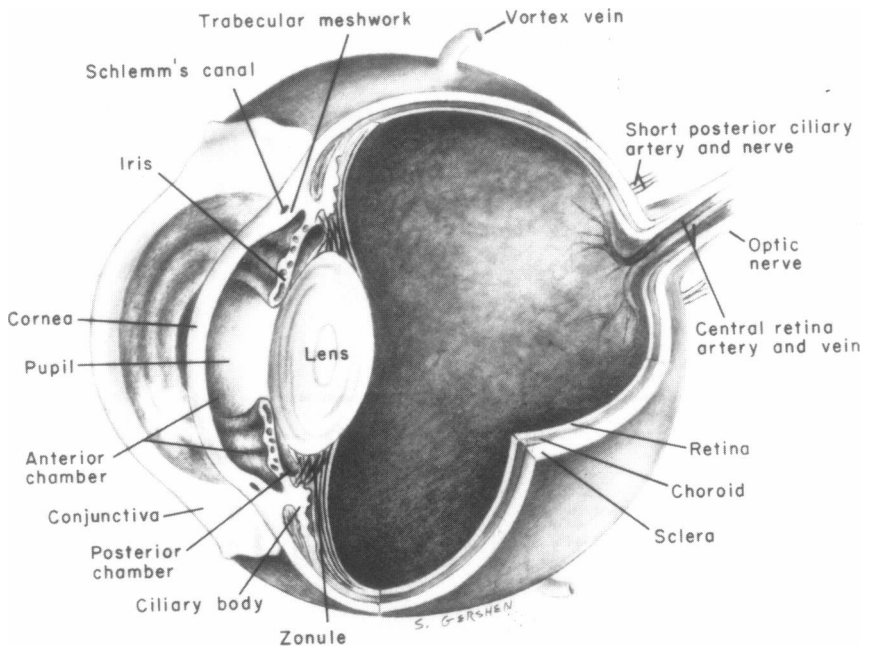

Fig. 1. Diagram of pertinent ocular structures.

ocular pressure in many, but not all glaucomas. Aqueous humor is produced primarily in the ciliary body and flows into the posterior chamber and then through the pupil into the anterior chamber (Figure 1). It leaves the eye through a connective tissue syncytium called the trabecular meshwork and then enters the Canal of Schlemm at the angle of the eye between the iris and the cornea (Figure 2) where it exits into a venous drainage network called the aqueous veins of Asher.[1]

Anticholinergic and parasympatholytic drugs block the action of cholinergic and parasympathetic innervation on the muscles of the iris and ciliary body. Parasympatholytic agents are commonly used topically to relax accommodation and to dilate the pupil. However, paralysis of accommodation (cycloplegia) and pupillary dilation may be unwanted, unpleasant, and even dangerous side effects of drugs administered systemically.[2]

Cycloplegia, from interference with the normal innervation of the ciliary muscle, can cause blurring of vision for near objects in young (less than 40 years old) patients. Blocking of parasympathetic innervation

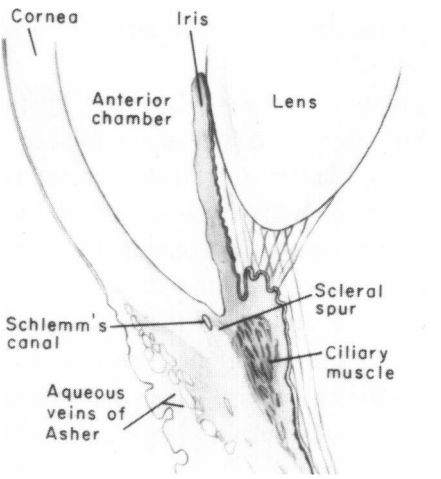

Fig. 2. Close-up of diagram of angle structures demonstrating the pathway of aqueous humor flow.

to the ciliary muscle can be dangerous to patients with borderline or actual, chronic open-angle glaucoma, because this may increase resistance to escape of aqueous humor from the eye and increase intraocular pressure. Normally, the physiologic tone of the ciliary muscle, dependent on parasympathetic innervation, assists in keeping open the channels for aqueous humor outflow by tension transmitted from the ciliary muscle through the scleral spur to the corneoscleral trabecular meshwork. In normal eyes with adequate channels for outflow of aqueous humor, the influence of ciliary muscle tone may be relatively insignificant, and blocking parasympathetic innervation locally or systemically will have little effect on facility of outflow or intraocular pressure. It has been shown, however, that topical administration of anticholinergics will cause intraocular pressure to rise more than 6 mm in 8% of normal adults.[6] However, in eyes with abnormal resistance to aqueous outflow, borderline or actual chronic open-angle glaucoma, the role of ciliary muscle tone in keeping open the outflow channels may be more critical, and parasympatholytic agents may cause an unwanted increase in outflow resistance and increased intraocular pressure.[3,4,5] In fact, Harris has demonstrated that 23% of patients with chronic open-angle glaucoma under medical control had an intraocular pressure elevation greater than 6

mm Hg after the topical application of the cycloplegic cyclopentolate.[6] There is a very high incidence of open-angle glaucoma in patients with diabetes mellitus (>18%).

The size of the pupil normally is regulated by the tone and state of parasympathetic innervation to the sphincter muscle of the iris. Interference with this innervation leads to mydriasis or pupillary dilation. In normal eyes this merely admits more light to the eye. A much more dangerous effect of dilating the pupils is encountered in certain eyes. Normally, the aqueous humor originating behind the iris in the ciliary processes flows forward through the pupil into the anterior chamber to reach the outflow channels of the trabecular meshwork and Schlemm's Canal in the angle of the anterior chamber. When the anterior segment is small or when the lens is disproportionately large or its anterior surface is further forward than ordinary, forming a shallow anterior chamber, the pupillary portion of the iris may be unusually closely applied to the anterior surface of the lens. In such eyes the aqueous humor encounters greater than ordinary resistance to flow through the pupil, and an abnormal billowing or forward bulging of the iris may result, sufficient to push the iris into actual contact with the trabecular meshwork, blocking the exit of aqueous humor and causing intraocular pressure to rise. This constitutes an attack of angle-closure glaucoma, which may be acute, painful, and extremely dangerous to the eye, and requiring immediate treatment.[8]

The potential role of parasympatholytic agents in precipitating such an attack is involved in the relationship between pupillary size, resistance to flow of aqueous humor from posterior to anterior chamber, and the resultant of forces acting on the periphery of the iris which govern its degree of forward bulging. In general, semidilation of the pupil most favors angle-closure. In semidilation there is likely enough slack or laxity of the iris and at the same time enough resistance to flow from the posterior to anterior chamber to cause the iris to bulge forward in the periphery and to close the angle. There is no reliably reproducible, safe test to preduct which eye[5] is at risk for the development of angle closure glaucoma.

Two of the most commonly used tests are the "darkroom provocative test" and the "prone provocative test." In the darkroom provocative test intraocular pressure is measured in the usual way, after which the patient sits in a darkened room for 20 minutes, at which time the pressure is remeasured. During this time, the pupil dilates somewhat and some pa-

tients may show precipitous elevation of the pressure. In the prone provocative test, the pressure is measured in the usual way, and then the patient lays face down for 20 minutes. During this time the lens-iris diaphragm falls forward in some patients and precipates glaucoma. Unfortunately, both false positive and false negatives occur with these tests. Clinical studies demonstrate that the eyes that will develop acute angle closure glaucoma usually belong to older patients (>60 years old) who are farsighted, with smaller eyes and anterior chamber depths less than 2.5 mm,[9] especially those who have had a previous attack of glaucoma in the fellow eye. It can be helpful to determine if an angle is occludable.

Gonioscopy, a technique whereby a contact lens is placed on the cornea, allows the ophthalmologist to view the actual area where the iris meets the cornea. (It must be emphasized that exceptions do occur to the above generalizations.)

Thus, atropine and other anticholinergics and parasympatholytics can cause elevation of intraocular pressure by the following mechanisms: In eyes with abnormally narrow anterior chamber angles, dilating the pupil may induce angle-closure glaucoma by allowing the iris to come in contact with the trabecular meshwork, blocking the aqueous outflow. In eyes with chronic open-angle glaucoma, the intraocular pressure may be raised without closing the angle independent of pupillary dilation through paralysis of ciliary muscle tone and subsequently increased aqueous outflow resistance through the trabecular meshwork.

When atropine is given orally or parenterally, its effects on the eyes are essentially the same as when applied directly to the eye, except that the amount reaching the eye from ordinary systemic doses appears generally to be relatively small and the effects accordingly much less. People receiving atropine or related drugs systemically may note enlargement of the pupils and weakened accommodation for near vision, usually associated with unpleasant dryness of the mouth. Specifically, Leopold and Comroe reported that atropine sulfate 0.6 mg injected intramuscularly in eight normal patients caused appreciable decrease in accommodation for near vision in 10 out of 16 eyes, but dilated the pupil in only 3 of the patients and not more than 1.5 mm in any.[10] Schwartz et al. studied the ocular effects of single dose intramuscular injections of atropine sulfate 0.5-0.6 mg in patients with either open-angle or narrow-angle glaucoma. Their topical medications were stopped 48 hours prior to the study, and intraocular pressures were measured every 20 to 30 minutes over two

hours after the atropine injection. In the open-angle glaucoma group, there was no change in intraocular pressure in seven of eight eyes, while one eye showed a 3 mm increase. In the narrow angle group (six patients in remission from previous attacks of angle closure glaucoma, five treated previously with peripheral iridectomies), there was no significant difference in intraocular pressure after the atropine injection. Pupillary size was measured in 15 eyes, 11 of which showed slight mydriasis up to 1 mm, averaging 0.5 mm of dilation. Four of 15 eyes had no mydriasis after atropine 0.5 mg intramuscularly. The authors concluded that "the safety of a single dose of parenterally given belladonna drug for preoperative medication in glaucomatous patients was clearly established."[10] However, they still recommended concurrent topical application of a miotic drop to counteract the potential mydriatic effect of the atropine and anesthetic agents.

Lazenby et al. demonstrated that while atropine sulfate 0.6 mg taken twice orally, four hours apart, had no significant influence on intraocular pressure in chronic open-angle glaucoma patients, a portion of these patients taking atropine sulfate 0.6 mg orally three times a day for seven days did have an increase in intraocular pressure after one week. Five of 12 patients not receiving antiglaucoma medication, and 4 of 9 patients taking topical medication had pressure elevations greater than 5 mm Hg but none greater than 14 mm Hg.[12,13] While the single injection of atropine seemed to have virtually no effect in Schwartz's open-angle glaucoma patients, a week of oral atropine three times a day had more significant effects in Lazenby's patients. Finally, in an evaluation of 25 patients with normal, nonglaucomatous eyes, Tammisto found no significant changes in intraocular pressure following the intramuscular injection of atropine sulfate 0.01 mg/kg.[14]

We therefore offer the following recommendations regarding the use of systemic atropine in glaucoma patients.

What questions then should the urologist ask of the patient who is to receive potential atropine? We propose the following: Have you ever had an attack of acute glaucoma in either eye? Has a glaucoma test on your eye ever been suspiciously high? Have you ever been diagnosed as having glaucoma, or is there a family history of glaucoma? Do you have diabetes?

If a patient is known to have narrow-angle glaucoma, while single dose systemic atropine has been shown to cause minor pupillary dilation (no more than 1 to 1.5 mm in some patients), a topical miotic should be

given concurrently to counteract potential mydriasis. Pilocarpine 2% should be given to both eyes one hour before systemic atropine is given.

If a patient is known to have open-angle glaucoma, while single dose systemic atropine had no major influence on intraocular pressure in such patients, the multiple-dose study reveals a pressure elevation in up to 44% of these patients. Therefore, while the ocular effect from ordinary systemic doses tends to be slight, it is expected to be outweighed by application of standard antiglaucoma medications: The open-angle glaucoma patient should continue with routine medical therapy.

If the diagnosis is unknown, Grant has estimated that in a racially heterogenous North American population not screened with regard to glaucoma, topical administration of an anticholinergic agent may be expected to induce acute angle-closure glaucoma in about one in 4,000 people over 30 years of age. It may also be expected to aggravate pre-existing or latent open-angle glaucoma in about one in 100 people older than 40.[15] The even rarer estimated occurrences of ocular effects reflecting the small concentration of parasympatholytic agents that may reach the eye via the systemic circulation (and then acting only in certain predisposed eyes) do not warrant routine antiglaucoma medication for an unscreened patient given a single dose of systemic atropine.

In short, systemically administered anticholinergic drugs are not likely to produce angle-closure glaucoma unless the patient is predisposed, having a shallow anterior chamber and an abnormally narrow angle, and the drug causes the pupil to dilate. Patients with the diagnosis of narrow angle glaucoma should receive a concurrent miotic eyedrop at the time of systemic atropine administration. Anticholinergic drugs given systemically to patients already known to have open-angle glaucoma are not likely to have an adverse effect unless the drug paralyzes the ciliary muscle. This paralysis, however, is expected to be outweighed by the patient's continuing use of topical antiglaucoma medications.

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