Autonomic ocular drugs
Desirable and undesirable effects

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At the present time most pharmacologists believe that acetylcholine is the activator and propagator of the chemical change present in all nerve conduction. This involves the axon and all synaptic junctions of both the sympathetic and the parasympathetic systems. At the sympathetic end organs, sympathin or norepinephrine is released as the effecter substance. Acetylcholine itself is the parasympathetic effecter substance. In ocular therapy it is possible to augment the action of the autonomic system by drugs having the same action on the end organ as does acetylcholine or sympathin. Other drugs augment autonomic action by interfering with the enzymes cholinesterase and methyl transferase which are responsible for the destruction of acetylcholine or sympathin, respectively. These sites of action provide a convenient method of classifying autonomic drugs. Only those most commonly used will be discussed.

Drugs stimulating the sympathetic nervous system

Cocaine, 1 to 10 per cent local anesthetic.
Cocaine activates the sympathetic nervous system by inhibiting amine oxidase, thus permitting a local buildup of sympathin. L-epinephrine, 0.1 to 2.0 per cent. This drug acts by direct stimulation of the sympathetic end organ, resulting in a moderate pupillary dilation. Intraocular tension is lowered by inhibition of aqueous production of approximately 30 per cent. This is in addition to the decreased formation which can be achieved by carbonic anhydrase inhibitors. After several months of use many eyes also have an increase in the facility of outflow. Epinephrine does not penetrate the barrier of the corneal epithelium easily and needs to be used in concentrated solutions to achieve adequate intraocular penetration. The currently available products are 1 per cent or 2 per cent solutions of the hydrochloride or the bitartrate salt of levo-epinephrine. These are acid salts with a pH of approximately 3, which cause some burning on instillation. The buffering action of the tears soon brings the pH to 7, at which point the alkaloid is active. Pharmacologists state that the bitartrate resists this buffering action longer than does the hydrochloride.

Most of epinephrine bitartrate solutions are 2 per cent. The actual epinephrine by weight in such a solution is less than in a 2 per cent solution of the hydrochloride salt such as Glaucon or Epifrin. The least expensive form of the drug is epinephrine HCl 1 per cent (Burroughs Wellcome &
Co.), which is usually used as a nasal spray in asthma. The most comfortable form is a 1 per cent epinephrine-borate complex called Eppy, which has a pH close to 7. All of these products tend to darken and lose potency by oxidation after they have been long opened. Those with a pH of 3 are more stable and can be further protected by refrigeration.

**Neosynephrine, 2½ to 10 per cent.** The action of Neosynephrine is similar to that of epinephrine. Its corneal penetration is good, and prompt pupillary dilation is accomplished. It does not inhibit aqueous production as well as epinephrine.

**Side effects.** Any of the sympathomimetic drugs can produce symptoms of sympathetic nervous system stimulation in predisposed persons. To avoid blood pressure elevation in the patient with hypertension, it is wise to hold the puncta closed to avoid rapid absorption from the nasal mucosa. This may also minimize the dryness of the nose of which some complain. Aching pain, particularly in the brow region, is a frequent complaint. Part of this is due to the local ischemia caused by severe vasoconstriction. Part may be the cramplike effect of the iris dilator fibers competing against the miotic pupil of the patient with glaucoma. Using epinephrine several hours after the miotic frequently diminishes the discomfort. The black melanin-like deposits in the conjunctiva which appear after prolonged use can be ignored. Of greater importance is a boggy chronically red conjunctiva occurring in some patients, which is caused by reactive hyperemia following the initial vasoconstriction. If severe, the use of epinephrine must be discontinued. Typical allergic conjunctivitis and dermatitis are also encountered.

In narrow-angle eyes these drugs are particularly dangerous and in most instances are contraindicated because of the risk of precipitating acute angle closure. If there is need to dilate the pupil in such eyes, the sympathomimetic drugs are safer than the parasymptolytic ones for two reasons. First, their duration of action is shorter and more easily overcome by parasympathetic stimulants than is the action of the parasymptolytics such as atropine or homatropine. Second, they produce a wider pupillary dilation which often breaks the pupillary block component and widens a narrow angle. The mid-dilated pupil is the most dangerous position because the pupillary block has not been completely relieved, yet the slack induced in the peripheral iris may permit it to drop against the trabecular meshwork resulting in an acute glaucoma.

In an eye with a dangerously narrow angle, any or all of the following procedures will help avoid angle closure if diagnostic pupillary dilation is mandatory. If the angle is critically narrowed, all three of the following preventive measures should be used.

1. As the dilating agent, use 1:1,000 epinephrine solution on a small wick of cotton placed in the lower cul-de-sac for two minutes. A pupil under parasympathetic miosis will usually dilate downward into a pear shape which will be large enough to examine the lens, disc, and macula. As soon as the pupil begins to dilate, parasympathetic drops should be added to prevent spread of the mydriasis.
2. Diamox, 250 mg. orally should be given one hour before dilation.
3. Glycerine, 50 per cent solution, 150 to 200 c.c., depending on the size of the patient, should be given one hour before dilation. This not only results in a soft eye, but in a widened angle in most instances. Miotics are ineffective if intraocular tension is materially elevated.

**Desirable side effects.** (1) In patients with nuclear cataracts, vision is sometimes improved by pupillary dilation. In eyes with open-angle glaucoma, the pressure-reducing effect is an additional benefit. (2) In secondary glaucoma due to iritis, parasympathetic stimulation is usually contraindicated and the pupil must be kept dilated. Again, sympathemimetic agents are helpful. (3) In young glaucoma patients, epinephrine is usually well tolerated while...
the accommodative myopia produced by parasympathetic-stimulating drugs is often intolerable. Miotics may be used at bedtime and epinephrine during the day. As previously stated, improvement in facility of outflow is often noted 2 to 12 months after beginning epinephrine therapy.

Parasympatholytic drugs

The parasympatholytic drugs cause pupillary dilation and paralysis of accommodation by paralysis of the parasympathetic end organs.

Atropine, 1 to 4 per cent acts for 5 to 12 days.
Scopolamine, 0.2 to 0.5 per cent, acts for 1 to 3 days.
Homatropine, 1 to 5 per cent, acts for 6 to 12 hours.
Cyclogyl, 0.5 to 2 per cent, acts for 6 to 10 hours.

In narrow-angle eyes, these drugs are particularly dangerous as they cause the mid-dilation of pupil which is most apt to result in angle closure as described in the preceding section. In eyes with open-angle glaucoma no disastrous rise in pressure is apt to result, but there may be significant rises of 5 to 20 mm. Hg or even higher because of the decrease in facility of aqueous outflow. They can safely be used systemically, as the small ocular concentration can usually be overcome by the miotic agents. In narrow-angle eyes even the slightest pupillary relaxation may be sufficient to trigger an acute glaucoma.

It is not uncommon for severe systemic poisoning to result from topical medication to the eye, particularly in infants. The symptoms are dilation of the pupils and paralysis of accommodation accompanied by dryness of the mouth, dryness and redness of the skin, increased pulse rate and temperature, and hallucinations. Circulatory collapse and death are possible.

Treatment is symptomatic with the specific use of physostigmine hypodermically in a dose of 2 mg, repeated as necessary.

Allergic conjunctivitis and dermatitis are not infrequent.

Desirable side effects. In glaucoma the atropinelike drugs are useful only in the treatment of postsurgical iritis or secondary iritic glaucoma and in the treatment of malignant glaucoma. In the latter, some cases will reform the anterior chamber when atropine and Neosynephrine are used topically as has been described by Chandler and Grant. This is due to breaking the pupillary block mechanism by pupillary dilation, and by pulling back the lens and the ciliary body when the zonular ligament is tightened by the release of parasympathetic stimulation.

Drugs stimulating the parasympathetic nervous system

These drugs produce an improvement of the facility of outflow and miosis either by direct stimulation of the parasympathetic nerve endings, the parasympathomimetic drugs, or by causing a buildup of acetylcholine at the end organ by inhibiting cholinesterase, the anticholinesterase drugs.

The parasympathomimetic drugs.
Pilocarpine nitrate or hydrochloride, 1 to 4 per cent solutions. This is the safest and most useful of the antiglaucoma drugs. Its action lasts from 4 to 12 hours, but usually is used every 6 to 8 hours.
Carbachol (carbamylcholine chloride, Carbolin, Doryl), 0.75 to 3.0 per cent solutions. Carbachol is a useful alternative drop if allergy or resistance develops to pilocarpine or other medications. Its action is similar but slightly stronger than pilocarpine. It does not penetrate the corneal epithelium as well and must be held against the cornea by Methocel, petrolatum, or its entrance must be facilitated by a wetting agent such as benzalkonium chloride (Zephiran), 1:5,000.
Metacholine chloride (Mecholyl), 10 to 20 per cent solution. This short-acting drug is seldom used and must be freshly prepared as it rapidly loses potency by hydrolysis.

The anticholinesterase drugs. By inhibiting the action of cholinesterase, these drugs permit the parasympathetic effecter,
acetylcholine, to build up at the end organ.

*Physostigmine (eserine)*, 0.25 to 1.0 per cent solution. Eserine was the first drug used in the treatment of glaucoma in the year 1876, by Laquer. Its duration of action is 4 to 12 hours. The drug has lost popularity because of its allergenic tendency. On standing, eserine solution gradually develops a red color due to the formation of a decay product, rubeserine, which is irritating.

*Prostigmine*, 3.0 to 5.0 per cent solution. Prostigmine is very similar in action to eserine. It is more stable but considerably more expensive.

*Isoflouraphate* (*Floropryl or DFP*), 0.01 to 0.1 per cent solution in peanut oil. Floropryl was the first of the long-acting cholinesterase-inhibiting agents. Like phospholine iodide and Humorsol, it forms a relatively irreversible union with cholinesterase. It is rapidly hydrolyzed and destroyed by water so that completely anhydrous peanut oil is needed to dilute it. Patients must be instructed to avoid contaminating the dropper bottle with tears. An ointment is also available. Floropryl's major action is against the nonspecific or "pseudo" cholinesterases, producing intense miosis and ciliary spasm, lasting 12 to 48 hours. Patients object to the oily vehicle to some extent. The peanut oil can become rancid if not refrigerated.

*Echothiophate* (phospholine iodide), 0.06 to 0.25 per cent solution. Phospholine iodide is soluble in water and stable for one month at room temperature. If kept refrigerated the solution remains active for one year. Its duration of action is like that of Floropryl and can usually be used once a day. Most patients prefer the water solution to the oil of Floropryl.

*Demecarium bromide* (Humorsol), 0.125 to 0.25 per cent solution. Humorsol is more stable than phospholine and does not need to be refrigerated. Unlike phospholine and Floropryl, whose actions are against the nonspecific cholinesterases, Humorsol has a unique effect on specific acetylcholinesterase. Its duration of action is also for 1 or 2 days but is usually prescribed daily. Tolerance to the drug and reduced effect seem to occur somewhat earlier than with the other two cholinesterase inhibitors.

*Use of miotics.* In general, it is wise to use the lowest percentage of the mildest miotic the least number of times which will guarantee that the patient will suffer no visual loss. Unfortunately, until there is loss the physician does not know how low the pressure must be held. In an eye with an excellent undamaged optic nerve, pressures above 20 mm. Hg can probably be tolerated for long periods of time. If the nerve is damaged, intraocular pressures must be held well below 20 mm. Hg to avoid further damage.

In prescribing antiglaucoma medication, the druggist should be instructed to place the name of the drug on the label so that the patient knows what he is taking. The time of medication should be "every 6 hours" rather than "4 times a day," or better yet, "1 drop at 7 A.M., noon, 5 P.M., and bedtime." The long-acting drops can usually be prescribed for bedtime or morning use.

If signs of progression of glaucoma are present, changes and additions to therapy should be made promptly. The doctor should know in two weeks whether or not a certain drug combination is giving satisfactory pressure reduction. Too often eyes are plied with drugs in various percentages, combinations, and timings for many months, when in retrospect it was obvious that surgical intervention was indicated. In the angle-closure eyes, of course, a medical regimen is pursued only to prepare the eye for iridectomy. In open-angle glaucoma eyes every effort should be made to control the disease by medications.

*Side effects.*

*Side effects related to the striated muscle effect.* The anticholinesterase action on the orbicularis muscle causes a spasm of the muscle during winking which can be quite annoying.

*Side effects due to miotic effect.* Because of the decreased pupilary size, diminished
brightness of objects and difficulty in adapting to dim illumination are frequent complaints. If a central cataract is present, there is often serious diminution of vision due to the small pupil. These complaints can be partially overcome by holding the pupil open with the addition of epinephrine. If this is inadequate, Neosynephrine can be safely used in eyes which do not have narrow angles. Fortunately, the facility of aqueous outflow seems to be independent of pupillary size. The vision of some anisometropic eyes is improved because of the stenopeic effect of a small pupil.

A dangerous side effect is noted in eyes with narrow angles. The smaller the pupil the greater the pupillary block. If this component exceeds the tightening effect on the peripheral iris, angle closure can result. This danger is aggravated by the stronger anticholinesterase drugs. It is much safer to use pilocarpine in such eyes.

Pupillary pigment cysts are caused by the anticholinesterase drugs. These rarely become large enough to occlude the pupil and may be ignored if they remain small. The use of epinephrine preceding the use of the drug is said to diminish cyst formation. When the drops are stopped the cysts promptly regress.

**Side effects related to ciliary body stimulation.** The long-acting cholinesterase inhibitors cause a particularly pronounced ciliary body stimulation which is aggravated into a true spasm of accommodation by the added acetylcholine production when reading or going into a brightly lighted area. Young patients are especially annoyed by induced myopia, although some prefer the steady state of the long-acting drugs to the variable myopia caused by such short-acting drugs as pilocarpine. Another frequent complaint is of severe pain in and about the eye lasting several hours after instillation. An occasional presbyopic patient may be pleased by his improved ability to read without glasses.

Posterior synechias can follow the prolonged use of the mildest of these miotics giving an added reason for dilating open-angle eyes once a year. Rarely a truly severe iritis may be precipitated if too heavy medication is incautiously prescribed. A vitreous separation is not infrequently precipitated and the patient will complain of muscae volitantes. Even without an iritis this symptom is frequently noted after starting miotics. It may be partly due to the shadow of a pre-existing vitreous opacity which is more easily visualized by the pencil of light coming through a small pupil.

In predisposed eyes, the contraction of the ciliary body can result in a retinal tear and retinal separation. Miotics must be used cautiously. In extremely narrow-angle eyes, in addition to the pupillary block caused by miosis, there is a forward movement of the lens and ciliary body which can be disastrous in an eye predisposed to malignant glaucoma.

Avoiding the side effects of ciliary body stimulation in the young glaucoma patient is often a thankless and impossible task. Where possible, the drug should be used at bedtime so that the greatest period of blur will be during sleep. Epinephrine is a useful daytime adjuvant. Varying strengths of minus clip-on lenses may be prescribed for the varying amounts of myopia present after medication. In all patients the various unpleasant side effects can be avoided or made somewhat more palatable by starting with very dilute solutions and gradually adding percentage strength and frequency of application until tension control is achieved.

As is true of any chronic medication, sensitivity can occur. Allergic conjunctivitis and dermatitis can seldom be treated by corticosteroids because of their pressure-producing tendencies. Stenosis of the lacrimal passages also has been noted after prolonged use.

**Side effects due to systemic parasym pathetic stimulation.** Although systemic poisoning is not common from these drugs, the possibility of ill-effects must be kept in mind. Patients have been known to have
Laparotomies for vague abdominal complaints while the true offenders, the eye drops, were assiduously continued throughout the hospitalization. Excessive salivation, nausea, diarrhea, and cramping discomfort are the usual symptoms of gastrointestinal toxicity. It should be emphasized that marked systemic poisoning can be present without having miotic pupils.

Parasympathetic stimulation also causes marked sweating, a bradycardia, decreased blood pressure, respiratory collapse, and death. Fortunately, the vital processes of the body can be carried on despite a considerable decrease of the various catalytic enzymes. No death definitely due to eye drops has been reported, but there have been deaths caused by overexposure to the cholinesterase-inhibiting insecticides. One of the fears is that glaucoma patients with depressed blood cholinesterase will be also exposed to these insecticides, resulting in a sudden onset of symptoms. Therefore, patients on cholinesterase inhibitors should have a determination of the blood cholinesterase level every 6 to 12 months. Signs of systemic poisoning do not appear until the cholinesterase level is depressed below 0.25 Δ.

There are two antidotes to anticholinesterase poisoning, atropine and Protopam, 2-pyridinealdoxime methachloride (pralidoxime) (Campbell Pharmaceuticals, Inc.). Atropine is a direct antagonist inhibiting the parasympathetic end organs. It must be used in full dosage, 1 to 5 mg. intravenously, repeated in 10 to 15 minutes until the signs of atropinization appear, dry, flushed skin and tachycardia as high as 140 per minute. A mild degree of atropinization should be maintained for 48 hours. Atropine should not be used in a cyanotic patient because of the danger of precipitating ventricular fibrillation.

Protopam, as an antidote, reacts chemically with the cholinesterase inhibitors and reactivates cholinesterase. In severe poisoning it can be used in doses of 1,000 mg. given slowly intravenously and repeated in one hour if muscle weakness has not been relieved. Five hundred milligram tablets are also available. At these dosages no significant toxic effects and no serious side effects of Protopam have been reported. It is particularly effective against phosphates which have a quaternary nitrogen such as phospholine iodide. It may be used in conjunction with atropine.

Conclusion
Despite the potential toxicity of these autonomic drugs, surprisingly few untoward actions occur. Physicians need to be aware of the symptoms of toxicity and to know the antidote. The other side effects are annoying but usually tolerable. The patient's willingness to accept discomfort and inconvenience will vary directly with the ophthalmologist's enthusiasm for a medical regimen and the patient's distaste for surgery.

Summary
The autonomic drugs commonly used in ocular therapeutics are discussed with particular emphasis on their side effects. Toxicity is considered and appropriate antidotes are suggested.