Pharmacology Of Ophthalmologically Important Drugs

James L. Tucker

Follow this and additional works at: https://scholarlycommons.henryford.com/hfhmedjournal

Part of the Chemicals and Drugs Commons, Life Sciences Commons, Medical Specialties Commons, and the Public Health Commons

Recommended Citation

Available at: https://scholarlycommons.henryford.com/hfhmedjournal/vol13/iss2/8

This Article is brought to you for free and open access by Henry Ford Health System Scholarly Commons. It has been accepted for inclusion in Henry Ford Hospital Medical Journal by an authorized editor of Henry Ford Health System Scholarly Commons. For more information, please contact acabrer4@hfhs.org.
PHARMACOLOGY OF OPHTHALMOLOGICALLY IMPORTANT DRUGS

JAMES L. TUCKER, JR., M.D.

Drug therapy in ophthalmology, like many specialties in medicine, encompasses the entire spectrum of pharmacology. This is true for any specialty that routinely involves the care of young and old patients, surgical and non-surgical problems, local eye disease (topical or subconjunctival drug administration), and systemic disease which must be treated in order to "cure" the "local" manifestations which frequently present in the eyes (uveitis, optic neuritis, etc.).

Few authors (see bibliography) have attempted an introduction to drug therapy oriented specifically for the ophthalmologist. The new resident in ophthalmology often has a vague concept of the importance of this subject, and with that in mind this paper was prepared. Revisions have been made in the original text which may allow this brief review of some important drugs to be of interest to other specialties.

The outline followed is:

I. Drugs Related to the Autonomic Nervous System

A. Cholinergic Drugs
   1. parasympathetic stimulants
   2. parasympathetic depressants

B. Adrenergic Drugs
   1. sympathetic stimulants
   2. adrenergic blocking agents (sympatholytic)

II. Miscellaneous Drugs in Ophthalmology

It is apparent that further sections could be written for antibiotics, topical and systemic, steroids, topical and systemic, tranquilizers, anesthetics, etc. These topics were not within the scope of this discussion.
I. Drugs Related to the Autonomic Nervous System

In general the sympathetic system corresponds to the adrenergic nervous system, and the parasympathetic nervous system to the cholinergic system, i.e., the adrenergic nerve endings act through the liberation of epinephrine and the cholinergic nerve endings act through the liberation of acetylcholine. Parasympathetic, sympathetic, mimetic and lytic are not particularly good terms for acetylcholine or epinephrine, since these are the substances released at the autonomic synapses. Acetylcholine also transmits impulses in all preganglionic synapses, both sympathetic and parasympathetic, in the myoneural junctions of the voluntary nervous system and probably all synapses of the central nervous system. Acetylcholine is rapidly inactivated by cholinesterase, and this action can be blocked by drugs with a urethane (carbamate) group that combines with esterase, such as physostigmine or prostigmine.

An early theory was that adrenergic nerve endings acted through the liberation of epinephrine which then combined with a substance to form sympathin which in turn initiated the action of the innervated cell. There was thought to be two types of sympathin produced, E and I — excitatory and inhibitory, for physiologists could readily demonstrate opposite sympathetic actions when epinephrine was administered intravenously.

Ahlquist in 1948 made a thorough study of the effects of epinephrine and his views are generally accepted today. He feels there are two types of receptors, alpha, associated with excitatory responses and beta, associated with inhibitory responses. Lands in 1952 added a third receptor, the undifferentiated, which he considers the receptor in the heart and must also include an undifferentiated receptor in the intestine, since it does not react in an alpha-beta pattern when adrenergic drugs are administered.

The action of any cell with an adrenergic nerve supply can be initiated either by stimulation of that particular nerve supply or by epinephrine reaching the nerve cell through the general circulation. A number of epinephrine derivatives possess qualitative actions somewhat similar to epinephrine but not exactly the same. Ephedrine probably acts directly on adrenergic structures to a limited extent, but at least the major portion of its effect is dependent on a cocaine-like action which is a sensitization of the structure to epinephrine. Other epinephrine derivatives intermediate between epinephrine and ephedrine with regards to the OH groups in the aromatic ring are also intermediate in their pharmacologic mode of action.

Introductory Definitions

1) Cholinergic Nerves — These include all nerves which release acetylcholine at their terminals. Thus included are not only the postganglionic parasympathetic fibers, but also all autonomic preganglionic nerves (whether they be parasympathetic or sympathetic).
2) Adrenergic Nerves — These are nerves that have impulses acting through the release of norepinephrine or epinephrine and consist only of postganglionic sympathetic fibers.

3) Acetylcholine Esterase — This enzyme destroys acetylcholine by hydrolysis.

4) Muscarine

\[
(CH_3)_3-N^+CH\backslashCH-O-H-CH_2-CH_3
\]

This drug, vagal in action, acts identically to acetylcholine and pilocarpine as a smooth muscle stimulant. Exocrine gland cells that are innervated by postganglionic cholinergic nerves are also activated by muscarine. It produces cardiac slowing and peripheral vasodilation. It also produces increased peristalsis, depression of blood pressure, salivation, bronchospasm, vasodilation, miosis, and sweating. Small doses of atropine completely abolish these responses to muscarine.

5) Nicotine — The major action of nicotine consists of a primary transient stimulation and a secondary more persistent depression of all sympathetic and parasympathetic ganglia. Acetylcholine is also called nicotinic in its actions on ganglia and skeletal muscles, since nicotine and acetylcholine can allow transmission of nerve impulses across synapses in autonomic ganglia and the transmission of impulses to skeletal muscles.

6) There are probably other classes of nerve fibers such as those sensitive to histamine, but very little is known of most of these responses and they are not considered within the scope of this presentation.

**Autonomic Innervation of the Eye**

The iris and ciliary body are innervated by the autonomic nervous system. The sympathetic nerves are the postganglionic fibers from the cervical chain and these reach the globe by the long ciliary nerves. The parasympathetic supply traverses the ciliary ganglion where there is a synapse and reaches the globe in the postganglionic fiber by way of the short ciliary nerves.
A. Cholinergic Drugs (These act on effector cells innervated by cholinergic nerves.)

1. parasympathetic stimulants

a. preganglionic (parasympathetic stimulatory miotics)

   (1) nicotine — direct action
   (2) acetylcholine — direct action
   (3) methacholine chloride — (mecholy l chloride) — direct action
   (4) carbachol — (Doryl) — direct and indirect action
   (5) urecholine — (bethanechol) — direct and indirect action
   (6) physostigmine — (Eserine) — indirect action
   (7) neostigmine — (prostigmin) — indirect action
   (8) DFP — (Floropryl) — indirect action
   (9) demecarium bromide — (Humorsol) — indirect action
   (10) echothiophate — (phospholine iodide) — indirect action

(1) nicotine

\[
\begin{align*}
\text{CH}_2 & \quad \text{CH}_2 \\
\text{CH} & \quad \text{N} \\
\text{CH}_2 & \quad \text{Cl}_3
\end{align*}
\]

The major actions of nicotine consist of a primary transient stimulation of all sympathetic and parasympathetic ganglia and a secondary more persistent depression of all sympathetic and parasympathetic ganglia. During the stage of excitation preganglionic nerve impulses are more effective, and during the stage of complete paralysis such impulses are wholly ineffective. Nicotine does not interfere with the release of acetylcholine in the ganglia by cholinergic preganglionic impulses, but it renders the ganglion cells temporarily more sensitive and then more resistant to acetylcholine. Both the initial excitation and the subsequent paralysis are due to a direct action on the ganglion cells. Nicotine and curare are similar in their impulse blocking, but nicotine much more in ganglia, and curare much more in skeletal
muscles. The expression "nicotinic action" in referring to the action of the choline esters on autonomic ganglia, adrenal medulla, and skeletal muscles arises from the similarity between the effects of nicotine and acetylcholine on these structures.

(2) acetylcholine

\[ (\text{CH}_3)_3\text{N-CH}_2\text{-CH}_2\text{-O-C-O-CH}_3 \]

Like other quarternary ammonium compounds acetylcholine possesses three distinct pharmacological effects; namely, muscarinic, nicotinic, and curariform.

Acetylcholine is actually preganglionic and postganglionic in its action. It acts directly on the sphincter muscle in the eye which is the effector organ.

Cells reacting to acetylcholine fall into two distinct categories according to whether they are innervated by:

(1) preganglionic cholinergic nerves: nicotinic actions, i.e., somatic autonomic ganglion cells, adrenal medullary cells, and skeletal muscle fibers. (The pharmacology of the autonomic ganglionic synapse bears many resemblances to that of the skeletal muscle end-plate).

(2) postganglionic cholinergic nerves, muscarinic action, i.e., cardiac muscles, smooth muscle cells (iris) and exocrine gland cells.

Acetylcholine is not official and is not described in the New and Nonofficial Remedies (N.N.R.) but can be obtained as the chloride or the bromide, which is a white odorless powder, hygroscopic and readily destroyed by heat. The chloride powder is packaged as 100 milligrams in an air-tight vial prepared by Merck and Company, Rahway, New Jersey; the Chemical Division.

Applied locally to the eye acetylcholine is not effective, i.e., it is not a miotic unless a 5% solution is used and massage is employed. It is most frequently used for miosis applied directly to the iris during surgery to obtain rapid miosis in spite of a retrobulbar nerve block. It is prepared by placing 1 cc. of normal saline in the vial of 100 milligrams and withdrawing 0.1 cc. of the solution. This 10 mg mixed with 9.9 cc. of normal saline, producing a dilution of 1:100, a concentration of one milligram per cc. Three to five cc. of this solution are used for maximum miosis. Acetylcholine is unstable in solution and must be prepared immediately before use.
(3) methacholine chloride — (mecholyl, acetylbetamethylcholine chloride), a synthetic substituted acetylcholine.

\[
\text{CH}_3\text{C}==\text{O}==\text{CH}==\text{CH}_2\text{N}^+\text{-(CH}_3\text{)}_3\text{Cl}^-
\]

Mecholyl is much more resistant to destruction by cholinesterase than is acetylcholine but it is still a short-acting drug.

Methacholine is a white crystalline or powdered chemical, deliquescent, fairly stable in aqueous solution if slightly acid.

Methacholine is used in 10-20% solutions (less than 5% has no effect) and like other choline derivatives penetrates corneal epithelium poorly. Absorption is enhanced by using a topical anesthetic first. (This tends to damage the epithelial cells enough to lower the surface tension). When applied to the conjunctival sac, it retains its maximal effect less than one hour and all effects are gone in several hours. Used in normal eyes, the intraocular pressure will fall 3-5 mm. Hg.

It is used with neostigmine or physostigmine so their anticholinesterase effect will allow the mecholyl to act without enzyme interference. It is used (but infrequently) to treat acute angle closure glaucoma, relieving the congestive attack. Mecholyl is also a vasodilator which increases the permeability of the blood-aqueous barrier but is rarely used for long-term administration. The drug is contraindicated in asthmatics, because of the possibility of bronchospasm. Reactions are not infrequent and include sweating, flushing, an increase in pulse rate and a fall in blood pressure.

(4) carbachol (doryl, lentin, carcholin, carbamyl chloride)

\[
\text{Cl}^-\text{-(CH}_3\text{)}_3\text{N}^+\text{CH}_2\text{CH}_2\text{O-CO-NH}_2
\]

Carbachol is a powerful synthetic parasympathomimetic drug, used in the therapy of chronic simple glaucoma. It acts preganglionically and postganglionically with a stimulatory effect. Carbachol not only has an acetylcholine-like action on the motor end plate, but also an inhibiting effect on cholinesterase. It is a derivative of choline and is not susceptible to destruction by cholinesterase.
Therefore, it is not enhanced nor prolonged in action by neostigmine or physostigmine which inactivate cholinesterase. This miotic may produce iris border cysts as do several other miotics, but these are not a permanent deterrent to vision. It is a urethane ester of choline and is more stable than methacholine. It is prepared as a 3/4% - 1 1/2% - 3% solution, and the brand available in our pharmacy is Isopto Carbachol by Alcon Laboratories. It is supplied in 15 cc. plastic bottles and administered one or two drops in each eye every four to eight hours. It is somewhat stronger than pilocarpine, but unfortunately does not penetrate the cornea as well. It is enhanced in its penetration by the use of a petrolatum base or with a wetting solution such as benzalkonium chloride 1:5000. Carbachol is a good replacement or alternate drug for pilocarpine or other miotics when resistance or intolerance has developed. This often permits carrying the patient along under control with later possibilities of returning to the original medication.

(5) urecholine (bethanechol, carbamylmethylcholine chloride)

Urecholine is prepared as a 1% solution and is approximately equal to 2% pilocarpine and 0.75% carbachol in its miotic effect in the treatment of chronic simple glaucoma. Both carbachol and urecholine should be used with caution in asthmatics where spasm of the bronchial musculature may occur. It is noted that these two drugs have both preganglionic and postganglionic actions. Urecholine, like carbachol, has direct and indirect action as a stimulant miotic acting on the motor end plate as does acetylcholine, and it inhibits cholinesterase.

(6) physostigmine (Eserine)
This is an alkaloid obtained from the Calabar bean (ordeal bean) which is the
dried ripe seed of Physostigma venenosum Balfour, a perennial woody climber growing
on banks of streams in tropical West Africa. It was brought to England in 1840
but not really investigated until 1855. The first therapeutic use was by Laqueur in
1875 for glaucoma. Although several alkaloids have been isolated from the Calabar
bean, physostigmine (Eserine) is the most important. Physostigmine salts and their
aqueous solutions in glass containers oxidize upon exposure to air and light and
turn at first pink and then reddish brown. Such colored solutions are decomposed
and should not be used. Addition of boric acid to the solution prevents this break­
down. Eserine acts primarily as a cholinesterase inhibitor and will not affect an
iris which has been cholinergically denervated. (Loss of cholinergic innervation to
the iris results in the absence of formation of acetylcholine.) Therefore, Eserine
administered in the presence of a retrobulbar block is not effective until the retrobulbar
anesthesia has worn off. By preventing the rapid enzymatic hydrolysis of acetylcholine,
Eserine allows the acetylcholine to exert its characteristic actions in an intensified
manner. Unlike neostigmine, Eserine shows no component of direct action on skeletal
muscle. Eserine is most often used in ophthalmology for miosis in the therapy of
chronic simple glaucoma. The drug is well tolerated, stable and effective, all features
that enhance its popularity.

Atropine blocks the muscarinic effects of Eserine and curare prevents the nicotinic
effects on skeletal muscle and nicotine prevents the nicotinic effects on the autonomic
ganglia. Although many drugs inhibit cholinesterase, few compare with Eserine and
DFP and their related compounds for the potency of their inhibition. Physostigmine
does not destroy the enzyme as does DFP, but inactivates it temporarily by the
formation of a readily dissociable complex.

Symptoms and signs of Eserine toxicity include defecation, increased peristalsis,
miosis, salivation, dysarthria, nausea, vomiting, colic, fasciculatory twitchings all over
the body, nystagmus, restlessness, weakness, distant objects are blurred (spasm of
accommodation), lacrimation, sweating, copious bronchial secretions, dyspnea, urinary
urgency, ashen skin, weak pulse and blood pressure at shock levels. Death is by
pulmonary edema or central respiratory depression.

For ophthalmological use, Alcon Laboratories (Fort Worth, Texas) prepare
Isopto Eserine, a sterile 0.25% solution of eserine salicylate in .5% methylecellulose.
As a preservative .1% sodium bisulfite and chlorobutanol 0.15% are also present.
Inactive ingredients include citric acid and sodium chloride. When applied to the eye,
miosis occurs in a few minutes and is maximal in 30 minutes. The effect persists
for 12-36 hours.

Eserine Ophthalmic Ointment is prepared for use in the eye as 0.25% eserine
sulfate and contains wool fat, light liquid petrolatum, and white petrolatum (Day-
Baldwin, Incorporated, Irvington, New Jersey).
Neostigmine is a synthetic substitute for physostigmine. It is available as the methylsulfate and is prepared as a 5% ophthalmic solution. Systemically administered neostigmine is without significant effect on the eye. Locally it produces miosis, but not in the parasympathetically denervated iris. Neostigmine is a potent cholinesterase inhibitor and its muscarinic properties are dependent upon an intact cholinergic nervous system (as with physostigmine). Neostigmine exerts less potency on the iris than does Eserine. Similar to acetylcholine, neostigmine in small doses stimulates, and in large doses depresses the autonomic ganglia and skeletal muscles. The muscarinic effects of neostigmine are decreased or blocked with atropine and the nicotinic effects by curare. Neostigmine finds its primary uses in the treatment of intestinal ileus, atony of the bladder and myasthenia gravis.

DFP (Di-isopropyl Fluorophosphate, Alkyl Fluorophosphate, Isofluorophosphate, and Isofluorophate)

This drug is marketed by Merck, Sharp and Dohme, under the trade name of Floropryl. Its pharmacological action is secondary to its inactivation of cholinesterase.

The inactivation of cholinesterase by DFP is irreversible, which is in contrast to physostigmine and neostigmine, although all these drugs have similar nicotinic and muscarinic actions. DFP is the most potent and persistent miotic known and its usefulness in the therapy of chronic simple glaucoma is limited primarily because there are effective drugs which are less expensive and more stable in solution.

DFP hydrolyzes in the presence of water and hence must not be diluted or it rapidly decomposes (even moisture on eyelids must be excluded from the drug when
applying it). It is prepared in a sterile .1% solution in anhydrous peanut oil, and as a .25% ointment. It is marketed only for ophthalmological use and the usual dosage is one drop in each eye for an adult every 12-72 hours, or one-fourth inch of the ointment every 12-72 hours in children. If it is used too frequently or for too prolonged a period of time, particularly in children, a high percentage of the eyes form iris cysts. These usually disappear on cessation of the drug. Used in the eye, there is a minimal systemic absorption. However, that the drug is absorbed systemically is fact, evidenced by a slight fall in the serum cholinesterase. But systemic effects rarely, if ever, occur when therapeutic concentrations are employed.

Occasionally, the intraocular tension is raised instead of lowered, especially in narrow angle glaucoma, or in open angle glaucoma with narrow angles. This may be due to an increase in the relative pupillary black and/or congestion of the iris root. This drug should not be used when the chamber angle is narrow. Pericorneal injection and congestive iritis sometimes occur early, but tend to disappear on continued use of the drug. If the tension does not fall in 48 hours, one should discontinue DFP and seek other measures for the control of the intraocular pressure.

The most common side effects are brow ache, blurred vision from ciliary spasm, headache or photophobia — and in 20% of the patients one or more of these symptoms force the discontinuance of the drug. Local irritation is uncommon.

Toxic symptoms include restlessness, weakness, skeletal muscular twitching, tremor, ataxia, pilomotor erection, salivation, defecation, diarrhea, bradycardia, convulsions, respiratory depression, and death from respiratory depression and vascular collapse.

Retinal detachment has occurred (rarely) irrespective of the amount of myopia present. Allergy to peanut oil has been reported, and in these cases one can use the ointment instead. Muscle twitching of the eyelids has been reported which is due to a locally increased muscle tonus. DFP is also used in treating accommodative esotropia. It reduces the centrally stimulated accommodation and its associated convergence by producing peripherally stimulated accommodation.

DFP can also be used as a diagnostic aid in evaluating strabismus to rule out the possibility of an accommodative element.

It is contraindicated in the patient with vasomotor instability, peptic ulcer, spastic GI symptoms, parkinsonism, bradycardia, asthma, recent myocardial infarction, or epilepsy.

The antidote for accidental poisoning in the adult is .4 to .6 milligram of atropine intramuscularly, and this may have to be repeated in order to reverse the toxic effects.
OPHTHALMOLOGICALLY IMPORTANT DRUGS

(9) demecarium bromide (Humorsol, BC-48, Tosmilen)

Marketed by Merck, Sharp and Dohme, this drug is a synthetic cholinesterase inhibitor. Humorsol is packaged for ophthalmological use only and is prepared as a 0.25% sterile aqueous solution. It is stable at room temperature, is relatively non-irritating, has a pH of 5-7, and when mixed with conjunctival fluid is isotonic. Recently MSD has made available .125% Humorsol.

Pharmacologically, it is a quaternary ammonium compound whose generic name is [decamethylenebis-(m-dimethylaminophenyl-N-methylcarbamate) dimethobromide]. In the structural formula, two neostigmine molecules are linked by a polymethylene chain.

Humorsol applied locally to the conjunctival sac appears to produce as prolonged inhibition of cholinesterase as DFP. (Both drugs marketed by MSD.) Its use in the therapy of glaucoma and strabismus parallels that of DFP.

The increase in acetylcholine that accumulates produces miosis with spasm of accommodation. This drug may produce hyperemia of the conjunctival vessels, increased capillary permeability in the ciliary body and increased permeability of the blood-aqueous barrier.

Humorsol is synergistic with several cholinesterase inhibitors. Prolonged side effects occur from systemic ingestion (parasympathetic stimulator). Toxic symptoms include nausea, vomiting, frequent urination, intestinal cramps, diarrhea, lacrimation, bronchoconstriction, shock and collapse. Humorsol is used exclusively in the conjunctival sac. Instillation of the 0.25% solution ranges from one or two drops once or twice a week to twice a day. It comes as a 5 cc. vial with a standardized dropper. The dosage is individual, and the drug should be reduced to an absolute minimum in order to avoid the formation of iris cysts.

Humorsol is used most often in the treatment of open angle glaucoma, for breaking of peripheral anterior synechias, and in accommodative esotropia. As with DFP, it should not be used in the presence of narrow chamber angles for fear of precipitating an attack of angle closure glaucoma. In accommodative esotropia it reduces centrally stimulated accommodation and its associated convergence by producing
TUCKER

a peripherally stimulated accommodation. Humorsol may be used as a diagnostic aid in determining if an esotropia has an accommodative element present.

The person administering Humorsol should be cautioned against overdosage, and should press on the lacrimal canaliculi for a minute or two after instilling a drop to prevent loss to the nasopharynx with subsequent systemic absorption from the nasal mucosa. (This is a technique that should be employed with all eye medications since it increases the length of time the eye is in contact with a drug.)

Early disagreeable symptoms, which usually disappear with continued use include headache, browache, congestion of the sclera and conjunctival vessels, photophobia, burning, induced myopia (blurred vision) and iridocyclitis. Complications that have arisen with the use of Humorsol include ciliary spasm — so severe as to produce retinal detachment, elevation of intraocular pressure instead of a lowering of the intraocular pressure, muscle twitching of the eyelids secondary to an increased tonus of the skeletal muscles locally. Again, this drug is contraindicated in persons with vasomotor instability, peptic ulcer, spastic GI symptoms, parkinsonism, bradycardia, asthma, recent myocardial infarction, and epilepsy.

As in DFP, the antidote for toxic symptoms is .4 to .6 milligram of atropine administered intramuscularly.

(10) echothiophate (phospholine iodide)

\[
\begin{align*}
\text{Pharmacologically, diethoxyphosphinylthiocholine iodine is a potent and relatively irreversable inhibitor of cholinesterase used only in ophthalmology.}
\end{align*}
\]

Phospholine iodine is a white crystalline solid. (Campbell Pharmaceuticals, Incorporated, 121 East 24th Street, New York 10, New York.) It is prepared in a 5 cc. vials of 0.06%, 0.125% and 0.25% concentration which is administered one drop every 12 to 48 hours and finds its greatest use in the treatment of open angle
glaucoma. Also contained in the sterile solution is 1.2% mannitol, .5% chlorobutanol, boric acid .06%, and disodium phosphate .026%. It has much the same action as DFP, but is water soluble and more stable. However, it should be refrigerated when in solution. The solution is stable for one month at room temperature but for about 12 months in the refrigerator.

It induces miosis in about 30 minutes which will last from several days to three weeks. It improves outflow facility and lowers pressure in both normal and most glaucomatous eyes. Fortunately, this drug is capable of lowering intraocular pressure by improving outflow facility in some glaucomatous eyes which are not controlled by other miotics and cholinesterase inhibitors. In many instances, Diamox and/or topical epinephrine compounds can be discontinued. Phospholine iodine may be used for diagnosis and/or therapy in accommodative esotropia. (See the similar section under DFP and Humorsol.)

Side effects of phospholine iodine include browache, dimness of vision, and ciliary and conjunctival injection which occur frequently when phospholine iodine is started, but usually disappear after a few days of continued treatment. Aphakic eyes may tolerate echothiophate better than phakic eyes. Rarely, retinal detachments have been reported with the use of the drug. Iris cysts occur only occasionally in adults but are fairly frequent in children. Phospholine iodine may activate or produce an iritis and slit-lamp evaluation at frequent intervals for one week is recommended.

Care should be used when a patient is receiving anticholinesterase drugs. The antidote is atropine 2 mgm. parenterally and artificial respiration if necessary if accidental overdosage is encountered.

b. postganglionic (parasympathetic stimulatory miotics)

(1) pilocarpine

\[
\begin{align*}
\text{C}_2\text{H}_5 & \quad \text{CH} & \quad \text{CH} & \quad \text{CH}_2 & \quad \text{C} & \quad \text{N} & \quad \text{CH}_3 \\
& \quad \text{O=\text{C}} & \quad \text{O} & \quad \text{CH}_2 & \quad & \quad & \\
\end{align*}
\]

\[\cdot \text{HNO}_3 \text{ or HCl}\]

Pilocarpine is the chief alkaloid obtained from the leaflets of the South American shrub known as Pilocarpus jaborandi and Pilocarpus microphilus. It was isolated by Hardy in 1871.

The autonomic activity of the drug is due to a highly selective action of pilocarpine on the cells innervated by postganglionic cholinergic nerves. This action is a direct one on the reactive substance and also occurs after complete nerve degeneration. Because of its effective miosis and infrequent idiosyncrasies it is a valuable drug in the therapy of chronic simple glaucoma, either alone or in combination with other drugs.
Atropine is the pharmacological antagonist to pilocarpine and prevents or counteracts all autonomic response to pilocarpine in the rather constant ratio of 1 to 10.

Particularly responsive to pilocarpine are the sweat and salivary glands. It is interesting that dependent as ophthalmologists are on pilocarpine, Goodman and Gilman’s pharmacology text is quoted “the alkaloid (pilocarpine) has few clinical uses and is perhaps not indispensable in medicine”.

Isopto Carpine is pilocarpine hydrochloride (Alcon) in a sterile 0.5% methylcellulose suspension with benzalkonium chloride 1:25,000 and phenylmercuric nitrate 1:75,000 as preservatives. It also contains for isotonicity boric acid and sodium citrate. The dosage for easily controlled open angle glaucoma is one drop in both eyes four times a day of the selected strength which most readily controls intraocular pressure in a given patient. This is determined by using the weakest dilution and increasing the strength and/or the frequency of pilocarpine until the pressure is controlled. Isopto Carpine is prepared in ½%, 1%, 2%, 3%, 4%, and 6% solutions.

A newer preparation* of pilocarpine HCl on the market is Pilocar, marketed by Smith, Miller and Patch, Incorporated of New York.

Allergan Pharmaceuticals markets P. V. Carpine which is pilocarpine nitrate in a polyvinyl alcohol (liquifilm) vehicle.

The following drugs have been discussed under preganglionic drugs, and it is pointed out that they are classified as preganglionic drugs, and postganglionic since 4-10 act indirectly by allowing acetylcholine to accumulate.

(2) acetylcholine
(3) methacholine — mecholyl
(4) carbachol — Doryl
(5) urecholine — bethanechol
(6) physostigmine — Eserine
(7) neostigmine — prostigmin
(8) DFP — Floropryl
(9) demecarium bromide — Humorsol
(10) echothiophate — phospholine iodide

2. Parasympathetic Blocking Agents — (parasympatholytic or depressor drugs)

a. preganglionic parasympathetic depressants — nicotine and curare are included in this discussion because standard texts compare the action of many pharmaceuticals to the action of these drugs

(1) nicotine

*Other pilocarpines include: Pilocimotin by Crookes Barnes Laboratory, Buf Opto Pilocel by Professional Pharmaceutical Company, and Almocarpine by Ayerst Laboratories (Ophthalmos Division). This example illustrates the large number of ophthalmological preparations available from many different drug companies.
OPHTHALMOLOGICALLY IMPORTANT DRUGS

The secondary action of nicotine is a more persistent depression of all sympathetic and parasympathetic ganglia. See remarks under 1. parasympathetic stimulants, for the formula and general pharmacology of nicotine.

(2) curare

Curare is a generic term for various South American arrow poisons (alkaloids), the first of which were derived from the plant Chondrodendron tomentosum.

Tubocurarine chloride

The pharmacological actions include paralysis of the skeletal muscle fiber by preventing its response to motor nerve impulses, i.e., to the acetylcholine liberated by such impulses. It probably acts on the motor end plate raising its threshold to acetylcholine. Curare, a quaternary ammonium compound, blocks autonomic ganglia and has an initial excitatory phase much as nicotine and differs from hexamethonium which is purely depressant. The main effects of curare are a highly selective paralysis of the motor end plates in skeletal muscles and a paralysis of ganglion cells of the autonomic nervous system. Thus, it blocks the nicotinic action of acetylcholine.

b. postganglionic parasympathetic depressants

(1) atropine (tropinyl tropate)

Atropine is one of the naturally occurring alkaloids which inhibit the effector organs innervated by the postganglionic cholinergic nerves. There are several other alkaloids of the belladonna plants which do the same, but by far atropine and scopolamine are the two most important clinically. Belladonna drugs are widely distributed in nature, especially in the deadly nightshade. Atropa belladonna (contains
mainly the alkaloids atropine and hyoscynamine). The same two alkaloids are also found in jimson-weed, stink-weed, thornapple and devil’s apple. The alkaloid, scopolamine (hyoscine) is found chiefly in the shrub Hyoscyamus niger, (henbane) and Scopolia carniolica. These alkaloids are organic esters formed by the combination of an aromatic acid, tropic acid, and complex organic bases either tropine (Tropanol) or scopin. Scopin differs from tropine only in having an oxygen bridge between the carbon atoms designated 6 and 7 in the structural formulas.

Atropine is the most useful drug available when complete cycloplegia, particularly for prolonged periods, (postoperative cataract surgery or iritis) is desired. Cycloplegia persists 8-12 days; mydriasis persists 7-10 days.

Isopto Atropine, a 1% sterile solution in .5% methylcellulose, is atropine sulfate (Alcon Laboratories, Fort Worth, Texas). For preservatives, it contains chlorobutanol .15% and it is buffered with boric acid in distilled water. Our department uses atropine ointment (Eli Lilly of Indianapolis) as the sulfate in a ½ ounce tube, ½% or 1% concentration. This ointment contains anhydrous lanolin, liquid petrolatum, white petrolatum, and purified water. Cycloplegic examination of children younger than 5 years of age is often accomplished by having the ½% ointment instilled in their eyes three times a day for 3 days prior to the examination.

Ocular effects are obtained after local or systemic administration of the alkaloids, but contrary to common opinion, the conventional dose of 0.6 mgm. of atropine injected intramuscularly causes minimal ocular effect. However, scopolamine in equal dosage causes definite mydriasis and a decrease in accommodative power. The significance of this is reflected when preoperatively medicated patients with shallow anterior chambers must be watched lest one precipitates an attack of acute angle closure glaucoma.

The site of action of atropine is purely peripheral. The fatal dose of atropine is probably higher than a usually recorded 100 milligrams for adults and 10 milligrams for children. One drop of 1% atropine solution contains approximately 0.5 milligrams of atropine. Thus, the absorption of two drops has caused systemic atropine poisoning. Atropine acts by preventing the effects of choline compounds, pilocarpine, and muscarine on structures innervated by cholinergic nerves. However, atropine neither destroys these compounds nor renders the innervated structure unresponsive to electrical stimulation.

Atropine does not prevent the effect of choline derivatives on the autonomic ganglion, the voluntary myoneural junction, or the central nervous system.

An interesting fact is that atropine will not dilate the pupil of a bird since the avian iris sphincter is striated muscle and, therefore, is paralyzed not by atropine but by curare.
(2) scopolamine (6,7-epoxytropinyl tropate)

Scopolamine is stated to be more toxic than atropine, although this is not well documented. Idiosyncrasies are more common with scopolamine than atropine. According to Goodman and Gilman, deaths from either scopolamine or atropine drops are exceedingly rare. Allergic reactions, local or systemic, are not infrequent.

The ocular effects of ½% (twice the concentration ordinarily used) scopolamine are mydriasis in 20 to 30 minutes which lasts 3 to 5 days and cycloplegia which occurs in one-half to one hour and lasts 5 to 7 days. This compares rather closely with 1% atropine sulfate which produces a mydriasis in 30 to 40 minutes that lasts 7 to 10 days and cycloplegia which has its onset in one to three hours and lasts 8 to 12 days. Like atropine, scopolamine acts by rendering tissues insensitive to acetylcholine.

Scopolamine is used in our department as Isopto Hyoscine, 0.25% scopolamine hydrobromide. It is in a sterile solution of .5% methylcellulose USP with .15% chlorobutanol as a preservative. (Alcon Laboratories of Fort Worth, Texas.)

The main danger in the use of the belladonna alkaloids for cycloplegia and mydriasis is an increase in intraocular pressure in persons with narrow angles. The belladonna alkaloids are most useful in cycloplegic refractions, cycloplegia for relief of ciliary spasm following corneal abrasions and postoperative intraocular surgery, as well as for the relief of ciliary spasm in uveitis.

(3) synthetic belladonna substitutes

(a) homatropine (tropyl mandelate)

This is a synthetic drug which differs from atropine by having mandelic acid substituted for the more complex tropic acid. It is both less effective and less toxic.
than atropine, and has a parasympatholytic potency of about one-tenth that of atropine (approximately 1/50 as toxic as atropine).

Homatropine mydriasis either as the hydrobromide or hydrochloride in a 5% solution has the advantage of rapid onset and relatively brief duration. The drug is preferable to atropine when an extended period of increased intraocular pressure must be avoided and when prolonged ocular effects are not necessary.

Maximum mydriasis is within 40-60 minutes and persists 1-2 days. Cycloplegia is present within one hour. Accommodation is usually normal within 1-2 days and homatropine is ineffective as a rule for the production of complete cycloplegia in children younger than 5 years.

Isopto Homatropine 5% (Alcon Laboratories of Fort Worth, Texas) is a sterile ophthalmic solution of the hydrobromide in .5% methylcellulose and distilled water. It contains chlorobutanol .15% as a preservative and the inactive ingredients include sodium phosphate dibasic and sodium phosphate monobasic. The dosage for routine cycloplegia is usually one drop in each eye every 5 minutes for 3 doses. Homatropine cycloplegia is used most frequently in the ages 7 to 15 years.

(b) cyclogyl (cyclopentolate hydrochloride)

More accurately cyclogyl is 2 dimethylamino-ethyl-l-hydroxy-alpha-phenyleclopentaneacetate hydrochloride.

In general, the usefulness of cyclogyl parallels that of homatropine:

1. Rapid onset of effect-cycloplegia usually is present within 30 to 60 minutes.
2. Effect is localized and specific.
5. Rapid decline of effect.
6. Low sensitivity and minimal intolerance reactions.
Cyclogyl for ophthalmic instillation (cycloplegic and mydriatic) is a sterile, clear solution of .5%, 1% and 2% strengths in Gifford's buffer. Gifford's buffer contains boric acid, potassium chloride, sodium carbonate monophosphate. Cyclogyl is manufactured by Schieffelin & Company, Pharmaceutical Laboratories Division, 28 Cooper Square, New York 3, New York. The .5% and 1% cyclogyl contains benzalkonium chloride as a preservative. The 2% cyclogyl is in a buffered base containing boric acid and sodium borate as well as polyvinylpyrrolidone (P.V.P.). The 2% cyclogyl has 0.5% chlorobutanol as a preservative. Cyclogyl is used for relaxing the cholinergically innervated muscles in the iris and ciliary body for refraction, for intraocular inflammatory reactions, keratitis, and for preventing or freeing existing synechia. Although complete recovery occurs in 24 hours, one or two drops of 2% pilocarpine reduces the recovery time to 6 hours or less. Caution should be exercised with this drug in cases where there is increased intraocular tension or where there is a shallow anterior chamber. In rare instances, atropine-like symptoms have been reported with the 2% solution in young children.

(c) euphthalmine (eucatropine hydrochloride)

Euphthalmine is a synthetic mandelic acid ester useful as a mydriatic in older patients. It is less active as a mydriatic than homatropine, and produces little cycloplegic effect. It is prepared in a 5-10% solution and presently is most often used in combination with phenylephrine in Mydriatin (Ayerst-Ophthalmos Division).

(d) mydriacyl (bis-tropicamide)

Mydriacyl (also tropicamide) is a synthetic drug, chemically defined as [tropic acid-N-ethyl-N-(gamma-picolyl) amide], (Alcon Laboratories of Fort Worth, Texas). It is a sterile isotonic solution containing boric acid 1.8% and phenylmercuric nitrate 1:50,000 as a preservative. The pH is approximately 6.2 and the white crystalline compound is only slightly soluble.

Mydriacyl is prepared in two strengths, .5% and 1%, and is pharmacologically a parasympatholytic or anticholinergic drug. Its action is unusual in that good cycloplegia and mydriasis are obtainable in 20-25 minutes, and the effects of the cycloplegia have worn off in 5-6 hours without use of a miotic.
Antrenyl's chemical names: 2-diethylaminoethyl-alpha-phenyl-alpha-cyclo-hexylglycolate methylbromide or diethyl (2-hydroxyethyl) methylammonium bromide-alpha-phenyl-cyclohexaneglycolate.

Antrenyl is a potent synthetic anticholinergic quaternary ammonium compound which is given in 5 mg. dose orally to relieve bronchospasm and reduce gastric secretions and intestinal motility. It has been prepared as a 1% solution for investigative use in ophthalmology for cycloplegia of patients allergic to atropine. It is prepared by Ciba and our chief interest is in its lack of allergic reactions. It is used for preanesthetic medication, especially in the presence of atropine sensitivity. (Also available in injectable solution in multiple dose vials as well as pediatric drops.)

B. Adrenergic Drugs (sympathomimetic) These drugs act on the effector cells innervated by adrenergic nerves. All of these drugs must be used with care in patients with hypertension.

1. sympathetic stimulants — None of the following drugs should be used in patients with narrow angles or shallow anterior chambers. Most of the adrenergic compounds have similar structures and are called catecholamines because the aromatic portion of the molecule is frequently catechol and the aliphatic portion is usually an amine.

Catechol (1, 2 dihydroxybenzene)

a. epinephrine (adrenalin or 3, 4 dihydro-oxyphenylethanolmethylamine)
Epinephrine (first hormone to be crystallized) can be prepared synthetically but it is difficult to separate the less active dextro-form from the more active levo-form. The levo-form occurs in the adrenal glands of animals and it is this source from which most adrenalin in this country is obtained. However, there is 1-norepinephrine (levarterenol) also in the adrenal glands of animals. Most clinically used epinephrine is contaminated with norepinephrine since the USP allows 4% contamination. However, Parke Davis epinephrine (adrenalin) has only 0.1% contamination with 1-norepinephrine and is the most popular brand of adrenalin.

Epinephrine is a light brown, microcrystalline, odorless, light sensitive powder, available as the hydrochloride in ampules of 1:1000 solution and in vials of 1:100 solution for inhalation, and 1:500 suspension in oil for intramuscular injection. The bitartrate salt which contains only 55% epinephrine is available (Suprarenin) in an ampule containing 91 mg. of the powder and in a 1:1000 solution.

Epinephrine has many uses in medicine and for these, as well as side effects and contraindications, the reader is referred to any standard text of pharmacology.

**Ophthalmic Preparations of Epinephrine**

1. **Local Anesthesia:** Approximately one drop of 1:1000 adrenalin (Parke Davis epinephrine) is placed in each cc. of local 2% or 4% xylocaine used for infiltrative anesthesia. The ensuing local vasoconstriction prolongs the anesthesia.

2. **Decongestant:** 1:1000 adrenalin is placed on each operative tray for hemostasis (constricts conjunctival vessels about the cornea) and for mydriasis (often in combination with cocaine or cyclogyl).

3. **Open Angle Glaucoma Therapy:** Topical epinephrine reduces aqueous formation and improves outflow by an obscure mechanism. It may be a direct action on the endothelial cells of the trabecular meshwork, the collagen or the mucoids. It may be that epinephrine acts by secondary mechanical effects mediated through the muscles of the ciliary body and iris, or secondary effects mediated through nerves in the trabecular meshwork or even by vascular or secretory effects of epinephrine. Refrigeration is not required for stability of any of the topical epinephrines used for open angle glaucoma therapy, but they deteriorate if left exposed to light.

(a) **Lyophrin:**

Lyophrin is a 2% solution of 1-epinephrine bitartrate (Alcon Laboratories, Fort Worth, Texas) and is a topically potent sympathomimetic amine. It is packaged as sterile lyophilized crystals to be reconstituted when dispensed (100 mg. of powder to 5 cc. of solution dispensed as Lyophrin diluent). The solution also contains sodium bisulfite .2% and chlorobutanol (chloral derivative) .15% as preservatives. Inactive ingredients include boric acid, disodium ethylenediaminetetraacetate. Lyophrin suppresses the secretion of aqueous, and the side effects include a slight burning or irritation in the eyes. Lyophrin finds its greatest use either alone or as an adjunct in the therapy of open angle glaucoma.
(b) **Eppy:**

Eppy is a 1% solution of 1-epinephrine in a 7.5 cc. bottle of free base complex of 1-epinephrine in a sterile ophthalmic vehicle (Barnes-Hind Laboratories, Incorporated, 895 Kifer Road, Sunnyvale, California). It has a pH of 7.4 and contains sodium bisulfite .3% as a preservative and oxine sulfate .01%. The natural color of Eppy is a pale yellow. The average dosage is two drops in each eye every 12 hours. There are no systemic effects noted, although occasional orbital pain is complained of. The indications and contraindications for Eppy are the same as Lyophrin and Glaucon.

(c) **Glaucon:**

Glaucon is a 2% solution of 1-epinephrine hydrochloride (Haug Drug Company, Milwaukee 3, Wisconsin). The preparation also contains .02% benzalkonium chloride and .2% sodium chloride and .3% sodium metabisulfite.

Glaucon has proved useful either alone or in combination with miotics and/or carbonic anhydrase inhibitors in cases of open angle glaucoma that respond poorly or not at all to other medications. There are no contraindications to the use of this drug with the exception of narrow angle glaucoma. Some patients with open angle glaucoma will obtain a drop in the intraocular pressure within one hour. The minimal dose is probably one drop a day, and the aqueous formation may be reduced by as much as 30% using Glaucon.

(d) **Epitrate:**

Ayerst brand of 1-epinephrine bitartrate prepared in 2% solution.

b. **phenylephrine** (Neo-syphrine)

![Chemical structure of phenylephrine](image)

Neo-syphrine is a synthetic vasoconstrictor and mydriatic which is rarely used in the therapy of glaucoma. Phenylephrine hydrochloride is manufactured by Winthrop Laboratories, 1450 Broadway, New York 18, New York. It is used in ophthalmology as a 10% solution in a 5 cc. bottle containing also sodium citrate, boric acid, dioctyl sodium sulfosuccinate, chlorobutanol .4% and sodium bisulfite .2%. The onset of action is more rapid than ephedrine, but less rapid than epinephrine, and the duration of action is longer than epinephrine. It finds its greatest usefulness for mydriasis of elderly patients but has the disadvantage of producing some epithelial stippling. When applied following ophthaine, a marked superficial punctate keratitis ensues.
Winthrop Laboratories also produces a viscous solution of 10% Neo-synephrine, which contains sodium citrate, methylcellulose, sodium chloride, chlorobutanol, and sodium bisulfite in 5 cc. bottles, and an emulsion of 10% phenylephrine hydrochloride in 4 cc. bottles which contains liquid petrolatum, acacia, glycerin, ascorbic acid, sodium benzoate, chlorobutanol, and sodium bisulfite.

c. levaterenol (1-norepinephrine, also levophed)

Levophed is obtained from the adrenal medullae of cattle and is prepared as the bitartrate available in 4 ml. ampules of 1:1000 (aqueous) solution.

Although rarely used in ophthalmology (most frequent use in intravenous therapy for raising blood pressure in hypotensive states), it is stated to have similar effects on the eye as 1-epinephrine, consideration being made for different dosage requirements.

d. ephedrine (1-phenyl-2-methylamino-propanol)

Ephedrine occurs naturally as an alkaloid but is usually prepared synthetically. It is available in capsules, elixer, syrup, and hypodermic tablets. Prepared for ophthalmological use in a 3% solution as sulfate it has no cycloplegic action. Ephedrine is not effective for mydriasis in the Negro.

e. amphetamine (Benzedrine)
dextro-amphetamine (Dexedrine)

Like ephedrine the amphetamines have many uses in medicine and having mydriatic effects are useful in ophthalmology. They are prepared as the sulfate in a 1% solution for this purpose. Benzedrine is useful as a synergist with homatropine and atropine, enhancing mydriasis but not cycloplegia.
Installation of cocaine into the conjunctival sac in a 2-10% solution produces slight to maximal mydriasis beginning within ten minutes, reaching its maximum within 45 minutes and disappearing with 4 hours.

The mechanism of motor action is not known except it enhances the response of sympathetically innervated structures to epinephrine probably by inhibiting the action of amine oxidase.

Cocaine is obtained from the leaves of shrubs of the Erythroxylon family or resynthesized from the base ecgonine obtained from the leaves.

Its effectiveness as a topical anesthetic is useful in surgery for conjunctival anesthesia.

2. Adrenergic Blocking Agents (sympatholytic miotics)
   a. dibenamine (N, N-dibenzyl-beta-chloroethylamine)

Dibenamine inhibits the response of the effector cells to epinephrine (and its related compounds) and to sympathetic nervous impulses. It is administered intravenously because of its local ineffectiveness and irritation. The drug induces a transitory miosis by relaxing the dilator fibers, dilates the conjunctival blood vessels, may narrow the palpebral fissure and slightly lowers the intraocular pressure in normal eyes. The usual dosage is 4-5 mg. per kg. and a lowering of the intraocular pressure occurs in 1-2 hours which usually remains for 24 hours. When used in ophthalmology it is in the preoperative management of angle closure glaucoma.
OPHTHALMOLOGICALLY IMPORTANT DRUGS

Dibenamine should not be used in the cardiac patient and it has produced atrial fibrillation. This drug should not be used in the treatment of acute narrow angle glaucoma except just prior to surgery when all other measures have failed to reduce intraocular pressure.

b. dibenzyline (phenoxybenzamine hydrochloride; N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl) benzylamine hydrochloride)

\[
\text{C}_6\text{H}_5\text{O} - \text{CH}_2 - \text{CH} - \text{CH}_3 \quad \text{N} - \text{CH}_2 - \text{CH}_2 - \text{Cl} \cdot \text{HCl}
\]

Dibenzyline hydrochloride (tertiary amine) has largely replaced dibenamine because it is locally less irritating.

Given systemically, dibenzyline blocks excitatory effects of adrenergic stimuli on smooth muscle (miosis) and glands but does not alter the inhibitory responses such as intestinal relaxation, bronchodilatation and vasorelaxation. Side effects include nasal congestion, miosis and orthostatic hypotension.

This drug is a colorless crystalline compound, insoluble in water, soluble in propylene glycol and available in capsules. Dibenzyline (Smith, Kline and French) is supplied in 10 mg. oral tablets as well as the parenteral form.

Dosage is started with 30 mg. daily to 200 mg. maximum, and caution is used with administration of this drug due to such side effects as hypotension with overdosage.

c. ergot alkaloids (ergotamine, ergocornine, ergochristine and ergocryptine) and the hydrogenated ergot alkaloids (dihydroergotamine, etc.)
TUCKER

Used by subcutaneous injection of .25 to .5mg. in 1% solution ergot alkaloids lower the intraocular pressure in 80-90% of simple glaucoma cases. For the most part, however, they have been abandoned for their unpredictable effects.

II. Miscellaneous Drugs

A. pyrimethamine (Daraprim; 2, 4-diamino-5(p-chloro-phenyl)-6-ethylpyrimidine)

A recent addition (1951-1952) to the synthetic antimalarials, Daraprim has been used (without clear-cut success) in the therapy of the protozoae, Toxoplasma gondii.

Toxic effects are primarily registered in the bone marrow were antifolinic acid properties produce a megaloblastic anemia and suppression of bone marrow elements, including platelets.

Management of the Patient taking Daraprim:

1. Daraprim dosage: There is no general agreement of what constitutes adequate Daraprim therapy in acute toxoplasmosis uveitis. A loading dose of 75-100 mg. (supplied in 25 mg. oral tablets) twice a day for 2 days, and then 25 mg. twice a day thereafter for 2-3 months is average. Then the patient may take 25 mg. daily for several months.

2. Additional therapy: Cortisone is frequently used to diminish the inflammatory reaction produced by the live as well as dead organism. A dosage of prednisone 10-15 mg. four times daily for a week followed by mg. four times daily for 4-6 weeks may be required or desired. The drug is then gradually tapered to discontinuance.

Sulfa enhances the effect of Daraprim and is given as terfonyl 2 gms. immediately and then 1 gm. four times a day, continued for several weeks to several months. The more potent Kynex may be substituted for triple sulfa (smaller dosage required to sustain blood levels).
Spiramycin has been advocated also as having an additive effect against toxoplasma when used with Daraprim. It is given in 250 mg. dosage four times a day and continued 4-6 weeks.

3. Precautions of therapy:

a. When using cortisone a negative history for duodenal ulcer and tuberculosis must be obtained. A negative chest x-ray report should be obtained.

b. Because of the danger of a megaloblastic anemia, a platelet count, white blood cell count, and hemoglobin are obtained once a week and preferably twice a week.

c. If a leukopenia is present (less than 3,000 cu. mm.) or the platelet count is less than 80,000 cu. mm. Daraprim must be discontinued at least temporarily. Leucovorin (folinic acid) may be given parenterally 5 mg. twice a day to hasten the return of a normal blood count. Patients may eat a yeast cake once or twice a day prophylactically. The folinic acid dosage is calculated at about one-fifth the Daraprim dosage.

d. A weekly urinalysis is obtained to rule out complications of sulfa therapy, i.e., crystalluria.

B. urea (Carbamide) i.e., diamide of carbonic acid.

\[ \text{H}_2\text{N}--\text{CO}--\text{NH}_2 \]

When Diamox and miotics have failed, urea intravenously is most valuable for lowering the intraocular pressure of acute angle closure glaucoma. The mechanism of action appears to be an osmotic influence on the blood-aqueous barrier. Oral urea was used as a diuretic as early as 1852. Intravenous urea is usually reserved for those cases unresponsive to other therapy or for lowering intraocular pressure just prior to surgery.

Urea for injection (Ureaphil, Abbott) is supplied as an anhydrous lyophilized, sterile powder. It is packaged in units containing 40 gms. of pyrogen-free urea in a 250 ml. bottle.

The solution is prepared as 30\% urea with total urea calculated at 1.0-1.5 gms. per kg. of the patient’s body weight. (Example: 80 gms. in 210 mls. = 30\% solution) The diluent may be 5 or 10\% glucose in water (dextrose or invert sugar) and the solution is prepared fresh for each case (ammonia develops in the solution with prolonged standing). It is administered no faster than 60 gfts/minute. The patient’s oral fluid intake should be restricted despite his extreme thirst or the desired osmotic effect will not be achieved.

In the presence of liver or kidney disease, urea should be administered with caution. In the adult a total dose should not exceed 120 gms. (In children, the dose is based on weight.) The dosage must, to some extent, be individualized to the
patient in order to prevent disorientation, circulatory collapse, etc. Inasmuch as the blood volume is markedly increased, this drug should not be used in patients with congestive heart failure.

Intraocular pressure will usually fall after I.V. urea in 20-30 minutes and remain down for 4-10 hours.

Marked diuresis is produced and patients going to surgery should, perhaps, have a Foley catheter inserted. Its diuretic effect is produced by the osmotic effect in the renal tubules lessening re-absorption of water. There are many other medical uses of intravenous urea which are not related to this paper, and the reader is referred to the literature.

Urevert is another I.V. urea preparation (Travenol Laboratories, Inc., Division of Baxter Laboratories, Inc., Morton Grove, Ill.) supplied as a 30% synthetic urea lyophilized powder with 10% invert sugar in a kit for simple mixing. Two sizes are available, 40 gms. and 90 gms. of urea per vial.

C. carbonic anhydrase inhibitors

The following four drugs are used either in the therapy of acute angle closure glaucoma or in difficult to control open angle glaucoma cases. The first of these drugs available was Diamox (acetazolamide) in the mid 1950's. It and the other drugs in the group (all are sulfonamides with substitutions at the benzene ring that characterizes the sulfonamides used as chemotherapeutic agents) were introduced as diuretics but all are now used for non-diuretic purposes. Because they are sulfonamide derivatives, it is possible for the reactions to occur which have been described for the bacteriostatic sulfonamides. These include crystalluria, renal calculus, leukopenia, rashes, hemolytic anemia, and bone marrow depression.

\[ \text{sulfanilamide} \]

1. *acetazolamide* (Diamox) Lederle Laboratories, Division of American Cyanamid Co., Pearl River, N. Y.

2-acetylamino-1, 3, 4-thiadiazole-5-sulfonamide
Diamox dosage orally varies from 125 mg. every 12 hours to 500 mg. every 4 hours, or in the case of an acute angle closure glaucoma 500 mg. intravenously. The most commonly used oral dose is 250 mg. every 6 hours, and this is decreased by patient intolerance or increased by patient need. More recently a sustained release capsule by Lederle containing 500 mg. of Diamox for 12 hour release has been made available. Each vial of Diamox parenteral contains 500 mg. of acetazolamide sodium and sodium hydroxide to pH 9.2. The solution should be reconstituted with at least 5 cc. of sterile distilled water (10 cc. very satisfactory) and intravenous route of injection is preferable although it can be given intramuscularly (one may give $\frac{1}{2}$ dose I.V. and $\frac{1}{2}$ dose I.M.).

Diamox will decrease production of aqueous and effect a lowering of intraocular pressure in $\frac{1}{2}$ to 3 hours and this effect lasts up to 6 hours, whereas Neptazane will not effect a lower pressure for 6-8 hours but will sustain its effect 8-10 hours. Intravenous Diamox will produce lowering of intraocular pressure in a few minutes that reaches its lowest level in $\frac{1}{2}$ - 4 hours.

There are other medical uses of Diamox not within the scope of this presentation and are therefore omitted. Side effects of Diamox include drowsiness, paresthesias, nausea, vomiting, etc. Contraindications include idiopathic hyperchloremic acidosis and known states of sodium or potassium depletion.

2. **methazolamide** (Neptazane) Lederle

5-acetylamino-4 methyl-$\Delta^2$-1, 3, 4-thiadiazoline-2-sulfonamide

Neptazane will decrease intraocular pressure with $\frac{1}{4}$ the dose of Diamox and it is reported that 50% of patients unable to tolerate the side effects of Diamox take Neptazane without difficulty. Also, 50% of those patients whose intraocular pressure failed to respond to Diamox reportedly responded to Neptazane. Effective dosage is 50-100 mg. 2 or 3 times a day. Neptazane is prepared only as a 50 mg. oral tablet. The pressure reaches its lowest level in 6-8 hours and is maintained at this level 8-10 hours. If tolerated, Diamox is the drug of choice.

![Chemical Structure of Ethoxyzoleamide](image)

Cardrase is a similar drug to Diamox (carbonic anhydrase inhibitor). It is supplied as an oral tablet in 62.5 and 125 mg. sizes.

The recommended dose is 62.5 to 125 mg. twice to four times a day; intermittent rather than continuous therapy in primary and secondary glaucomas because of the possibility of electrolyte imbalances being produced. For best results miotics are used with Cardrase. The same side effects and contraindications apply for Cardrase as are listed for Diamox.

4. *dichlorphenamidine* (Daranide, Oratrol) Merck, Sharp & Dohme

![Chemical Structure of Dichlorphenamidine](image)

Daranide is another carbonic anhydrase inhibitor that may successfully be substituted for Diamox in the patient who experiences intolerable side effects from Diamox in glaucoma therapy.

The dosage varies from 50-200 mg. every 6-8 hours. (A priming dose of 100-200 mg. is given at the start of therapy.) It is said to produce less metabolic acidosis but may induce a more pronounced renal loss of potassium. It is supplied only in 50 mg. tablets for oral administration.

Daranide has been noted to be more effective when combined with a cholinesterase inhibitor in glaucoma therapy.

Side effects and contraindications are identical with those listed for Diamox. Short-term therapy is recommended.
At the present time the most convenient hypertonic agent is 1, 2, 3-propanetriol or “glycerol”. Of the hypertonic agents currently in vogue, urea has the disadvantage of being poorly tolerated orally — usually making the nausea and vomiting of already sick, acute glaucoma patients worse — and when given intravenously has the definite risk of causing a slough if the I.V. infiltrates. Glycerol is used orally, a 50% solution made up in normal saline or water and flavored with a citrus fruit extract, makes a passably palatable cocktail. 1-2 gm. per kg. of body weight is an appropriate dose which will drop intraocular pressure dramatically within about 40 minutes. A handy rule of thumb is to use 1.50 cc. per pound of a 50% “cocktail”.

E. ethylenediamine acetic acid (EDTA or Versene)

EDTA belongs to a class of chemical agents known as chelate compounds or chelating agents. Such compounds will inactivate a metallic ion with the formation of an inner ring structure in the molecule, the metallic ion becoming a member of the ring. Thus is formed a stable soluble complex with calcium ions and certain heavy metals.
In ophthalmology it is practical to remove the calcium from corneal tissue in band keratopathy by chelation. The calcium deposit most frequently lies between the epithelium and Bowman's membrane, and after removal of the corneal epithelium the calcium deposit is vulnerable.

A .01 molar solution is used and the cornea is irrigated with 100 cc. for 15 minutes by placing a corneal irrigation cup over the cornea and removing the EDTA with a suction bulb to replace fresh Versenate. (Solutions up to a concentration of .05 molar may be used in the cup.)

REFERENCES