RESEARCH/RECHERCHE

Newer Approaches to Glaucoma Management *

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Abstract

Traditional drug treatment of glaucoma tends to produce sequential periods of overdose and underdose. Methods of avoiding this pulsed sequence are becoming available. The aim is to achieve zero order kinetics instead of first order kinetics. The result should be smoother control of intraocular pressure with a smaller dose of drug. Laser treatments are replacing some of the older surgical procedures for treating glaucoma. No current treatment modality is totally successful and free of problems for all patients.

Résumé

Le traitement traditionnel du glaucome par médicaments a tendance à produire des périodes séquentielles de dose excessive et de dose insuffisante. Certaines méthodes visant à éviter ces séquences pulsatoires deviennent accessibles. Leur but: atteindre la cinétique d'ordre zéro au lieu de la cinétique de prèmier ordre. Le résultat escompté: une maîtrise plus souple de la pression intraoculaire, par une dose réduite de médicaments. Les traitements au laser remplacent certaines interventions chirurgicales habituelles du glaucome. Aucun traitement actuel ne réussit à cent pour cent sans occasionner de problèmes à certains patients.

Glaucoma encompasses a group of diseases involving the optic nerve and resulting in a visual field loss. The glaucomatous signs (visual field reduction, damage to nerve fiber layer and sometimes disc changes) are likely to be accompanied by increased intraocular pressure. However, there is no simple relation between intraocular pressure (IOP) and impaired functioning of the optic nerve. Many eyes with an IOP over 21 mmHg never develop visual field loss from glaucoma,[1] while a few patients who do develop glaucoma have an IOP below 21 mmHg.[2] A pressure which fluctuates considerably during the day is likely to be as harmful as a constant high pressure.[3] Normal eyes show a diurnal fluctuation of about 4 mmHg but glaucomatous eyes undergo wider swings in pressure. Perfusion of the capillaries supplying the nerve head and the retina is influenced by the blood pressure and by the intraocular pressure.[4-8] A ratio between blood pressure and intraocular pressure which results in inadequate perfusion of these capillaries results in nerve fiber damage.[8, 9] Although the etiology of glaucoma remains obscure there is a strong vascular component.[8, 10]

Early confusion about the prevalence of glaucoma partly resulted from a failure to recognize that about 11% of the population have a slightly elevated IOP but of this group only 1% a year develop visual field losses.[11] Current estimates indicate that between 0.5% and 1% of the population have glaucoma[12-14] Most of those who have primary open-angle glaucoma are over 55 years of age.[7] Improved diagnostic techniques and the increasing longevity of patients will increase the number of people requiring treatment.[15]

There are many types of glaucoma but since 1940 it has been possible to divide primary glaucoma into two types based on the anatomical size of the angle between the anterior surface of the iris and the trabecular region.[4] Gonioscopy and to a lesser extent the slitlamp and penlight methods of estimating the angle width are employed.[16, 17]

The most common type is open-angle glaucoma. Gonioscopy reveals an open angle, early manifestations are insidious and drug treatment is usually lifelong. In most populations the incidence of open-angle glaucoma is more than twice that of angle-closure glaucoma.[8]

Angle-closure glaucoma occurs in eyes with a pre-existing narrow angle and is generally ameliorated by prompt surgery,[4] after the pressure has been reduced by appropriate drugs.

Drugs and surgical procedures seek to prevent damage to the optic nerve by controlling the IOP either by facilitating the escape of aqueous humor from the eye or by decreasing the rate of formation of this fluid[4] (Tables 1 and 2). This paper describes some newer approaches to the management of open-angle glaucoma including presently available drugs and some new formulations. Laser treatment of both open-angle and angle-closure glaucoma is the only surgical procedure discussed.

Fundamental Concepts of Ocular Pharmacology

When an eyedrop such as pilocarpine is instilled how much of it is physiologically available? How accurately can we predict the magnitude and time course of drug action? A drop of pilocarpine (50 to 75 μL) is many times larger than the normal tear film volume (6.5 to 8.5 μL) or the maximum capacity of the conjunctival sac (25 to 30 μL). As a result approximately 80%[22] of the instilled drop does not enter conjunctival-corneal

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Table 1
Drugs to Lower Intraocular Pressure

	Onset of pressure reduction	Duration of pressure reduction*	Decreases aqueous production (inflow)	Facilitates aqueous escape (outflow)	Extent of pressure reduction	Reported compliance	Discontinued because of unwanted effects	Had signficant unwanted effects	Comments
acetazolamide (Diamox) 270 or 127 mg (q.i.d.) orally	½ to 2 h; max 3 to 5 h	6 to 10 h	40 to 70%	yes	About 30%; about 10 mmHg, range 3 to 22 mmHg.	?	40 to 50% [Methazolamide (Neptazane) 50 or 100 mg t.i.d. causes fewer unwanted effects.]	yes	Gastrointestinal effects, acidosis, gout, drowsiness paresthesias, potassium depletion, kidney stones, blood dyscrasias and up to 8D of myopia. Depression has been reported.
acetazolamide (Sequel) 500 mg (b.i.d.) orally	2 h; max 8 to 18 h	22 to 39 h	50%	yes	About 10 mmHg.	?	?	?	Sustained release form.
acetazolamide 250 mg i.v.	From 5 to 10 min; max ½ to 4 h	½ to 4 h	50%	—	5 to 10 mmHg.	100%	?	?	Employed sometimes to treat an acute glaucoma episode.
carbachol 1.5% or 3% topically. (b.i.d. or t.i.d.)	4 h	8 to 12 h	probably	yes	5 to 10 mmHg.	?	?	?	Causes sweating and palpitation. Can raise IOP if angle is narrow. Ciliary spasm. Myopia. Penetrates the cornea poorly.
N-demthylated carbachol, 3% or 6% topically	?	8 h	probably	presumably	By 30 to 35%; about 10 to 12 mmHg.	?	?	few	No ciliary spasm, no decrease in acuity, no effect on pupil size.
demecarium bromide (Humorsol) 0.125% or 0.25% topically every other day. For eyes with open angles only.	30 min; max at 30 to 36 h	9 days	no	121%	45%	?	?	yes	Causes bradycardia, bronchoconstriction, ciliary spasm, increased rate of cataract development. Causes iris cysts and local congestion. Rarely used.
dipivefrin hydrochloride (Propine) (dipivalyl epinephrine) 0.1% (b.i.d.) topically	30 min; max at 4 to 8 h	similar to epinephrine i.e., about 12 h	yes Probably by 25%	yes Penetrates cornea IOX more readily than epinephrine	From 20% to 25%; about 7 mmHg.	Good	5%	yes in 8% to 25%	Intraocular effects similar to epinephrine but systemic effects less. Adverse effects on the ocular surface do occur with dipivefrin. Can cause cystoid maculopathy especially in aphakic eyes. Do not use if angle is narrow.
echothiophate iodide, (Phospholine Iodide), 0.03% or 0.06% once or twice a day, topically.	4 to 6 h; max 10 to 28 h	12 to 72 h	no effect	125%	Usually 10% range 4% to 50%; 10 to 16 mmHg.	?	?	yes	Shallows anterior chamber progressively. Cysts at pupillary margin. Cataract in 50% in 1 yr. Ciliary spasm and risk of retinal detachment. Induced myopia possibly not all due to ciliary spasm. Do not use if angle is narrow.
epinephrine, adrenalin. Many trade names. 1% or 2% (b.i.d.) topically	60 min; max 2 to 4 h	12 to 24 h	By 25% to 37% but briefly increases production for 2 to 5 h	By 50% if drug treatment is continued for some days	From 25% to 30%; 3 to 36 mmHg, mean 12 mmHg. About 50% show 5 mmHg lower IOP.	30% to 80%	20% to 70%	yes in 83%	Lowers IOP in 70% of open-angle eyes, and in 31% of secondary glaucoma cases. Can cause extrasystoles, arrhythmia, and hypertension. Allergic reactions occur in 20%.

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Table 1 continued

	Onset of pressure reduction	Duration of pressure reduction*	Decreases aqueous production (inflow)	Facilitates aqueous escape (outflow)	Extent of pressure reduction	Reported compliance	Discontinued because of unwanted effects	Had signficant unwanted effects	Comments
ethyl alcohol. 3 fluid ounces of spirits. (50% alcohol) (orally); 2 to 3 ml/kg spirits.	15 min; max 1 to 2 h	4 to 5 h	slightly	yes	20%. As much as 5 to 35 mmHg reduction if IOP elevated.	excellent	—	yes	Inhibits anti-diuretic hormone, raises the osmotic pressure of the plasma. Probably also has a central effect on IOP. Can be repeated but can cause intoxication.
gylcerol (glycerin) 1.5 grams/ kg (orally). About ½ a cupful. Dose can be repeated if necessary. One ml of the solution contains 0.62 grams.	10 to 30 min; max 30 to 60 min	3 to 5 h	?	yes	At least 20%.	?	rarely	Unpleasant to swallow	Raises level of blood glucose and osmotic pressure. Also has a central effect on IOP. Caution if diabetic. Can cause nausea but will lower IOP if the glycerol is not lost by vomiting until 5 or 10 min after ingestion.
guanethidine (3%) plus adrenaline (0.5%) (b.i.d.) (topically). Other proportions are available. (1% to 5%) guanethidine plus 0.2% to 1% adrenaline.	1 to 2 h	12 to 24 h	yes	yes	25%; About 9 mmHg; range 2 to 10 mmHg.	good	?	?	Guanethidine produces a type of chemical sympathectomy so the epinephrine has more effect. Can cause punctate epitheliopathy: conjunctival hyperemia, pigmentation and raise blood pressure. Use only for eyes with open-angle glaucoma.
levobunolol hydrocholoride (Betagon) 0.5% once a day.	30 min; max at 2 to 4 h	16 to 24 h	yes	not likely	About 25% 7 mmHg.	?	About 5%		Like timolol blocks beta₁ and beta₂ sites. Slows heart 5 to 10 beats a min, lowers BP about 4 mmHg. Stings and may cause blepharitis.
marijuana, cannabis, tetrahydrocannabinol, Δ⁹ THC (smoked). Probable dose from one cigarette is 1 mg.	within 1 h	up to 5 h	Probably dilates efferent vessels from ciliary processes and constricts afferents to to ciliary processes.	yes	15% to 24% or 20% to 40%	?	?	?	Has a central effect and lowers blood pressure so may actually worsen effect of glaucoma. Topical tetrahydrocannabinol may or may not lower IOP.
nadolol 2% topically (b.i.d.)	max at 4 h	12 h							A non-selective beta blocker. Lowers IOP about as well as 0.5 timolol b.i.d. but causes more unwanted systemic effects.
pilocarpine nitrate or hydrochloride 1% to 6%. Usually 2% (q.i.d.) topically.	30 to 60 min; max reduction evident at 75 min	4 to 8 h	up to 25% eventually	over 30%	10 to 40% 5 to 10 mmHg	50 to 70%	30%	yes	Lowers IOP in 80% with open or closed angle. Shallows anterior chamber by about 10% promptly. Causes up to 10D myopia. Decreases AC/A by 20%. Hastens cataract formation; poorer vision in dim illumination.
pilocarpine Ocusert® Topically once a week.	max 2 h.	7 to 9 days	probably	probably	Lower IOP in a.m. than with pilo 2%.	Better than with drops.	38%	few	Releases pilocarpine at 20 or 40 μg/hr for a week. Causes 0.5 to 1.4D of myopia in young patients, may fall out; costs more.

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Table 1 continued

	Onset of pressure reduction	Duration of pressure reduction*	Decreases aqueous production (inflow)	Facilitates aqueous escape (outflow)	Extent of pressure reduction	Reported compliance	Discontinued because of unwanted effects	Had signficant unwanted effects	Comments
physostigmine, eserine, 0.25% or 0.5% solutions (q. 4 or 6 hr) or 0.25% ointment (hs.) Topically.	15 min	8 to 12 h	?	slightly	?	?	?	?	Ciliary spasms. Poorer vision in dim illumination. No longer used to treat glaucoma
thymoxamine HC1 0.1% to 0.5% (topically)				slightly	very little			not at these low concentra- tions.	Is an alpha, blocker useful in angle-closure glaucoma. Reverses phenyle- phrine mydriasis. Causes miosis.
timolol maleate (Timoptic) 0.25% or 0.5% (b.i.d.) topically	20 min; max 1 to 2 h	7 to 14 h	15% to 40%	Possibly with long term use but this is doubtful.	20% to 30%; 2 to 16 mmHg.	90%	9% (or in about 40% of those who get side effects.)	15% to 23% bradycardia, asthma, bronchitis	About 10% do not respond and 25% do not respond ade- quately. Lowers IOP in over 80% of open-angle cases but pres- sure tends to escape from con- trol to some extent in a few months. Timolol is less effective in other types of glaucoma. Can cause bradycardia, hypotension, syn- cope, worsen asthma and bron- chitis and cause mental depression.

*When administered at the usually indicated dose and recommended regimen. All values are based on reports by a number of investigators and are approximations because of various clinical variables.

tissues but rather flows into the nasolacrimal duct (within 30 s) or down the cheeks.[18-22] With a normal blink rate and instillation of a much smaller drop up to 80% more of the drug remains in the ocular area for 5 min.[23]

From 12% to 25% of the tear fluid is replaced every minute by new secretion. (Table 3). The normal tear production rate is 1.2 to 3.8 μL/min but can reach 5.7 μL/min or more[24, 25] following irri- tation or rapid blinking (the latter also hastens tear drainage.[18]) Some of the instilled drug enters the conjunctival tis- sue and its blood vessels[26] but most of the drop does not penetrate the eye.[27] It is possible to predict how much drug has penetrated the cornea at any time after drug instillation — providing the instil- lation is performed correctly and tear production and blink rates are known. For example less than 1% of the pilocar- pine in an aqueous solution enters the cornea.[28] Pilocarpine reaches its peak concentration in corneal epithelium within 2 min,[29] in cornea in 15 min[28] and in aqueous in 35 min.[30] For most drugs less than 0.1% of the instilled drug penetrates the cornea and actually enters the anterior chamber.[20, 31-34] Drug con- centration in the anterior chamber rises rapidly during the first 10 to 20 min reaches a peak in 20 to 40 min and then begins to decline.[34] Initially the rate of decline is rapid but then becomes slower i.e. first order kinetics are observed. The concurrent or prior application of ben- zalkonium chloride (0.01% or 0.001%) or other preservatives can damage the epithelium and increase pilocarpine penetration into the aqueous by as much as 50%.[20] Elimination of topically instilled aqueous solutions of pilocarpine from the tear film occurs at a steady rate (most is lost in 30 min[35]). Instilled drops become diluted by tear fluid to half their original strength in 45 s and typically reach 1/1000 of their initial concentration in 8 min.[36]

Many ocular drugs are more effective in an eye with a lightly pigmented iris[37] possibly because pigmented tissues bind the drug more firmly[38] or because the rate of drug hydrolysis is faster in heav- ily pigmented eyes.[39-42] Heavily pig- mented irides are more dense,[42] so penetration of the drug is impeded. Peak drug effect is reached later and persists longer in dark eyes.[43, 44] The pharmaco- logic action of pilocarpine (4%) or epinephrine (2%) is more pronounced (i.e. decreased IOP) in lightly pigmented than in heavily pigmented subjects.[45] Similar pharmacokinetics apply to most topically instilled ocular drugs.[44]

Most drugs when taken orally undergo extensive metabolism by the liver so that less than 50% of the drug reaches the sys- temic circulation. Topically instilled drugs bypass liver metabolism and enter the blood stream directly via the capil- laries of the nasolacrimal passage. Drugs instilled on the eye reach peak concen- trations in the blood in about 90 min.[33]

Drugs to Control Glaucoma

(a) **Parasympathomimetics (Cholinergics)**
For over 100 years, pilocarpine has been used to promote the escape of aqueous humor from the eye.[4] A drop of a 2% aqueous solution of pilocarpine is effective for only 6 h thus requiring four applications daily.[16] Pilocarpine is usually effec- tive[46] but poor compliance[46a] is a common problem because of the need for frequent instillations and the side effects such as headache, blurred vision (induced myopia), reduced vision in dim light and reduced vision when cataract is present.[15, 47, 48] In most patients the side effects diminish after a week on the drug. Multiple daily instillation

of a drug and its preservatives can induce an allergic response or produce cumulative damage to the corneal epithelium.[49]

(b) **Sympathomimetics (Adrenergics)**

Epinephrine, an adrenergic agent, also has a long history of use in the treatment of glaucoma.[4, 46] Its topical use was abandoned for a time because, by producing mydriasis, it precipitated angle closure in a few eyes. The use of epinephrine was resumed (about 1945) when practitioners became able to identify those eyes which had anatomically narrow angles. Adrenergic agents such as epinephrine are believed to lower the IOP by increasing aqueous outflow and by slightly decreasing aqueous production.[4, 15, 50, 51] Possibly epinephrine also promotes the endogenous production of prostaglandins.[52] The pressure lowering effect of epinephrine is blocked by concurrent administration of indomethacin an inhibitor of cyclo-oxygenase and prostaglandin production.

Adrenergic drugs have several advantages over pilocarpine because they require only twice a day instillation, do not blur the vision and dilate rather than constrict the pupil. This helps vision in dim light and permits patients with cataract to make the best use of their remaining vision.[15] Epinephrine (1%) when given to a patient who is receiving pilocarpine usually lowers the IOP even further.[4] However epinephrine can raise blood pressure, cause adrenochrome pigment deposits in ocular tissues[53] and cause cystoid macular edema[4, 51] (in about 20% of aphakic eyes,[54]) so caution is advised.

(c) **Beta Adrenergic Blocking Agents**

Paradoxically both stimulating and blocking certain adrenergic receptor sites in the eye will lower IOP.[17] In the past seven years timolol maleate, a non-selective "β-blocker", has become widely used to treat glaucoma.[4] Timolol (0.25% or 0.5%) when instilled twice a day lowers the IOP without affecting pupil size or accommodation. Timolol decreases aqueous production and smooths out diurnal variations in pressure.[55, 56] The action of timolol persists longer in heavily pigmented eyes.[57]

Table 2
Aqueous Humor Production and Outflow in the Normal Adult Eye

- capacity of the anterior chamber = 190 to 265 μL (about 4 to 5.5 drops).
- capacity of the posterior chamber = 60 μL (about 1.0 drop) (Capacity of the vitreous chamber is about 4.4 mL).
- total volume of aqueous in an eye = 250 to 325 μL (about 5.0 to 6.5 drops).
- aqueous production rate = 2 to 3.5 μL/min = 120 to 210 μL/hr (each eye). The rate is lower during sleep and declines with increasing age.
- total daily production of aqueous = 3 mL (about 60 drops each eye).
- aqueous outflow by the trabecular route is 2.4 to 3.0 μL/min (each eye). Aqueous outflow facility declines slightly with increasing age.
- aqueous outflow by the uveoscleral route is 0.2 to 0.5 μL/min (each eye). This route provides 5 to 15% of the total aqueous outflow.
- aqueous turnover time is 80 to 120 min.
- aqueous turnover rate is about 1.5%/min.
- in normal eyes the diurnal variation in IOP is 4 to 6.5 mmHg.

However, the ability of timolol to control the IOP diminishes slowly after some months of therapy.[58] Timolol can be added to the regimen of those receiving topical pilocarpine or oral acetazolamide but may or may not help when given to those who are receiving topical epinephrine.[50, 59] When used with epinephrine, the epinephrine should be instilled before the timolol.[50, 60] Timolol slows the heart rate, especially in patients with heart disease and can precipitate an asthma attack and bronchitis in patients with respiratory disease. At least a dozen other adrenergic blockers are presently being investigated for the control of IOP[15], for example, levobunolol, betaxolol, metipranolol and nadolol.

(d) **Carbonic Anhydrase Inhibitors**

Acetazolamide or methazolamide can be administered orally to treat glaucoma.[46] Acetazolamide can also be given intravenously. Carbonic anhydrase inhibitors are used primarily to lower very high IOP in acute angle-closure glaucoma prior to surgery. Carbonic anhydrase inhibitors, which are also diuretics, decrease aqueous production but their unwanted effects (drowsiness, headache, anorexia, nausea, lethargy, transient myopia, paresthesias and rarely renal calculi and blood dyscrasias) make their long term use undesirable.[61] Attempts to develop topical preparations of carbonic anhydrase inhibitors have created some interest.[62]

Other methods (some experimental) of administering drugs to treat ocular conditions are:

- subconjunctival injection[63]
- a spray system;[64] with aerosols
- iontophoresis, the use of a direct electric current to cause drug ions to penetrate tissue. Duke-Elder[65] provides a long list of drugs, including pilocarpine, which have been administered this way.

Prolonging Drug Release

In an effort to minimize the problems associated with repeated instillation of drugs (which subject the patient to a cycle of overdoses and underdoses) various methods have been designed to prolong the duration of the effect of single doses.[25, 66-70] Fifteen minutes after drug instillation the proportion of drug remaining in the conjunctival sac was shown[69] to depend on the vehicle and for the following vehicles was: saline 23%, methylcellulose 24%, polyvinyl alcohol 30%, and ointment 38%. Pilocarpine in an aqueous vehicle is lost from the tears at rate of at about 10% a minute.[44] Another study[20] compared drug retention time with various vehicles and reported for aqueous 60 s; for 0.5% hydroxypropyl methylcellulose 140 s, for 1% hydroxypropyl methylcellulose 210 s; and for 1.4% polyvinyl alcohol 70 s.

Ideally a controlled drug delivery system[22, 70-72] should:

- require less frequent administration
- avoid the overdose/underdose sequence
- diminish the extent of the fluctuations in IOP
- require less total drug per day
- produce fewer unwanted effects
- avoid the use of preservatives

Table 3
Tear Production and Tear Drainage in the Normal Eye

- total tear volume is 6.5 to 8.5 μL (each eye).
- tear production rate is from 1.2 to 3.8 μL/min (usually 2.5 μL/min) but can reach 5.7 μL/min (each eye). Tear production during sleep is negligible. Tear production declines as age increases.
- daily tear production is from 1.7 to 8.2 mL (about 35 to 145 drops) (each eye).
- tear fluid turnover time is 4 to 6 min.
- tear turnover rate is 12% to 25%/min, generally about 15%/min.
- maximum capacity of the conjunctival sac of an adult is 25 to 30 μL, providing blinking does not occur. A typical drop of pilocarpine contains about 50 μL so half is immediately spilled out. Blinking and drainage into the puncta soon reduce the quantity of fluid retained in the conjunctival cul-de-sac to about half the maximum capacity value, i.e. to about 12 μL in an adult eye.
- normal blink rate is 10 to 20/min. Each blink expresses one to two microliters of fluid from the tear volume.
- maximum capacity of the conjunctival sac of a child is up to 10 uL, providing blinking does not occur.
- about 2% of the tear fluid is lost by evaporation and the remainder enters the nasolacrimal drainage pathway.
- absorptive surface of the conjunctiva of an adult is about 16 cm^2 each eye. Surface area of the cornea is about 1.5 cm^2.
- tears contain 1% protein, have a pH of 7.1 to 7.6, a surface tension of 40 dyne/cm and an osmolarity of about 300 mOsm/L. Probably eyes with a tear tonicity above 312 mOsm/L will be associated with dry eye symptoms.
- the tears have some buffering capacity. Instilled solutions in the pH range 6.5 to 9 cause little discomfort.

- permit use of newer drugs, some of which have such short half-lives that they would require too frequent administration.
- improve compliance. Patient compliance is notoriously poor especially for pilocarpine.[46a]

Formulations employed to prolong drug release or increase corneal penetration include:

(a) **Ointment vehicles**

The turnover rate of a drug in an ointment in the conjunctival cul-de-sac[19] is about 0.5%/min compared to at least 50%/min for a drug in solution.[24, 36] Ointments retain a lipid soluble drug in the tear film nine or ten times as long as an aqueous solution.[19, 73, 74] Pilocarpine is lost from an ointment about 20 times slower than from an oily vehicle.[44] Ointments prolong drug contact with the ocular surface[19, 44, 67, 74] are less diluted by tears and less readily drained away. Often a given drug will be prescribed in an aqueous solution for use during the day and in an ointment for use at night.[18, 70, 75] Ointments (especially, large doses) produce a greasy appearance, and blur the vision slightly.[22, 71, 75, 76]

(b) **Soluble gel vehicles**

A gel vehicle, poloxamer 407 (a polymer of ethylene oxide and propylene oxide), when combined with pilocarpine, enables a single night-time dose to control IOP for 24 h.[76-78] Poloxamer gels become more viscous when they reach body temperature but the drug-gel combination dissolves in the tears in less than 5 min.[79] Compliance is improved but drug delivery is still somewhat pulsed.[78]

Pilocarpine 4% in a gel vehicle, carbopol 940 (Pilogel, Pilopine H.S.) was introduced by Alcon. The gel contains a carboxylated (acrylic) polymer and the preservative is benzalkonium chloride 0.008%. A half-inch ribbon of gel applied at bedtime controlled IOP for 24 h.[80] Pilopine H.S. controlled IOP with once a day administration but 10 to 28% of eyes developed a persistent superficial corneal haze.[78, 78a] Viscous preparations and gels increase bioavailability since they provide about 8 h exposure to the drug. Very little aqueous solution of a drug remains in contact with the cornea for longer than 15 min.[81]

A carboxypolymethylene gel (Gel Tears) has been developed by Alcon for the treatment of dry eyes.[82] This polymer of acrylic acid has an ointment-like consistency and remains in the conjunctival sac for 6 to 12 h where it melts and absorbs and retains fluid. Gel Tears could serve as a drug vehicle.

(c) **Addition of soluble polymers to the drug**

Hydroxypropyl methylcellulose (0.5%)[75, 80] and polyvinyl alcohol (1.4%)[22, 35, 66, 68, 69, 83-86] increase tear viscosity and delay tear drainage.[62] Adding one of these agents to a drug will extend the duration of contact time by 8 or 10 min[87, 88] but provides minimal clinical benefit.[18, 89-92] The bioavailability of pilocarpine increases two fold when the drug has a hydroxypropyl methylcellulose vehicle compared to an aqueous vehicle.[44] Pilocel (Professional Pharmacol Co.) contained methylcellulose while Isopto vehicle (Alcon) uses 0.5% hydroxypropyl methylcellulose. Retention time of drugs placed in the conjunctival cul-de-sac is mostly determined by the rate of tear production.[92] The Adsorbobase vehicle (Alcon) with 1.67% polyvinyl pyrrolidone and other soluble polymers plus 1% hydroxypropyl methylcellulose prolongs drug bioavailability.[20, 93] Adsorbocarpine (Burton Parsons) given twice a day achieved better control of IOP than regular pilocarpine administered four times a day.[94] Soluble polymers increase the thickness of the tear film.[95] A drug in an aqueous solution enters the nose in 60 s but in polyvinyl alcohol it requires 70 s and in 0.5% methylcellulose 140 s.[96] Even when combined with methylcellulose twice a day dosing with pilocarpine is inadequate.[97, 98] A polyvinyl alcohol vehicle has been reported to provide longer drug contact time than a methylcellulose vehicle,[86] but not all investigators agree.[66]A polyvinyl alcohol vehicle produces a concentration of the drug in the anterior chamber which is 4 times higher than that produced by an aqueous vehicle.[83] Viscous solutions (60 cps) increase the amount of drug absorbed by a factor of 2 or 3.[99]

(d) **Aqueous emulsion**

When pilocarpine is bound in an aqueous emulsion to a polymer salt (i.e. in Piloplex by Allergan), 80%

of the drug is released in 6 h as compared to 80% in one hour from an aqueous solution.[31, 77, 100, 101] This 3.4% pilocarpine emulsion permits twice a day administration[102] and lowers IOP by about 8%. The maximum effect occurs 12 to 14 h after application, therefore treatment is still somewhat pulsed. Combining pilocarpine with a polymeric vehicle produces a clinical benefit,[103] but the improvement is small.[20] Pilocarpine has been prepared as a water-in-oil emulsion, and controlled IOP with twice a day applications.[98] Piloplex produces a slight blurring of vision.[101] Emulsifying agents are potentially toxic to the corneal epithelium.

(e) Oily vehicles

Oily vehicles for pilocarpine have also been suggested.[43, 90] Oily preparations (e.g. with castor oil) are more comfortable and achieve good control of IOP with twice a day application.[91] In oily solutions the pilocarpine is non-ionized and therefore penetrates the corneal epithelium readily.[43] Oil suspensions retain the drug in the tear film about 3 times longer than aqueous solutions.[19]

(f) Presoaked matrices

Soft contact lenses[35, 104-110] soaked in 2% pilocarpine release 50% to 90% of the drug within 30 min yet keep IOP controlled for nearly 24 h.[19, 110] The half-life of most water soluble drugs in hydrophilic matrices is 20 to 30 min.[18, 69] About 80% of the pilocarpine is· released in one hour from drug-soaked contact lenses,[35] but complete elution of the drug requires 4-1/2 to 5 h.[21, 111,] Ellis et al.[106] found that use of contact lenses did not increase the concentration of pilocarpine in the anterior chamber of rabbits at 30 min. The effect of pilocarpine lasts about three times longer when it is administered by a pilocarpine-soaked contact lens than by instillation of an aqueous solution.[35] Although pulsed administration occurs when using the contact lens method[70, 75] drug bioavailability is increased and the total daily dose of pilocarpine required to control the IOP is less than that provided in an aqueous solution.

Polyvinyl alcohol disks impregnated with pilocarpine were developed in Russia.[22] They were worn in the conjunctival sac for 3 h then removed. The drug effect was prolonged but the disks were uncomfortable to wear.[72] Six hours after insertion the drug concentration in the anterior chamber was 17 times greater than when the drug was instilled in an aqueous vehicle.[72] Drug-impregnated polyvinyl alcohol membranes have been designed to dissolve in 30 to 90 min.[84] Others[85] have employed 50 mm long rods of acrylic plastic which have had one end dipped into a solution of the drug and then dried. The disposable rod releases its thin layer of drug when the rod is rotated briefly in the conjunctival sac. The advantages of such a system are that preservatives are not required and a smaller quantity of the drug (e.g. 500 ug of pilocarpine) is needed.

(g) Lamellae and other soluble drug inserts

Soluble, solid-state drug carriers such as gelatin wafers containing atropine have been available for years.[36] Soluble ophthalmic drug inserts made from polymers of acrylamide, ethylacrylate and vinyl pyrrolidone were developed in Russia,[22, 84] and contained 2.6 mg of pilocarpine. The disc dissolved in 30 to 90 min but provided a longer pulse of drug availability.[22] Pilocarpine (2%) in a matrix of hydroxypropyl cellulose lowered IOP for 24 h although the disc itself dissolved within 12 h.[71] Soluble inserts prolong drug contact time[112] but the effect is still pulsed.[108]

Small rods of hydroxypropyl cellulose (Lacrisert by Merck Sharp & Dohme) have been developed to treat dry eyes.[113, 114] (See also Gel Tears).

(h) Drug adsorbed onto particles

Pilocarpine can be adsorbed onto 0.3 μm diameter particles of cellulose acetate hydrogen phthalate latex.[71] An aqueous suspension of these particles has a low viscosity so it can be instilled as eyedrops. When instilled the change in pH causes the latex particles to coagulate and resist drainage from the eye. The drug then leaches from the particles during the next 4 h. Other aqueous suspensions consist of fine particles of the drug held in a dispersed form in an aqueous medium, which allows the particles to remain for a long time in the conjunctival sac.[18]

(i) Collagen inserts

Inserts made of soluble, succinylated, enzyme-solubilized collagen containing a drug are under investigation.[109] The oval 6 × 12 mm wafer dissolves in 6 or 7 h,[109] rapidly at first then more slowly so a slow pulsed effect is produced.[114]

(j) Incorporating the drug in liposomes

Liposomes are small (0.01 to 10 μm) uni-or multilamellar spheres of lipid enclosing an aqueous drop.[115, 116] Liposomes are made by combining phospholipids (normally insoluble) with water by means of dispersion with high energy sound waves. The liposomes enhance corneal penetration· by adsorbing to the corneal epithelium[115, 117] and the drug enters cells by endocytosis. This formulation works better than an aqueous solution for penicillin (4× better), idoxuridine and inulin but not for epinephrine.[118] Liposomes are relatively unstable and expensive. When liposomes are 1.5 μm or less in diameter they disappear almost as rapidly as an aqueous solution.[117]

(k) Use of a prodrug

Dipivalyl epinephrine (Propine) becomes converted to epinephrine and pivalic acid within the eyeball by enzymes in the cornea and aqueous humor.[4, 71, 119, 120] The released epinephrine then acts in the usual way in the eye and the pivalic acid is non toxic.[18] Propine enters the eye at least 10× more readily[18] than epinephrine so a much smaller dose is required (one drop of 0.1% vs. 1%). There are fewer unwanted systemic effects[119] but the probability of unwanted ocular effects (especially maculopathy and pigment deposition) is about the same as with epinephrine.[15]

(l) Chemical modification to enhance penetration

Removing a methyl group from the quaternary nitrogen of carbachol improves[121] the corneal penetration of the drug. After 20 min the concentration of the instilled N-demethylated carbachol in the aqueous humor reached about 0.25%.

(m) Combination with adrenergic blocking agents

Guanethidine initially acts as an adrenergic agent and produces a fall

in IOP. However, the hypotensive action is brief since guanethidine depletes adrenergic drug-sensitive sites of their normal levels of catecholamines and the IOP then returns to the pretreatment level.[15] If a small quantity of epinephrine is now instilled, the IOP falls again for several hours. This procedure makes use of the phenomenon of "denervation supersensitivity". By combining guanethidine (1%) and epinephrine (1%) the effect of epinephrine is potentiated and the IOP is lowered.[123] Hoyng and Dake[123] using 8% guanethidine and 0.5% adrenaline achieved about 10% reduction in IOP with twice a day instillation. Aqueous outflow is improved by over 40%.[124] Tachyphylaxis does not seem to develop.[15] Even 1% guanethidine combined with 0.2% epinephrine lowered IOP more than timolol did. However, side effects such as conjunctival hyperemia and punctate epitheliopathy are more of a problem with the guanethidine-epinephrine combination.[124]

Systems Designed to Provide Controlled Release of Drugs

The goal for newer methods of drug administration is to achieve a delivery such that the amount of drug released per unit time is independent of the amount remaining i.e. zero order, as opposed to first order kinetics.[70-72] The following systems have been reported:

(a) **Diffusional systems, reservoir devices**
In this system the drug is enclosed in a barrier membrane having a specified thickness which allows drug release at a controlled rate either 20 μg/hr or 40 μg/hr for a week.[37] Ocusert (R) by Alza Corp. contains pilocarpine bound to alginic acid and enclosed in a hydrophobic, ethylene-vinyl acetate polymer membrane which allows the drug out but not water in.[28] Drug release is a little higher in the first 30 min but then stabilizes,[28, 70, 109, 125] and the drug effect persists for a day or so after the Ocusert is removed. The total daily dose is $1/10$ to $1/5$ that of the dose provided by 4 times a day drops[37, 70, 75, 125] and thus causes less miosis, myopia and shallowing of the anterior chamber.[37, 48, 126] About

70% of patients can use Ocuserts comfortably.[70] In a few cases the device falls out without the patient noticing it.[63]

(b) **Osmotic systems, pumping devices**
Osmotic pumps can provide continuous drug delivery.[127] A salt is enclosed in a semi-permeable pocket occupying a small space at one end of the unit and separated by an elastic wall from the drug which is in an impermeable pocket at the other end. As the salt takes up water the salt-containing compartment swells and forces the drug out through a small opening in the drug pocket.[70] Therapeutic levels of drug release can be maintained for two weeks when an osmotic pump unit is worn in the conjunctival sac.

(c) **Bioerodible systems, three types are mentioned**
i. The drug is incorporated in an erodible hydrophobic matrix[116] from which it is released by surface hydrolysis from contact with the tears.[71] While remaining in the conjunctival sac the system is consumed layer by layer but very little leaching of the drug occurs.[70] Drug administration remains at a constant rate until the device is almost completely eroded.

ii. biodegradable polymer systems
The drug is attached to a polymer by a hydrolytically labile linkage and is released by hydrolysis of this linkage and by drug diffusion through the matrix. The polymer dissolves in 5 to 24 h.[83, 128]

iii. ionic interaction systems
This system depends upon an ionic interaction between a salt of the drug and a soluble polymer matrix. A hydroxypropyl cellulose matrix linked to pilocarpine pamoate will release only the pilocarpine.[71]

Other Methods of Controlling IOP

(a) Smoking marihuana has been promoted as a means of reducing IOP but the effect is modest and transient,[129, 130] and the side effects and legality of its use present problems.[131, 132] To control glaucoma would require smoking 6 cigarettes a day.[129] Topical application of Δ^9 tetrahydrocannabinol (THC) does not lower IOP,[132, 133] however attempts are being made to develop a marihuana derivative for topical application.

Intravenous THC will lower IOP dramatically but is not practical. Oral ingestion of THC lowers IOP[130] and can be effective in control of glaucoma.[129]

(b) Experiments at Cornell University in 1984 indicated that the application of ultrasound to the sclera near the limbus could reduce IOP. The production of aqueous appears to be decreased and aqueous outflow from the eye increased but the mechanism is unknown. Retrobulbar anesthesia is required.

(c) Cryotherapy (cyclocryothermy) has been tried especially in aphakic patients. The aim is to damage the ciliary processes enough to diminish aqueous production.[134] This procedure may be used when other methods of controlling IOP have failed but there is a risk of producing phthisis.

(d) Laser trabeculoplasty or trabeculopexy can be performed for patients with open-angle glaucoma, who have failed to respond to maximal medical therapy. Trabeculoplasty involves putting a series of laser burns (up to 100) in the mid-trabecular region. Presumably each burn causes local shrinkage of trabecular tissue and thereby causes adjacent regions to become more porous. The argon laser emits dichromatic radiation in the wavelength bands 488 and 514 nm and these wavelengths are absorbed by melanin, hemoglobin, and xanthophyll.[135] Peak absorption by melanin is at 450 nm. Some use an argon laser producing monochromic green (514.5 nm), or argon blue (488 nm) or krypton yellow (568.2 nm) or red (647.1 nm). A few weeks after the initial transient rise in IOP (probably due to release of prostaglandins) the IOP falls 7 to 10 mm Hg in about 85% of eyes. Laser trabeculoplasty is also effective in eyes with pigmentary glaucoma or with pseudoexfoliation glaucoma and is more effective in phakic eyes than in aphakic eyes. Some loss of IOP control occurs in time.[136, 137] Continued glaucoma medication is often required and there is a risk of downgrowth of endothelial cells from the cornea.

For patients with angle-closure glaucoma traditional surgery has involved cutting a hole in the iris near its root, a peripheral iridectomy. It is possible to use a laser[138] to produce

a hole in the iris. This is called a laser iridotomy. Q-switched Nd:YAG laser (blue-green, 582 nm) or Q-switched ruby laser[139] iridotomies have success rates of over 75%. YAG lasers cause mechanical disruption of tissue. Continuous wave argon lasers produce an iridotomy by a thermal process and require less energy than the ruby laser.[140] The technique is not easy, the small hole sometimes closes spontaneously in about a month, and the long term effects are not known. The small lens opacity which forms seems to be stationary.[139] The technique can not be done if the cornea is hazy. The laser beam might accidently damage the macula. There is a small transient rise in pressure and sometimes mild iritis but the operation is easy on the patient, requires no general anesthetic, is performed as an outpatient procedure, and avoids the risks of regular surgery.

Lasers are also used for treating other glaucoma-related conditions. A trabeculectomy i.e. removal of a block of scleral and trabecular tissue can be done by a laser. This surgery improves aqueous outflow by allowing the aqueous to have direct access to subconjunctival and scleral tissues where it is readily absorbed in the same manner as after conventional filtration surgery.

Conclusion

The treatment of glaucoma presents challenges to all those involved. At present most glaucoma patients receive timolol or pilocarpine. Too often the patient fails to instill the drug as instructed.[46a, 141] Some benefit from adrenergic drugs and many new beta blockers are being studied. Although reduction of IOP does not always halt the progression of field loss it is currently the only therapeutic approach available. One of the principal benefits sought by new formulations and ways of administering drugs is the improvement of compliance. Improved methods of drug delivery, more effective drugs and the use of laser surgery in selected cases offer more dependable and effective control of IOP than was available a decade ago.

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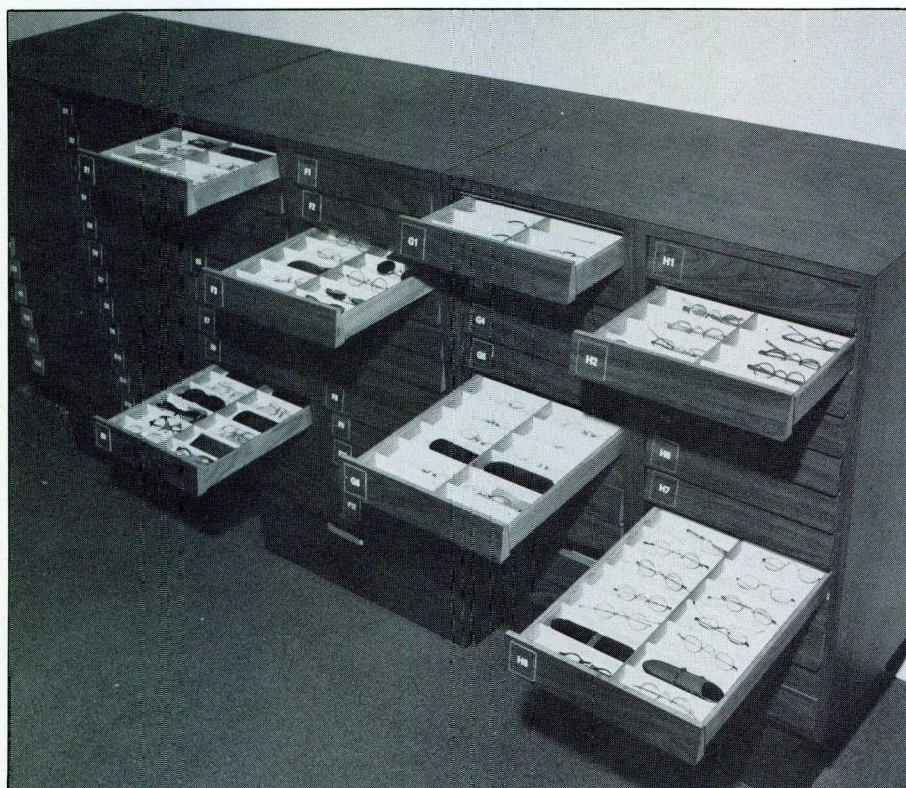
Display case of spectacle collection.

Other early books of some interest which are found in the museum include:

Lawson, The Eye — 1873
Second edition
(Signed "Presented to F.P. Cooke by Dr. W.G. Scott, Hull, May, 1892")
Wright, J.W. Ophthalmology
Trauger, Columbus 1896
Maddox, E.E. Tests and Studies of the Ocular Muscles
Wright and Co., Bristol 1898
Tscherning, M. Physiological Optics
Keystone Press, Philadelphia 1904
Worth, C. Squint Blakiston's
Philadelphia 1906
Sheard, C. Dynamic Ocular Tests
Lawrence Press, Columbus 1917

> **Every continent is represented on the guest list, as well as every Canadian province and many States.**

The Museum serves a large and varied audience. Apart from the students in Optometry, there are classes from other departments in the University who attend lectures in the adjacent Visual Science Demonstration theatre and look over the exhibits between lectures. Many local groups of senior citizens, recreational, school and church organizations are given special tours. Casual visitors are welcomed frequently and are requested to sign the guest register. Every continent is represented on the guest list, as well as every Canadian province and many States.

It would be of considerable benefit to the continued improvement of the Museum of Visual Science and Optometry if all readers would be alert to locate any unusual optical instruments, documents, licenses, certificates, books or other artifacts which may have historical significance to visual science or the profession. Even postage stamps having some optical connection would augment the present collection. Continued contributions to the museum will help to preserve and document the early history of Optometry in Canada. It is suggested that contact be made with the writer before sending any larger pieces in order to confirm that they are not duplications.

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