Comparison of action of cholinergic and anticholinesterase agents in glaucoma

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The cholinergic agents have the advantages of systemic safety, fewer undesirable local side effects, and usefulness in angle-closure and narrow-angle glaucoma. The powerful cholinesterase inhibitors, on the other hand, produce better diurnal reduction of intraocular pressure, require less frequent administration, and can control many cases whose pressures cannot be otherwise brought to heal. Neither group constitutes the ideal agent, and the search for this must therefore continue. It must always be kept in mind that the agents used are powerful toxic drugs and for some people may be incapacitating. One must not be afraid to use them when indicated, but they should not be used indiscriminately.

Experience with the treatment of the glaucomas with both cholinergic agents and cholinesterase inhibitors dates back for nearly a century. Physostigmine, an anticholinesterase agent, was introduced as a medication in 1875; pilocarpine, which has a direct effect, was first used in 1877. During the last 20 years, the new group of powerful cholinesterase inhibitors has made its entry into the armamentarium of glaucoma therapy. It is quite clear that the ideal drug has not yet been found. There are advantages and disadvantages in the use of both groups of these agents.

We are not at a stage when we can meaningfully compare the effects of the two groups of agents on the progression or prevention of the field changes, which must be our aim, but we can compare them in terms of: (1) the mechanism of action, (2) the effect on ocular dynamics, and (3) the toxicity and side effects.

The cholinergic agents, exemplified by pilocarpine and carbachol, have direct effects on target cells. Their effects are similar to the muscarine action of naturally released acetylcholine. They are not dependent on release of acetylcholine, and act on denervated tissues. The cholinesterase inhibitors, such as physostigmine, mintacol, DFP, echothiophate iodide, and demecarium bromide (and to some extent carbachol) inhibit cholinesterases and potentiate the action of acetylcholine released at nerve endings. They appear to have no effect on denervated tissues, and will not produce an appreciable effect in tissues where a local anesthetic has temporarily abolished nerve conduction.

Both groups of drugs lower intraocular pressures and decrease the resistance to outflow as measured tonographically. In eyes with open angles, this is independent of the myosis produced. It is presumed to be caused by the effect of the ciliary muscle on the outflow channels or on the vessels supplying and draining that segment of the eye. Perfusion studies have suggested that pilocarpine may also have
a direct histaminelike action on the endothelial cells of the trabeculum.\(^9\)

The long-acting cholinesterase inhibitors have a more marked action and longer duration of action on intraocular pressure and outflow facility, which means that: (1) these agents will influence intraocular pressure when the cholinergic agents alone or in combination with sympathomimetic agents have failed, and (2) they dampen the diurnal swings of intraocular pressure in a more effective way than can be achieved with cholinergic agents.

In order to compare the effect of 4 per cent pilocarpine with 0.06 per cent echothiophate iodide on the diurnal intraocular pressure variations, 20 eyes of 13 patients in varying stages of ocular hypertension and chronic simple glaucoma were studied.\(^7\) Pilocarpine was administered to the patients in this group 4 times daily, at 8 A.M., 2 P.M., 6 P.M. and 10 P.M., whereas echothiophate iodide was administered at 7 A.M. and 10 P.M. Diurnal tension curves a month of echothiophate 0.06 per cent, were carried out on no therapy, after a month of pilocarpine 4 per cent, and after

The results show (Figs. 1 and 2) that pilocarpine reduced intraocular pressure less effectively than echothiophate iodide, and that 70 per cent of pilocarpine-treated eyes showed peaks of intraocular pressure over 24 mm. Hg, whereas only 20 per cent of the echothiophate-treated eyes showed similar peaks. Four of the 13 patients preferred the echothiophate, whereas 6 preferred pilocarpine and 3 expressed no preference. This comparison dealt only with the effects of these drugs on intraocular pressure. The practical application is that, when it has been decided in an individual that meticulous pressure reduction is indicated, the cholinesterase inhibitor does this more reliably than the cholinergic agent. This is important when no facilities are available for measurements of intraocular pressure around the clock. These results do not mean that these powerful agents should be used as the first line of therapy in very early cases, when the decision to treat has been made, but when critical pressure control may be much less important.

Single-dose responses of echothiophate iodide on intraocular pressure and outflow facility were studied in 11 patients with either ocular hypertension or advanced open-angle glaucoma.\(^8\) These patients had intraocular pressures checked around the clock. Single doses of 0.03, 0.06, 0.125 and 0.25 per cent echothiophate were instilled in one eye, and the other was used as a control. Drug effects were calculated by comparing the logarithms of the pressure in the treated and the untreated eye at various times after the instillation of the drug, and allowing for intraocular pressure differences at the same time of day in the untreated state. There was a clear-cut dose response to echothiophate iodide with a latent period of some 13 to 21 hours. The maximal effect occurred 27 hours after the instillation of the drug, and there was a second peak of action 24 hours later. Echothiophate iodide, 0.03 per cent, although its action was only barely significant, followed the pattern of other con-

Fig. 1. Each line represents the maximum and minimum levels of intraocular pressure in the 20 eyes recorded without therapy, on pilocarpine 4 per cent four times a day, and on echothiophate iodide 0.06 per cent twice a day.
centrations and can be considered active. These findings do not necessarily reflect the cumulative action of the various drug concentrations when used repetitively; they show only a dose response to single instillations (Fig. 3).

A comparison of the two groups of drugs would not be complete without a discussion of the side effects, which can be divided into local and systemic effects.

**Side effects**

**Local.**

*Accommodative spasm.* This is produced by both cholinergic agents and cholinesterase inhibitors. It is more marked with cholinesterase inhibitors, but it is more even with these agents. Some young patients prefer weak solutions of long-acting cholinesterase inhibitors, which are less incapacitating than the cholinergic agents, for this reason.

*Headache.*

*Browache.*

*Visual difficulty due to myosis.*

*Vascular dilatation.*

*Iritis and posterior synechiae.* These occur mainly with cholinesterase inhibitors.

*Cysts.* These occur particularly with cholinesterase inhibitors and are often referred to as pupil margin cysts, but in fact any part of the pigment epithelium may be involved. Some of the bowing of the iris, particularly when it is localized to one segment, may be caused by the formation of a cyst. Following iridectomy, one can see the cysts go all the way to the ciliary body.

*Pupillary block.* This is an important side effect which is much more marked with the long-acting cholinesterase inhibitors. The cholinergic agents do, however, produce it as well. The cholinesterase inhibitors are therefore contraindicated in
Effects of cholinergic and anticholinesterase agents

very narrow angles which can be converted from an open- to a closed-angle mechanism. It is not uncommon to find good pressure-lowering effects when the drugs are first used which gradually, and sometimes rather quickly, give way to poor control again. Some of these apparent "resistances" to the drug are due to development of pupil block or forward displacement of the entire lens iris diaphragm which compromises the outflow mechanism. A peripheral iridectomy will relieve the situation in those cases where pupil block was the cause of the phenomenon, and the drug following such a procedure will again be very effective in controlling pressure.

Retinal detachments. Both groups of agents can be incriminated, although the cholinesterase inhibitors are much more frequently responsible for this complication. It must be remembered that many glaucoma eyes have degenerative retinal areas and even tears, and that the miotic is usually only the precipitating cause which induces the progressive retinal separation.

Tolerance or resistance. These occur much more frequently in the case of the cholinergic agents, although the cholinesterase inhibitors may enjoy a period of pressure control and finally lose their effect. When a powerful cholinesterase inhibitor no longer controls intraocular pressure, a switch to the cholinergic agents may again produce reasonable control. The possibility of pupil block as a cause of resistance has been discussed.

Lens opacities. All ophthalmologists

Fig. 3. The mean effect of single doses of varying concentrations of Phospholine iodide on intraocular pressure in eleven glaucomatous eyes. One eye was treated and the other used as a control. A rise in the log ratio (fall on the graph) indicates a fall in intraocular pressure produced by the drug. The mean diurnal curve pattern at the bottom of the figure was that obtained during the 24 hours prior to instillation of the drug. The pattern has been empirically repeated for illustrative purposes for 4 days.

1.5
1.6
1.7
1.8
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
0.03% 0.06% 0.125% 0.25%

TR = IOP PRIOR TO ECHOTHIOPHATE
TR = IOP AFTER ECHOTHIOPHATE
CONT = IOP CONTROL EYE AT SAME TIMES 1 AND 2

Fig. 3. The mean effect of single doses of varying concentrations of Phospholine iodide on intraocular pressure in eleven glaucomatous eyes. One eye was treated and the other used as a control. A rise in the log ratio (fall on the graph) indicates a fall in intraocular pressure produced by the drug. The mean diurnal curve pattern at the bottom of the figure was that obtained during the 24 hours prior to instillation of the drug. The pattern has been empirically repeated for illustrative purposes for 4 days.
using the powerful cholinesterase inhibitors have encountered patients who have developed rapid visual deterioration due to myosis in eyes already affected by lens opacities. When the drug was discontinued, some of these patients' visual acuity does not return to its previous level. Most of these cases have a posterior subcapsular opacity with some nuclear sclerosis. Recent reports from Sweden suggest that echothiophate iodide produces lens opacities very frequently, and these are a combination of specific anterior subcapsular white opacities in addition to senile nuclear sclerosis. There are many factors which could influence this situation. The coexistence of glaucoma and lens opacities is of a very high order. The Scandinavian workers usually report a very high incidence of pseudoexfoliation in their glaucomatous patients, and these factors may have a bearing on the results which they presented. If a powerful cholinesterase inhibitor is used with proper indication, when control with other agents is not possible, and the alternative is a surgical one, the incidence of gradually occurring lens opacities following fistulizing surgery and even peripheral iridectomy is probably very much higher than the reported opacities on echothiophate iodide. Experience of the past 9 years with this agent suggests that lens opacities undoubtedly can occur either produced by the drug, accelerated by the drug, or merely coincidentally in patients who are using the drug, but the tremendously high incidence of opacities reported must be proved to be due to the drug in a study carefully designed to this end.

**Systemic.** Systemic side effects can occur with both groups of agents. Ocular pilocarpine or carbachol may produce asthmatic attacks in patients who suffer from this disease. Occasional nausea and colicky abdominal pains are well known, and lacrimation, rhinorrhea, and salivation are quite common. Eserine has also produced signs of systemic parasympathetic overstimulation. The long-acting cholinesterase inhibitors do, however, constitute a much more serious and potential danger. The majority of people on ocular medication with these drugs show depression of acetylcholinesterase in the red blood cells and of serum pseudocholinesterase. Fortunately, the vast majority of these patients have no systemic side effects of acetylcholine accumulation. The more closely one looks for mild side effects the more frequently they are found. The commonest effects are gastrointestinal, and increased secretions from lacrimal, salivary, and mucosal glands. More rarely, respiratory and cardiovascular effects are seen, and occasional cases of neurologic disturbances have been reported. There is no doubt that patients on these agents must be liable to acetylcholine accumulation after vagal stimulation. They are also at risk to organophosphorous insecticides or when treated for myasthenia. Pharmacogenetic studies may also show differences in the cholinesterase of those people who show systemic symptoms from ocular instillation. The depression of pseudocholinesterase may be responsible for prolonged apnea when succinylcholine is used to aid general anesthesia.

**REFERENCES**

8. Stockstill, P., and Drance, S. M.: Dose re-