Anticholinesterase Miotics in the Management of Accommodative Esotropia

Webb Chamberlain, M.D.
Cleveland, Ohio

Anticholinesterase miotics have gained wide acceptance in the management of accommodative esodeviations since DFP (Floropryl isoflorophate) was introduced by Abraham in 1949. The effectiveness of these miotics has been amply confirmed by Knapp and Capabianco, and Costenbader, Miller, Schlossman, Breinin and Wheeler. A divergence of opinion continues, however as to the proper role of anticholinesterase miotics.

Recent reports have suggested again the significance of adverse local and systemic effects. It is the purpose of this study to evaluate the current status of DFP (isoflorophate) and phospholine iodide (echothiophate) in the diagnosis and treatment of accommodative esotropia.

LITERATURE

This investigation has been prompted by Axelsson and Nyman's 1970 report of transient anterior subcapsular lens opacities appearing in two young persons while receiving anticholinesterase miotics for accommodative esotropia. A 19-year-old patient was given 0.125 percent DFP twice daily for three months and a six-year-old child received 0.125 percent phospholine iodide twice daily for six months. These opacities were similar to those described in the case reported by Harrison in 1960. It should be noted that Axelsson and Nyman used higher concentrations of these drugs and instilled them more frequently than is usually recommended in the therapy of accommodative esotropia. Numerous investigators have studied the apparent cataractogenic properties of anticholinesterase miotics in older adults under treatment for glaucoma, including Axelsson, Axelsson and Holmberg, Shaffer and Hethington and de Roeth.

Jones and Watson in 1967 reported a single case of angle closure glaucoma in a seven-year-old boy using 0.125 percent phospholine iodide daily for accommodative esotropia. The elevated intraocular tension was quickly normalized by the instillation of atropine sulfate. This is apparently the only report of angle closure glaucoma related to the use of anticholinesterase miotics in a child. There have been no instances of retinal detachment occurring in children while receiving these medications.

Iris cysts of the pigment epithelium have been investigated in detail by Swan, Christensen, Swan and Huggins, Abraham, and Chin, Gold and Breinin. In general, the formation of iris cysts has been found less common with phospholine iodide than with DFP, as has been indicated by Miller and Chamberlain and Caldwell. The occurrence of iris cysts has been controlled by minimizing the dosage or by adding phenylephrine five percent as has been suggested by Abraham and Breinin. The use of phenylephrine is also presumed helpful in avoiding irreversible miosis as described by Roy and Hanna and Apt. Axelsson has observed depigmentation of the iris border and tissue adjacent to the site of iris cysts.

A minor complaint is brow ache or

Presented at the One Hundred Tenth Annual Meeting of The American Ophthalmological Society, May 21, 1974.

Requests for reprints should be addressed to Webb Chamberlain, M.D., 1324 Hanna Building, Cleveland, Ohio 44115.
headache occasionally experienced at the beginning of treatments. Local reactions of lesser significance include conjunctivitis, blepharitis and rarely keratitis or iritis. These are usually relieved by reducing the dosage or omitting the medication.

Systemic toxicity is associated with depressed cholinesterase levels and is encountered primarily with phospholine iodide as has been established by Leopold,44 de Roeth, et al,25 Humphreys and Holmes 26 and Ripps.27 Most reports of systemic toxicity to phospholine iodide relate to adults under intensive treatment for glaucoma. This includes the documented case of cardiac arrest recorded by Hiscox and McCulloch 28 in a patient who received 0/125 percent phospholine iodide three times daily. Leopold 44 and Apt 33 have listed the various signs of systemic involvement. Apt points out that complaints in children such as nausea, abdominal discomfort and diarrhea are infrequent and are usually mild and of short duration. He has also described rhinorrhea simulating an upper respiratory infection as a finding in children on anticholinesterase miotics.

Systemic toxicity of significant proportions following instillation of phospholine iodide is rare in children. Atropine usually gives prompt relief. In case of accidental swallowing of eye drops prompt administration of pralidoxime chloride (Protopam) is an effective antidote. The neutralization of cholinesterase inhibition by the oximes and atropine has been studied by Hunter and McCulloch.29 The management of systemic toxicity is well presented by Havener 38 in his text "Ocular Pharmacology."

The possibility of systemic reactions to the instillation of phospholine iodide is considerably enhanced by exposure to organophosphorus insecticides as noted by Goldstein.31 The significant depression of cholinesterase levels by these insecticide compounds has been documented by Klenedshoj and Feldstein,32 Ellis,33 and Williams, Griffiths and Sterns.34 This is particularly important in fruit growing areas. Ferrer 35 has observed a child on phospholine iodide who developed pallor and nausea only when exposed to antimosquito spray.

In contrast to phospholine iodide DFP has been found to produce minimal or insignificant depression of cholinesterase levels by Leopold,44 Leopold and Comroe,45 Humphreys and Holmes,26 Ellis and Esterdahl 37 and Samson and Hermann.38 The absence of a comparable depression of cholinesterase by DFP has been attributed by Leopold 39 to the difference in absorption characteristics. Phospholine iodide is dispensed in an aqueous solution which easily passes into the nasopharynx where it is absorbed through the mucosa. The DFP, on the other hand, is usually prepared in an ointment base which does not favor ready passage into the nasopharynx. Furthermore, DFP is readily hydrolyzed on contact with tears and rapidly becomes ineffective.

In the presence of low cholinesterase levels there is the possibility of prolonged apnea with the use of succinyl choline in general anesthesia. This may be encountered following the instillation of phospholine iodide and for this reason drops are usually discontinued several weeks before anticipated surgery. It is important to recognize, however, that there are other potential causes for low cholinesterase levels. There are various inherited abnormalities of the cholinesterase enzymes that can also lead to a delayed hydrolysis of succinyl choline and produce a similar prolonged apnea. Kalow 40 has found that two thirds of these patient have atypical serum pseudocholinesterases. When choline apnea is suspected, the patient and members of the family are immediately investigated as to cholinesterase levels following an established routine as noted by Crawford.41 These cholinesterase variants must also be differentiated from low production of cholinesterase such as is encountered in hepatic disease and anemias by an estimation of cholinesterase activity.

S U R V E Y

To determine the current status of treatment with anticholinesterase miotics in accommodative strabismus.
questionnaires were sent to more than 100 ophthalmologists with special interest in strabismus. Geographic areas included were North and South America, Western Europe, South Africa and Australia. The survey is based on 81 completed returns. The questions covered diagnostic and therapeutic use, selection of miotics, dosage and various local and systemic complications.

As to the specific survey question of cataract formation there were no reports of lens opacities developing in any young person receiving anticholinesterase miotics for accommodative strabismus. Similarly, there were no instances of angle closure glaucoma or retinal detachment occurring in children.

Regarding the general utilization of anticholinesterase miotics in the management of accommodative strabismus, there were 23 ophthalmologists who routinely used phospholine iodide or DFP either diagnostically or therapeutically. There were 13 who never used miotics to diagnose the accommodative factor but only three who never prescribed miotics at least occasionally for treatment (Table I).

As for the selection of specific anticholinesterase miotic, many more utilized phospholine iodide than DFP. There were 52 ophthalmologists who prescribed phospholine iodide alone, whereas 19 used only DFP and seven employed both medications (Table II). This apparent preference for phospholine iodide is affected by the unavailability of DFP in South Africa, Australia and some South American countries.

As to the preferred concentration of miotics, DFP is used almost exclusively in the 0/025 percent concentration and most often in the ointment form, whereas phospholine iodide is prescribed in various strengths, e.g., 0/125 percent, 0/06 percent and 0/03 percent. A slight majority favored the 0/125 percent over the 0/06 percent concentration, but a surprising number found the 0/03 percent phospholine iodide to be effective and one reported using 0/01 percent.

Many ophthalmologists indicate the importance of reducing the dosage of anticholinesterase miotics to the minimal effective concentration once a satisfactory response has been attained. With DFP this is usually accomplished by decreasing the frequency of instillation of the 0/025 percent ointment, whereas with phospholine iodide the concentration of the drug is progressively reduced to accomplish this end.

An important question relates to the incidence of systemic toxicity. Less than half of the reporting ophthalmologists have ever recognized systemic complaints and only four of these interpreted the reactions as severe. There was one instance of jaundice in a two-year-old child following the use of DFP 0/025 percent which cleared on omitting the drug; no cholinesterase studies were available. One eight-year-old child developed nausea and vomiting after instillation of 0/06 percent phospholine iodide.

A particularly significant aspect of systemic reactions relates to the question of prolonged apnea which may be encountered when succinyl choline is used in conjunction with general anesthesia. Among the survey group there was only one report suggesting a possible relationship to anticholinesterase miotics. A child had been given a trial with 0/025 percent DFP ointment every third night but this medication had been discontinued six weeks before strabismus surgery. Succinyl choline was used as an adjunct in the general anesthesia and a prolonged apnea of 1 1/2 hours was experienced. It was not possible to obtain cholinesterase blood levels from this patient or to screen.

### Table I

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Occasional</th>
<th>Routine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic:</td>
<td>13</td>
<td>55</td>
<td>13</td>
</tr>
<tr>
<td>Treatment:</td>
<td>3</td>
<td>55</td>
<td>23</td>
</tr>
</tbody>
</table>

### Table II

<table>
<thead>
<tr>
<th>Selection Anticholinesterase Miotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFP only</td>
</tr>
<tr>
<td>PI only</td>
</tr>
<tr>
<td>DFP and PI</td>
</tr>
</tbody>
</table>
members of the family for a possible familial cholinesterase anomaly at that time.

Many ophthalmologists prescribing phospholine iodide favor a "medical alert" card indicating that the child has been receiving this medication and suggest direct communication with the anesthesiologist in case of anticipated surgery. There is a consensus that phospholine iodide should probably be discontinued four to six weeks before scheduled surgery. On the other hand, with DFP such precautions are apparently not deemed essential, although many also prefer to omit the medication in advance of planned strabismus surgery.

As has been noted, the possibility of significant systemic reaction to phospholine iodide is considerably enhanced by any exposure to an organophosphorus insecticide which by itself may depress the cholinesterase levels. Among these 81 ophthalmologists there were three reporting systemic symptoms in patients where such an exposure may have been a factor. These complaints were not severe and omission of the medication resulted in rapid alleviation of the symptoms.

As to minor reactions, two thirds of the ophthalmologists reported some degree of blurring of distant vision and about half recorded mild headaches as an occasional complaint. Severe headache was reported in a child receiving 0/125 percent phospholine iodide drops. Conjunctivitis and blepharitis were occasional findings and there was one report of superficial punctate keratits involving two patients.

The actual frequency of iris cysts is partly a matter of definition. One observer reports that all his patients on anticholinesterase miotics for an extended period show at least minimal cyst formation when evaluated by slit lamp and corneal microscope. Another ophthalmologist has never seen iris cysts among his patients on phospholine iodide. Certainly, significant iris cysts are not found in all patients on these medications. Occasionally the miotic pupil may be occluded by the encroachment of cysts and this has been seen by 22 observers. Of the ophthalmologists questionable 34 utilized phenylephrine as a means of minimizing cyst formation and avoiding pupillary occlusion. There were no reports of iris atrophy developing in relation to the iris cysts and no specific instance of the cysts persisting as such for appreciable periods after omitting the medication. One observer reported shrunken "raisin-like" tags still quite obvious eight years after discontinuing DFP.

**DISCUSSION**

As for the initial question of cataract formation in children, it is significant that none of the 81 ophthalmologists surveyed had encountered this complication. To further study this problem a series of 50 young patients who had been on anticholinesterase miotics for at least six months were examined by me with the slit lamp and corneal microscope. The pupils were dilated with repeated instillations of mydriatic. No anterior subcapsular lens opacities were found.

It is interesting that no instances of angle closure glaucoma in children were uncovered in this survey and similarly there were no cases of retinal detachment related to anticholinesterase miotics.

While iris cysts are not a cause for great concern, large cysts that encroach on the pupil are undesirable. The addition of phenylephrine five percent continues to be a satisfactory means of avoiding major cyst formation.

Systemic toxicity may be encountered after instillation of phospholine iodide due to depression of the cholinesterase levels. As DFP does not produce a comparable lowering of the cholinesterase levels, symptoms of systemic toxicity are not likely to be experienced with this drug.

Since phospholine iodide can depress the cholinesterase levels this medication should probably be discontinued four to six weeks before anticipated surgery. When surgery must be performed on a patient receiving phospholine iodide the anesthesiologist should be so informed. In pediatric anesthesia the possibility of "choline apnea" should be recognized as an inherited anomaly of the cholinesterases which can also lead to
prolonged apnea when succinyl choline is used. Such patients and their families should be identified by proper evaluation techniques.

It is worthy of note that exposure to organophosphorus insecticides by itself can create significant lowering of cholinesterase levels which may be accentuated by the instillation of phospholine iodide.

CONCLUSION

In the management of accommodative strabismus in children, significant adverse reactions to anticholinesterase miotics are rare. With proper supervision these drugs continue to be a useful diagnostic and therapeutic adjunct.

REFERENCES

35. Ferrer J: Personal communication.
39. Leopold IH: Personal communication.
41. Crawford JS: Personal communication.