OXYPHENONIUM AS AN ATROPINE SUBSTITUTE IN OPHTHALMOLOGY*

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ATROPINE, perhaps the drug most used in ophthalmology, is prone to cause contact-irritation, often at a time when continued mydriasis is essential, in patients on long-term treatment. Unfortunately, most substitutes are less effective in producing mydriasis, and not infrequently contact-irritation is developed to these substitutes in rapid succession.

Lachescine (E3) was developed in Great Britain during the war because of the possibility of a serious shortage of the usual mydriatics. It was found to have an effect mid-way between that of atropine and homatropine with cocaine. Since this time, Lachescine has been found very useful in clinical practice where atropine irritation has occurred. Its difference from the atropine group of mydriatics (Figure) made it almost free from producing irritation. Its usefulness in cases of atropine sensitivity has been suggested in recent ophthalmic text-books, and, in her original article on this subject, Mann (1946) reviews 42 cases of atropine irritation.

FIGURE

When Lachescine was being developed, MacDonald (1947) described the development of Dibutolin in America (Di-n-butylcarbamylocholine). The formula for Lachescine is benzilyl-oxyethyl-dimethyl-ethyl-ammonium chloride.

Now that Lachescine has been withdrawn from production, oxyphenonium (Antrenyl) deserves consideration as an atropine substitute. In fact, it has an action much stronger than that of Lachescine and more prolonged than that of atropine itself.

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This article is based on a series of 57 cases treated at the Birmingham and Midland Eye Hospital.

Mydriatic Effect

Experimental work on the mydriatic and cycloplegic effect of oxyphenonium is somewhat contradictory. Plummer, Barrett, Rutledge, and Yonkman (1946) make the following statements:

Two drops of a 2 per cent. solution of Antrenyl instilled at 15-minute intervals into the conjunctival sac of the eye of the rabbit caused no observed mydriasis . . . atropine in 0.5 per cent concentration applied similarly produced maximal pupillary dilatation after two applications.

The mydriatic action of Antrenyl is definitely less marked than that of atropine when each is applied locally to the eye of the rabbit, for a 0.5 per cent. solution of atropine sulphate causes maximal pupillary dilatation, while four times this concentration in Antrenyl produced no obvious changes in pupil size.

These authors conclude that:

Antrenyl possesses less marked mydriatic and anti-salivary activity than atropine.

Havener and Falls (1953) found excellent mydriasis in rabbits, which persisted for 4 to 8 days after a single instillation of 5 per cent. oxyphenonium, and complete mydriasis for 2 days after the instillation of a 1 per cent. solution. They conclude:

In rabbits, the mydriatic effect of oxyphenonium is very much more marked and prolonged than that of atropine; however, the rabbit can detoxify belladonna drugs much more rapidly than can man.

Whatever the conflicting results in rabbits may be, there seems no doubt of the strength of the action of this drug in man. Abrahamson and Hurwitz (1954) state that:

Oxyphenonium mydriasis was slightly more rapid in onset and was completed in the same time as with atropine. Oxyphenonium mydriasis began in 15 to 35 minutes, whereas with atropine it commenced in 20 to 30 minutes. The completion time ranged from 35 to 55 minutes with both drugs. Mydriasis with oxyphenonium lasted 15 to 20 days, with atropine 11 to 14 days. The mydriasis was maximal with both drugs.

This statement applies to both mydriasis and cycloplegia but refers to 5 per cent oxyphenonium and 1 per cent. atropine.

Irritant Effects

Although few volunteer this information, most patients, when asked directly, state that the drops sting on instillation, but they are happy to continue with the treatment. A few patients find the drops too painful to use because of burning and notice that the eye flushes after instillation.

In 100 cases treated with a 5 per cent. solution by Abrahamson and Hurwitz

(1954), there was no complaint other than that of a burning sensation, which was severe enough in fourteen cases to lead to the withdrawal of the drug. Other authors (Havener and Falls, 1954) advise against the use of 5 per cent. solutions and have found that 1 per cent. or 0.5 per cent is not irritating to the human eye, and is not strong enough to produce smarting or conjunctival discharge. They have found 1 per cent. solutions of oxyphenonium and atropine comparable in effect.

Report of Cases

57 patients began treatment between May and August, 1956, and these cases were followed until the end of October, 1956. There were 27 males and 30 females, with a slight preponderance of older women of over 60, and of younger men between 20 and 60 years of age. In some of these cases continuous treatment with oxyphenonium was given for over 4 months, fourteen were treated for more than 2 months, and 26 for more than 1 month. At the end of the period of survey, nine patients were still continuing with treatment.

The duration of the condition for which the patients were being treated was less than 1 year in twenty patients, between 1 and 5 years in sixteen patients, and over 5 years in 21 patients.

Oxyphenonium was frequently used when previous irritation had taken place. 39 cases with irritation to atropine or some other mydriatic were treated with oxyphenonium; sixteen of them had previously been treated with Lachescine and were put on to oxyphenonium when the supply of Lachescine became exhausted. Two other cases had been treated with Lachescine without any previous irritation, and in sixteen cases oxyphenonium was used as the first mydriatic.

33 cases had previously had irritation with atropine, twelve with homatropine, four with hyoscine, and three with an antibiotic. In four cases, there had been multiple irritations:

Case 1	(Iridocyclitis)	Homatropine, Lachescine, penicillin, Eumydrin Duboisine, and atropine.
Case 2	(Secondary Glaucoma)	Eserine, Butacaine, homatropine, and hyoscine.
Case 3	(Scleritis)	Atropine, hyoscine, homatropine, and yellow oxide of mercury.
Case 4	(Rosacea Keratitis)	Atropine, homatropine, hyoscine, sulphacetamide and penicillin.

Oxyphenonium proved satisfactory in these cases and produced no irritation, although the length of treatment was 14 weeks, 5 weeks, 2 weeks, and 11 weeks respectively.

In all, there were 10 cases with irritation to more than one drug: in two cases the reaction to oxyphenonium was uncertain from the records, and in the remaining eight it proved satisfactory. Of the other 29 cases, oxyphen-

onium was satisfactory in 23, uncertain in four, and withdrawn because of discomfort in two.

In the whole series of 57 cases oxyphenonium was satisfactory in 45, uncertain in nine, and was withdrawn because of discomfort in three.

One of these was a case of trachoma with recurrent keratitis, previously treated with Lachescine; in this patient oxyphenonium produced the appearances of a chemical conjunctivitis in the lower fornix, with some chemosis.

The other two cases were being treated for uveitis, and oxyphenonium was used after atropine irritation had occurred; these patients complained of discomfort lasting for a few minutes after instillation, and were put on to another mydriatic.

In all the other cases, oxyphenonium proved satisfactory, although in answer to a leading question patients would usually agree that smarting was noticeable on instillation but passed off very soon and was not enough to cause concern. It may be relevant to note that a patient with Behçet's syndrome, had quite marked smarting to begin with, but after 3 months was finding the drops more comfortable; in this case, mydriasis with oxyphenonium was much more satisfactory than with the Lachescine, which had previously been used after atropine irritation. In no case did an irritation occur with a clinical appearance similar to that with atropine, and experience suggests that oxyphenonium is less likely to produce irritation than the other older atropine substitutes.

When treatment is discontinued, mydriasis lasts as long as, if not longer than, with atropine. One patient with hypopyon iritis, who was sensitive to atropine and homatropine, was treated with oxyphenonium 3 times daily from May 31 until August 15, 1956, when mydriasis was discontinued; the pupil was still moderately dilated on October 3, 1956.

In a few cases, oxyphenonium was used as a mydriatic and cycloplegic for refraction in children. Guttae Antrenyl were instilled in one eye and guttae atropine (1 per cent.) in the other. It was found that after a 1 per cent. solution had been used for one or two instillations, atropine produced a greater and more rapid mydriasis, and it was usually necessary to increase the dosage of Antrenyl to 2 per cent. in order to obtain an equal effect. There would seem to be little advantage in using Antrenyl in these circumstances. There is no doubt that it serves its most useful purpose when used as an atropine substitute after irritation has taken place.

In an attempt to overcome the smarting sensation on instillation of the drops, pH and tonicity of oxyphenonium were investigated. It was found that a 1 per cent. Antrenyl solution in distilled water, with 1.35 per cent. boric acid, gave a freezing point depression of 0.526°C., which would make it almost exactly isotonic with the lacrimal secretion. With this preparation the pH was 4.7, but in spite of this acidity the manufacturers thought it would be satisfactory for instillation and would not prove to be particularly uncomfortable. It was, however, felt necessary to include an anti-bacterial

agent, and the drops used in this series were made up as follows: Antrenyl 1 per cent.; benzalkonium chloride 1/5,000; distilled water to 100 per cent., giving a pH of 6·8. Sodium chloride 0·75 per cent. has since been added, to make the drops more nearly isotonic. This gives a freezing point depression of 0·540°C. and a pH of 5·98, and seems more comfortable in use.

Summary

After a brief review of atropine substitutes, a series of 57 cases treated with oxyphenonium is recorded. It is suggested that oxyphenonium is a satisfactory substitute for atropine, particularly in patients showing contact-irritation to atropine and other atropine substitutes.

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