

AUREOMYCIN IN OPHTHALMOLOGY*

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AUREOMYCIN has now become established as an important and powerful antibiotic and has proved itself effective in several ophthalmological infections which failed to respond to other treatment. A preliminary report has already been made from this clinic on the use of this drug in ophthalmology (Duke-Elder and others, 1950). The present communication describes our further experiences with this drug. In particular it has been found effective in resistant cases of conjunctivitis, blepharo-conjunctivitis, follicular conjunctivitis, and trachoma, and in some cases of keratitis and corneal ulceration.

The main disadvantage of aureomycin in ocular therapeutics is its poor penetration into the eye, whether given topically, subconjunctivally, or systemically. Experimental studies of the penetrability of aureomycin into the eye of the rabbit have been made by de Roeth (1949) and by Bellows and others (1950). Their results were similar. They found that a barely therapeutic level of aureomycin in the aqueous was obtained after a very large intravenous dosage (50mg./kg. bodyweight). Subconjunctival injection did not lead to a therapeutic level in the aqueous. Local administration of drops 0.5 per cent. to the conjunctival sac did not lead to any penetration in the intact eye. In cases of corneal ulceration or abrasion, however, aureomycin was found to penetrate into the cornea and aqueous. Theoretically intra-ocular injection is the only possible means of its introduction into the eye, but the direct injection of aureomycin into the anterior chamber is said to produce a severe iritis, which, however, gradually settles, whereas injection into the vitreous leads to retinal degeneration and fibrous tissue formation (Azzolini and Faldi, 1950; Pritikin and others, 1950).

Methods of Administration and Toxicity

In the series under review the four following methods of administration were employed:

(1) **Drops.**—0.5 per cent. aureomycin borate was used, administered at hourly intervals. In some cases of severe conjunctivitis

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in children the treatment was started by an intensive course, *i.e.*, one drop every minute for half an hour, one every five minutes for one hour, then hourly. No untoward effects were produced, there being no evidence of corneal damage or allergic response.

(2) **Ointment.**—In cases of blepharitis it was thought desirable to use an ointment. In addition it was necessary to find some preparation of aureomycin which remained stable for a considerable period. The fact that the drops deteriorated rapidly and were only effective for 24-48 hours, even if refrigerated, made outpatient administration difficult.

An anhydrous ointment was prepared, using 5 mg. aureomycin per gram of a eucerine base. This lasted for at least a month without appreciable loss of potency. A smoother ointment was prepared by first mixing the aureomycin with a very small amount of water, before adding to the eucerine. This latter ointment was still highly active after a week, but after three weeks its potency was reduced almost to nil. It was, however, less irritating to use.

In several cases a slight allergic response occurred as a result of the use of the anhydrous ointment. In one case the reaction was severe and necessitated cessation of treatment.

There is now a commercial preparation of aureomycin ointment 1 mg. per gram (Lederle). Only six tubes, obtained as samples, have been used, but it appears to be effective in this low concentration and no allergic response has been noted.

(3) **Systemic Administration.**—500-750 mg. were given orally. Mild diarrhoea occurred in all cases. Nausea was common but actual vomiting only occurred in one case. In only one case was there a more severe toxic reaction, with vertigo and severe headache. The vertigo improved immediately the drug was stopped but the headache persisted for three weeks.

(4) **Sub-Conjunctival Administration.**—This method was used in three cases, 0.5 ml. of 0.5 per cent. aureomycin borate being given. Severe pain lasting for half an hour resulted, but there was no untoward reaction. In the case of a patient who had had six such injections, two days after the last one there was no chemosis, no scarring and only slight hyperaemia.

Clinical Applications

Conjunctivitis.—Eight cases of simple conjunctivitis were treated. All had had penicillin treatment, and three had had albucid and two oxycyanide of mercury in addition, without effect. All were left for two days without treatment and cultures taken. Five gave no growth on blood agar, although there was mucopurulent discharge at the time of taking the cultures. Three grew *Staph. aureus*, which was resistant to penicillin but sensitive to aureomycin (*in vitro*). All the

cases with "no growth" responded rapidly to aureomycin drops, being cured in from 3 to 10 days.

One particularly striking case was that of an infant, who had had two intensive courses of penicillin drops and in addition systemic penicillin therapy, all without effect. Four days of guttae aureomycin hourly eradicated the infection. At no time in this case was there any growth from cultures of the mucopurulent discharge.

Of the three cases apparently due to penicillin resistant *Staph. aureus* one cleared up rapidly and completely, but the remaining two recurred immediately treatment was stopped, even though systemic aureomycin was given and the lacrimal sacs were syringed.

Follicular Conjunctivitis.—Under this head are included thirteen cases of conjunctivitis characterized by the presence of small follicles of the palpebral conjunctivae and a thin mucopurulent discharge. In four cases there was a marginal ring of superficial corneal vascularization with small corneal ulcers. From three cases there was obtained a growth of *Staph. aureus*, but in the others cultures were sterile. Scrapings from the conjunctivae revealed inclusion bodies in five of the "sterile" cases.

Of ten cases which responded to aureomycin treatment, seven required only local treatment, but in three a cure was not effected until after a course of oral administration. Cures were effected in from 12 to 25 days. Of the three which were unsuccessful, two had had the condition for 2½ and 6½ years respectively and, although aureomycin, given intensively both locally and systemically, cleared up the condition, it recurred immediately treatment was stopped. Two out of the four cases with corneal vascularization responded.

Blepharitis.—Fourteen cases of long-standing blepharitis were treated. All had had numerous previous treatments. Cultures were taken in every case after at least 48 hours without treatment. In two cases there was no growth, but in eleven *Staph. aureus* (in nine cases insensitive to penicillin) was revealed. The remaining case grew penicillin-insensitive Friedländer bacillus.

The patients were all treated by aureomycin ointment given 2-hourly, and six received systemic therapy in addition. The results were most satisfactory, ten of the fourteen treated being clinically cured. In three cases the cure was effected only after a second course, and in one it was necessary to persist with treatment for over 6 weeks. The case in which culture showed Friedländer bacillus (and in which the blepharitis had been present for 6 years) cleared after 12 days' aureomycin ointment and did not recur.

Of the remaining four, two showed no response. Two improved but the infection was not eradicated and the condition recurred in spite of persistent treatment. All four unsuccessful cases had systemic administration in addition to local therapy. Only two out of the ten successful cases required systemic therapy.

One remarkable success occurred in a woman who had had blepharitis for 26 years and had had treatment with ungu. hydrarg. ox. flav., ichthyol, ungu. hyd. ammon. dil., lotio hyd. oxycyan., albugid, penicillin, and possibly other drugs. A good growth of *Staph. aureus*, slightly sensitive to penicillin but more so to aureomycin, was obtained. Twelve days' treatment with aureomycin ointment caused complete subsidence of the inflammation. Except for slight scarring of the lids causing irregularity of the hair follicles, nothing abnormal can be detected and there has been no recurrence during four months.

Trachoma.—It has been impossible in London to find entirely fresh cases of acute trachoma, but six cases of active trachoma have been treated. All showed pannus, follicles, and scarring. In five at least there was no doubt as to the diagnosis. Inclusion bodies were found in only two.

In four cases immediate improvement occurred after local therapy, and in 14 to 21 days the follicles had disappeared and the pannus was less vascular. In the main, however, the long-standing pannus did not appear greatly altered, though all ulceration became inactive. Discharge and lacrimation ceased and the comfort of the patients has been greatly increased.

Two cases were slow in response and required systemic administration. After this, one improved considerably but the other showed little change. This last

was an unusual case in that, although the appearance was typical trachoma, the condition was unilateral and the patient had no symptoms except those from a slight ptosis. Now, 6 months after treatment, the follicles are less in number, but still present, and the pannus is unchanged. The patient remains symptom-free.

The above cases were not ideal material for clinical research, but there is no doubt that the improvement was very marked and immense relief was afforded to the patients.

Superficial Punctate Keratitis.—Eight cases of this condition were treated by local administration. In all except one there was subjective improvement during treatment, but in none was a cure effected.

Dendritic Ulcer.—Eleven cases were treated without result.

Keratitis with Lid Ulcer.—This case does not fit into any of the above categories but the results were so striking that it deserves mention:

Ten days after vaccination (which resulted in a normal "take") acute conjunctivitis developed. When the patient attended hospital a corneal ulcer about 3 mm. diameter was found and an ulcer of about the same size on the lower lid. There was hyperaemia around this ulcer but the edges were not raised. A culture showed *Strep. viridans*, *Staph. albus*, and *B. xerosis*. Treatment with penicillin and atropine was given but after a week there was no improvement but rather deterioration. A second culture gave no growth. The patient was admitted to the ward and intensive local aureomycin given for 2 hours, after which the drug was applied hourly. After 36 hours the site of the lid ulcer was only marked by an area of hyperaemia and the cornea showed a minute stain. Aureomycin drops were continued hourly, and after a total of three days' treatment the condition was quiescent.

Whether or not this was a vaccinal kerato-conjunctivitis is difficult to say, but there is no doubt that aureomycin rapidly proved effective in curing a dangerous ulcer in which penicillin had failed to effect an improvement.

Disciform Keratitis.—Five cases of this condition were treated. Three cases treated by topical application only showed no improvement. Two treated by sub-conjunctival administration both improved: in one, this change for the better was only slight, but the condition is still gradually settling; in the other the state of the cornea improved rapidly and at the end of a fortnight appeared quiet. The last patient has now been observed for 10 weeks since treatment ceased and there has been no sign of further activity. The nebula is gradually clearing, the vision having improved from 6/36 to 6/18.

Discussion

The cases in this series were selected rather for their difficulty than for their simplicity. Only cases unresponsive to other drugs were treated.

The excellent results in certain cases of conjunctivitis and blepharitis are due to the wide field of action of aureomycin. Many bacilli and cocci insensitive to penicillin are sensitive to this abiotic, and in addition aureomycin is effective against certain viruses. With regard to conjunctivitis, it seems that aureomycin is particularly effective in those cases in which, although infection is obviously present, careful cultures reveal no organism. It may well be that such cases are due to virus infection. The cases of follicular conjunctivitis may also have a virus aetiology, as may the case recorded as "keratitis with lid ulcer". Trachoma, almost certainly a virus disease, also responded well.

Several reports of the effectivity of aureomycin in virus diseases

of the eye have appeared in the literature. Boase (1950) reports success in trachoma. Bellows (1950) and Bellows and others (1950) report successes in epidemic kerato-conjunctivitis. Sheehan (1950) mentions a cure in a case of presumed Newcastle (Philippine Fowl) disease causing conjunctivitis in a chicken farmer, though Gettes (1950) treated a proved case of Newcastle's conjunctivitis without success.

The previous report from this clinic described nine cases of dendritic ulcer in none of which local aureomycin produced a cure. Since this report only two further cases have been treated and they were also unsuccessful. These findings are in sharp contrast to those of Thygeson and Hogan (1950), who gave a 60 per cent. cure rate in from 4 to 7 days, and Zeller and O'Conner (1950) whose seven cases all healed.

The toxic effects of the drug when given orally are found to be more unpleasant than serious, and local application rarely causes any ill effects. In this series only one case of severe allergic reaction was encountered and this was with ointment. There was no case of allergy to the drops. It is to be noted, however, that Burstein (1950) reported an allergic response to guttae aureomycin 0.5 per cent. in a case with rosacea.

Summary

(1) Eight cases of resistant conjunctivitis were treated with aureomycin, six successfully.

(2) Thirteen cases of follicular conjunctivitis, four with corneal vascularization and ulceration, were treated; ten recovered.

(3) Ten of the fourteen cases of long-standing blepharitis treated were clinically cured. Eight of the successes were achieved by local administration only.

(4) Six cases of active trachoma received aureomycin; five showed great improvement.

(5) Superficial punctate keratitis did not respond to treatment given locally.

(6) A case of corneal ulceration and lid ulceration occurring 10 days after vaccination responded dramatically.

(7) Local administration of drops produced no benefit in three cases of disciform keratitis. Two cases received subconjunctival injection and one improved rapidly. Sufficient cases have not been so treated to give any conclusive results.

(8) Treatment of dendritic ulcers has not been successful.

(9) The value of aureomycin in external ophthalmological infections is considerable, particularly in conditions caused by

organisms resistant to the older antibiotics and in several types of infection caused, or presumably caused, by viruses. From the general point of view its therapeutic effect in trachoma is probably its most important application; long-term observations with pathological controls will be necessary before its true value in this disease can be properly assessed, but the preliminary observations are encouraging.

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REFERENCES

- AZZOLINI, U., and FALDI, S. (1950). *G. ital. Oftal.*, **3**, 24.
 BELLOWS, J. G. (1950). *Amer. J. Ophthalm.*, **33**, 909.
 ——— RICHARDSON, V. M., and FARMER, C. J. (1950). *Ibid.*, **33**, 273.
 BOASE, A. J. (1950). *British Journal of Ophthalmology*, **34**, 627.
 BURSTEIN, F. (1950). *Amer. J. Ophthalm.*, **33**, 973.
 DE ROETHH, A. (1949). *Arch. Ophthalm., Chicago*, **42**, 365.
 DUKE-ELDER, S., AINSLIE, D., and BOASE, A. J. (1950). *British Journal of Ophthalmology*, **34**, 30.
 GETTES, B. C. (1950). *Arch. Ophthalm., Chicago*, **43**, 1088.
 PRITIKIN, R. I., DUCHON, M. L., and FARMER, H. S. (1950). *Eye, Ear, Nose. Thr. Mon.*, **29**, 310.
 SHEEHAN, G. A. (1950). *Arch. Ophthalm., Chicago*, **43**, 772.
 THYGESON, P., and HOGAN, M. J. (1950). *Amer. J. Ophthalm.*, **33**, 958.
 ZELLER, R. W., and O'CONNOR, E. F. (1950). *Ibid.*, **33**, 619.