

Keratitis due to *Aspergillus flavus* successfully treated with thiabendazole

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SUMMARY A case of *Aspergillus flavus* keratitis treated successfully with 4% suspension of thiabendazole is reported. This seems to be the first case of successful treatment of keratomycosis with thiabendazole. All other reported cases treated with this drug either had their eyes removed or did not retain any useful vision. Its ability to penetrate ocular tissues, ability to remain in concentrations higher than the minimal inhibitory concentration of many fungi, and broad spectrum of activity make it a worthwhile drug for further investigation in keratomycosis.

Various species of the genus *Aspergillus* are among the commonest cause of keratomycosis (Locatcher-Khorajo and Seegal, 1972). There are few reports of keratomycosis treated with thiabendazole and none of its use in aspergillus infections of the eye. We describe the clinical and mycological features of an *Aspergillus flavus* keratitis treated successfully with thiabendazole ocular suspension.

Case report

A 24-year-old man, a country dweller, woke up on the morning of 21 August 1977 with a red and painful right eye. The symptoms gradually worsened, with watering and blurring of vision. He consulted an eye surgeon on 26 August 1977. He was diagnosed as having a corneal ulcer of possibly bacterial origin and treated with atropine and framycetin eye drops 3 times a day. He also received a combination of 400 000 units of penicillin and 0.5 g streptomycin intramuscularly daily. As there was no improvement after 5 days of treatment the patient was referred to one of us (M. P. U.).

Examination on 2 September 1977 showed his vision was only of hand movements, the right upper lid was swollen with blepharospasm, and there was marked circumcorneal congestion. Slit-lamp examination of the cornea showed a dead white plaque of cheesy excrement material (Fig. 1), which came off easily leaving a large fluorescein-staining corneal ulcer. The anterior chamber showed fair number of

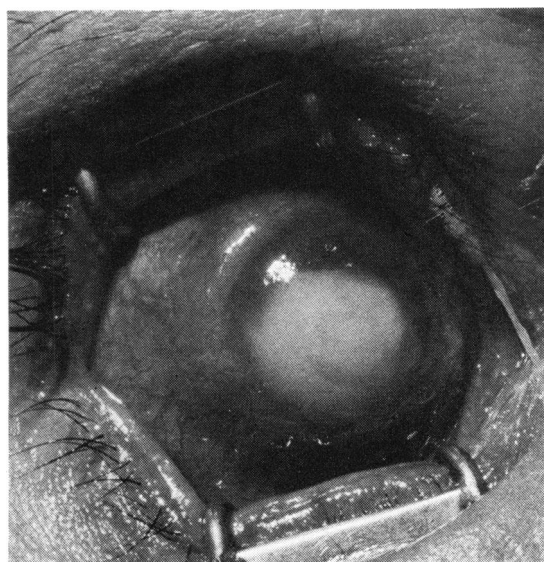


Fig. 1 Patient's eye, showing white plaque

cells, with flare. Intraocular pressures were normal to finger palpation.

The patient was treated with framycetin drops hourly during the day and 2-hourly by night, 2 tablets twice daily of Seprin (sulphamethoxazole, trimethoprim, and co-trimoxazole), and vitamin B-complex and vitamin C twice daily. Once bacterial cultures were reported negative, Seprin was stopped and framycetin reduced to 4 times a day. Fungal culture was reported as a rapidly growing fungus with following sensitivity: amphotericin-

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Fig. 2 *Aspergillus flavus* isolated from patient

B, 15 µg/ml; thiabendazole 5 µg/ml; clotrimazole 1 µg/ml; pimarinic 15 µg/ml; miconazole 10 µg/ml; and econazole 5 µg/ml. On 10 September 1977 the patient was started on 4% thiabendazole suspension every 2 hours. Three days later the lesion appeared smaller but a white plaque again formed on the surface of the ulcer. A second corneal scraping on 14 September 1977 showed a fungus on direct smear which was subsequently grown and identified as the one in the original scraping. Thiabendazole was continued. A third scraping taken on 23 September failed to show fungus on direct smear as well as culture.

The patient was allowed home on 28 September with advice to continue thiabendazole 4 times a day with a quiet eye and a vision of 6/18. A week later the eye remained quiet, vision having improved to 6/12 with pinhole. A month later the condition was essentially unchanged. Five months later, on 17 March 1978, he still had a quiet eye with a vision of 6/12 with pinhole, having been on no medication for 3 months. A faint corneal nebula remains.

MYCOLOGICAL STUDIES

A smear of the corneal scraping was examined microscopically by direct wet mount and Gram's stain. Under magnification of 100× both slides showed abundant presence of branching, thick-walled fungi. Another portion was inoculated into a Sabouraud's dextrose agar (SDA) slant at the time of scraping. Incubation at room temperature showed growth of a flat, velvety, white fungal colony. With further incubation the colony developed a yellow-green colour, with radial furrows. The reverse was

golden in colour. Microscopically (Fig. 2) it showed growth of septate hyphae with unbranched conidiophores terminating in an enlarged conidial head covered with flask-shaped sterigmata producing chains of conidia. The hyphae were thick-walled and hyaline and the conidiophores rough and pitted. The isolate was consequently identified as *Aspergillus flavus* and this identification was confirmed by Dr Y. M. Clayton at the Institute of Dermatology in London. Sensitivity tests were run on the fungal isolate by the agar slant method (Holt, 1975). A 10 mm colony was suspended in 0.01 M phosphate buffer. This suspension was then used to inoculate tubes of SDA containing 0.5 to 15 µg/ml of the various test drugs with each tube receiving a loopful of the suspension. A control tube containing no drug was similarly inoculated. Results were read at 48 hours after incubation at room temperature.

Discussion

Keratomycosis due to the genus *Aspergillus* accounts for nearly 50% of all reported cases of oculomycosis (Locatcher-Khorajo and Seegal, 1972; Jones, 1975). The steady increase in the number of fungal infections has not, however, been matched by an increasing availability of useful antifungals. At the time of writing only 3 antifungal drugs are freely available commercially for use in ophthalmology, namely, amphotericin-B, nystatin, and more recently pimarinic. The last, however, has not reached many parts of the world where fungal eye infections are commonly seen. Amphotericin has been shown to have severe corneal and systemic toxicity (Jones, 1975; Upadhyay, in press). Nystatin, because of its inability to penetrate the cornea and lack of absorption from the gut (Goodman and Gilman, 1970) is not of much value in ophthalmology except for the most superficial corneal infections. In countries in which clotrimazole is available this imidazole would appear to be the drug of first choice for aspergillus infections of the eye (Jones *et al.*, 1974). Similarly miconazole and econazole have a high level of activity and are effective against ocular aspergillus (Jones, 1975).

However, we were keen to test a drug which is more freely available in many parts of the world and which is known to be non-irritant to the eye and to penetrate the ocular tissues well from topical administration.

Thiabendazole is a well-known broad spectrum anthelmintic and its in-vitro antimycotic activities were reported by Robinson *et al.* (1964). In-vivo antifungal effects were reported by Fleischmajer *et al.* (1965). Thiabendazole has been shown to be an effective antifungal against both pathogenic and

saprophytic fungi. The latter is of greater relevance to ophthalmologists, as most reported cases of oculomycosis have been caused by saprophytes. Thiabendazole has both fungistatic and fungicidal properties (Robinson *et al.*, 1964). The fungi that are particularly sensitive to the drug are dermatophytes *Microsporium* and *Trichophyton*. Fungi with moderate sensitivity include *Cladosporius*, *Phialospora*, *Fonsecaea*, *Madurella*, and *Parenechacha* (Robinson *et al.*, 1969). Strains of *Aspergillus flavus*, including those known to produce aflatoxins, are highly susceptible. Robinson and his associates reported on thiabendazole's ability to penetrate ocular tissues (Robinson *et al.*, 1966). It has been shown that, if applied locally to the rabbit eye in concentrations up to 4%, it is non-irritating (Robinson *et al.*, 1965). This was confirmed in our case both subjectively by patient inquiry and objectively by daily slit-lamp examination of the eye.

Wilson and his associates investigated the effect of a topical application of thiabendazole in a corneal infection due to *Phialophora verrucosa*. Although in vitro tests had shown the isolate to be sensitive to thiabendazole, this drug could not eradicate the corneal infection (Wilson *et al.*, 1966). Sensitivity of *Fusarium* species to thiabendazole was reported by Jones (1975), but in this case, although infection was eliminated, the eye could not be saved, having to be removed due to advanced fungal malignant glaucoma. Ocular penetration from topical administration has been demonstrated (Robinson *et al.*, 1966). Thirty minutes to 1 hour after application of 20 mg of the ¹⁴C drug as 0.5 ml of a 4% suspension the cornea contained 42 to 52 µg/g, the aqueous 18 to 28 µg/g, vitreous 0.5 to 1 µg/g, and the lens 2 to 3.4 µg/g.

For the last year we have been testing the in-vitro sensitivity to thiabendazole of various ocular isolates. Of the 27 isolates tested only 6 required thiabendazole in concentrations more than 15 µg/ml (minimum inhibitory concentration 15 µg/ml). The other isolates have all been sensitive at concentrations lower than 5 µg/ml (unpublished data). Encouraged by these studies and the reasonable sensitivity (MIC 5 µg/ml) of this patient's isolate

to thiabendazole we wanted to see the in-vivo effect of this drug. The result has certainly been encouraging.

Dr L. N. Prasad referred the case. Dr C. M. Anklesaria of Merk, Sharpe & Dohme (India) supplied the powder. The ocular suspension was prepared by Anand Deo Shrestha of the Royal Drugs Ltd. We thank them all. Thanks are also due to Dr Y. M. Clayton of the Institute of Dermatology, University of London, for her help in identification. We also record our gratitude to Dr Y. M. S. Pradhan, medical superintendent of Bir Hospital, for allowing us to report this case and for his constant encouragement.

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