

Topical silver sulphadiazine—a new drug for ocular keratomycosis

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SUMMARY The efficacy of silver sulphadiazine in human keratomycosis has not been evaluated so far. Encouraged by the success of an earlier experimental trial, a prospective, controlled, randomised double masked clinical study was designed to evaluate the efficacy of 1% silver sulphadiazine ophthalmic ointment in 20 eyes of mycotic keratitis. Miconazole 1% was used for comparative evaluation in another 20 eyes. Silver sulphadiazine had a higher success rate (80% vs 55%) than miconazole. It had broad antifungal activity and was found to be effective in fusarium keratitis. Absence of side effects, economy, and its efficacy in deeper and extensive lesions were additional advantages. It is concluded from this study that silver sulphadiazine is a safe and effective broad spectrum antifungal agent which can be used for the treatment of human keratomycosis.

Fungal keratitis still remains a diagnostic and therapeutic challenge for the ophthalmologist. The management is restricted by the relative unavailability of effective antifungal agents, the extent to which they can penetrate the cornea, and their ocular side effects.¹⁻³ Newer and more potent antifungal agents are thus required for the treatment of mycotic corneal ulcers.

Silver sulphadiazine, a topical antimicrobial, has been shown to be beneficial in both the prophylaxis and the treatment of infections of the skin following burns.^{4,5} It has a powerful antibacterial and antifungal activity.⁶ In a recent experimental study conducted by us silver sulphadiazine was found to be very effective in the control of fungal infections of the rabbit cornea produced by *aspergillus* and *fusarium*.⁷ Encouraged by the results of this experimental study, a prospective, controlled, randomised, and double masked clinical trial was designed to study the efficacy of silver sulphadiazine in the treatment of mycotic keratitis. Miconazole 1% ophthalmic ointment, a known antifungal agent^{1,3,8} was used for comparison.

Subjects and methods

The study material comprised of 43 smear-positive cases of fungal corneal ulcers. On the patient's initial visit a detailed history including the presence of any predisposing factors such as diabetes, trauma, use of topical steroids, and antimetabolites was elicited. A detailed ophthalmic examination was carried out, and a record of the severity of symptoms and ocular signs, the presence and extent of hypopyon if any, and of digital intraocular pressure was made. The ulcer was graded from grade I to grade V and hypopyon from + to +++ according to Mohan's classification (Table 1).⁹ Corneal scrapings were examined for the presence of fungus by KOH and Gram's stain and also cultured on Sabouraud's agar.

After explaining the nature of the study an informed written consent was obtained from all the subjects prior to starting treatment. The patients were assigned alternately to each of two groups. Group I consisted of 22 fungal corneal ulcers treated with 1% miconazole ointment, while group II comprised 21 fungal ulcers treated with 1% silver sulphadiazine ointment.

The two ointments were coded and supplied to the

Table 1 Grading of ulcers and hypopyon

Grading of ulcer	
O	: No ulcer
I	: Extension less than 4 mm
II	: Extension up to 5 mm
III	: Extension up to 7 mm
IV	: Extension up to 10 mm
V	: Extension more than 10 mm

Grading of hypopyon	
H0	: Absent
+	: Less than 2 mm
++	: Less than 5 mm (filling up to half of anterior chamber)
+++	: 5 mm or more (filling more than half of anterior chamber)

patients in identical packings. The patients were advised to apply the given ointment five times a day to the affected eye. In addition, cycloplegics, anti-glaucoma medications, and supportive vitamins were given where indicated. The clinical response to therapy was noted every second day on the slit-lamp by two independent observers. In the event of absence of any obvious clinical improvement or further progression of the lesion following treatment for one week, the patient was switched to the other drug. Disappearance of hypopyon and circumcorneal congestion, absence of fluorescein staining, and a negative report of repeat culture were the necessary criteria for a healed ulcer. However, the treatment was continued for a further period of two weeks after clinical healing of the ulcer. The development of any local or systemic adverse effects was carefully recorded. At the end of the study the code was broken and the results analysed.

Results

Three patients (two on miconazole and one on silver sulphadiazine) developed local allergic reactions, possibly to the ointment base. They were excluded from further analysis and do not form a part of the study material.

Of the remaining 40 patients studied 31 were males and nine females. Their ages ranged between 14 and 68 years. A preceding history of trauma with organic matter was forthcoming in 19 cases, 15 patients had used topical steroids, and another three had diabetes mellitus.

Three eyes were in grade I, 15 in grade II, 13 in grade III, and nine in grade IV. None of the ulcers in the study belonged to grade V (Table 2). Hypopyon was present in 21 eyes. It was H+ in 13 and H++ in eight. Fungus could be cultured on Sabouraud's agar in 32 of the 40 smear-positive cases. The predominant organisms cultured were aspergillus from 14 ulcers followed by fusarium from seven ulcers.

Silver sulphadiazine 1% was found to be effective in 16 of the 20 ulcers (80%), while 1% miconazole was successful in 11 of the 20 ulcers (55%); $p < 0.05$. Figs. 1A and B show a representative case of a fungal corneal ulcer which responded favourably to silver sulphadiazine therapy. The therapeutic response of both these drugs with regard to the ulcer grading and morphology is shown in Table 2. Five of the nine non-responders to miconazole in group I showed a good therapeutic response when switched over to silver sulphadiazine. In contrast, none of the four cases in group II, resistant to silver sulphadiazine initially, could be improved with miconazole therapy (Table 2; NS).

The efficacy of the drugs with regard to the various fungi isolated on culture (a total of 32 cases) is shown in Table 3.

In group I eight of the 15 (53.3%) culture-positive cases responded to miconazole therapy, whereas silver sulphadiazine showed a higher efficacy of 82.3% (14 out of 17 ulcers; NS). With both the drugs a comparable response of 60% (group I) and 66.6% (group II) was observed for aspergillus. The remaining cases of aspergillus keratitis with poor results on initial treatment with miconazole therapy responded well when switched over to silver sulphadiazine therapy.

Table 2 Efficacy of miconazole and silver sulphadiazine in relation to ulcer morphology (40 eyes)

Grade of ulcer (I-V)	Group I miconazole		Group II silver sulphadiazine	
	Primary response to miconazole/total number of cases	Response of miconazole-resistant cases to silver sulphadiazine after cross-over/total number of cases crossed over	Primary response to silver sulphadiazine/total number of cases	Response of silver sulphadiazine-resistant cases to miconazole after cross-over/total number of cases crossed over
I	2/2	—	1/1	—
II	3/7	2/4	7/8	0/1
III	5/7	1/2	5/6	0/1
IV	1/4	2/3	3/5	0/2
V	0/0	—	0/0	—
Total	11/20	5/9	16/20	0/4

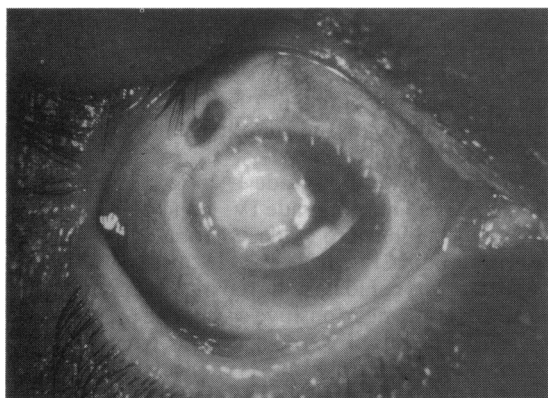


Fig. 1A Showing an active fungal corneal ulcer in a patient on long-term topical steroids following IOL implantation. Iris-supported claw lens, steel sutures, and filtering bleb of glaucoma surgery are clearly visible.

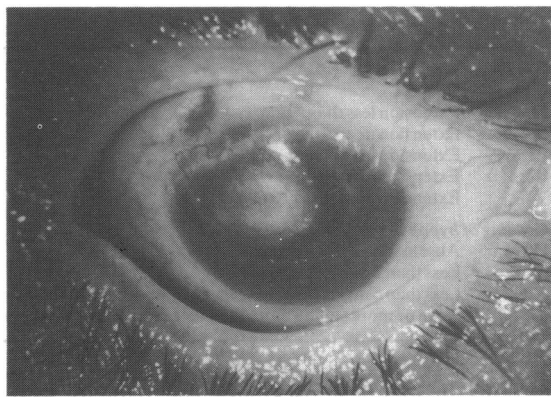


Fig. 1B Same case three weeks after initiating topical silver sulphadiazine therapy. Note the resolution of the ulcer and the absence of activity after therapy.

For fusarium keratitis miconazole was found to be entirely ineffective, while silver sulphadiazine was successful in curing all the four fusarium ulcers in group II on initial treatment. It was also effective against two of the three ulcers resistant to miconazole in group I when switched over to silver sulphadiazine (Table 3). The results for the other cultured fungi were by and large comparable for the two drugs. The mean duration of resolution of the ulcers which responded was 20.7 days for miconazole and 23.9 days for silver sulphadiazine (NS).

No significant ocular or systemic adverse effects apart from the above mentioned local allergic reactions in three eyes were observed during the study period.

Discussion

During the past 10 years there has been a major change in the management of fungal infections of the cornea. Better diagnostic methods, more effective and less toxic antifungal agents, and an increased awareness of the pathogenic mechanisms involved in the corneal inflammations have been responsible for this.¹⁰ The problem of keratomycosis in tropical countries like India is more acute because of the humid environment, poverty in a primarily agrarian economy, illiteracy, and ignorance. The problem is compounded further by the unavailability of effective antifungal agents. In India only amphotericin B and nystatin are commercially available for ocular use. Both of these suffer from the drawbacks of a relatively narrow spectrum of action and inefficacy in deeper corneal lesions.^{11,12}

Recent evidence suggests that miconazole is a relatively safe, non-toxic, and effective antifungal

agent against candida and aspergillus keratitis.¹¹⁻¹³ Silver sulphadiazine is a drug which combines the powerful antimicrobial activity of silver and sulphadiazine.¹⁴ It derives synergistic benefits from sulphonamides and heavy metals and functions as an organic base heavy metal release system by liberating silver.¹⁵ The antimicrobial activity of silver halides is known. Silver sulphadiazine differs from other silver compounds in that it does not react with chlorides, amino acids, or sulphhydryl groups in the body tissues and is thus not inactivated. Silver sulphadiazine, however, reacts rapidly with the DNA of the microorganisms and silver becomes bound to it. This prevents the unzipping of the DNA helix, thereby inhibiting the replication of the pathogens.¹⁶ Since no reduced silver is liberated within the tissues, there is a negligible possibility of silver being deposited to cause argyrosis. Conspicuous epithelial regeneration occurs in the presence of silver sulphadiazine. There is over 100 times more DNA in mammalian cells than in bacterial and fungal cells. Thus the ratio of silver sulphadiazine to micro-organismal DNA is high enough to prevent their division, but the corresponding ratio of silver sulphadiazine to epithelial DNA is too low to block epithelial cell regeneration (healing), which is facilitated by the suppression of micro-organismal proliferation.¹⁶ Its efficacy as a potent antimicrobial agent is thus well established.

Both miconazole and silver sulphadiazine were effective against most fungi, namely, aspergillus, yeast-like fungi, and the brown dematiaceous filamentous fungi. Fusarium corneal ulcers were, however, found to be resistant to miconazole therapy, as has been previously observed.^{12,13} In contrast, an excellent response of 85.7% (including cross-overs) was observed with silver sulphadiazine therapy in

Table 3 Therapeutic response of various fungi to miconazole and silver sulphadiazine (total 32 eyes)

Fungus isolated	Group I miconazole		Group II silver sulphadiazine	
	Primary response to miconazole/total number of cases	Response of miconazole-resistant cases on cross-over to silver sulphadiazine/total number of cases crossed over	Primary response to silver sulphadiazine/total number of cases	Response of silver sulphadiazine-resistant cases on cross-over to miconazole/total number of cases crossed over
Aspergillus	3/5	2/2	6/9	0/3
Fusarium	0/3	2/3	4/4	—
Phialophora	1/1	—	1/1	—
Candida	2/2	—	1/1	—
Harmodendrum	1/1	—	0/0	—
Rhodotorula	1/1	—	0/0	—
Phycomyces	0/0	—	1/1	—
Curvularia	0/0	—	1/1	—
Monosporium	0/2	0/2	0/0	—
Total	8/15	4/7	14/17	0/3

patients with fusarium keratitis. Apart from its distinct advantage for fusarium keratitis, silver sulphadiazine also caused the successful resolution of five out of nine (total cases) and four out of seven (culture-positive) corneal ulcers resistant to initial miconazole therapy when crossed over. In contrast, miconazole had no beneficial effect on the non-responding corneal ulcers of the silver sulphadiazine group after being switched over to miconazole. This differential response on cross-over seen for all cases (Table 2), as also for culture-positive cases alone (Table 3), was not statistically significant but needs further investigation.

Nevertheless this clinical trial, possibly the first in the literature, corroborates our previous experimental study and has demonstrated silver sulphadiazine to be a potent, safe, and effective antifungal drug with a wide spectrum of activity. The ready availability and relative cheapness of silver sulphadiazine are further points in favour of its routine use for the management of human mycotic keratitis.

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