Corneal changes in patients treated with clofazimine

P.-E. WALINDER, L. GIP, AND M. STEMPA
From the Eye and the Dermatological Clinics, Sundsvall’s Hospital, Sweden

Clofazimine (Lamprene) is a phenazine derivative (Barry, Belton, Conalny, Dennen, Edward, O’Sullivan, Twomey, and Winder, 1957) which is active against mycobacteria (Vischer, 1969). It has been used in the treatment of leprosy for more than 10 years (Browne, 1965a) and recently it has also been tried in different dermatological diseases including psoriasis and pyoderma gangrenosum (Gip and Stempa, 1976). A common side-effect is a reddish-brown discoloration of the skin (Browne, 1965b), and there have been reports of pigmentation of the conjunctiva (Browne, 1965b, 1969; Schultz, 1972) and of the cornea (Ohman and Wahlberg, 1975), although such changes have also been denied (Imkamp, 1968). The possibility that clofazimine treatment in psoriatic patients causes corneal changes is discussed.

The study comprised 19 patients who were being given clofazimine as a treatment for psoriasis; their mean age was 45 years. The dose was usually 400 mg daily for one to two months. Ocular examinations covered visual acuity, slit-lamp microscopy (Haag-Streit 900 slit lamp using ×16 ocular) ophthalmoscopy, applanation tonometry, Goldmann perimetry, and colour vision tests. The first ocular examination was performed between two days and two months after the clofazimine therapy had ceased.

Two patients, Cases 1 and 2, showed obvious corneal changes.

Case 1
A 47-year-old man with psoriasis pustulosa was treated with clofazimine 100–400 mg daily for two months (total dose 20 g). The psoriatic lesions improved, but the skin showed a reddish-brown discoloration which lasted six months after the clofazimine therapy had stopped.

At the first ocular examination two days after the end of the treatment the visual acuity, visual fields, and colour vision were normal. Slit-lamp microscopy revealed several fine brownish, branched lines in the most superficial layers of both corneas (Fig. 1). Sometimes the border of the line was well marked, but at other times the brownish colour merged into the surrounding cornea. Using high magnification (×16 ocular) the lines showed a fine granular appearance. The changes were localized to the lower part of the cornea and there were no epithelial defects. No pigmentation was seen in the deeper layers of the cornea or in the conjunctiva. The lens and fundus were normal except for a very fine granular pigmentation scattered over both macular regions.

Repeated examinations during a one-year follow-up period showed a gradual decrease in the corneal changes. However, at the last examination, a few, very fine, brownish lines could still be seen in both corneas.

Case 2
A 29-year-old woman with psoriasis pustulosa was treated with clofazimine 100–400 mg daily for two months (total dose 20 g). The psoriatic lesions improved. The patient noted a slight reddish-brown discoloration of the skin and small dry spots on the legs. The discoloration had disappeared two to three months after the end of the treatment but some of the dry spots still remained six months later.

At the first ocular examination two weeks after the end of the treatment the visual acuity, visual fields, and colour vision were normal. The slit-lamp microscopy revealed fine, brownish lines in the superficial layers of both corneas similar to those observed in Case 1 (Fig. 2). The conjunctiva, the deeper corneal layers, the lens, and fundus were normal.

Two months later there was a slight regression of the corneal changes and six months later the corneal lines had disappeared.

Both these patients denied having used any other drugs, for example chloroquine or phenothiazine derivatives.

Cases 3, 4, 5, and 6
In four patients, aged 70, 45, 37, and 32 years, both corneas showed a very fine, brownish line horizontally placed across the lower half at the site for lid closure. Using high magnification the line appeared slightly granular; it resembled a common change in the cornea called the Hudson-Staehli line. Visual acuity, visual fields, and colour vision were normal. At examination six to eight months later the line could hardly be seen in one patient (aged 37) but was unchanged in the other three.

Among the 19 patients in this study were two with...
known cataracts. Intraocular pressure was normal in all patients except in one with unilateral, secondary glaucoma. Three of the men had defective colour vision but normal visual acuity, visual fields, and fundus. One patient had a brown pigmentation of the conjunctiva similar to a conjunctival naevus. The pigmentation of the conjunctiva was unaltered six months after the treatment had finished.

There were no severe side-effects. Some of the patients showed a marked reddish-brown staining of the skin. Three patients had erythoderma, and a few complained of nausea and fatigue.

Discussion

There are several kinds of superficial lines in the cornea similar to those observed in the present study. The most common is the Hudson-Staeohl line in which iron is deposited in the cornea (Gass, 1964). Corneal lines are also observed after exposure to certain substances, for example, atebrin, and are a well-known complication during treatment with chloroquine and its analogues. In certain corneal diseases there are brownish lines caused by deposition of melanin. The morphological resemblance and possible relationship between these changes are discussed by Bron (1973).

In the present study microscopical examination of 19 psoriatic patients given clofazimine revealed bilateral corneal changes in six cases. Two patients showed between five and 10 brownish, curved lines in the superficial part of both corneae. The changes resembled chloroquine keratopathy except for the brownish colour. None of the patients in this series had used any drugs known to cause corneal opacities nor had they any corneal disease.

The other four patients showed very slight changes, usually there was one brownish corneal line, which it was not possible to differentiate from a Hudson-Staeohl line. This line is common in old people, but may be seen by the third and fourth decades (Gass, 1964). The brownish lines in these four patients may thus be a 'normal' finding. However, the fact that in one patient the lines diminished when the clofazimine treatment ended suggests some relationship with the drug.

Eye complications in psoriatic patients are rare. Kerato-conjunctivitis has been described (Horowitz, 1949), but the symptoms and clinical appearance are different from the corneal changes observed in this study.

The excretion of clofazimine has been shown to be very slow in animals (Vischer, 1969). The pigmentation of the skin in humans has been reported to last for a long time (Browne, 1965b), and this is confirmed by one of our patients (Case 1) who had a brown discoloration of the skin which lasted for six months. It is feasible that the skin pigmentation and the corneal pigmentation are of the same origin, thus explaining why the corneal changes in Case 1 persisted for at least one year.

Conjunctival pigmentation has been reported in some lepromatous patients during clofazimine therapy, but was not observed in our study.

There have been no reports of corneal changes in lepromatous patients given clofazimine. The reason may be that the changes are minimal and seen only by microscopical examination. In a study by Imkamp (1968), however, the patients were examined by slit lamp and yet no corneal opacities were found compared to the two cases found in our series. This difference could possibly be due to the fact that Imkamp's patients had been treated mainly with a lower daily dose of clofazimine (100 mg).

Recently, Ohman and Wahlberg (1975) observed brownish lines in the cornea in 10 of 26 patients given clofazimine as treatment for some dermatological disorders. They also found two cases with macular pigmented changes compared with only one dubious case in our series (Case 1). The clinical appearance and the reversibility of the corneal changes in their series are in agreement with our findings.

Summary

Fine, brownish lines, similar to chloroquine keratopathy, were observed in two of 19 psoriatic patients given clofazimine. There was no functional disturbance and the changes were reversible.
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