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Clofazimine-Resistant Leprosy,[1] a Case Report

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In 1962 Browne and Hogerzeil first reported on the efficacy of clofazimine (Lamprene®, B663) in leprosy patients ([2]). A bactericidal effect of the drug of *Mycobacterium leprae* has been suggested by Levy ([9]) and was later confirmed ([6, 8]). In the mouse foot pad system multiplication of *M. leprae* is inhibited by feeding mice 0.0001% clofazimine in the diet, a dosage amounting to 0.1 mg per kg body weight per day ([9, 11]). The most commonly used dosage of 50 mg to 100 mg per day has indeed been found effective in human leprosy. Browne and Hogerzeil referred to the possibility of clofazimine resistance after 12 months' treatment ([3, 4]), but this was not confirmed by Browne in a report on three years of clofazimine therapy ([5]), and so far no cases of clofazimine resistance have been reported.

A preliminary report is presented here on a patient who experienced a clinical and bacteriological relapse while on clofazimine 100 mg three times weekly and whose *M. leprae* exhibit resistance to clofazimine in the mouse foot pad sensitivity test.

CASE HISTORY

The patient is a 56-year-old Ethiopian male who was diagnosed at the All Africa Leprosy and Rehabilitation Training Centre (ALERT) as having lepromatous leprosy in 1963 and subsequently started on dapsone. After two years and nine months, his treatment became very irregular due to serious recurrent attacks of erythema nodosum leprosum (ENL) reactions, which at that time were interpreted as being a complication of dapsone treatment. He received, therefore, in the period 1966–1968 no leprosy treatment, but was on and off of glucocorticosteroids. For another two years he was given thiambutosine monotherapy in doses varying between 0.5 and 2 grams daily. In May 1970 dapsone treatment was resumed with a low oral weekly dosage, which was slowly increased to a dosage of 200 mg weekly.

Bacteriological negativity was never achieved, and by October 1972 an erythematous plaque was noted on the face, suggesting reactivation of the disease. The dapsone dosage was increased to 100 mg daily, but despite regular treatment the disease progressed, and in March 1973 histoid nodules were noted on the trunk and buttocks and a scleral leproma appeared on the left eye. Drug sensitivity determination in the mouse foot pad failed. However, since the patient had clinically dapsone-resistant leprosy, treatment was changed to clofazimine 100 mg daily. In November 1973, after eight months of clofazimine treatment, the patient again experienced serious recurrent ENL, requiring short courses of glucocorticoids for a total of 190 days. The

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ENL was controlled after the clofazimine dosage was increased to 200 mg daily as from December 1975. After nine months it was decreased again to 100 mg daily. The patient's clinical response to clofazimine was good and in March 1977 he was clinically quiescent and bacteriologically negative for the first time. In September 1977 the clofazimine dosage was further reduced to 100 mg three times a week. The drug was faithfully collected every two months, and the patient affirmed to take a capsule on alternate days three times a week.

It is very likely that his experience of ENL reactions motivated him to take the drug as prescribed. The serum clofazimine concentration prior to admission in December 1979 was 50 ng per ml and was identical to that found 2½ weeks after admission (determined by CIBA-GEIGY Laboratories, by courtesy of Dr. W. Vischer).

During October–December 1979 innumerable histoid nodules with a pearly appearance developed on the face, trunk (also the abdomen), extremities (including the flexor side of elbows and knees), and one lesion appeared at the limbus of the right cornea. The Bacteriological Index (BI) in the lesions was 5+, with 4% to 8% solid forms. The histoid character was confirmed by histology. He was hospitalized for four weeks and treated with clofazimine, 100 mg three times per week. Treatment and observation then continued on an outpatient basis. Although some lesions seemed to atrophy, none disappeared. Slit-skin scraping carried out in January, May, August, and November 1980 revealed in most examined nodules a Bacteriological Index of 5 to 6+, with solid forms up to 6%.

In November some of the nodules had extended into plaques and a biopsy was taken for a clofazimine sensitivity study and histological examination. The histology showed an advanced relapse with a BI of 5+ and 10% solid forms. In June 1981 the clofazimine dosage was increased to 100 mg daily and was taken under supervision as from September. The disease failed to respond, clinically and bacteriologically, and treatment was therefore changed to rifampin 600 mg daily from 6 January 1982. A regression of the nodules was already noticeable after two weeks. Cross-resistance with rifampin seemed, therefore, unlikely and multiple drug treatment was started on 26 January after obtaining a skin specimen to perform a viability study in mice.

MOUSE FOOT PAD STUDIES

Locally bred Swiss albino mice were inoculated in both hind foot pads with 5×10^3 *M. leprae*, isolated from a punch biopsy. Preparation of the inoculum, inoculation of mice, and harvesting of *M. leprae* from the foot pad tissues were accomplished by the method described by Rees [10], and the counting of the harvested organisms was performed according to the method reported by Shepard and McRae [12].

The clofazimine was received through Dr. W. A. Vischer, CIBA-GEIGY, Basel. The drug was dissolved in absolute ethanol, mixed with the locally available powdered feed in concentrations of 0.003%, 0.001%, and 0.0001% w/w and fed continuously from the 60th day after inoculation. Harvesting of control and drug-treated animals was carried out between nine and ten months after inoculation. At that time only four mice in each group of treated mice were available for harvesting, and six of the control mice were sacrificed. The hind foot pads of each mouse were pooled, and the average number of bacilli per foot pad calculated. The lower limit of detectability is 1.3×10^4 acid-fast bacilli (AFB) and multiplication was considered to have occurred if 10^5 or more AFB were harvested per foot pad.

The results of the present study are given in The Table. Multiplication of *M. leprae* occurred in all concentrations tested.

Bacilli obtained from the control mice were passaged into various strains of mice in our laboratory and the laboratories of Dr. L. Levy (Jerusalem) and Dr. S. R. Pattyn (Antwerp). The results will be available at the end of 1982.

DISCUSSION

This is, to our knowledge, the first case of clofazimine-resistant leprosy, confirmed by mouse foot pad testing. Whereas most investigators start to feed drug-containing diets from the first day after inoculation, some do so from the 21st day (S. R. Pattyn, personal communication). In the present test, drug-containing diet was started on day 60. This is still well within the lag phase of the growth curve. Levy [9] reported that no

THE TABLE. *Number of acid-fast bacilli (AFB) harvested per mouse foot pad.*

Months after inoculation	Controls	Clofazimine treated mice[a]		
		0.0001%	0.01%	0.03%
9 months	4.6×10^5	3.9×10^5	1.8×10^5	1.6×10^5
	6.6×10^5			
9½ months	6.1×10^5	3.6×10^5	1.0×10^5	2.6×10^5
	4.8×10^5			
10 months	8.0×10^5	1.3×10^5	2.0×10^5	1.3×10^5
	5.2×10^5	1.8×10^5	2.6×10^5	1.0×10^5

[a] Percentages refer to w/w concentrations of clofazimine in powdered feed, fed continuously from the 60th day after inoculation until sacrifice.

multiplication of *M. leprae* occurred in mice fed 0.0001% clofazimine in the diet from day 60 after inoculation.

It has been assumed that up until now no cases of secondary clofazimine-resistant leprosy have been observed because the drug had not been used for a sufficiently long time in a large enough number of patients or because the frequency of initially resistant mutants is less than that encountered with thiambutosine, rifampin, and dapsone ([7]).

The case presented in this report responded initially to clofazimine, and resistance appeared after 7½ years of monotherapy, given successively in the following dosages: 33 months of 100 mg daily, 9 months of 200 mg daily, 12 months of 100 mg daily, and 38 months of 100 mg three times weekly. Reactivation occurred after 25 months' treatment with 100 mg three times weekly.

The question will be raised whether the inefficacy of the administered clofazimine may be due to an abnormally low absorption rate of the drug in this patient. His clofazimine serum level while on supervised treatment (50 ng/ml) is rather low for someone taking 100 mg of the drug thrice weekly. Banerjee, *et al.* ([1]) reported an average of about 500 ng per ml serum in a small number of patients treated with the same dosage. Levy, however, found in three leprosy patients treated with 100 mg three times weekly, serum levels between less than 170 ng per ml (lower limit of sensitivity of the assay) and 400 ng per ml ([9]). In all our ten patients in whom clofazimine serum concentrations were measured by CIBA-GEIGY laboratories at Basel, considerably lower concentrations were found than reported by Banerjee in patients receiving a comparable dosage. In one patient, clinically improving very well on 300 mg weekly, the serum clofazimine level was even as low as 13 ng per ml. The serum concentration resulting from a certain dosage of clofazimine seems to vary appreciably from one patient to another and in the same patient from time to time (Levy ([9]) and our personal observation.)

Although the patient presented in this study did not show distinct red discoloration of the skin or pigmentation of the lesions, his initial response to clofazimine in a dosage of 100–200 mg daily was good. The orange color, noticed in the fatty tissue of a skin biopsy taken from a nodule prior to the change of treatment (January 1982), suggests deposition of clofazimine.

There is generally little known about the relationship between the serum concentration of clofazimine, crystalline deposits in fatty and reticulo-endothelial tissues, and the therapeutic efficacy of this drug. Further studies on the pharmacodynamics of clofazimine in various ethnic groups are obviously needed.

One wonders if the intermittent administration of glucocorticoids on 190 days during the first three years of clofazimine treatment has promoted the multiplication of clofazimine-resistant mutants, which had the opportunity to multiply during the treatment with clofazimine 100 mg three times weekly. Clinical observation during three weeks of rifampin monotherapy suggests susceptibility to this drug, in contrast to the finding of Tsutsumi and Morrison in a clofazimine-resistant laboratory strain of mycobacteria ([13]). Results of further mouse foot

pad studies on *M. leprae* from this patient are awaited to confirm the clinical finding.

SUMMARY

A preliminary report is presented on the findings in a patient with lepromatous leprosy who experienced a clinical and bacteriological reactivation after 7½ years of clofazimine monotherapy. Mouse foot pad studies confirmed clofazimine resistance.

RESUMEN

Se presenta un informe preliminar acerca de un paciente con lepra lepromatosa que desarrolló una reactivación clínica y bacteriológica de su enfermedad después de 7.5 años de tratamiento con clofazimina. Los estudios en el cojinete plantar del ratón confirmaron el desarrollo de resistencia a la clofazimina.

RÉSUMÉ

On présente ici un rapport préliminaire relatant les observations faites chez un malade atteint de lèpre lépromateuse, qui avait présenté un réactivation clinique et bactériologique après sept ans et demi de monothérapie par la clofazimine. Les études menées dans le coussinet plantaire de la souris ont confirmé une résistance à la clofazimine.

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