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Dapsone-resistant leprosy in a population of Bamako (Mali)

G BAQUILLON,* C FERRACCI,* P SAINT ANDRE* & S R PATTYN†

**The Marchoux Institute, BP 251, Bamako, Mali;*
†Institut de Medecine Tropicale Prince Leopold, Nationalstraat 155, B-2000, Antwerpen, Belgium.

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Summary Prevalence of dapsone resistance among 105 previously multibacillary patients, living in the vicinity of the Marchoux Institute in Bamako, Mali, was 5.7%. Patients had been treated for 10–29 years with a mean of 21 years. It is possible that although the amount of drug administered was only 56% of that prescribed, these long incubation times are the result of a year-long practice of administering dapsone by injections. It is possible that the technique of patient selection did not detect the appearance of resistant relapses at the earliest stages. The need for training in the early diagnosis of relapses is stressed.

Introduction

The Marchoux Institute was founded in 1933 as a research, teaching and reference centre for leprosy in French West Africa. Since 1960 it has been integrated into the Organisation de Coordination et de Coopération pour la lutte contre les Grandes Endémies (OCCGE) whose headquarters are in Bobo-Dioulasso (Upper Volta). Member states are Benin, Guinea, Ivory Coast, Mali, Mauritania, Niger, Senegal, Togo, Upper Volta and France.

During the years a great number of leprosy patients were hospitalized in the Institute or lived for shorter or longer periods in one of the 90 houses belonging to the Institute. After discharge, many patients went back to their home villages, but a number of them settled with their families in the vicinity of the Institute, creating a new village on the outskirt of the city. Patients continue their treatment at the out-patient clinic of the Marchoux Institute. In 1978 a patient from this population developed a relapse of lepromatous leprosy proven

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to be dapsone resistant (Pattyn *et al.*, 1979). It was then decided to conduct a dapsone-resistance survey among the remaining patients from this population.

Materials and methods

Starting in early 1979, smears were prepared from both earlobes and the nasal mucosa of all originally multibacillary patients treated for more than 5 years. If the bacterial index (average of the three smears) was 2 or more, a possibly active skin lesion was biopsied and sent on ice by air to the Institute for Tropical Medicine, Antwerp, where the bacilli, if present in sufficient numbers, were inoculated into mouse foot pads and screened against a full range of dapsone concentrations in the mouse diet: 0.1%, 0.001% and 0.0001%. Concentrations were checked for each new batch of food.

At 6 months after inoculation a control mouse was examined. If the count reached 5.10^5 acid-fast bacilli per foot, 4 more control mice were examined and 5 mice of each of the drug-treated groups. If in the control group no or insufficient multiplication was observed at 6 months, new harvests were performed at 7–9 and 12 months.

Results

Of the 105 originally multibacillary patients living in the village, who had a BI $\geqslant$ 2, 12 were biopsied. Five of these biopsies were not inoculated into mice because in smears prepared from the suspensions only 1–5 acid-fast bacilli (AFB) were observed. Six biopsies contained a mean of 6.10^7 AFB per gram of tissue (range $3.7\ 10^7 - 1.10^8$) and a seventh $9.2\ 10^5$ AFB per gram of tissue. These were inoculated into mouse foot pads. Table 1 shows the results. Bacilli from the biopsy with the lower bacterial load did not multiply in the control mice. One strain was fully dapsone sensitive. No low-grade resistance, e.g. multiplication only in mice fed dapsone at 0.0001% in the diet and in the controls, was observed; 3 strains were resistant to the 0.001% and 2 strains to the 0.01% dapsone concentration. In some instances only part of the mice fed a given concentration of dapsone showed bacterial multiplication with scores of 2 or 3 positive mice out of 5 examined. This points to the existence in the biopsy specimen of mixed populations of sensitive and resistant bacteria to the particular concentration of dapsone. For the final analysis these results were interpreted as resistant.

Discussion

In this study the primary selection of patients was based on the results of the bacteriological examination of the earlobes and the nasal mucosa. This resulted

Table 1. Results of mouse foot-pad tests for dapsone resistance in 7 patients

Degree of resistance	Number	Mean BI	Duration of therapy (yrs)	
			Mean	Range
Resists dapsone 0.01% in mouse diet	2	4.5	22	15–29
Resists dapsone 0.001% in mouse diet	3	4.5	20	10–26
Sensitive to dapsone 0.0001% in mouse diet	1	4		22
No multiplication of *Mycobacterium leprae*	1	3		28

in the discovery of 12 patients revealing a BI $\geqslant 2$ (in fact of 4–4.5, see Table 1), 5 of which harboured dapsone-resistant *Mycobacterium leprae* in their skin.

Clinical examination of these patients at the end of 1979 revealed that all showed relapsing skin lesions. It is impossible to know when these clinical relapses started. These patients present themselves more or less regularly to the out-patients clinic to collect their drug, and certainly their relapsing lesions were not noted by the paramedical worker responsible. At the end of 1979, 3 patients, the two with high dapsone-resistant *M. leprae* and one of those with intermediate resistance (3 positive mice out of 5 fed 0.001% dapsone), had multiple small skin nodules. The two remaining patients had solitary skin lesions. It was furthermore noted that all the relapsing lesions had a rose to red colour, whereas normally lepromatous lesions on a black skin are black.

The patients whose skin biopsy contained only very few AFB, and were therefore not inoculated into mice, had a BI lower than the skin biopsy positive group: mean 2.8, range 2–3.5, they had been treated for 5, 6, 8, 20 and 20 years respectively. Examination of these patients in December 1979 did not reveal any active skin lesions. It would have been interesting to isolate in mice the bacilli excreted through the nose.

The patient with dapsone-sensitive *M. leprae* had a BI of 4 and had been treated since 1957. The patient whose bacilli did not multiply had a BI of 3 and had been treated for 28 years (Table 1). The only explanation possible is that both must have stopped their treatment for some time in the past, the second having restarted his treatment some months before the biopsy was taken. Since no urine tests to detect dapsone were performed it is impossible to support this hypothesis.

The shortest incubation time for the appearance of resistance was 10 years after the start of treatment, 2 occurring within 15 years and 3 between 15 and 29 years. All the patients had received dapsone injections once every 2 weeks, 1.25 g in chaulmoogra oil since 1971–72, and dapsone tablets distributed once every 2 weeks since 1977–78. Examination of the files, taking into account the injections of dapsone only, allowed to calculate that on an average 56% of the drug had been administered with a range of 41–67%. For comparison, regularity of treatment was calculated in the same way for 10 randomly selected patients treated for more than 10 years but showing no evidence of

relapse or drug resistance, the percentage of drug administered in this group was on the average 45% with a range of 27–58%.

There was no significant difference in the bacterial indices nor in the duration of treatment between the fully resistant (0.01% dapsone in the diet corresponding to the administration of 100 mg to man) and the medium-resistant strains (see Table 1).

Two patients, one with fully resistant and one with sensitive *M. leprae* had belonged in 1958 to an experimental group (described by Languillon & Clary, 1959) who had been given a combination of dapsone and thiosemicarbazone injections for an unknown period.

The prevalence of dapsone resistance among this population, taking into account the one case studied previously (Pattyn *et al.*, 1979), is 5.7% and should be compared with figures obtained elsewhere: 2.5% in Malaysia (Meade *et al.*, 1973), 6.8% in Costa Rica (Peters *et al.*, 1976), 3.7% in Israel (Levy *et al.*, 1977), 3% per year in Ethiopia (Pearson *et al.*, 1976). Our results do not allow a calculation of the incidence of dapsone resistance. Compared with the other prevalence studies mentioned, it seems that in the population studied, resistance developed after longer incubation times. It is possible that this is the result of the year-long practice of dapsone injections, which produce discontinuously high peaks of serum dapsone levels (Schneider *et al.*, 1959). Pearson *et al.* (1979) showed evidence that patients with various levels of dapsone resistance were still improving clinically for several years when given injections of dapsone (375 mg once weekly).

It should also be mentioned that the technique of patient selection followed in the present study may not have detected some early cases of dapsone resistance if resistant relapses start as solitary skin lesions from where bacilli invade the whole body producing, at a later stage only, high BI values in ear lobes and nasal mucosa. This point deserves further study.

Our results also illustrate the need for additional training of the paramedical workers for the earlier detection of relapses and clinical suspicion of dapsone resistance.

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