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Further Data on the Effect of Ethionamide and Prothionamide in Experimental Leprosy

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Experiments carried out in mice using intermittent administration of ethionamide and/or prothionamide indicate that the efficacy of these drugs are substantially impaired if they are given less frequently than 3 times a week. Irregular administration of these drugs could lead more rapidly to the emergence of resistance than is the case for dapsone. Results of the total minimal inhibitory test show that treatment of paucibacillary leprosy with prothionamide during 9 or 12 weeks can be envisaged.

Introduction

Ethionamide (α-ethyl thioisonicotinamide) and more recently prothionamide (α-propyl thioisonicotinamide) have been quite extensively used as second-line drugs in the treatment of tuberculosis. Using the proportional bactericidal test, Colston, Hilson and Banerjee (1978) have demonstrated that when either drug is fed to mice for 45 days at 0.1% in the diet, 98.6% of the inoculated leprosy bacilli were killed. This proportion is only surpassed by rifampicin.

The commercial production of ethionamide has now been discontinued, since prothionamide was found to be as active against *Mycobacterium tuberculosis* as ethionamide but better tolerated in man (Chambatte *et al.,* 1965; Martin-Lalande *et al.,* 1966; Lesorbre *et al.,* 1968; Mycskowska-Wilska and Pawelc, 1968; Glatthaar and Van Der Merwe, 1970). Against *Mycobacterium leprae* the 2 drugs have also an identical activity (Colston *et al.,* 1978*a*). In this paper the results of ethionamide-prothionamide in intermittent therapy and the total minimal inhibitory test are presented. Ethionamide was used at the start of the experiments, and it was replaced by prothionamide when ethionamide was no longer available.

Material and Methods

M. leprae strain 17547 isolated in our laboratory was used (Pattyn *et al.,* 1972) and mice inoculated with 5.10^3 bacilli. Treatment started 3 weeks post-infection. When ethionamide or prothionamide were given for periods of more

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than 2 consecutive days, they were administered in the diet at a concentration of 0.1%. For regimens once, twice or thrice weekly drug administration, it was given by gastric cannula, 0.25 mg per mouse.

When multiplication in untreated control mice had reached 5.10^5 bacilli per footpad, the drug treated animals were killed and footpads examined for the presence of acid-fast bacilli.

Results

(A) INTERMITTENT ADMINISTRATION OF ETHIONAMIDE-PROTHIONAMIDE

As shown in Table 1 control treatment with continuous prothionamide inhibited completely the growth of *M. leprae* strain 17547. All intermittent regimens except the one of 3 administrations per week, were only partially active.

TABLE 1
Effect of intermittent administration of ethionamide prothionamide on the multiplication of M. leprae

Controls continuous treatment†	0/9*	A
3 days p. week‡	0/4	A
2 days p. week‡	5/10	P
1 day p. week‡	4/6	P
1 day every 2 weeks†	4/6	P
1 day every 3 weeks†	4/7	P
1 day every 4 weeks†	3/6	P
1 week every 3–4–6–8 and 12 weeks†	all positive	I

* Number of footpads positive/number of footpads harvested.
† Ethionamide given during initial 64 days, followed by prothionamide.
‡ Prothionamide.
A = active; P = partially active; I = inactive.

(B) TOTAL MINIMAL EFFECTIVE DOSE

Table 2 shows the results of treatment during 6–9 or 12 weeks. Clearly a 6-week treatment resulted only in a growth delay, whereas a 12-week treatment, was sufficiently bactericidal to result in absence of multiplication during the following 16 weeks of observation.

Discussion

Ethionamide-prothionamide are after rifampicin the most potent bactericidal antileprosy drugs. They are however rapidly excreted, and serum levels only exceed the MIC for about 24 h (Colston *et al.*, 1978*b*). We have previously shown that the efficacy of rifampicin in the mouse is still maintained when administered intermittently once every week, once every 2 weeks and even once every 4 weeks provided the dose administered is 2.5–10 times the

TABLE 2
Total minimal effective dose of ethionamide prothionamide

Duration of treatment	At plateau*	Plateau + 16 weeks†
Controls, untreated	12/12	
6 weeks	0/3	5/9
9 weeks	0/3	0/9
12 weeks	N.E.‡	0/9

* When bacterial multiplication reached 5.10^5 bacilli per footpad in the control mice.
† 16 weeks later.
‡ Not examined.

MED (Pattyn and Saerens, 1974). The efficacy of once weekly administration of rifampicin in man has also been studied (Pattyn *et al.*, 1975). In this experiment with prothionamide, the drug was administered at 10 to 3 times the MED, but intermittency could not be lowered beneath 3 administrations per week. This is unfortunate because there may be an advantage in supervised weekly intermittent treatment. The results of the intermittent experimental therapy with prothionamide and the studies of Colston *et al.* (1978*b*) suggest that irregular treatment with this drug could lead more rapidly to the emergence of resistance than with dapsone. In the total minimal inhibitory test, mice were followed for 16 weeks after the plateau phase of multiplication was reached in the control group. Although this length of follow-up could be too short to prove definitely complete sterilization of the infection, it is certainly reduced to such low levels that can be taken care of by the existing immunological defences in the paucibacillary human patient. It is generally accepted that in almost all infections chemotherapy does not kill absolutely all parasites, but that a minimal surviving fraction is eliminated by the host defence mechanisms. Only in the lepromatous patient with his immune deficiency should chemotherapy aim at a complete sterilization of the infection. It can therefore be concluded from the present results that 3–6 months prothionamide treatment courses (500 mg daily) of paucibacillary leprosy should be considered: previous experiments showed that a short course treatment of a paucibacillary infection with dapsone (Pattyn, 1977) was insufficiently bactericidal.

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