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Letter to the Editor

Cross-resistance Amongst Thiambutosine, Thiacetazone, Ethionamide and Prothionamide with *Mycobacterium leprae*

Thiambutosine and thiacetazone have been quite widely used in the treatment of leprosy, and the rapid emergence of thiambutosine- or thiacetazone-resistant *Mycobacterium leprae,* when the drugs are used in monotherapy, has been well documented (Davey, 1960; Rees, 1967*a*, *b*; Garrod and Ellard, 1968; Waters, Pearson and Rees, 1976). The use of the thioamides ethionamide and prothionamide for the treatment of leprosy has been much less extensive, but in the search for alternative drugs for use in combined drug therapy, interest in these compounds has been renewed (Colston, Ellard and Gammon, 1978). In view of the several reports of cross-resistance with *M. tuberculosis* between thiacetazone and ethionamide (Rist, Grumbach and Libermann, 1959; Bartmann, 1960; Grosset and Benhassine, 1970), it was important to establish whether such a phenomenon exists for *M. leprae.*

Five strains of *M. leprae* were tested for sensitivity to ethionamide, prothionamide, thiambutosine and thiacetazone. Strains L25 and L30 were obtained from patients in North Africa who had relapsed during treatment with ethionamide (Pattyn *et al.,* 1975). Strains 144/62, L21 and 22491, had been shown to be resistant to thiambutosine by mouse footpad testing. These strains of *M. leprae* were inoculated into the left hind footpads of mice and the 4 drugs administered at a dietary concentration of 0.1%. When counts of *M. leprae* in control mice had reached a maximum, drug-treated mice were examined histologically for bacillary growth. In the case of strains L25 and L30, bacillary growth was determined on the basis of counts of total numbers of AFB per footpad. The results are shown in Table 1.

The two strains which were clinically resistant to ethionamide (L25 and L30) were found to be resistant also to prothionamide, thiacetazone and thiambutosine. The 3 thiambutosine-resistant strains, however, were sensitive to prothionamide, and strain L21 was also sensitive to thiacetazone.

For *M. tuberculosis,* cross-resistance between the thioamides and thiacetazone is two-way, at least for strains developing resistance *in vivo* (Bartmann, 1960; Grosset and Benhassine, 1970). Cross-resistance between ethionamide and prothionamide is to be expected since the parts of the molecules responsible for antibacterial activity are identical. Thiambutosine and thiacetazone are also closely related compounds, and cross-resistance is shown by both *M. leprae* and *M. tuberculosis* (Rees, 1967*a*, *b*). Of the small number of strains available for this study, ethionamide-resistant strains (L25 and L30) were also resistant to thiacetazone and thiambutosine, whereas thiambutosine-resistant strains (144/62, L21 and 22491), although not tested

TABLE 1

Sensitivity of thiambutosine- and ethionamide-resistant strains of M. leprae *to thiambutosine, thiacetazone, ethionamide and prothionamide*

Strain of *M. leprae*	Drug treatment				
	Control	Thiambutosine (0.1%)	Thiacetazone (0.1%)	Ethionamide (0.1%)	Prothionamide (0.1%)
L25*	6/6§	6/6	6/6	6/6	6/6
L30*	6/6	6/6	6/6	6/6	6/6
144/62†	6/6	6/6	NT	NT	0/7
L21†	6/6	2/3	0/7	NT	0/9
22491†	9/9	4/8	NT	NT	0/5

*Strains from patients clinically resistant to ethionamide.

†Strains demonstrated to be resistant to thiambutosine by mouse footpad testing. Strains 144/62 and 2249 were isolated from old "lepromatous" cases and details of treatment were not available; patient L21 had been treated for 1 year with thiambutosine.

§Number of footpads showing growth of *M. leprae*/number of footpads harvested.

NT, Not tested.

against ethionamide, were sensitive to prothionamide. This suggests that development of resistance to these drugs is a penicillin-type (multiple-step) process, and that the first step is a small one. The ratio of peak serum level to MIC for thiambutosine is much lower than that for thiacetazone, ethionamide and prothionamide (Colston *et al.*, 1978; Colston, Ellard and Gammon, 1978), thus even a small decrease in sensitivity would result in clinical resistance to thiambutosine, but not necessarily to thiacetazone, ethionamide or prothionamide. On the other hand, the decrease in sensitivity required for clinical resistance to ethionamide would certainly result in resistance to thiacetazone and thiambutosine.

This demonstration of cross-resistance with *M. leprae* amongst thiambutosine, thiacetazone, ethionamide and prothionamide emphasizes that these drugs should be considered as alternatives to each other when devising antileprous drug regimens, and that where past treatment with one of the drugs is known to have occurred, sensitivity testing in the mouse footpad is advisable when considering one of the drugs for inclusion in a treatment regimen.

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