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THE BACTERICIDAL EFFECT OF RIFAMPICIN ON M. leprae IN MAN: a) SINGLE DOSES OF 600, 900 AND 1200 mg; AND b) DAILY DOSES OF 300 mg.

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Rifampicin has been shown to be a potent bactericidal agent that is extraordinarily effective in the treatment of patients with multibacillary (LL, LI and BL) leprosy in terms of the rate at which M. leprae are rendered non-infective for mice (1-4). We had previously shown that rifampicin, in a single 1500 mg dose or in a daily dosage of 600 mg, reduced the proportion of infective organisms to less than 1 per 1000 within three or four days (3). The purpose of this study was to measure the rate at which M. leprae were rendered non-infective for mice after the administration of smaller single doses of rifampicin -- 1200, 900 and 600 mg, and during treatment with a smaller daily dose -- 300 mg.

The methods were much the same as those we have used in previous trials. For the comparison of three single doses of rifampicin, previously untreated patients with multibacillary leprosy who volunteered to participate were given at random a single dose of 600, 900 or 1200 mg rifampicin by mouth. No other antimicrobial treatment was administered for one week. Skin biopsy specimens obtained before treatment and again after 3 or 4 and 7 days were used to inoculate mice. For the second trial, previously untreated patients with multibacillary leprosy were treated with 300 mg rifampicin daily for two weeks. Skin biopsy specimens were obtained for mouse inoculation before treatment and at intervals of 3 or 4, 7 and 14 days during treatment. As in our earlier trials, patients were treated in San Francisco; skin biopsy specimens were shipped by air on wet ice to Atlanta, where mice were inoculated.

The results of these trials are summarized in Table 1. As shown in the first row of this table, the administration of a single 1500 mg dose of rifampicin in a trial already reported (3) rendered all of the inocula non-infective for mice. As shown in the next three rows, no mice were infected by inocula prepared from the specimens of five patients given 1200 mg rifampicin in a single dose, whereas the organisms recovered from three specimens obtained from patients administered single doses of 900 or 600 mg multiplied in mice. In all three cases, the multiplication was scored "plus-minus". That is, a monthly section was positive, whereas no evidence

TABLE 1. Rate of killing of M. leprae after rifampicin administration.

Dose of Rifampicin (mg)	Mouse Results for Specimens Taken on Day No.									
	0		3-5			7-9			11-15	
	+	-	+	±	-	+	±	-	+,±	-
1500	14				14			9		13
1200	5				5			5		
900	4			1	3		1	3		
600	6			1	5			6		
600 daily	15				4			13		14
300 daily	12		3		5	2		7		8

TABLE 2. Analysis of results.

A. Rifampicin Dose	Number of Patients: Mouse Results After 3 to 5 and 7 to 9 days ±	-	Total
1500 mg 1200 mg	0	33	33
900 mg 600 mg	3	17	20
TOTAL	3	50	53

P = 0.049

B. Rifampicin Dosage	Mouse Results After 3 to 5 and 7 to 9 days +	-	Total
600 mg/day	0	17	17
300 mg/day	5	12	17
TOTAL	5	29	34

P = 0.022

of multiplication was found in harvests performed subsequently from the same groups of mice. This kind of result suggests that only some of the inoculated mice received the minimal infective dose of M. leprae, indicating that the inocula contained barely detectable proportions of infective organisms. Combining the results for the 3 to 5 day and 7 to 9 day specimens for the larger and smaller doses yields the 2 x 2 table shown in the upper panel of Table 2. Calculation of the exact probability demonstrates that this distribution may be encountered by chance with a probability less than 0.05; therefore, killing of M. leprae is more rapid after single doses of 1200 and 1500 mg rifampicin than after single 600 and 900 mg doses.

As shown in the fifth row of Table 1, rifampicin in a daily dose of 600 mg was fully effective in a trial already reported (3), in that no biopsy specimen was found to contain a proportion of infective M. leprae sufficient to multiply in mice. On the other hand, the incomplete results of a trial of 300 mg rifampicin daily, shown in the last row, demonstrate that the organisms from five of 17 specimens obtained between 3 and 9 days after beginning treatment multiplied in mice. The analysis of these results, shown in the lower panel of Table 2, is consistent with the conclusion that M. leprae are killed more rapidly during treatment with 600 mg rifampicin daily than with 300 mg daily.

In summary, we have shown that rifampicin in a single dose of 1200 mg is about as effective as a single dose of 1500 mg or a daily dose of 600 mg. Single doses of 900 and 600 mg and a daily dose of 300 mg are somewhat less rapidly effective in terms of the rate at which M. leprae are killed. Even the less effective regimens are very effective, however, in that the proportion of infective organisms fell to undetectable levels within one or two weeks after initiating treatment, an end-point achieved only after treatment with dapsone for three months (5).

Two obstacles to the wide use of rifampicin in the treatment of leprosy patients are the great expense of the drug and the toxicity associated with intermittent administration. The results of this study suggest that rifampicin may be administered in a daily dose smaller than 600 mg without important loss of efficacy, permitting the use of less expensive daily regimens. The toxicity of intermittently-administered rifampicin appears to be dose-dependent; significantly less toxicity is associated with 600 and 900 mg doses than with doses of 1200 mg or larger (6). Our demonstration that individual 600 and 900 mg doses are not much less effective than larger doses suggests that the use of these smaller doses may provide effective intermittent regimens that are less toxic than those using larger doses.

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