Minimal Inhibitory Concentrations of Lomefloxacin and Minocycline Against Drug-Sensitive and Drug-Resistant Isolates of *M. tuberculosis* Compared on L-J and 7H11 Media

TO THE EDITOR:

Rifampin derivatives, ß-lactam antibiotics with ß-lactamase inhibitors, and fluoroquinolones are the newer and highly promising drugs against tuberculosis. Among them, little is known about the activity of lomefloxacin, a new difluoropiperazinyl quinolone ([10, 11, 14]), and minocycline, a long-acting tetracycline derivative, against *Mycobacterium tuberculosis.* Minocycline has been studied with respect to its effect on *M. leprae* only ([4, 6–8]).

In the present study, we have tested a total of 97 *M. tuberculosis* strains for their susceptibility to lomefloxacin and minocycline by the minimal inhibitory concentration (MIC) method using both Lowenstein-Jensen (L-J) medium and 7H11 medium to see if the high protein content of L-J medium would have any effect on the MICs. The strains tested included 46 *M. tuberculosis* strains resistant to S (streptomycin) H (isoniazid) R (rifampin) /HR and 51 susceptible to SHR isolated from patients. Their susceptibility to ciprofloxacin

TABLE 1. *Frequency distribution of MICs of lomefloxacin on L-J and 7H11 against 46 drug-resistant (SHR/HR) and 51 drug-sensitive (SHR) strains of* M. tuberculosis.

MIC μg/ml	L-J		7H11	
	No. SHR/HR res. strains	No. SHR sens. strains	No. SHR/HR res. strains	No. SHR sens. strains
0.5	0	0	0	0
1.0	0	0	0	0
2.0	1	2	5	5
4.0	11	8	14	18
8.0	16	23	13	14
16.0	17	18	14	14
32.0	1	0	0	0
Total	46	51	46	51

and ofloxacin had been determined previously in our Centre ([17]).

Lomefloxacin (Torrent Phamaceuticals) and minocycline [Cyanamid of Great Britain Limited (Lederle), kindly provided by Dr. M.D. Gupte, Officer-in-Charge, CJIL Field Unit, Avadi] at the final concentrations of 16.0, 8.0, 4.0, 2.0, 1.0, 0.5 and 0.25 μg/ml, and 64, 32, 16, 8, 4, 2 and 1 μg/ml, respectively, were tested in L-J medium and 7H11 medium containing oleic acid-albumin-dextrose (OADC) enrichment using standard procedures. The inoculated media were incubated at 37°C with the 7H11 plates kept in 5% CO_2, and read at the end of 4 weeks. The lowest concentration of the drug which inhibited growth to <20 colonies compared to at least ++ (numerous discrete colonies) growth on drug-free medium was taken as the minimal inhibitory concentration (MIC).

RESULTS AND DISCUSSION

Lomefloxacin. The MIC for the standard *M. tuberculosis* strain H37Rv was 4 μg/ml on L-J and 2 μg/ml on 7H11. For the other strains, the range of MICs was 2–32 μg/ml on L-J and 2–16 μg/ml on 7H11 (Table 1). A highly significant difference between the mean MICs of lomefloxacin on L-J and 7H11 was observed, MICs being generally higher on L-J. Of the 46 resistant strains, 16 had the same MICs on L-J and 7H11, 22 had higher MICs on L-J and only 8 had lower MICs on L-J (Table 2). Similarly, of the 51 sensitive strains, 21 had the same MICs on L-J and 7H11, 23 had higher MICs on L-J while only 7 had lower MICs on L-J. The geometric mean MICs for SHR/HR-resistant and SHR-sensitive strains were 0.84 and 0.82, respectively, on 7H11, and 0.94 for both resistant and sensitive strains on L-J. The differences in MICs on L-J and 7H11 were highly significant for both resistant and sensitive strains together ($p = 0.0013$), for resistant strains alone ($p = 0.0209$) and for sensitive strains alone ($p = 0.0251$). It has been reported earlier that the MICs of quinolones (norfloxacin, perfloxacin, ciprofloxacin and ofloxacin) may not vary much when the agar or broth dilution methods are used ([15]).

Fluoroquinolones have promising *in vitro* activity and low toxicity and no crossresistance has been reported between fluoroquinolones and other anti-tuberculosis drugs ([12]). In earlier studies comparing the activities of different fluoroquinolones, the activity of lomefloxacin has either been less ([10]) or has compared favorably ([14]). In the present study, the MICs of lomefloxacin (geometric mean MIC 0.94) were significantly higher than those of ciprofloxacin

TABLE 2. *Comparison of the MICs (μg/ml) of lomefloxacin on L-J and on 7H11 media.*

MIC on 7H11	MICs on L-J											
	SHR/HR-resistant strains						SHR-sensitive strains					
	2	4	8	16	32	Total	2	4	8	16	32	Total
2	0	5	0	0	0	5	1	2	2	0	0	5
4	1	2	7	5	0	15	0	4	10	4	0	18
8	0	2	6	4	0	12	0	2	7	5	0	14
16	0	2	3	8	1	14	1	0	4	9	0	14
Total	1	11	16	17	1	46	2	8	23	18	0	51

(geometric mean MIC 0.3) and ofloxacin (geometric mean MIC 0.3) on L-J for the same strains reported in an earlier study from this Centre ([17]). The MIC ranged from 2–16 μg/ml for lomefloxacin compared to 1–4 μg/ml for ciprofloxacin and ofloxacin for the same strains. However, these concentrations of lomefloxacin are probably within the levels achieved in tissues and macrophages because of its pharmacokinetic features, which include a high degree of tissue distribution, a lack of significant metabolism, good oral absorption, long serum half-life, good tolerance on oral administration, and high tissue and intracellular concentrations ([1, 2, 3, 5, 9, 13]). Thus, the activity of lomefloxacin against *M. tuberculosis* merits further study.

Minocycline. The MIC of minocycline was >64 μg/ml for all of the strains tested both on L-J and 7H11. There was more than 1+ growth (>100 colonies) of all the strains tested even at the concentration of 64 μg/ml of minocycline, indicating no activity at all of this drug at these concentrations against the *M. tuberculosis* strains tested. There is to date very meager information on the activity of minocycline against mycobacteria other than *M. leprae*. In an earlier report, of 5 *M. tuberculosis* strains tested, 4 were inhibited at 6.5 μg/ml, and all 5 at 12.5 μg/ml when Ogawa egg medium was used ([16]). The serum level is about 2 g/ml after a single oral dose of 150 mg of minocycline. Thus, the results of the present study suggest that minocycline may not be useful in the treatment of tuberculosis.

SUMMARY

The *in vitro* activity of lomefloxacin and minocycline was tested against 46 strains of *M. tuberculosis* resistant to streptomycin (S), isoniazid (H) and rifampin (R) or SHR and 51 strains sensitive to SHR by the minimal inhibitory concentration (MIC) method on two different media, namely, Lowenstein-Jensen (L-J) and Middlebrook 7H11. The results of the study showed that, irrespective of the medium used, minocycline had little activity against the strains tested and the MIC was >64 μg/ml. The MIC of lomefloxacin in 7H11 medium ranged from 2 to 16 μg/ml. There were highly significant differences in the MICs of lomefloxacin in L-J compared with 7H11. The results suggest that the activity of lomefloxacin against *M. tuberculosis* merits further study.

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