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Ciprofloxacin (4-quinolone) and *Mycobacterium leprae*

D K BANERJEE
Department of Medical Microbiology, St George's Hospital Medical School, London SW17 0RE

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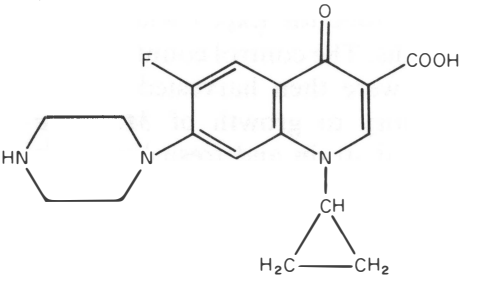
Summary A new synthetic antimicrobial agent, ciprofloxacin (4-quinolone compound), active against a wide variety of bacteria including *Mycobacterium tuberculosis* was tested in the mouse footpad system against *M. leprae*. At doses tested, ciprofloxacin was found to be ineffective in suppressing the growth of *M. leprae*.

Introduction

Dapsone has been the mainstay of treatment of leprosy for over 40 years especially in areas where the disease occurs most commonly. Other more active bactericidal drugs have been introduced during the last 15 years but these are much more expensive for use in national programmes and some like clofazimine cause unsightly skin pigmentation problems. Dapsone resistance, both secondary and primary, is now posing a real threat to the control programmes and a search for new, safe and cheap compounds including development of new bactericidal drugs has been strongly emphasized.[1] A new group of synthetic quinolone compounds related to nalidixic acid has recently been developed, some of which have been found to be actively bactericidal against a wide variety of Gram-negative and Gram-positive organisms.[2] Most active amongst these, so far, is ciprofloxacin (see below).



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This, in common with other 4-quinolone compounds, acts by interfering with DNA gyrase (topoisomerase) enzymes which are needed to supercoil strands of DNA in order to fit these long filaments in the bacterial cell.[3] Ciprofloxacin also affects RNA synthesis at higher concentrations. In *in vitro* studies ciprofloxacin has been found to be inhibitory to the growth of *M. tuberculosis*.[4] A further quinolone, ofloxacin was found to have similar antimycobacterial activity *in vivo*[5] but was markedly less active in treatment-failure cases of cavitary tuberculosis with a high incidence of resistance development during treatment.[6] In preliminary *in vitro* studies in our laboratory, ciprofloxacin has also been found to have bactericidal activity against *M. tuberculosis* (unpublished data) and the present work describes experiments to determine activity of this compound against *M. leprae* in the mouse footpad.

Materials and methods

Two strains of *M. leprae* were used in this study, 1 (Experiment 1) isolated from an untreated lepromatous leprosy patient and subsequently found to be dapsone sensitive and the other (Experiment 2) a mouse passage dapsone-sensitive strain. The detailed methods of mouse inoculation, assessment of bacillary growth in footpad homogenates, and drug–diet preparation have been previously described.[7–9] In brief, 5000 acid-fast bacilli were inoculated in 20 μl volume into the hind footpads of groups of mice. The drug was administered in dosages of 0·01%, 0·001% and 0·0001% (wt/wt) mixed with powdered mouse food from day 30 to day 90 in Exp. 1 and from day 45 to day 105 in Exp. 2 following the kinetic method.[10] When the bacillary numbers had reached about 5×10^5 in the control animals, groups of three mice were harvested from the drug-treated groups, the footpads from these mice were homogenized, slides prepared, stained and counted by an established technique.

Results

Bacterial count in the untreated control mice in Exp. 1 reached $3{\cdot}5 \times 10^5$ after 6 months but only $1{\cdot}5 \times 10^5$ in Exp. 2 (mouse passage strain). Treated animals were therefore harvested at this time for Exp. 1 while a further control harvest was made for Exp. 2 at 9 months. The control count in Exp. 2 at this time was 8×10^5 and the treated animals were then harvested also. Neither concentration of ciprofloxacin was inhibitory to growth of *M. leprae* in the mouse footpad (Figure 1). Mouse-passaged strain and fresh human isolate behaved similarly. There was a slight reduction in the numbers of acid-fast bacilli at the highest concentration in Exp. 1, but was not considered significant. No acute or chronic toxic manifestations were observed at any drug concentrations.

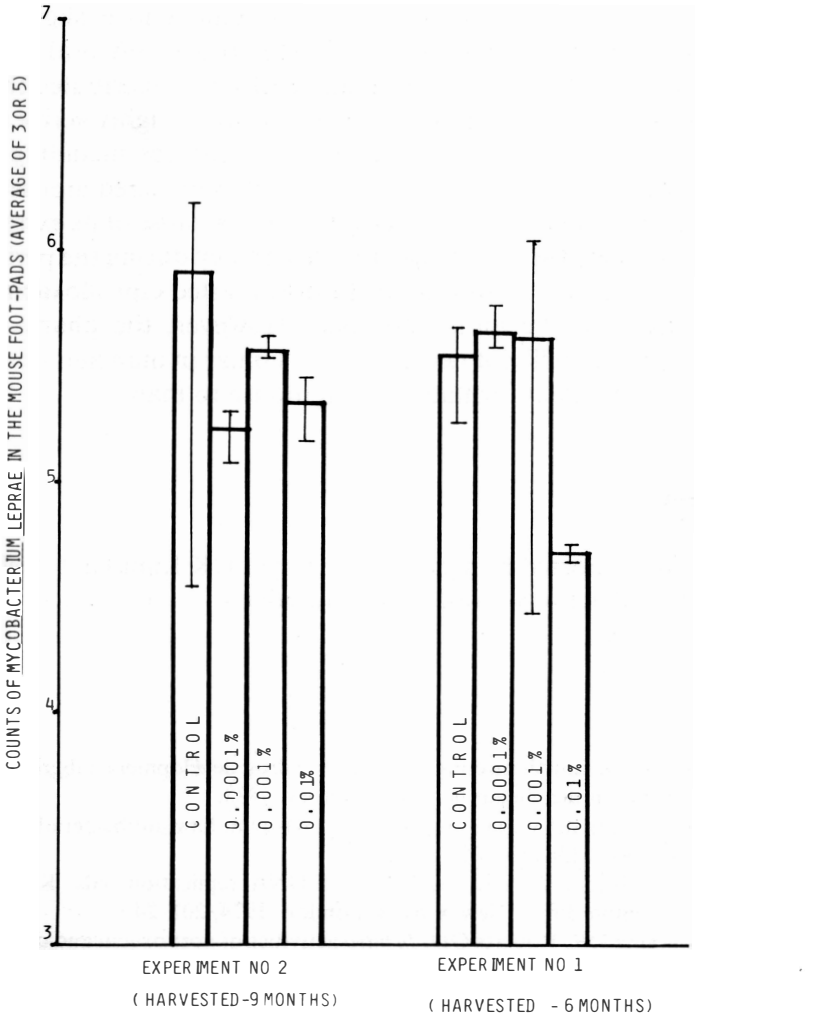

Figure 1. Effect of graded dosages of ciprofloxacin on *Mycobacterium leprae* infection in the mouse footpad. Ciprofloxacin was given for a limited period of 60 days starting 30 days after infection in Exp. 1 and 45 days after infection in Exp. 2.

Discussion

Despite its antibacterial activity against *M. tuberculosis* in *in vitro* studies, ciprofloxacin failed to inhibit growth of *M. leprae* in the mouse footpad. This is not entirely unexpected as antitubercular drugs are known to produce variable effects on *M. leprae*. Antileprosy drugs like dapsone and clofazimine, have no effect on the growth of *M. tuberculosis* while rifampicin is equally active against both organisms. The highest level of the drug, i.e. 0·01% used in this study was

equivalent to 1·5 g of the drug for a 60-kg human. This is slightly in excess of manufacturer's recommended dose, i.e. 500 mg twice daily orally in tablet form. The drug is well absorbed from the gut and uniformly distributed throughout the body (manufacturer's information). Ciprofloxacin is highly stable in acid and in aqueous solution it is stable at different temperatures including 37°C. In the present experiment ciprofloxacin was mixed with powdered mouse food, enough for about 2 weeks, and left at room temperature. Because of its extreme stability it seems highly unlikely that the drug will lose potency during the period of storage. It can therefore be concluded that at the doses tested ciprofloxacin is ineffective against *M. leprae* in the mouse footpad. However, the pharmacokinetics of ciprofloxacin in mice will not necessarily be similar in man and it is therefore not possible to extrapolate information from mouse to man.

Acknowledgment

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