Activity against *M. Leprae* of Lincomycin and Two Derivatives, of Amicetin, Phosphonomycin and Two Derivatives of Tetrahydronaphthylaminopropylpiperidine[1]

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In continuing studies of drugs against *Mycobacterium leprae* in mice we have tested the following compounds: lincomycin, clinimycin (7-(S)-chloro-7-deoxylincomycin, clindamycin), U-24729A (4′-pentyl-N-demethyl-7-chlorolincomycin), amicetin, phosphonomycin, ABT-29666 (1-{3-[4-(p-chlorophenyl-azo)-5, 6, 7, 8-tetrahydro-1-naphthylamino] propyl} piperidine), ABT-38396 (1- {3-[4-(6-methoxy-3-pyridyl-azo) 5, 6, 7, 8-tetrahydro-1-naphthylamino] propyl} piperidine).

MATERIALS AND METHODS

The methods have been described ([7,-8]). In brief, the drugs were administered for a limited period during the logarithmic phase of growth of *M. leprae* in mouse foot-pads. Activity against *M. leprae* is manifested as a delay in the appearance of bacterial growth in the treated mice in comparison with the control mice. In this experiment, the time the growth curves passed $10^{5.4}$ was taken for the measurement of the delay. The drugs were all administered as additions to the diet in dosages thought to be near the maximum tolerated dosage.

RESULTS

The results are given in Figure 1 and Table 1. Only the two derivatives of lincomycin had any activity for *M. leprae*. The amount of growth delay was longer than the period of drug administration; this finding indicates that the anti-bacterial effect was more than simple bacteriostasis. Although growth did begin as soon as the drug was stopped (Figure 1), it appeared to occur at a slow rate and took longer to reach plateau levels. Nevertheless, the anti-bacterial effect was much less than that observed for the distinctly bactericidal drugs, dapsone, ethionamide, clofazimine, B1912, and especially rifampin.

TABLE 1. *Activities of several drugs against M. leprae in man.*

Drug[a]	Growth delay (days)
Lincomycin HCl, 0.1%	11
Clinimycin HCl, 0.1%	91
U–24729–A, 0.05%	178
Amicetin, 0.01%	0
ABT 29666, 0.01%	2
ABT 38396, 0.01%	0
Phosphonomycin, 0.3%	0

[a] The drugs were administered as additions to the diet in the concentrations shown from the 70th to the 133rd day after inoculation with *M. leprae*.

The results with amicetin, phosphonomycin, ABT-29666, and ABT-38396 were very similar to those with lincomycin; at each of the three intervals the counts of *M. leprae* were not significantly different from the control curve.

DISCUSSION

Lincomycin is an antibiotic active principally against gram-positive bacteria. Clinimycin and U-242729A are semi-synthetic derivatives of lincomycin with approximately 4- to 8-fold lower minimal inhibitory concentrations than lincomycin against sensitive organisms. Their activities are also greater against experimental infections in

1 Received for publication March 8, 1971.

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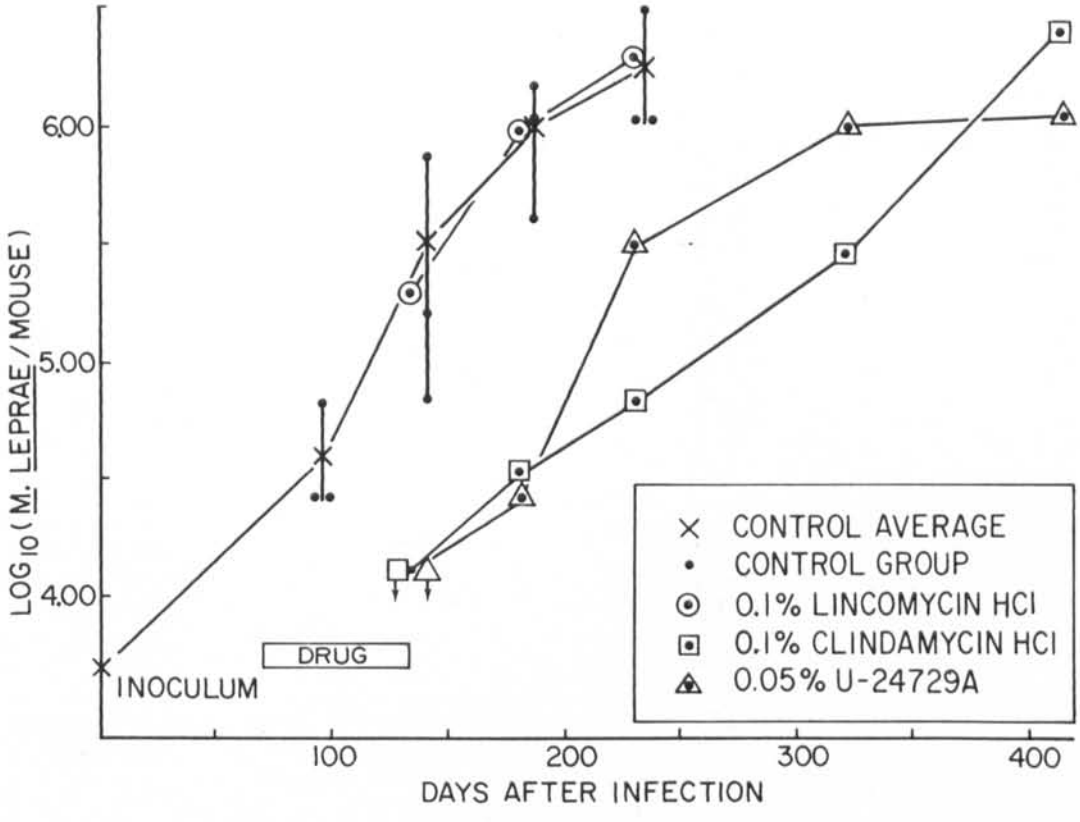

FIG. 1. Effect of lincomycin, clindamycin, and another lincomycin derivative (U-24729A) on the multiplication of *M. leprae* in mice. The drugs were administered in the diet in the indicated concentrations from the 70th to the 133rd day after infection.

mice ([6]). Presumably these derivatives act in the same way as lincomycin, by binding to the 50S subunit of the bacterial ribosome and thereby inhibiting the binding of aminoacyl SRNA ([1]).

Amicetin is an antibiotic with activity for gram-positive bacteria and mycobacteria ([3, 5]). It is active against *M. tuberculosis in vitro* and in mice. Phosphonomycin, a new antibiotic, is active against gram-positive and gram-negative bacteria and possesses very low toxicity ([4]). ABT-29666 and ABT-38396 are representatives of a group of synthetic compounds with activity for *M. tuberculosis in vitro* and *in vivo* ([9]). They are also effective in *M. lepraemurium* infections in mice ([2]).

The combined results again illustrate the difficulty in predicting a drug's action against *M. leprae* from its action against any other mycobacterium.

SUMMARY

Clinimycin and U-24729-A, two semisynthetic derivatives of lincomycin, were active against *M. leprae* in mice, but they were not distinctly bactericidal. The following compounds were not active: lincomycin, amicetin, phosphonomycin, and ABT-29666 and ABT-38396 (two derivatives of tetrahydronaphthylaminopropylpiperidine).

RESUMEN

La clinimicina y la U-24729-A, dos derivados semisintéticos de la lincomicina fueron activos contra el *M. leprae* en ratones, pero no fueron claramente bactericidas. Los siguientes compuestos no fueron activos: lincomicina, amicetina, fosfonomicina y ABT-29666 y ABT-38396 (dos derivados de la tetrahidronaftilaminopropilpiperidina).

RÉSUMÉ

Deux dérivés semi-synthétiques de la lincomycine, la clinimycine et l'U-24729-A, sont actifs contre *M. leprae* chez la souris; néanmoins, ils ne sont pas notablement bactéricides. Les composés suivants se sont révélés inactifs: la lincomycine, l'amicétine, la phosphonomycine, l'ABT-29666 et l'ABT-38396 (ces deux derniers produits étant des dérivés de la tétrahydronaphthylaminopropylpipéridine).

Acknowledgments. This work was supported in part by an interagency agreement with the National Institute of Allergy and Infectious Diseases, National Institutes of Health, under the U.S.-Japan Cooperative Medical Science Program. We are indebted to the following for supplies of the drugs: Dr. Joseph E. Grady and Dr. George B. Whitfield, the Upjohn Company, Kalamazoo, Michigan, for lincomycin, clinimycin, U-24729A, and amicetin; Dr. David E. Hendlin, Merck Institute for Therapeutic Research, Rahway, New Jersey for phosphonomycin; and Dr. Edward F. Elslager, Parke Davis and Company, Ann Arbor, Michigan.

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