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Efficacy of Clarithromycin versus That of Clindamycin for Single-Dose Prophylaxis of Experimental Streptococcal Endocarditis

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Clarithromycin is compared with clindamycin for single-dose prophylaxis of streptococcal endocarditis in rats. Human-like kinetics of the two antibiotics prevented endocarditis in animals challenged with both small and large amounts of bacterial inocula. Clarithromycin was marginally superior to clindamycin against small amounts of inocula. Clarithromycin may be considered for endocarditis chemoprophylaxis in human.

Most authorities recommend that patients with cardiac valve abnormalities take antibiotic prophylaxis before procedures that might induce bacteremia (3, 4, 16, 17). In the case of dental surgery, the recommendations include high doses of either oral amoxicillin, erythromycin, or clindamycin for penicillin-allergic patients (3, 4, 16, 17). Newer acid-stable macrolides produce more-prolonged antibiotic concentrations in the serum and fewer gastrointestinal side effects than erythromycin and clindamycin (18, 19) and thus might present some advantages for the prevention of streptococcal endocarditis. In our experiments, the new acid-stable macrolide clarithromycin was compared with clindamycin for single-dose prophylaxis of streptococcal endocarditis in rats. Clindamycin was utilized as a control because this drug is recommended both in the United States and in Europe for endocarditis prophylaxis for penicillin-allergic patients (3, 4, 16, 17).

Three previously described streptococcal isolates susceptible to erythromycin were used in the animals (Table 1) (5, 6). Bacteria were grown at 35°C either in brain heart infusion broth (Difco Laboratories, Detroit, Mich.) or on Columbia broth plates (Becton Dickinson, Cockeysville, Md.) supplemented with 3% blood. Clarithromycin was obtained from Abbott Laboratories Ltd. (North Chicago, Ill.), clindamycin was obtained from The Upjohn Company (Kalamazoo, Mich.), and erythromycin was obtained from Sigma Ltd. (St. Louis, Mo.). MICs and MBCs of the antibiotics were determined by a previously described broth macrodilution method (5, 15). Time-kill curves were determined in liquid cultures with 10^6 to 10^7 CFU/ml as the original inoculum amount (5). The antibiotics were added to the cultures at final concentrations approximating the peak drug levels in sera during prophylaxis for humans (see below). Samples of the cultures were appropriately diluted before plating, thus permitting the minimization of antibiotic carryover.

Sterile aortic vegetations were produced in rats as previously described (10). An intravenous line was inserted into the superior vena cava and connected to a programmable infusion pump to deliver the antibiotics (6). Bacterial endocarditis was induced 24 h after catheterization by intravenous challenge of the animals with 0.5 ml of saline containing either the minimal amount of inoculum producing endocarditis in 90% of untreated controls (the 90% infective dose [ID_{90}]) or 100 times the ID_{90}. Antibiotic prophylaxis was started 2 h before inoculation. The drugs were administrated at changing flow rates through the pump to simulate in rats the human kinetics in serum produced by an oral dose of 500 mg of clarithromycin or 600 mg of clindamycin. This drug administration required a total of 58.5 mg of clarithromycin per kg of body weight per 24 h and of 82.5 mg of clindamycin per kg per 12 h. The animals were sacrificed 3 days later, and quantitative cultures of the vegetations, the spleens, and the blood were performed. The limit of detection was ≥ 2 $\log_{10}$ CFU/g of tissue. Rats with sterile vegetations were considered uninfected. Bacteria recovered from infected vegetations were retested for the MIC of the prophylactic drug. Antibiotic levels in the serum were determined in groups of three to six rats by an agar diffusion method and with *Micrococcus luteus* ATCC 9341 as the indicator organism. The limits of detection were 0.08 mg/liter for clarithromycin and 0.3 mg/liter for clindamycin. Standard curves were linear ($r \geq 0.995$), and intraplate and interplate variations were $\leq 10\%$. No attempt was made to distinguish between the activity of clarithromycin and that of drug metabolites. Inhibitory titers in serum and bactericidal titers in serum were measured in groups of six rats as previously described (12). The incidence of valvular infection among treatment groups was compared by the χ^2 test with Yates' correction. All reported significant differences ($P \leq 0.05$) were determined by two-tailed tests.

Table 1 shows the MICs and MBCs of erythromycin, clarithromycin, and clindamycin for the three test organisms. MBCs were low except for *Streptococcus intermedius*. In time-kill experiments, peak levels in serum of either erythromycin (2 mg/liter) (11), clarithromycin (2 mg/liter) (2), or clindamycin (10 mg/liter) (7) could reduce the cultures' viable counts by ≥ 2 $\log_{10}$ CFU/ml/24 h (data not shown). Figure 1 depicts antibiotic concentrations in the sera of rats during simulation of the human kinetics produced by a single oral dose of 500 mg of clarithromycin or 600 mg of clindamycin (2, 7). Clarithromycin was detectable for ≥ 24 h after administration, whereas clindamycin became barely measurable after 12 h. Clarithromycin also generated a more prolonged antistreptococcal activity than clindamycin in sera, as shown by determinations of inhibitory titers in sera (Fig. 1, bottom panel). No bactericidal titers in sera were detected. Figure 2 shows that both antibiotics

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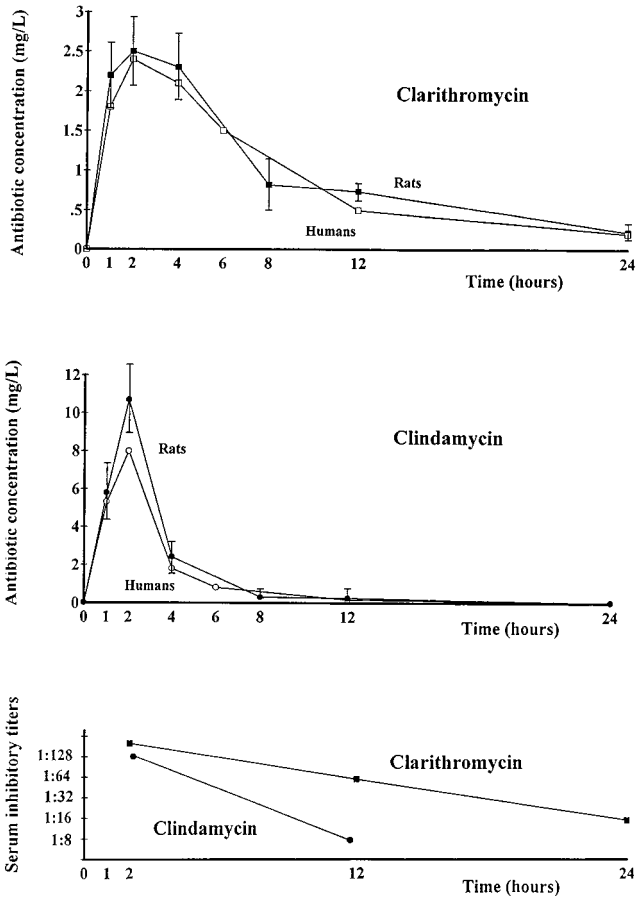

FIG. 1. Antibiotic concentrations in the sera of rats (means ± standard deviations for ≥10 separate animals per point; closed symbols) during simulation of the humans kinetics (open symbols) produced by a single oral dose of either 500 mg of clarithromycin (upper panel) or 600 mg of clindamycin (middle panel). The lower panel depicts the inhibitory titers in sera of rats treated with either of the two compounds. Note that identical inhibitory titers in serum were found for each of the three test organisms.

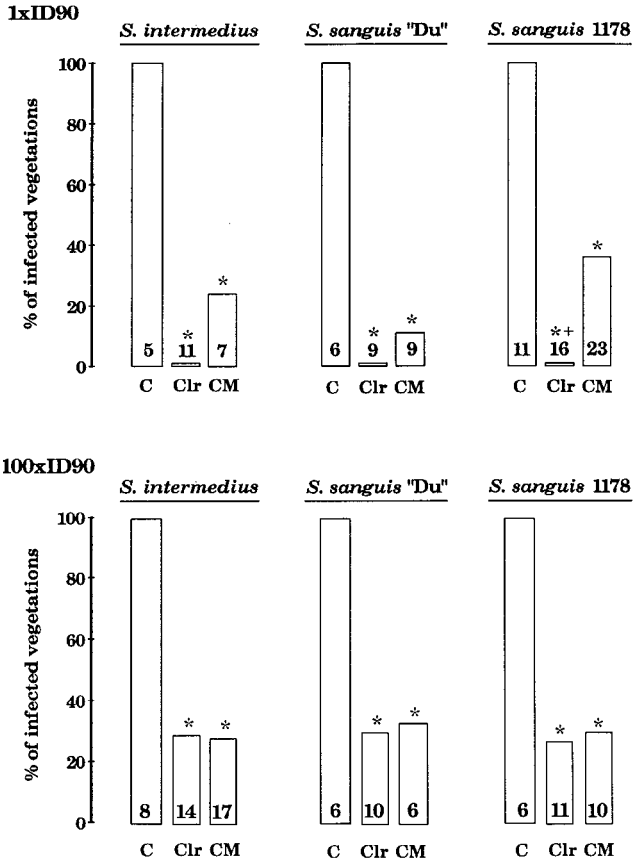

FIG. 2. Results of antibiotic prophylaxis of experimental streptococcal endocarditis. The columns indicate percentages of infected vegetations. The test organisms are indicated at the top of the figure. The treatment groups and numbers of animals per group are shown at the bottoms of the columns. C, untreated control; Clr, clarithromycin; CM, clindamycin. The * symbols indicate a P value of <0.05 when compared with untreated controls, and the + symbol indicates a P value of <0.05 when compared with clindamycin prophylaxis.

successfully prevented endocarditis in animals challenged with either the ID_{90} or 100 times the ID_{90} of the three test organisms, although clarithromycin tended to be more effective than clindamycin at the smaller inoculum amount. Spleen and blood cultures were positive only in infected animals. No resistant bacteria were detected.

Thus, single-dose prophylaxis with either clarithromycin or clindamycin successfully prevented experimental streptococcal endocarditis produced with both large (ID_{90}) and very large (100 times the ID_{90}) inoculum amounts. This wide range of protection was probably derived from the combination of both a prolonged inhibition of bacterial growth and some killing effects of the drugs. The contribution of these two mechanisms to successful prophylaxis was previously documented (1, 6, 8, 12). While inoculum amounts as large as 100 times the ID_{90} are unlikely to be released during dental procedures on humans (9, 13), these experiments provide a stringent test for antibiotic efficacy. The protection afforded by clarithromycin and clindamycin in these studies suggests a wide—yet theoretical—margin of safety for the utilization of these antibiotics for endocarditis prophylaxis in humans. Because clarithromycin is sustained in serum longer than erythromycin and clindamycin, clarithromycin might also help to simplify the recommendations for endocarditis prophylaxis in the United States, which advocate a second antibiotic dose after 6 h to ensure prolonged antibiotic activity (3). Clarithromycin might also be superior to single-dose prophylaxis with clindamycin, which is recommended in Europe (4, 16, 17). Thus, these observations and the good pharmacokinetics and levels of tolerance for new macrolides suggest that clarithromycin might be an excellent candidate for prophylaxis of streptococcal endocarditis in humans.

TABLE 1. MICs and MBCs of erythromycin, clarithromycin, and clindamycin for the three streptococcal strains tested in in vivo experiments

Strain	MIC/MBC (mg/liter) of:		
	Erythromycin	Clarithromycin	Clindamycin
Streptococcus intermedius	0.064/32[a]	0.032/4[a]	0.032/0.25
Streptococcus sanguis "Du"	0.008/0.125	0.032/0.064	0.016/0.064
Streptococcus sanguis 1178	0.016/0.125	0.016/0.032	0.064/0.12

[a] Considered "tolerant" to erythromycin and clarithromycin as defined by a MBC/MIC ratio of ≥32 (14).

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REFERENCES

1. **Bayer, A. S., and J. Tu.** 1990. Chemoprophylactic efficacy against experimental endocarditis caused by β-lactamase-producing, aminoglycoside-resistant enterococci is associated with prolonged serum inhibitory activity. Antimicrob. Agents Chemother. **34:**1068–1074.
2. **Chu, S. Y., Y. Park, C. Locke, D. S. Wilson, and J. C. Cavanaugh.** 1992. Drug-food interaction potential of clarithromycin, a new macrolide antimicrobial. J. Clin. Pharmacol. **32:**32–36.
3. **Dajani, A. S., A. L. Bisno, K. J. Chung, D. T. Durack, M. Freed, M. A. Gerber, A. W. Karchmer, H. D. Millard, S. Rahimtoola, S. T. Shulman, C. Watanakunakorn, and K. A. Taubert.** 1990. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. JAMA **264:** 2919–2922.
4. **Endocarditis Working Party of the British Society for Antimicrobial Chemotherapy.** 1990. Antibiotic prophylaxis of infective endocarditis. Lancet **335:**88–89.
5. **Entenza, J. M., M. Blatter, M. P. Glauser, and P. Moreillon.** 1994. Parenteral sparfloxacin compared with ceftriaxone in treatment of experimental endocarditis due to penicillin-susceptible and -resistant streptococci. Antimicrob. Agents Chemother. **38:**2683–2688.
6. **Flückiger, U., P. Francioli, J. Blaser, M. P. Glauser, and P. Moreillon.** 1994. Role of amoxicillin serum levels for successful prophylaxis of experimental endocarditis due to tolerant streptococci. J. Infect. Dis. **169:**1397–1400.
7. **Gatti, G., J. Flaherty, J. Bubp, J. White, M. Borin, and J. Gambertoglio.** 1993. Comparative study of bioavailabilities and pharmacokinetics of clindamycin in healthy volunteers and patients with AIDS. Antimicrob. Agents Chemother. **37:**1137–1143.
8. **Glauser, M. P., J. P. Bernard, P. Moreillon, and P. Francioli.** 1983. Successful single dose amoxicillin prophylaxis against experimental endocarditis: evidence for two mechanisms of protection. J. Infect. Dis. **147:**568–575.
9. **Hall, G., S. A. Hedstrom, A. Heimdahl, and C. E. Nord.** 1993. Prophylactic administration of penicillins for endocarditis does not reduce the incidence of postextraction bacteremia. Clin. Infect. Dis. **17:**188–194.
10. **Heraief, E., M. P. Glauser, and L. Freedman.** 1982. Natural history of aortic valve endocarditis in rats. Infect. Immun. **37:**127–131.
11. **Lode, H., M. Boeckh, T. Schaberg, K. Borner, and P. Koeppe.** 1993. Pharmacology, p. 61–67. *In* H. C. Neu, L. S. Young, and S. H. Zimmer (ed.), The new macrolides, azalides and streptogramins. Pharmacology and clinical applications. Marcel Dekker, Inc., New York.
12. **Moreillon, P., P. Francioli, D. Overholser, P. Meylan, and M. P. Glauser.** 1986. Mechanisms of successful amoxicillin prophylaxis of experimental endocarditis due to *Streptococcus intermedius*. J. Infect. Dis. **154:**801–807.
13. **Moreillon, P., C. D. Overholser, R. Malinverni, J. Bille, and M. P. Glauser.** 1988. Predictors of endocarditis in isolates from cultures of blood following dental extractions in rats with periodontal disease. J. Infect. Dis. **157:**990–995.
14. **Sabath, L. D., N. Wheeler, M. Laverdiere, D. Blazevic, and B. J. Wilkinson.** 1977. A new type of penicillin resistance of *Staphylococcus aureus*. Lancet **i:**443–447.
15. **Sahm, D. F., and J. A. Washington II.** 1991. Antibacterial susceptibility tests: dilution methods, p. 1105–1116. *In* E. Balows, W. J. Hausler, K. L. Herrmann, H. D. Isenberg, and H. J. Shadomy (ed.), Manual of clinical microbiology, 5th ed. American Society for Microbiology, Washington, D.C.
16. **Schweizerische Arbeitsgruppe für Endokarditisprophylaxe.** 1984. Empfehlungen der Schweizerischen Arbeitsgruppe für Endokarditisprophylaxe. Prophylaxe der bakteriellen Endokarditis. Schweiz. Med. Wochenschr. **114:**1246–1252.
17. **Simmons, N. A.** 1993. Recommendations for endocarditis prophylaxis. J. Antimicrob. Chemother. **31:**437–438.
18. **Steigbigel, N. H.** 1990. Erythromycin, lincomycin, and clindamycin, p. 308–317. *In* G. L. Mandell, R. G. Douglas, and J. E. Bennett (ed.), Principles and practice of infectious diseases, 3rd ed. Churchill Livingstone, New York.
19. **Swartzberg, J. E., R. M. Maresca, and J. S. Remington.** 1976. Gastrointestinal side effects associated with clindamycin. Arch. Intern. Med. **136:**876–879.