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# Activities of Taurolidine In Vitro and in Experimental Enterococcal Endocarditis

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**In vitro, the antimicrobial agent taurolidine inhibited virtually all of the bacteria tested, including vancomycin-resistant enterococci, oxacillin-resistant staphylococci, and *Stenotrophomonas maltophilia*, at concentrations between 250 and 2,000 μg/ml. Taurolidine was not effective in experimental endocarditis. While it appears unlikely that this antimicrobial would be useful for systemic therapy, its bactericidal activity and the resistance rates found ($<10^{-9}$) are favorable indicators for its possible development for topical use.**

With the continuing emergence of multiply antibiotic-resistant organisms, the need to develop new therapeutic agents remains evident. Taurolidine [bis-(1,1-dioxoperhydro-1,2,4-thiadiazinyl-4)methane], a derivative of the amino acid taurine, is an antimicrobial agent which inhibits and kills a broad range of microorganisms in vitro, albeit at high concentrations (3, 4, 9, 11, 13). This compound acts through mechanisms unlike those described for other currently available antimicrobials. Specifically, it is believed that methylol derivatives interact with components of bacterial cell walls resulting in irreparable injury (4). Taurolidine also appears to have immunoregulatory properties, blunting lipopolysaccharide-induced tumor necrosis factor and interleukin-1 release from human peripheral blood mononuclear cells (2) and also reducing adherence of bacteria to human epithelial cells in vitro (5). The compound has been given to humans both intravenously (i.v.) and by peritoneal lavage (1, 12).

The purpose of the present study was to examine the in vitro activity of taurolidine against a broad variety of bacterial species, including antibiotic-resistant strains. We also evaluated the activity of taurolidine in vivo in experimental endocarditis using two strains of enterococci, one of which was a vancomycin-resistant strain of *Enterococcus faecium*.

Most of the bacterial strains used in this study were routine isolates collected by our clinical microbiology laboratory during 1997. Additional strains from our collection were included based upon specific resistance traits. Taurolidine was provided by Wallace Laboratories, Cranbury, N.J. Antimicrobial reference standards of ciprofloxacin, imipenem, and cefotaxime were provided by Bayer Corporation, West Haven, Conn.; Merck & Co., Inc., West Point, Pa.; and Hoechst Marion Roussel, Inc., Kansas City, Mo., respectively. Vancomycin was obtained from Eli Lilly & Co., Indianapolis, Ind. MICs were determined by agar dilution (7, 8) on Mueller-Hinton II agar (BBL Microbiology Systems, Cockeysville, Md.) except as noted otherwise. Agar was supplemented with 5% sheep blood for streptococci and diphtheroids. Inocula were ca. $10^4$ ($10^5$ for anaerobes) CFU/spot. Plates were incubated in room air and read at 18 to 20 h, except for lactobacilli, *Leuconostoc* spp., *Pediococcus* spp., and pneumococci, which were incubated in 5% $CO_2$, and examined for growth at 24 h. Anaerobes were incubated for 48 h on brucella agar in an atmosphere produced by GasPak Plus (BBL). Time-kill studies were carried out with Mueller-Hinton broth with no antibiotic or with taurolidine at the MICs and four times the MICs for individual strains. No attempt was made to inactivate or remove the antimicrobial, except by dilution. To test for the emergence of resistant subpopulations, suspensions of organisms grown overnight in broth were concentrated fivefold and 0.1 ml of each suspension was laid onto the surface of an agar plate containing taurolidine at two and four times the MIC for each organism. The plates were examined for growth at 48 h of incubation.

Experimental endocarditis was established as described previously (6). Two enterococcal strains were used in these experiments: vancomycin-susceptible strain *E. faecalis* 1310 and vancomycin-resistant (Vanb) strain *E. faecium* A1222. The characteristics of these organisms have been described recently (10). Mean injected inocula were $2.2 \times 10^7$ and $1.1 \times 10^7$ CFU, respectively. Treatment was started 24 h after inoculation and continued for 3 days. Taurolidine or a placebo (excipients only) was delivered by continuous i.v. infusion via an indwelling central venous catheter. Taurolidine was given intravenously at a dose of 720 mg/kg/day, which was the maximum feasible dose, given the formulation. In several experiments, i.v. taurolidine was supplemented with intraperitoneal (i.p.) administration of 2 ml of a 2% solution of taurolidine in saline (total, 40 mg/dose) twice daily, yielding a total daily dose (i.v. plus i.p.) of ca. 1,120 mg/kg. Animals were sacrificed approximately 1 h after discontinuation of i.v. infusions. For animals receiving i.p. injections, the last dose was given 14 h before sacrifice. Aortic valve vegetations were aseptically removed, homogenized, and serially diluted in sterile saline for bacterial colony counts. Only animals having received at least 4 days of therapy and with correct placement of the aortic valve catheter determined at necropsy were included in the evaluation.

Agar dilution MICs of taurolidine and comparison agents are shown in Table 1. Virtually all of the organisms tested were inhibited by taurolidine at concentrations between 250 and 2,000 μg/ml. Included among the enterococci were 43 vancomycin-resistant *E. faecium* and 21 vancomycin-resistant *E. faecalis* isolates. Activity of taurolidine against oxacillin-resistant staphylococci (including two glycopeptide-intermediate *S. aureus* isolates) was equivalent to that against oxacillin-susceptible strains. Occasional strains of gram-positive bacteria, including all 10 strains of *Clostridium difficile*, were inhibited at

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