In Vitro Activity of N-Formimidoyl Thienamycin and Other β-Lactam Antibiotics Against Methicillin-Resistant Staphylococcus aureus

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Of 43 isolates of methicillin-resistant Staphylococcus aureus, 90% were inhibited by 8 μg or less of N-formimidoyl thienamycin per ml by the agar-dilution technique. Cefamandole, cefotaxime, cefoperazone, moxalactam, and cefsulodin showed relatively poor activity. Vancomycin was the most active compound by weight, inhibiting 93% of strains at 1 μg/ml.

Strains of Staphylococcus aureus exhibiting intrinsic resistance to penicillinase-resistant penicillins have been recognized since the introduction of methicillin 20 years ago (7). In many European hospitals, the strains became established as prevalent nosocomial pathogens during the 1960s, accounting for 30 to 50% of the S. aureus isolates in some centers (8). In the same period, outbreaks of methicillin-resistant S. aureus (MRSA) infection in hospitals in the United States were rarely reported (1, 13). However, several lines of evidence suggest that MRSA are now widely dispersed throughout the United States and are becoming increasingly prevalent as endemic hospital pathogens. Sixteen hospital outbreaks have been reported since 1976, including two documenting interhospital transmissions. A recent survey of 62 hospital epidemiologists indicated that 37% had noted MRSA to be nosocomial bloodstream pathogens at their institutions during 1979 (4). Additionally, surveillance data reported by hospitals participating in the National Nosocomial Infections Study demonstrated that the proportion of MRSA that were isolated from patients with nosocomial S. aureus infections increased from 2.4% in 1975 to 4.9% in 1980 (4).

MRSA strains are always resistant to multiple antibiotics, although the spectrum of resistance is variable. In vitro resistance is often demonstrated not only to all penicillins but also to many other antistaphylococcal agents, including first-generation cephalosporins, aminoglycosides, erythromycin, clindamycin, and chloramphenicol. Trimethoprim-sulfamethoxazole and rifampin frequently show activity for MRSA, yet clinical experience in treating serious staphylo-

tical infection with these agents is limited. Vancomycin, uniformly active against all MRSA strains, is the only antimicrobial agent currently available that can be recommended for the treatment of serious MRSA infections.

Third-generation cephalosporins, including cefoperazone, cefotaxime, and cefsulodin, are generally less active than cephalothin against staphylococci and other gram-positive organisms (12). Moxalactam, a 1-oxa cephalosporin, resembles these compounds in its spectrum of activity (12). Recently a unique β-lactam, N-formimidoyl thienamycin (MK0787) has been shown to be very active against facultative gram-positive cocci. The minimum inhibitory concentration of N-formimidoyl thienamycin against over 350 methicillin-susceptible S. aureus isolates was less than 1.0 μg/ml, with at least 90% of the strains in five studies inhibited by 0.125 μg/ml (6, 9, 10, 15, 16). The purpose of this study was to compare and contrast the in vitro activity of the compounds against MRSA strains isolated from patients at a university medical center.

A total of 43 clinical isolates of MRSA submitted to the University of Virginia clinical microbiology laboratory was used in the study. These isolates of S. aureus were selected based upon their resistance to nafcillin, using disk diffusion by the method of Bauer et al. (2) and by minimum inhibitory concentration susceptibility procedures. The 43 isolates were cultured from 27 wounds, 3 lower respiratory secretions, 2 blood cultures, and 11 miscellaneous sites, including urine, peritoneal fluid, stool, and catheter tips. Laboratory providers were supplied by the following manufacturers: N-formimidoyl thienamycin by Merck & Co., Inc., Rahway, N.J.; vancomycin, cefamandole, and moxalactam by Eli Lilly & Co., Indianapolis, Ind.; nafcillin by

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Wyeth Laboratories, West Chester, Pa.; cefsulodin by Abbott Laboratories, Chicago, Ill.; cefotaxime by Hoechst-Roussel Pharmaceuticals, Inc., Sommerville, N.J.; and cefoperazone by Pfizer Laboratories, Inc., New York, N.Y. All isolates were tested for antimicrobial susceptibility by an agar-dilution technique (5). S. aureus (ATCC 25923) served as the control strain. Overnight cultures of the isolates in tryptic soy broth were diluted 1:100 in physiological saline and inoculated onto Mueller Hinton agar plates by the use of a Steers replicating device delivering a 1- to 2-μl inoculum containing 10^6 colony-forming units. The Mueller Hinton agar plates were prepared with stock solutions of each antibiotic made on the day of use to yield twofold serial dilutions ranging from 32 to 0.125 μg/ml. After incubation at 35°C for 18 h, the minimum inhibitory concentration was interpreted as the lowest concentration of antibiotic which permitted no visible growth.

The in vitro activities of the newer β-lactam compounds (N-formimidoyl thienamycin, moxalactam, cefaperazone, cefsulodin, and cefotaxime) against MRSA were compared with those for nafcillin, cefamandole, and vancomycin (Fig. 1). Vancomycin was the most active by weight, inhibiting more than 90% of the strains at 1 μg/ml. N-formimidoyl thienamycin inhibited 50% of the isolates at 2 μg/ml and 90% at 8 μg/ml. All other compounds failed to demonstrate activity against these strains.

There have been marked temperature and inoculum effects demonstrated in some in vitro studies of the activity of cephalexopins against strains of MRSA (3, 11). Although other investigators have not shown these effects (14), it seems prudent to interpret in vitro data on the activity of newer cephalosporins and other β-lactam antibiotics with caution. Furthermore, there is a marked difference in the in vitro susceptibility of methicillin-susceptible versus methicillin-resistant strains of S. aureus for N-formimidoyl thienamycin, suggesting a parallel resistance which may also have relevance with regard to its in vivo activity.

The in vitro activity of N-formimidoyl thienamycin against MRSA has been previously reported in only 12 isolates. N-formimidoyl thienamycin inhibited 90% of the 11 isolates studied by Verbist and Verhaegen at 1 μg/ml (16) and 1 isolate reported by Kropp et al. at 20 μg/ml (10). Our results suggest that N-formimidoyl thienamycin is unique among the newer β-lactam compounds in its in vitro activity against these strains. However, serum levels attainable in animals or humans have not yet been defined. In vivo studies are warranted to further evaluate its pharmacokinetics and therapeutic efficacy.

**LITERATURE CITED**


