Comparative In Vitro Activities of N-Formimidoyl Thienamycin and Moxalactam Against Nonfermentative Aerobic Gram-Negative Rods

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N-Formimidoyl thienamycin was the most active drug against strains of Pseudomonas aeruginosa with a 90% minimum inhibitory concentration of 1.25 μg/ml. With the exception of P. maltophilia, thienamycin was as active or more active than moxalactam against other species of pseudomonads and against other genera of nonfermenters.

Moxalactam is a new beta-lactam antimicrobial agent with a broad spectrum of activity against aerobic and facultative gram-negative rods (2, 4, 5, 8, 16). Although there are fewer reports on N-formimidoyl thienamycin, this new more stable derivative of thienamycin also has an expanded spectrum of activity (7, 14, 17). Except for Pseudomonas aeruginosa (6, 8, 13, 15, 19) and a few other common Pseudomonas species (9, 11), there are relatively few data available on the susceptibility of significant numbers of well-characterized nonfermentative gram-negative rods to these antimicrobial agents. This report is the result of an investigation of the in vitro activity of N-formimidoyl thienamycin and moxalactam against common and less commonly occurring species of nonfermenters. In addition, the susceptibility of aminoglycoside-resistant species of Pseudomonas is included.

The organisms studied included 323 clinical isolates of nonfermentative gram-negative rods obtained from the Hospital for Joint Diseases and Medical Center, New York, and from the Medical College of Ohio and affiliated hospitals. Aminoglycoside-resistant P. aeruginosa were obtained from the Medical College of Ohio and affiliated hospitals. Resistance was determined by the standard Kirby-Bauer disk assay and confirmed by minimum inhibitory concentration (MIC) determinations. The identity of all isolates was confirmed by conventional methods in our laboratories.

Staphylococcus aureus ATCC 25923 and ATCC 29213, Escherichia coli ATCC 25922, P. aeruginosa ATCC 27853, and Streptococcus faecalis ATCC 29212 were included as control organisms in all tests.

Standardized antibiotic powders or solutions were kindly provided by their respective manufacturers: moxalactam by Eli Lilly & Co. and N-formimidoyl thienamycin by Merck Research Laboratories.

MICs for all antibiotics were determined simultaneously for each strain by the microdilution method. Microtiter trays containing twofold dilutions of the antibiotic in Mueller-Hinton broth supplemented with calcium (50 μg/ml) and magnesium (25 μg/ml) were inoculated with 0.05 ml of an overnight culture of the organism diluted in cation-supplemented broth to contain 2 × 10⁵ organisms per ml. The MIC was read as the lowest concentration of the drug inhibiting visible growth of the organism after incubation at 37°C for 24 h.

The effect of inoculum size on the MIC was determined for representative organisms from each group. The inocula used ranged from 10⁶ to 10⁷ organisms per ml.

The results of the in vitro activity of N-formimidoyl thienamycin and moxalactam are recorded in Table 1. These results show that the 50% MIC (MIC₅₀) for moxalactam against P. aeruginosa was 32 μg/ml, whereas the MIC₅₀ was 128 μg/ml. Only 19% of the isolates was susceptible to moxalactam at 8 μg/ml; 73% was inhibited at 32 μg/ml. In contrast, the MIC₅₀ for N-formimidoyl thienamycin was 0.625 μg/ml, and the MIC₉₀ was 1.25 μg/ml. N-formimidoyl thienamycin clearly was more active than moxalactam; 90% of the isolates was inhibited at 1.25 μg/ml.

In general, N-formimidoyl thienamycin was as active or more active than moxalactam against the other species of Pseudomonas. The MIC₉₀ for N-formimidoyl thienamycin against P. cepacia was relatively high (10 μg/ml). P. acidovorans was equally susceptible to moxalactam and...
N-formimidoyl thienamycin. Only *P. maltophilia* was more susceptible to moxalactam than to N-formimidoyl thienamycin.

Against the remaining species of nonfermenters, N-formimidoyl thienamycin was more active. This was especially true for the genus *Acinetobacter*. The MIC\(_{90}\) for N-formimidoyl thienamycin against *A. calcoaceticus* var. *anitratus* and *A. calcoaceticus* var. *lwoffii* was 0.31 and 0.15 \(\mu\text{g/ ml}\), respectively, whereas the MIC\(_{90}\) for moxalactam was more than 100-fold higher.

The size of the inoculum had only minimal effects on the MICs of moxalactam and N-formimidoyl thienamycin when inocula of 10\(^5\), 10\(^6\), and 10\(^8\) were tested. However, an inoculum of 10\(^8\) organisms per ml significantly increased the MIC for moxalactam against most species, whereas the MIC for N-formimidoyl thienamycin showed little change (data not shown).

The in vitro activity of moxalactam and N-formimidoyl thienamycin against aminoglycoside-resistant strains of *P. aeruginosa* was also tested. Organisms were divided into three groups according to their pattern of resistance: resistance to gentamicin alone, to gentamicin and tobramycin, and to gentamicin, tobramycin, and amikacin. Aminoglycoside resistance is defined as \(\geq 8\ \mu\text{g/ ml}\) for gentamicin and tobramycin and \(\geq 32\ \mu\text{g/ ml}\) for amikacin. The MIC\(_{90}\) for moxalactam and N-formimidoyl thienamycin against each of three groups of aminoglycoside-resistant isolates were 128 and 1.25 \(\mu\text{g/ ml}\), respectively. These results are similar to those of the aminoglycoside-sensitive strains.

Our results indicate that the MIC\(_{90}\) for moxalactam against *P. aeruginosa* is relatively high.
(128 μg/ml). These results are in contrast to the earlier reports of Barza et al. (2) and of Trager et al. (16), who both demonstrated an MIC<sub>90</sub> value of 32 μg/ml. Our data are consistent with the more recent report of Jones et al. (8), who obtained an MIC<sub>90</sub> of >32 μg/ml. With the criteria of Barry et al. of >64 μg/ml for resistance (1), approximately one-fourth of our P. aeruginosa isolates would be considered resistant.

Our results indicate that both P. maltophilia and P. cepacia are also relatively resistant to moxalactam. These results are similar to those reported by Fass and Barnishan (6). The susceptibility of the remaining species of pseudomonads to moxalactam has not been well studied. We have found that P. acidovorans, P. putrefaciens, and P. stutzeri are quite susceptible to moxalactam; in contrast, P. fluorescens and P. putida are relatively resistant.

Both species of Acinetobacter are moderately resistant or resistant to moxalactam. The data are similar to those reported by Fass and Barnishan (6) and Jorgensen et al. (9). We have found that all isolates of the genera Acromobacter, Flavobacterium, and Moraxella are relatively susceptible to moxalactam.

Our results of the susceptibility of P. aeruginosa to N-formimidoyl thienamycin are in agreement with those of others (12, 17), but lower than those reported by Tally et al. (15). Kesado et al. (11) has reported data on a limited number of species of other nonfermenters, but otherwise little comparative data exist. With the exception of P. maltophilia, all species that we examined had MIC<sub>90</sub> to N-formimidoyl thienamycin that were equal to or lower than those for moxalactam.

With the exception of strains of P. aeruginosa, the effect of inoculum size on in vitro activities of moxalactam and thienamycin has not been reported. For this species, our data are similar to those of other investigators (3, 18), who showed an increase in MICs at high inocula of 10<sup>7</sup> organisms per ml. Our data show that this inoculum effect also is seen for most other species when tested with moxalactam. The inoculum effect is clearly less evident when N-formimidoyl thienamycin is tested.

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LITERATURE CITED


