In Vitro Activity of Carumonam (Ro 17-2301; AMA-1080) versus Enteropathogenic and Nonfermentative Gram-Negative Rods and Legionella pneumophila

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The in vitro activity of carumonam (Ro 17-2301; AMA-1080) was tested against 355 single-patient isolates, by and large enteropathogenic or nonfermentative rods. The new monobactam was inhibitory and bactericidal against the majority of diarrhea-causing members of the family Enterobacteriaceae at concentrations of less than and equal to 8 μg/ml. Although known to be active against Pseudomonas aeruginosa, it generally did not exhibit clinically useful activity against other nonfermenters or against Legionella pneumophila, thus confirming its narrow spectrum of activity.

Carumonam (Ro 17-2301; AMA-1080) is a parenterally administered monocyclic beta-lactam (monobactam) currently under clinical development. This new agent has been shown to be active in vitro against many, predominantly gram-negative, aerobic rods, primarily members of the families Enterobacteriaceae and Neisseriaceae, Haemophilus spp., and Pseudomonas aeruginosa (1, 5, 7). Because the activity of carumonam has not been unequivocally defined with regard to its use for enteric and for nosocomial infections, the purpose of the present study was to determine its in vitro activity against the most ubiquitous causative agents of acute bacterial diarrhea, against the main nonfermentative gram-negative rods (except P. aeruginosa), and against Legionella pneumophila.

A total of 355 clinical isolates from the culture collection of the Department of Medical Microbiology at the University of Zürich were selected for the study. The MIC of carumonam was determined by the microbroth dilution technique following widely accepted recommendations (8) in wells with 0.1-ml final volume by using cation-unsupplemented Mueller-Hinton broth (Difco Laboratories). The MIC was read with the unaided eye and taken as the lowest concentration of antibacterial agent that suppressed visible bacterial growth. Faintly turbid wells were disregarded. Halophilic Vibrio spp. were tested in Mueller-Hinton broth supplemented with 6.5% NaCl. Susceptibility testing of Campylobacter jejuni was carried out by agar dilution under microaerophilic conditions by using Mueller-Hinton agar (final amount, 2.5% agar) enriched with 7% horse blood incubated in an anaerobic jar without catalyst at 35°C for 48 h (12). Determination of Legionella pneumophila susceptibility (MIC only) was carried out on enriched charcoal-yeast extract agar in room air with added 10% CO2 (2) for 48 h.

To obtain the MBC, clear wells at and just above the MIC were subcultured (20 μl) on blood agar plates. Plates were incubated for 24 h at 37°C in room air. The MBC was based on a 99.9% reduction of the initial colony count (9).

Carumonam laboratory powder (lot no. 403005) with a potency of 894 μg/mg was obtained from an in-house source and reconstituted in sterile water. Four control strains (Escherichia coli ATCC 25922, P. aeruginosa ATCC 27853, Staphylococcus aureus ATCC 25923, and Staphylococcus aureus ATCC 29213) were included in the study.

The MICs and MBCs of carumonam for the 149 enteropathogenic strains (17 species) are shown in Table 1. For the members of the Enterobacteriaceae Escherichia coli, Aeromonas spp., Plesiomonas shigelloides, and Shigella spp., MICs for 50% of the strains (MIC50) (MICs for 90% of the strains [MIC90]) were 0.125 (0.5), 0.25 (0.5), 0.125 (0.25), and 0.5 (1) μg/ml. Data for other organisms were as follows: Yersinia spp., 1 (8) μg/ml; Vibrio spp., 16 (16) μg/ml; and Salmonella spp., 1 (>128) μg/ml. For Campylobacter jejuni, which was still more resistant to the compound, the MIC50 (MIC90) was 8 (128) μg/ml.

Results with 191 nonfermentative rods (27 species) are not tabulated, since these bacteria were quite resistant to carumonam. Sixteen of the 27 species tested, currently or formerly, were classified as belonging to the genus Pseudomonas: P. maltophilia (Xanthomonas maltophilia) (10 isolates), P. fluorescens (10 isolates), P. cepacia (9 isolates), P. putrefaciens, P. putida (8 isolates), P. aeruginosa, Pseudomonas group Ve (Pseudomonas group Ve-1: P. luteola; CDC group Ve-1; and/or Pseudomonas group Ve-2: P. oryzihabitans; CDC group Ve-2) (8 isolates), P. pseudoalcaligenes (7 isolates), Pseudomonas group Va-1 (CDC group Va-1) (7 isolates), P. picketti (CDC group Va-2) (7 isolates), P. pseudoalcaligenes (7 isolates), P. diminuta (6 isolates), P. acidovorans (Comamonas acidovorans) (5 isolates), P. alcaligenes (5 isolates), P. putrefaciens (Alteromonas putrefaciens) (4 isolates), P. vesicularis (4 isolates), and P. medocina (3 isolates). Five species belonged to the genus Flavobacterium or a related group: Flavobacterium group IIb (Flavobacterium gleum; CDC group IIb) (8 isolates), F. odoratum (6 isolates), CDC group II (Weeksella virosa) (6 isolates), F. meningosepticum (5 isolates), and F. multivorum (5 isolates). Finally, there were Acinetobacter calcoaceticus subsp. anitratus (12 isolates), Acinetobacter calcoaceticus subsp. lwoffi (8 isolates), Alcaligenes denitrificans subsp. xylosoxidans (8 isolates), Alcaligenes faecalis (8 isolates), Alcaligenes denitrificans subsp. denitrificans (4 isolates), Achromobacter (CDC group Vd) (8 isolates), and Moraxella urethralis (Oligella urethralis) (6 isolates). All nonfermenter species examined, with the exception of P. stutzeri (MIC50, 8 μg/ml) and Oligella urethralis (MIC50, 4 μg/ml), had MIC90s and

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TABLE 1. In vitro activity of carumonam against enteropathogenic bacteria

<table>
<thead>
<tr>
<th>Organism (no. tested)</th>
<th>MIC (µg/ml)</th>
<th>MBC (µg/ml)</th>
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<tr>
<td></td>
<td>50%</td>
<td>90%</td>
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<tr>
<td><em>Escherichia coli</em> (28)*</td>
<td>0.125</td>
<td>2</td>
</tr>
<tr>
<td>Aeromonas spp. (20)</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>Plesiomonas shigelloides (10)</td>
<td>0.125</td>
<td>0.25</td>
</tr>
<tr>
<td>Shigella spp. (20)*</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Yersinia spp. (14)*</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>1</td>
<td>&gt;128</td>
</tr>
<tr>
<td>S. typhimurium (9)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other serovars (13)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vibrio spp. (15)*</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Campylobacter jejuni (20)</td>
<td>8</td>
<td>128</td>
</tr>
</tbody>
</table>

*Toxin assay results were as follows: not assayed, 16; heat-labile and heat-stable enterotoxin positive, 9; toxin negative, 3.

MBCs of 16 µg/ml or greater (Alteromonas putrefaciens, 16 µg/ml; *P. stutzeri*, 64 µg/ml; all other species, ≥128 µg/ml). The corresponding MICs and MBCs for *Legionella pneumophila* were 16 and 32 µg/ml, respectively.

The MICs for the *Escherichia coli* ATCC 25922 strain were within the quality control range suggested by the National Committee for Clinical Laboratory Standards; those for *P. aeruginosa* ATCC 27853 (data not shown) were generally 1 dilution step higher than the upper limit of quality control values recommended by Jones et al. (6).

Our results confirm that carumonam encompasses only the narrow spectrum of activity of the early monobactams delineated by others, which appears to restrict the clinical usefulness of this monobactam, as well as to infections caused by members of the *Enterobacteriaceae* and *P. aeruginosa*. While the compound showed sufficient activity to be of clinical promise against the bulk of enteropathogenic members of the *Enterobacteriaceae* (based on the recently proposed susceptibility-interpretative criteria that advocate a MIC breakpoint for susceptibility of ≤8 µg/ml of carumonam per ml (6)), it has, on the basis of the same interpretative criteria, little or no activity against *Vibrio cholerae* or against the occasional extraterrestrially acquired traveler's diarrhea, multiply resistant members of the *Enterobacteriaceae* (e.g., *Salmonella typhi* and *Salmonella paratyphi*).

Likewise, carumonam had very limited activity against a much larger spectrum of nonfermenters than suggested by earlier publications (3, 4, 11, 13). Provided that sequential clinical isolates emanating from routine diagnostic testing in a hospital are as resistant to carumonam (MICs) as the strains in this study and thus more resistant to carumonam than strains belonging to identical species in earlier studies (3, 4, 10, 13), the new monobactam is very unlikely to be of use in difficult-to-treat nosocomial infections caused by nonfermentative bacilli other than *P. aeruginosa*. Thus, it behaves differently from the aminoglycosides, quinolones, and some of the other newer beta-lactams such as cepazidime and imipenem, which are all active against many of these rods.

**LITERATURE CITED**


