Comparative In Vitro Activity of Imipenem against *Haemophilus influenzae* and *Haemophilus parainfluenzae*

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A microdilution broth method was used to test 77 clinical isolates of *Haemophilus influenzae* and *Haemophilus parainfluenzae*, including β-lactamase-positive and -negative strains, for susceptibility to ampicillin, chloramphenicol, and imipenem. Except for ampicillin against β-lactamase-producing strains (MIC for 90% of strains [MIC₉₀], ≥ 128 μg/ml), all three antimicrobial agents had comparable in vitro activity (MIC₉₀, ≤ 1 μg/ml) against these bacterial strains.

The role of *Haemophilus influenzae* in human diseases is well established, whereas the pathogenicity of *Haemophilus parainfluenzae*, a routine isolate of normal upper respiratory flora, is still somewhat controversial. Nevertheless, due in part to improved methods of identification (5, 7), *H. parainfluenzae* has been increasingly recognized as an opportunistic human pathogen. It has been implicated in a variety of serious infections including meningitis, endocarditis, septicemia, pneumonia, septic arthritis, otitis media, epiglotitis, and abscesses (2, 3, 8, 14-16; J. B. McClain, R. D. Almanza, and J. F. Keiser, Clin. Microbiol. Newsl. 5:31, 1983).

The antibiotic susceptibility of *H. parainfluenzae* has been investigated previously (2, 5, 8) and was found, in general, to parallel that of *H. influenzae*. Like resistance by *H. influenzae*, resistance by *H. parainfluenzae* to ampicillin, the current drug of choice for bacterial infections caused by these organisms, is widespread and appears to be closely related to β-lactamase production. In some areas, the prevalence of β-lactamase-producing strains of *H. parainfluenzae* has been reported to be as high as 76% (13). Imipenem is almost totally resistant to virtually all known types of β-lactamases (6, 10), with the exception of an inducible penicillinase from *Pseudomonas maltophilia* (11) and one from *Bacteroides fragilis* (10). Since available data on the susceptibility of *H. parainfluenzae* to imipenem are still extremely limited (1), we decided to study the activity of this drug in comparison to that of other agents against both β-lactamase-producing and non-β-lactamase-producing strains of *H. influenzae* and *H. parainfluenzae*.

<table>
<thead>
<tr>
<th>Strain (no. tested)</th>
<th>MIC (μg/ml) of:</th>
<th>Imipenem</th>
<th>Ampicillin</th>
<th>Chloramphenicol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>MIC₅₀</td>
<td>MIC₉₀</td>
<td>Range</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-lactamase positive (9)</td>
<td>0.25-1</td>
<td>1</td>
<td>8→128</td>
<td>0.5→1</td>
</tr>
<tr>
<td>β-lactamase negative (36)</td>
<td>0.12-1</td>
<td>0.5</td>
<td>0.25→8</td>
<td>0.25</td>
</tr>
<tr>
<td><em>H. parainfluenzae</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-lactamase positive (26)</td>
<td>0.25-1</td>
<td>0.5</td>
<td>16→128</td>
<td>32</td>
</tr>
<tr>
<td>β-lactamase negative (6)</td>
<td>0.12-2</td>
<td>0.5</td>
<td>0.25-8</td>
<td>1</td>
</tr>
</tbody>
</table>

Ampicillin (Bristol Laboratories, Syracuse, N.Y.) was dissolved in distilled water, chloramphenicol (Parke, Davis & Co., Ann Arbor, Mich.) was dissolved in a 50% aqueous solution of N,N-dimethylacetamide with tartaric acid and sodium tartrate, and imipenem (Merck & Co., Inc., Rahway, N.J.) was dissolved in 0.01 M phosphate buffer. β-Lactamase production was determined by the use of nitrocefin-impregnated disks (Cefinase; BBL Microbiology Systems, Cockeysville, Md.).

With the MIC-2000 System (Dynatech Laboratories, Alexandria, Va.), MICs were determined by the microdilution broth method as outlined previously (9), except that 5% CO₂ was used during incubation. Cation-supplemented Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) was enriched with 5% lysed horse blood and 10 μg of NAD per ml. The inocula, grown overnight at 37°C, were appropriately diluted to achieve a final inoculum density of approximately 5 × 10⁵ CFU/ml. The MIC was defined as the lowest concentration of the drug yielding no visible growth after a 24-h incubation.

The results summarized in Table 1 show that imipenem, ampicillin, and chloramphenicol had comparable MICs for 90% (MIC₉₀) of the 36 strains of non-β-lactamase-producing *H. influenzae* tested; e.g., the MIC₉₀ was 1.0 μg/ml for all three drugs. The MIC ranges for the 6 strains of non-β-lactamase-producing *H. parainfluenzae* and the 36 strains of non-β-lactamase-producing *H. influenzae* were fairly similar for each antibiotic. Except for one strain each of *H. influenzae* and *H. parainfluenzae* which required an MIC of 8 μg of ampicillin per ml, all non-β-lactamase-producing strains included in this study required MICs of ≤ 2 μg of each antimicrobial agent tested per ml.
Both imipenem and chloramphenicol had an MIC\textsubscript{90} of 1.0 \(\mu\text{g/ml}\) for the 26 \(\beta\)-lactamase-producing strains of \textit{H. parainfluenzae} and MIC ranges of 0.25 to 1 and 0.5 to 1 \(\mu\text{g/ml}\), respectively, for the 9 \(\beta\)-lactamase-producing strains of \textit{H. influenzae} tested. Ampicillin exhibited very poor activity against these organisms, resulting in an MIC\textsubscript{90} of 128 \(\mu\text{g/ml}\) for the 26 strains of \textit{H. parainfluenzae} and an MIC range of 8 to >128 \(\mu\text{g/ml}\) for the 9 strains of \textit{H. influenzae}. Of 77 isolates tested, none was found to be resistant to either imipenem or chloramphenicol, whereas 37 isolates (48%) were resistant to ampicillin (MIC, \(\geq 4 \mu\text{g/ml}\)).

The clinical efficacy of Primaxin (imipenem-cilastatin) against strains of \textit{H. influenzae} (1, 4, 12) and \textit{H. parainfluenzae} (1) with undefined \(\beta\)-lactamase activity has been established previously. The data presented here indicate that, at least in vitro, imipenem is equally very active against \(\beta\)-lactamase-negative and \(\beta\)-lactamase-positive strains of these bacterial species, regardless of their susceptibility responses to ampicillin. The superior antibacterial activity of imipenem compared with that of ampicillin may be due, in part, to its marked resistance to enzymatic degradation.

**LITERATURE CITED**