Carbenicillin for Treatment of \textit{Bacteroides fragilis} Infections: Why Not Penicillin G?

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Carbenicillin has been advocated for treatment of infections caused by \textit{Bacteroides fragilis} and other anaerobic bacteria. Wide-scale use of the drug in this setting could result in a substantial increase in carbenicillin-resistant \textit{Pseudomonas aeruginosa}, an effect that would have serious implications. Thirty-four strains of \textit{B. fragilis}, one-half from bacteremic infections, were tested in vitro, and penicillin G was found to be twice as active as carbenicillin on an equal weight basis; 94\% of the strains were inhibited by 32 \textmu g of penicillin/ml, a level easily achieved therapeutically. Penicillin killed \textit{B. fragilis} organisms as rapidly as carbenicillin. In two subjects given equivalent doses (100 mg/kg intravenously) of carbenicillin and aqueous penicillin G, the bactericidal activity of serum against \textit{B. fragilis} after administration of each drug was the same. Controlled clinical trials of treatment of anaerobic bacterial infections with penicillin G in high dosage, carbenicillin (or closely related ticarcillin), clindamycin, and chloramphenicol should be undertaken. Carbenicillin (and ticarcillin) for the present would seem better reserved for \textit{P. aeruginosa} infections.

Chloramphenicol and clindamycin are generally considered to be the drugs of choice for serious infections caused by \textit{Bacteroides fragilis} [1–3]. Carbenicillin, carboxybenzyl penicillin, has been shown to have in vitro activity against \textit{B. fragilis} [4–8], and clinical trials indicate that the drug is effective in \textit{B. fragilis} infections [9–11]. In 1975 carbenicillin was approved by the Food and Drug Administration (Washington, D.C.) for use in anaerobic infections. Since that time, it has been advocated increasingly for general use in all infections that may be caused by anaerobes.

\textit{B. fragilis} is considered by most clinicians and microbiologists to be resistant to penicillin G [1, 2, 5, 6]. This study was undertaken to determine the relative in vitro activities of carbenicillin and penicillin G against 34 clinical isolates of \textit{B. fragilis}, half of which were from bacteremic infections. We also tested the bactericidal activity against \textit{B. fragilis} of serum from two subjects who received equivalent therapeutic doses of carbenicillin and penicillin.

Materials and Methods

\textit{Strains studied.} Thirty-four strains of \textit{B. fragilis} recovered from patients hospitalized in the University of Wisconsin Hospitals with anaerobic bacterial infections were obtained for study. Sixteen strains (48\%) had been recovered from blood cultures, and the rest were from intraabdominal abscesses or anaerobic pulmonary infections. The identity of each strain was confirmed by the methods and criteria of the Virginia Polytechnic Institute [12]; 17 of the strains were \textit{B. fragilis} subspecies \textit{fragilis}.

\textit{Determination of antibiotic susceptibilities.} Each strain was simultaneously tested for susceptibility to carbenicillin and penicillin G by an agar dilution technique and an inoculum of \~{}10\textsuperscript{5} organisms [13].

\textit{Rates of bacterial killing.} Killing curves for carbenicillin and penicillin G were determined for four strains of \textit{B. fragilis} (MICs, 16–256 \textmu g of carbenicillin/ml and 8–64 \textmu g of penicillin/ml). An overnight culture in prereduced pep-
Table 1. Susceptibility of 34 strains of Bacteroides fragilis to carbenicillin and penicillin G.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Cumulative percentage of strains inhibited at indicated concentration (μg/ml)</th>
<th>Geometric mean MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 1 was diluted to a concentration of approximately $3 \times 10^8$ cells/ml. A volume of 4 ml was added to 4 ml of broth containing enough antibiotic to yield a final antibiotic concentration equal to twice the organism’s MIC. At zero-time and after 2, 4, 6, and 8 hr, aliquots were removed, and counts of viable organisms were determined.

Serum bactericidal activity in treated subjects. Equivalent therapeutic doses (100 mg/kg) of sodium carbenicillin (Roerig, New York, N.Y.) and four days later, aqueous potassium penicillin G (E. R. Squibb and Sons, Princeton, N.J.) were given to two of the authors. Each drug was administered iv over 0.5 hr. Blood specimens were obtained 15 min and 3.5 hr after administration of the drug.

Serum bactericidal assays were performed by a microtiter method adapted from that recommended by Ruttle et al. for susceptibility testing of anaerobes [14], using a strain of B. fragilis subspecies fragilis with a relatively high MIC for both carbenicillin (64 μg/ml) and penicillin G (82 μg/ml). (Only 9% of the 34 strains studied had MICs exceeding these values.) The final concentration in each well was $\sim 10^8$ viable organisms/ml.

Serum levels of penicillin G and carbenicillin were determined by a standard well diffusion bioassay using Bacillus subtilis ATCC strain 6633 (American Type Culture Collection, Rockville, Md.).

Results

Antibiotic sensitivities. Table 1 shows the range of MICs of carbenicillin and penicillin G for the 34 strains of B. fragilis. A commonly accepted MIC above which laboratories regard an organism to be resistant to penicillin G is 2.0 μg/ml. None of the strains was susceptible to this concentration of penicillin. However, at a concentration of 92 μg/ml, penicillin inhibited 94% of the strains, whereas only 68% were inhibited by this concentration of carbenicillin. At 128 μg/ml, a concentration above which B. fragilis is generally regarded as resistant to carbenicillin [5, 8], 97% of the strains were inhibited by both carbenicillin and penicillin. The geometric mean MIC of penicillin G, 21.1 μg/ml, was less than one-half that of carbenicillin, 46.5 μg/ml.

Rates of bacterial killing. At a drug concentration twofold greater than the MIC, penicillin

![Figure 1. Killing curves for penicillin G and carbenicillin against four strains of Bacteroides fragilis. Each strain was tested against an antibiotic concentration that was twice the MIC.](image-url)
G reduced the concentration of viable *B. fragilis* organisms slightly more rapidly than did carbenicillin (figure 1).

**Serum bactericidal activity in treated subjects.**
As shown in table 2, 15 min after administration of the same dose by weight (as shown by comparable peak blood levels), the maximal (peak) bactericidal dilution of serum against the test *B. fragilis* strain was the same for carbenicillin and penicillin in both subjects (1:16 in subject no. 1 and 1:32 in no. 2). The trough bactericidal dilution (3.5 hr later) was slightly higher for carbenicillin (1:4) than for penicillin G (1:2) in both individuals.

**Discussion**
Aqueous penicillin G is generally considered to be the drug of choice for infections caused by all types of anaerobic bacteria with the exception of *B. fragilis* [1–3, 5, 6]. This species appears to be unique among anaerobic pathogens in terms of its greater virulence [2, 3] and because it is considerably more resistant to penicillin G. For these reasons, in serious infections that may be caused by *B. fragilis*, such as supplicative intra-abdominal or gynecologic infections, clindamycin or chloramphenicol has come to be regarded as the drug of choice [1–3]. Each of these drugs, however, has been implicated in rare but serious idiosyncratic reactions: aplastic anemia with chloramphenicol [15] and pseudomembranous enterocolitis with clindamycin [16].

Sutter and Finegold reported that carbenicillin inhibited 96% of *B. fragilis* strains at a concentration of 100 µg/ml [6], although Tally et al. [8] found that only 60% of strains were inhibited by 128 µg/ml. These concentrations are readily attainable with iv doses of 400–500 mg/kg per day, dosages required for treatment of systemic infections caused by *Pseudomonas aeruginosa* [18–20]. Clinical trials of carbenicillin in pulmonary and intraabdominal infections due to anaerobes suggest that the drug is efficacious when given in these doses [9–11]. Very recently, ticarcillin, a new antipseudomonal penicillin more potent than carbenicillin, has also been shown to have activity against *B. fragilis* [21], and early clinical trials suggest that it is also effective clinically in anaerobic bacterial infections [17].

Since the Food and Drug Administration approved carbenicillin for treatment of anaerobic bacterial infections, we have observed increasing use of the drug in all types of anaerobic infections, primarily because of promotion on the part of its manufacturers. We question the advisability of regarding carbenicillin (or ticarcillin) as a first-line drug for treatment of these infections, particularly infections of soft tissue, lung, genital tract, and abdomen, which are characterized by large populations of aerobic gram-negative bacilli, often including *P. aeruginosa*. *P. aeruginosa* strains readily develop resistance to carbenicillin, particularly when large microbial populations are present, such as in pneumonias or soft tissue infections [22–27] and burn wounds [28, 29]. We are concerned that wide-scale use of carbenicillin for treatment of anaerobic bacterial infections could result in a

<table>
<thead>
<tr>
<th>Subject, drug</th>
<th>Blood level (µg/ml)</th>
<th>MBC*</th>
<th>Blood level (µg/ml)</th>
<th>MBC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject no. 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>596</td>
<td>1:16</td>
<td>122</td>
<td>1:4</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>482</td>
<td>1:16</td>
<td>9.3</td>
<td>&lt;1:2</td>
</tr>
<tr>
<td>Subject no. 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>622</td>
<td>1:32</td>
<td>108</td>
<td>1:4</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>457</td>
<td>1:32</td>
<td>19.4</td>
<td>1:2</td>
</tr>
</tbody>
</table>

**NOTE:** The peak level was measured 15 min after administration of the drug, and the trough level was measured at 3.5 hr.

*Maximal bactericidal dilution when tested against a strain of *B. fragilis* with MBCs of 64 µg of carbenicillin/ml and 32 µg of penicillin/ml.
significant increase in the prevalence of carbenicillin-resistant *P. aeruginosa*. Such an effect would have serious implications since evidence suggests that carbenicillin, when combined with an aminoglycoside such as gentamicin or tobramycin, has had a major impact in reducing the mortality from *P. aeruginosa* sepsis, particularly in patients with leukemia [18–20]. In several centers where carbenicillin has been extensively used since 1970, but primarily only for treatment of presumed or suspected *P. aeruginosa* infections, the prevalence of carbenicillin resistance has remained stable [27, 30].

*B. fragilis* is often regarded by clinicians to be resistant to penicillin G because most strains are not inhibited by concentrations of 2–10 μg/ml [1, 2, 5, 6]. The present study of clinical isolates, nearly one-half from bacteremic infections, confirms the findings of prior studies [4–8] that penicillin G is more active in vitro against *B. fragilis* on an equal weight basis than carbenicillin (table 1). Furthermore, penicillin is as rapidly bactericidal as carbenicillin (figure 1). The bactericidal activity against a *B. fragilis* strain with relatively high MICs suggests that penicillin might be as effective as carbenicillin for treatment of *B. fragilis* infections.

The pharmacology of penicillin G and sodium carbenicillin is similar except that penicillin G has a shorter 1/2 (≈0.5 vs. 1.0 hr) [31]. Dosages of 20–30 × 10^6 units of aqueous penicillin G per day have long been safely used for treatment of subacute bacterial endocarditis. Weinstein et al. [32] in 1963 reported that serious complications were infrequent even with very high dosages of aqueous penicillin, averaging 40–80 × 10^6 units per day, which produced serum levels of up to 737 units/ml. Seizures occurred in several patients with renal insufficiency or neurologic disorders. In this study Weinstein and his colleagues found that aqueous penicillin G alone, in large dosages, was effective in treating sepsis caused by aerobic gram-negative bacilli with MICs of penicillin in the range of 2.5–625 μg/ml, organisms that are conventionally regarded as resistant. More recently, Benner [33] reported a highly favorable experience with benzylpenicillin treatment of 117 patients with severe infections due to *Bacteroides* species, 61 of whom had bacteremia; all but one patient survived. The penicillin dosage was designed to provide a serum level of 250–400 μg/ml. It is almost certain that many of these infections, particularly those of the abdomen or pelvis, were caused by *B. fragilis*.

We do not advocate the use of penicillin G for treatment of serious infections caused by *B. fragilis* because both clindamycin and chloramphenicol have well-established efficacy, and life-threatening adverse reactions associated with each of these drugs are infrequent or, in the case of chloramphenicol, rare [15]. Furthermore, in studies with several well-defined animal models of anaerobic infection, clindamycin was superior to high-dosage penicillin in protection against late abscess formation by anaerobes [34]; penetration of benzylpenicillin into anaerobic abscesses appeared to be poor [35].

We suggest, however, that because of the aforementioned considerations, the use of sodium carbenicillin (or ticarcillin) as a first-line drug for treatment of anaerobic infections should be critically reexamined. Carbenicillin and ticarcillin would seem better reserved for *P. aeruginosa* infections, for mixed anaerobic infections in which *P. aeruginosa* is likely or known to be a pathogen, and possibly for *B. fragilis* endocarditis [36, 37].

Should resistance of *B. fragilis* to clindamycin and chloramphenicol increase or drug toxicity associated with these two agents become more problematic, high-dosage aqueous penicillin G, because of its at least equivalent in vitro activity against *B. fragilis* and much lower cost, would seem preferable to carbenicillin for treatment of anaerobic infections caused by *B. fragilis*. Comparative randomized clinical trials of penicillin G, carbenicillin (or ticarcillin), clindamycin, and chloramphenicol in treatment of *B. fragilis* infections should be undertaken.

References

1294, 1974.


33. Benner, E. J. Benzylpenicillin therapy in bacteroides infections [abstract no. 196]. In Programs and abstracts of the 14th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1974, San Fran-


