Interactions of Carbenicillin and Ticarcillin with Gentamicin

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The in vitro inactivation of gentamicin by carbenicillin and a new semisynthetic penicillin, ticarcillin (BRL 2288), has been demonstrated. Gentamicin half-lives have been studied in eight patients with end-stage renal failure, and a 25 to 74% reduction in half-life has resulted from the concomitant administration of therapeutic doses of carbenicillin and ticarcillin.

The penicillin and aminoglycoside groups of antibiotics are often used in combination. Gentamicin and carbenicillin are widely used in the treatment of gram-negative infections, particularly those caused by Pseudomonas pyocyanae. The in vitro inactivation of gentamicin by carbenicillin was clearly demonstrated by McLaughlin and Reeves (5), who suggested that some antagonistic effect might take place in vivo by a combination that had hitherto been regarded as additive or synergistic (1, 3, 7, 8). No inactivation was apparent when the two drugs were given to patients with normal renal function, provided the antibiotics were administered separately via different injection sites (6, 9). Riff and Jackson (6) studied the half-life of gentamicin in four patients receiving hemodialysis. They found a half-life of 60 h in one patient, whereas in the remaining three patients the half-life concentration was not reached in the interval between hemodialyses. When carbenicillin and gentamicin were administered concomitantly in a dosage ratio of 80:1, the half-life of gentamicin was reduced to 24 to 30 h.

A new semisynthetic penicillin, ticarcillin (BRL 2288), with a chemical structure and antimicrobial range similar to carbenicillin was reported recently (4). Its similarity to carbenicillin suggests that it might have some antagonistic effects on gentamicin. This report compares the antagonistic activity of ticarcillin and carbenicillin against gentamicin. The activity was assessed in vitro and in patients on maintenance dialysis.

MATERIALS AND METHODS

Informed consent was obtained from the patients who took part in this study. All had end-stage renal failure and no history of penicillin allergy. Each patient served as his own control.

A single intramuscular injection of gentamicin was given in doses varying from 60 to 80 mg according to the patient's weight. Blood was taken at intervals over the ensuing 48 h. After a period varying from 2 to 28 days, during which time the patients received at least one 8-h hemodialysis or 48-h peritoneal dialysis, a second injection of gentamicin was given. In addition, the patient received 2 g of carbenicillin or ticarcillin every 8 h by intravenous injection over 3 to 5 min. Blood samples were taken over 48 h. For the assay of gentamicin, blood samples were collected into tubes containing penicillinase. Serum was separated, frozen, and stored at −20 C until assays could be performed. Eight patients were studied; three received carbenicillin and five received ticarcillin.

In vitro experiments, 10 µg of gentamicin per ml and either 200 µg of carbenicillin or 200 µg of ticarcillin per ml were used. The mixtures were prepared in phosphate-buffered saline (pH 7.3) and shaken at 37 C. Samples were withdrawn at timed intervals, penicillinase was added, and the samples were frozen at −20 C until the gentamicin assays were performed.

Gentamicin assays were carried out by the technique of Bennett et al. (2) with Bacillus subtilis spores. Carbenicillin and ticarcillin assays were carried out by the technique of Bennett et al. (2) with Pseudomonas pyocyanae NCTC 10701 which was resistant to gentamicin.

RESULTS

Figure 1 illustrates the concentrations of gentamicin in a patient who received a single intramuscular injection of the antibiotic. This was compared with the concentrations attained in the same patient when he received concomitantly an intravenous injection of carbenicillin every 8 h. This regimen resulted in carbenicillin levels ranging from 68 to 390 µg/ml with a mean value of 180 µg/ml over 48 h. By 24 h significant inactivation of gentamicin had occurred, and by 48 h the gentamicin level had dropped to 1.2

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μg/ml of serum. Figure 2 presents these data as a semilogarithmic plot of gentamicin concentration against time and the best line drawn from regression analysis. Confidence limits have been included, and the correlation coefficients are significant ($P < 0.05$).

The effect of ticarcillin on gentamicin in a second patient is shown in Fig. 3. Ticarcillin levels ranged between 120 and 244 μg/ml over the 48-h period. Inactivation of gentamicin was apparent by 24 h, and at 48 h gentamicin levels were 50% of the control. Figure 4 represents a more detailed analysis of the data with confidence limits of the logarithmic inactivation of gentamicin and the correlation coefficients that are significant ($P < 0.05$).

Calculation of the gentamicin half-life in each patient was made from the semilogarithmic plots (Fig. 2, 4, and 5). These results, together with the concomitant levels of carbenicillin or ticarcillin, are shown in Table 1. The gentamicin half-life was reduced by 22 to 31 h in three
patients receiving carbenicillin and by 8 to 50 h in patients receiving ticarcillin. When expressed as a percentage of the control values, the half-life of gentamicin was reduced by 25 to 74% in all the patients studied.

From the data in Fig. 2, 4, and 5 regression coefficients were analyzed by Student's t test. A comparison of gentamicin activity under control and test conditions indicated statistical significance (P < 0.005).

The in vitro rate of inactivation of 10 μg of gentamicin per ml in the presence of 200 μg of ticarcillin per ml at 37 C is shown in Fig. 6. There was approximately 20% inactivation under control conditions, whereas the gentamicin concentration fell below 50% after 15 h in the mixture, and by 45 h no detectable levels of gentamicin were found. Figure 7 shows the results of an experiment with carbenicillin. A similar effect was seen, but there was a suggestion that the rate of inactivation was slower since 50% of active gentamicin remained at 30 h and detectable levels were still present at 60 h.

**DISCUSSION**

Ticarcillin is a new semisynthetic penicillin (carboxyl-3-thienyl methyl penicillin) with a wide antibacterial activity against gram-positive and gram-negative bacteria including *P. pyocyanea*. It is similar to carbenicillin, which is often used in combination with gentamicin, and it seems likely that a gentamicin-ticarcillin combination may also be used for the treatment of serious gram-negative bacterial infections. The possibility must also be considered that under certain circumstances adverse interactions may take place analogous to the inactivation of gentamicin by carbenicillin (5, 6). Our in vitro studies suggest that gentamicin is inactivated by both carbenicillin and ticarcillin at 37 C. Although complete inactivation by carbenicillin seemed to be slower, both penicillins

### TABLE 1. Gentamicin half-lives and concentrations of carbenicillin or ticarcillin achieved in patients with renal failure

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gentamicin half-life (h)</th>
<th>Reduction in half-life (%)</th>
<th>Concen of carbenicillin or ticarcillin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Along</td>
<td>With penicillin</td>
<td>Mean (μg/ml)</td>
</tr>
<tr>
<td>R.F.</td>
<td>42</td>
<td>11</td>
<td>74</td>
</tr>
<tr>
<td>M.L.</td>
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<td>11</td>
<td>67</td>
</tr>
<tr>
<td>P.H.</td>
<td>50</td>
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<td>56</td>
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<tr>
<td>B.H.</td>
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</tr>
<tr>
<td>J.S.</td>
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<td>23</td>
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<tr>
<td>J.P.</td>
<td>32</td>
<td>24</td>
<td>25</td>
</tr>
</tbody>
</table>

* The penicillin used was carbenicillin; the remainder received ticarcillin.

* Standard deviation.
over 24 h, which provided a carbenicillin concentration of 1,000 µg/ml in the blood. Riff and Jackson (6) have shown that in patients receiving hemodialysis inactivation of gentamicin took place when carbenicillin and gentamicin were administered concomitantly at a dosage ratio of 80:1. The carbenicillin concentrations in the serum were not mentioned. We have studied the concentrations of gentamicin in patients who received doses of carbenicillin at 8-h intervals resulting in mean drug concentrations of 180 to 205 µg/ml of serum. In five patients who received ticarcillin, the mean drug concentrations in the serum were between 97 and 177 µg/ml. We would consider these concentrations to be potentially therapeutic but still high enough to produce significant reduction in the half-life of gentamicin. Although the number of patients studied was small, there did not appear to be any appreciable difference in the antagonistic activity of ticarcillin and carbenicillin.

The reduction in the half-life of gentamicin produced by carbenicillin and ticarcillin is of importance in patients with severe renal failure, receiving gentamicin at 48- to 72-h intervals. In dialysis patients receiving combination therapy, regular monitoring of the concentrations of gentamicin in serum is essential to ensure adequate therapeutic levels as well as to avoid ototoxicity. The advantages of ticarcillin relate to its superior antimicrobial activity and to the fact that, in our experience, the injections are far less painful.

ACKNOWLEDGMENT

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LITERATURE CITED