Comparison of the Effects of Mezlocillin, Carbenicillin, and Placebo on Normal Hemostasis

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Mezlocillin was compared with carbenicillin and 0.9% NaCl as placebo in a double-blind manner to determine its effect in vivo on hemostasis in normal volunteers. Eighteen subjects were randomized to receive mezlocillin, 4 g every 6 h; carbenicillin, 7.5 g every 6 h; or placebo, 50 ml every 6 h, each given for 20 intravenous doses unless the template bleeding time after 10 doses was >15 min. Template bleeding times were determined before the dose 1 and 1 h after doses 10 and 20. Five of six (83%) subjects receiving carbenicillin developed template bleeding time prolongation to >21 min, and two of six (33%) subjects receiving mezlocillin and one of six (17%) subjects receiving carbenicillin had mild template bleeding time prolongations of <13 min. Coagulation studies (prothrombin time, partial thromboplastin time, and thrombin time) were normal in all subjects, and blood salicylate levels were negative. Thus, in standard therapeutic doses, mezlocillin was less likely than carbenicillin to prolong the template bleeding time above normal (P = 0.04) and, when prolongation occurred with mezlocillin, it was mild. These data support the selective use of mezlocillin in patients at increased risk for bleeding and who require therapy with an antipseudomonal penicillin.

Carbenicillin, ticarcillin, and other commonly used penicillins can cause platelet dysfunction (3–5, 8) and a bleeding diathesis (1, 5, 9, 12), which has been more apparent in patients with renal failure (1) and in those undergoing surgery (5, 9). Patients with preexisting hemostatic defects, such as thrombocytopenia due to cancer chemotherapy or hematological malignancies, are also at increased risk for hemorrhage. Antipseudomonal penicillins, including carbenicillin and ticarcillin, are routinely prescribed when these thrombocytopenic patients develop severe granulocytopenia and fever (2). Therefore, it would be desirable to identify antipseudomonal penicillins which lack platelet-inhibitory properties.

Mezlocillin is a new, broad-spectrum acylureidopenicillin with excellent in vitro activity against Pseudomonas aeruginosa (7). Two in vitro studies (13, 14) failed to show that high concentrations of mezlocillin inhibited the ADP- and collagen-induced aggregation of normal platelet-rich plasma. To assess the relative risk of inducing in vivo platelet dysfunction or coagulopathy with mezlocillin, we prospectively compared the bleeding times and coagulation studies of normal volunteers randomized to receive mezlocillin, carbenicillin, or placebo.

(MATERIALS AND METHODS

Volunteer subjects. Eighteen healthy adults, nine women and nine men ranging in age from 22 to 35 years, from The M. S. Hershey Medical Center staff and student body volunteered for the study. Each subject gave informed consent before enrollment. A detailed history and physical examination was completed before treatment. Pre- and post-study safety tests included complete blood count, differential, platelet count, prothrombin time, partial thromboplastin time, thrombin time, electrolytes, renal and liver function tests, calcium, phosphorus, uric acid, cholesterol, and urinalysis. Criteria for exclusion included history of penicillin allergy; abnormal bleeding history or systemic illness; use of any medication, including oral contraceptives, within the preceding 3 weeks; pregnancy or breast feeding; and abnormality of screening laboratory tests. Women who were using a method of birth control other than oral contraceptives were eligible.

Extraneous drugs, including alcohol, salicylates, and non-steroidal antiinflammatory agents, were prohibited during the study. Blood studies for salicylate levels were obtained before and during the study to monitor for inadvertent use of drugs. Volunteers were permitted to continue their daily occupations and were evaluated for adverse reactions every 6 h by one of the physician-investigators.

Study design. A computer-generated randomization code was used to assign volunteers to one of three groups receiving (i) mezlocillin, 4 g intravenously every 6 h; (ii) carbenicillin, 7.5 g intravenously every 6 h; or (iii) 0.9% sodium chloride injection, USP, as placebo, 50 ml intravenously every 6 h. Antibiotics were reconstituted by a hospital pharmacist according to the manufacturer's instructions and then diluted to a final volume of 50 ml with 0.9% sodium chloride injection, USP. The pharmacist coded and dispensed the drugs and placebo in identical-appearing plastic bags in such a manner that neither volunteers nor the investigators knew the study group assignments. Each dose was administered by an investigator over 15 min through a forearm vein. Volunteers received a total of 20 doses over 5 days unless the template bleeding times (TBTs) after dose 10 (2.5 days) exceeded 15 min, at which time the volunteer was removed from the study. TBT determinations were repeated at 48 to 96 h after discontinuation of the study drug in volunteers with TBTs of >15 min.

Clotting studies. Platelet counts, TBT determinations, and blood coagulation studies (prothrombin time, partial thromboplastin time, and thrombin time) were performed before
dose 1 and 1 h after doses 10 and 20. Platelet counts were performed by an automated cell counter on whole blood anticoagulated with EDTA. The TBTs were determined by two of the investigators using the Simplate II device (General Diagnostics, Warner-Lambert Co.). A blood pressure cuff was inflated to 40 mmHg, and two standardized incisions, 6 mm in length and 1 mm in depth, were made parallel and 5 to 8 cm distal to the antecubital crease on the volar forearm at a site free of veins and hair. Blood exuding from the wound was blotted with filter paper every 30 s, and care was used to avoid the wound margins. The time required for cessation of bleeding was recorded with a stopwatch and expressed as the average time for the two incisions to stop bleeding. When possible, the same arm was used for each determination. TBT determinations were immediately repeated when a value exceeded the protocol limit of 15 min. The normal range, established by testing 20 normal volunteers taking no medications, was 2.5 to 8 min.

Blood for coagulation tests was drawn into tubes containing a 0.1 volume of 3.8% sodium citrate, and the platelet-poor plasma was obtained by centrifugation at 2,000 × g for 15 min. Prothrombin time, activated partial thromboplastin time, and thrombin time were measured by standard methods (17).

**Drug assays.** Blood samples for antibiotic and salicylate concentrations were drawn before dose 1 of the test drug and 1 h after doses 10 and 20, corresponding to the timing of TBT determinations. Sera were flash-frozen and shipped on dry ice to Miles Pharmaceutical Laboratories for bioassays in which an agar well diffusion technique and *Bacillus subtilis* ATCC 6633 as the test organism were used.

**RESULTS**

Demographic data for the study population are summarized in Table 1. Age and sex distribution was similar for the three groups. Mean body weight was least for the placebo group and greatest for volunteers who received mezlocillin. Total daily dose of mezlocillin was 16 g, and the mean dose according to body weight (± standard deviation) was 205.2 ± 37 mg/kg per day, compared with 50 g per day and 475.2 ± 115 mg/kg per day for carbenicillin.

Platelet counts and blood coagulation studies remained normal for all volunteers throughout the study, and serum salicylates were not detected. Serial TBTs of subjects randomized to each of the three study groups are shown in Fig. 1. Values for volunteers receiving placebo were within the normal range throughout the study. All subjects treated with mezlocillin or placebo completed all 20 doses, but 4 of 6 subjects receiving carbenicillin were removed from the study after 10 doses because TBTs exceeded 15 min (actual TBTs were >21 min in all four subjects). One additional carbenicillin volunteer had developed a TBT prolongation of >21 min when measured 1 h after dose 20. Thus, five of six (83%) subjects who received carbenicillin had TBTs of >21 min at some time during the study. Two of six (33%) subjects randomized to the mezlocillin group and one of six (17%) subjects in the carbenicillin group had mildly prolonged TBTs of 11.5, 12.5, and 11.5 min, respectively, after either 10 or 20 doses of the test drug. Mezlocillin was, therefore, less likely than carbenicillin to prolong the TBT above the upper normal limit (P = 0.04, Fisher's exact test).

Table 2 shows a comparison of body weight, dosage, drug level in serum, and TBTs for individuals in the mezlocillin and carbenicillin groups. Mean body weight was higher for the mezlocillin group than for the carbenicillin group; however, within each group neither dose, in milligrams per kilogram of body weight, nor serum drug level was predictive of which volunteers would develop prolonged TBTs. Markedly prolonged TBTs (>21 min) in five carbenicillin volunteers returned to normal only after an interval of 72 to 96 h after the final dose.

None of the volunteers developed clinical bleeding; the only side effect was mild diarrhea in six volunteers receiving either mezlocillin (four subjects) or carbenicillin (two subjects). Post-study screening laboratory tests were normal except in two volunteers who received carbenicillin. One had a serum glutamic pyruvic transaminase of 50 IU and a serum glutamic oxalacetic transaminase of 43 IU, and in the other, serum potassium was 3.4 meq/liter.

**DISCUSSION**

The objective of this investigation was to assess the effect of mezlocillin on normal hemostasis compared with the effect of carbenicillin, using a controlled, double-blind study design. To simulate current clinical practice, the daily dosages of both antibiotics were those recommended for the treatment of severe infections and were not based on body weight. Platelet function was monitored with the standardized TBT, since it has been shown that in vivo platelet function correlates best with this test (11).

![Graph showing TBTs of subjects in each study group](http://aac.asm.org/)

**FIG. 1.** Serial TBTs of subjects in each study group performed immediately prestudy and 1 h after doses 10 and 20 (normal range shaded).

**TABLE 1.** Demographic characteristics of study population

<table>
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<th>Study group (n)</th>
<th>Mean ± SD age (yr)</th>
<th>Sex (no. female/no. male)</th>
<th>Mean ± SD wt (kg)</th>
<th>Total dose (g per day)</th>
<th>Mean ± SD dose (mg/kg per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (6)</td>
<td>28.7 ± 4.7</td>
<td>4/2</td>
<td>60.6 ± 9.2</td>
<td>16</td>
<td>205.2 ± 37</td>
</tr>
<tr>
<td>Mezlocillin (6)</td>
<td>27.5 ± 3.8</td>
<td>2/4</td>
<td>79.9 ± 13.0</td>
<td>16</td>
<td>457.2 ± 115</td>
</tr>
<tr>
<td>Carbenicillin (6)</td>
<td>25.7 ± 3.3</td>
<td>3/3</td>
<td>69.0 ± 13.9</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>
During the study, blood coagulation tests and platelet counts remained normal, but several volunteers developed evidence of platelet dysfunction. All six subjects receiving carbenicillin (30 g per day) developed abnormal TBTs and, in five of these, TBTs exceeded 21 min. In contrast, only two of six subjects receiving mezlocillin (16 g per day) showed abnormal TBTs, but the degree of prolongation was less than 13 min in each.

Other investigators have shown that several antibiotics of the β-lactam class interfere with platelet activation and aggregation in vitro at concentrations higher than those usually achieved in vivo (15). More importantly, human volunteer studies have confirmed that standard doses of penicillin G and carbenicillin (5), ticarcillin (4), and piperacillin (8) impair in vivo platelet function. Although it has been difficult to estimate the true incidence of hemorrhage occurring in patients treated with these drugs, it is clear that surgery (5, 9), renal insufficiency (1), and other coexistent hemostatic defects increase the likelihood of bleeding.

Mezlocillin, unlike other antipseudomonal penicillins, was shown not to interfere with ADP- and collagen-induced aggregation of normal platelet-rich plasma, even in concentrations of up to 10 mg/ml (13, 14). Furthermore, the results of our investigation and of a recently completed study (6) that was not placebo controlled demonstrate that, in standard therapeutic doses given to normal volunteers, mezlocillin is less likely than carbenicillin to prolong the TBT above normal. In another study (16), nearly identical in design to ours, mezlocillin was shown to be less likely than ticarcillin to impair platelet aggregation in vitro or in vivo. Although data obtained from these studies do not prove that therapy with mezlocillin will reduce the incidence of hemorrhage in patients with preexisting risks for bleeding, there is reason to believe that the potential for bleeding may be less in patients treated with mezlocillin compared with other available antipseudomonal penicillins.

Although there are in vivo antibacterial differences among the antipseudomonal penicillins (7) and the sodium content varies with each, comparative studies in febrile granulocytopenic patients who were also receiving an aminoglycoside have failed to show greater efficacy or less hypokalemia with any particular regimen (10, 18). The results of our study do suggest that there may in fact be a hematological safety factor associated with mezlocillin and that it should be used selectively in patients at increased risk for bleeding and who require an antipseudomonal penicillin.

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LITERATURE CITED


