In Vitro and In Vivo Studies of the Effect of Aztreonam on Platelet Function and Coagulation in Normal Volunteers

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Received 2 December 1985/Accepted 11 April 1986

The in vitro effects of aztreonam on platelet aggregation were compared with those of cefotaxime, moxalactam, piperacillin, and carbenicillin. In addition, the in vivo effects of intravenously administered aztreonam on blood coagulation and platelet function were examined in 10 normal male volunteers in a randomized crossover study. In vitro, at concentrations of >6.25 mM (2.7 mg/ml), aztreonam inhibited ADP-induced platelet aggregation in a dose-dependent manner. The effect was less than that produced by equimolar concentrations of cefotaxime, moxalactam, piperacillin, or carbenicillin. At all concentrations tested, aztreonam and cefotaxime inhibited epinephrine-induced aggregation least. All antibiotics inhibited collagen-induced aggregation, but only at inordinately high concentrations (25 mM). In vivo studies in 10 male subjects, randomly infused intravenously with 2 g of aztreonam or saline placebo every 6 h for 21 consecutive doses in a single-blind crossover study, revealed no evidence of bleeding or visible adverse side effects. Although plasma coagulation and platelet adhesion remained within normal limits in all subjects throughout the study, inhibition of ADP-induced platelet aggregation significantly (P < 0.0001) increased on days 3 and 6, but still was below 40%. With the exception of one subject who had a mean template bleeding time of 7.3 min (normal, 2 to 7 min at 95% confidence limits) on day 6 of aztreonam administration, all volunteers exhibited bleeding times within the normal range. No abnormalities in platelet morphology were observed. Mean peak serum aztreonam concentrations on days 1 and 6 were 90.1 ± 16.7 and 95.9 ± 13.7 µg/ml, respectively; accumulation did not occur. Thus, in normal volunteers, aztreonam produced no significant recognizable abnormalities of hemostasis after 6 days of maximal recommended doses.

Abnormalities of hemostasis and the potential for spontaneous hemorrhage exist with beta-lactam antibiotics. Major offending agents include penicillin G, carbenicillin, ticarcillin, and moxalactam; all have been observed to reduce platelet aggregation in a dose-dependent manner (1-5, 10-12, 14, 16, 18, 22). In addition, moxalactam may prolong the prothrombin time if doses exceed 4 g/day (2, 7, 19, 24).

Aztreonam, the first of a new class of beta-lactam antibiotics identified as monobactams, lacks the thiazolidine and dihydrothiazine rings which constitute the nuclei of penicillin and cephalosporin, respectively. Since aztreonam differs chemically from the penicillins and cephalosporins, we examined its effects on coagulation in vitro, comparing it with carbenicillin, piperacillin, cefotaxime, and moxalactam, and in vivo in normal volunteers.

(This paper was presented in part at the 14th International Congress of Chemotherapy, 25 June 1985, Kyoto, Japan.)

MATERIALS AND METHODS

Subjects. After giving informed consent, 10 healthy, male volunteers (ages 23 to 28 years) were enrolled in a randomized crossover study to receive either 21 consecutive doses of intravenous (i.v.) aztreonam (2 g) suspended in 100 ml of normal saline every 6 h, followed by a 14-day drug-free “washout,” followed by 21 consecutive doses of 100 ml of i.v. normal saline (placebo) administered every 6 h; or 21 consecutive doses of placebo, followed by a washout, followed by 21 consecutive doses of aztreonam. Before infusion, all volunteers underwent complete physical examinations and blood tests, which included multiple chemistry profiles, complete blood counts, urinalyses, and coagulation and platelet function studies (see below). Subjects with abnormal laboratory values or a history of bleeding tendencies, including easy bruising and telangiectasia, recent transfusions, acute infections, or previous allergic reactions to beta-lactam antibiotics, were excluded. No volunteers were receiving medications on a chronic basis before or during the study period. All subjects abstained from aspirin, aspirin-containing products, and alcohol within 1 week of enrollment and for the duration of the study.

In vitro antibiotic study. Solutions of each of the following antibiotics were prepared from sterile powder in barbitol-buffered saline (0.15 M, pH 7.34): aztreonam arginine (E. R. Squibb & Sons, Princeton, N.J.; lot MNB-864-H/C 73); moxalactam (Eli Lilly & Co., Indianapolis, Ind.; lot 7LR52C); cefotaxime (Hoechst-Roussel Pharmaceuticals, Inc., Somerville, N.J.; lot L458/190182); carbenicillin (Pfizer, Inc., New York, N.Y.; lot 22074), and piperacillin (Lederle Laboratories, Pearl River, N.Y.; lot 743-306). Three concentrations of each antibiotic were tested: 25, 12.5, and 6.25 mM (corresponding to 10.9, 5.4, and 2.7 mg of aztreonam per ml; 16.5, 8.2, and 4.1 mg of moxalactam per ml; 12.0, 6.0, and 3.0 mg of cefotaxime per ml; 11.9, 5.9, and 3.0 mg of carbenicillin per ml; and 16.5, 8.2, and 4.1 mg of piperacillin per ml, respectively).

Coagulation studies. Plasma prothrombin time, partial thromboplastin time, thrombin time, fibrinogen content, and total platelet counts were performed by standard methods as previously described (13, 20). Fibrin split products were analyzed with a Thermo-Wellco-Test (Wellcome Research Laboratories, Beckenham, England).

* Corresponding author.
TABLE 1. In vitro inhibition of platelet aggregation

<table>
<thead>
<tr>
<th>Antibiotic concn (mM)*</th>
<th>Mean % inhibition ± SD for aggregating agent**</th>
<th>Cefotaxime (5 µg/ml)</th>
<th>Pipeperacillin (11 or 22 µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6.25</td>
<td>8.5 ± 8.6</td>
<td>2.4 ± 4.9</td>
<td>27.2 ± 18.0</td>
</tr>
<tr>
<td>&gt;12.5</td>
<td>18.1 ± 12.9</td>
<td>2.7 ± 7.9</td>
<td>50.2 ± 16.4</td>
</tr>
<tr>
<td>25.0</td>
<td>42.8 ± 17.5</td>
<td>16.8 ± 31.7</td>
<td>76.8 ± 13.6</td>
</tr>
<tr>
<td>Moxalactam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6.25</td>
<td>34.1 ± 10.2</td>
<td>4.5 ± 5.8</td>
<td>41.8 ± 16.9</td>
</tr>
<tr>
<td>&gt;12.5</td>
<td>59.7 ± 10.8</td>
<td>2.2 ± 3.7</td>
<td>67.3 ± 13.7</td>
</tr>
<tr>
<td>25.0</td>
<td>83.4 ± 10.3</td>
<td>17.6 ± 29.1</td>
<td>88.2 ± 10.1</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6.25</td>
<td>35.1 ± 9.7</td>
<td>2.3 ± 5.0</td>
<td>23.2 ± 14.4</td>
</tr>
<tr>
<td>&gt;12.5</td>
<td>57.0 ± 12.6</td>
<td>14.7 ± 16.1</td>
<td>40.9 ± 13.5</td>
</tr>
<tr>
<td>25.0</td>
<td>79.0 ± 5.9</td>
<td>94.9 ± 11.3</td>
<td>73.5 ± 12.0</td>
</tr>
<tr>
<td>Carbenicillin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6.25</td>
<td>16.1 ± 7.9</td>
<td>2.9 ± 5.7</td>
<td>34.3 ± 18.4</td>
</tr>
<tr>
<td>&gt;12.5</td>
<td>42.0 ± 10.6</td>
<td>4.6 ± 6.2</td>
<td>58.6 ± 11.0</td>
</tr>
<tr>
<td>25.0</td>
<td>74.4 ± 6.9</td>
<td>47.9 ± 32.3</td>
<td>95.5 ± 7.8</td>
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<tr>
<td>Piperacillin</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6.25</td>
<td>19.4 ± 13.9</td>
<td>2.2 ± 3.3</td>
<td>51.2 ± 18.6</td>
</tr>
<tr>
<td>&gt;12.5</td>
<td>46.1 ± 14.9</td>
<td>5.6 ± 8.6</td>
<td>78.2 ± 12.6</td>
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<tr>
<td>25.0</td>
<td>83.6 ± 8.5</td>
<td>14.4 ± 16.5</td>
<td>92.4 ± 15.5</td>
</tr>
</tbody>
</table>

** Antibiotic concentrations tested (see text).
** Expressed as final % inhibition.
*** 76 rather than 190 µm/ml was used for cepotaxime and carbenicillin studies.

Bleeding time and platelet adhesion. Platelet adhesion was studied by the method of Bowie et al. (9), and the template bleeding time was performed in triplicate by the method of Mielke et al. (17), always by the same investigator (T.A.T.), and mean values were calculated.

Platelet aggregation studies. Whole blood was mixed with sodium citrate (3.8%) to produce an anticoagulant/blood ratio of 1:9. Platelet-rich plasma (PRP) and platelet-poor plasma were prepared by centrifugation at 1,200 x g for 5 and 15 min, respectively, at room temperature (23°C). Platelet counts in the PRP test were adjusted to 180,000 platelets per ml. For each determination of platelet aggregation, the PRP test mixture contained 0.4 ml of test PRP and 0.05 ml of antibiotic solution or buffer (control).

Platelet aggregation was measured in duplicate with an automatic platelet aggregometer (dual channel, model 440; Chrono-Log Corp., Havertown, Pa.) by the turbimetric method of Born and Cross (8). Heights of aggregation were measured at predetermined times after maximal response (ADP, 4 min; collagen, 8 min; epinephrine, 6 min). Responses of test PRP without antibiotics (control) were determined frequently (three to four times) throughout each aggregation run. Percent inhibition of platelet aggregation was calculated with the following formula: % inhibition = (control aggregation [mm] - antibiotic aggregation [mm]/control aggregation [mm]) x 100. All platelet aggregations were studied within 3 h of venipuncture.

In vitro protocol. PRP obtained from each volunteer was mixed in vitro with various concentrations of aztreonam, moxalactam, cefotaxime, carbenicillin, and piperacillin (see above). Antibiotic-PRP mixtures were incubated for exactly 10 min at 37°C before the addition of 0.05 ml of the aggregating agents ADP (Sigma Chemicals, St. Louis, Mo.), collagen (Biodata; lot 081085B), and epinephrine (Parke, Davis & Co., Detroit, Mich.; lot 02183P). (Preliminary work had demonstrated that 10 min was sufficient for maximum in vitro antiplatelet effect of the antibiotic.) The final concentrations of each aggregating agent in the PRP test mixtures were as follows: ADP, 5 M; collagen, 76 or 190 µg/ml; and epinephrine, 11 or 22 µg/ml.

In vivo protocol. Subjects were admitted to the Clinical Research Ward of the Medical College of Virginia Hospitals and were randomly assigned to receive aztreonam or placebo in a single-blind crossover study. Aztreonam was administered at a maximum dose of 2 g, which was given every 6 h for 21 consecutive doses. The antibiotic was dissolved in 100 ml of 0.9% normal saline and was infused over 30 min. Subjects assigned to placebo treatment received 21 consecutive, 100-ml doses of 0.9% normal saline i.v. over 30 min every 6 h. A 14-day drug-free period (washout) was interposed between the two treatment periods of placebo and aztreonam.

The following tests were performed before commencement of the study and 30 min after completion of the infusion of dose 1 on days 1, 2, 3, and 6 of each study period: complete blood counts (hemoglobin, leukocytes, and platelets), prothrombin time, partial thromboplastin time, thrombin time, fibrin split products, plasma fibrinogen, platelet adhesion, platelet aggregation, and bleeding time. Blood smears were prepared for evaluation of platelet morphology by light microscopy. In addition, peak (30 min after completion of infusion) and trough (30 min before infusion) serum aztreonam concentrations were obtained on study days 1, 2, 3, and 6. Aztreonam concentrations were analyzed by E. R. Squibb & Sons, with a reverse-phase high-performance liquid chromatography procedure previously described (23). Vital signs were monitored three times daily throughout the study period.

One week after the aztreonam treatment period, all of the aforementioned tests, including a multichemistry profile and urinalysis, were repeated, as was a complete history and physical examination.

Statistical analysis. In vitro inhibition of platelet aggregation was analyzed by a one-way analysis of variance and 120

FIG. 1. Mean peak serum level of aztreonam on days 1, 2, 3, and 6 of therapy (x±S.E.M.) and corresponding in vivo mean bleeding times (○-○) in 10 normal male volunteers receiving 2 g of aztreonam i.v. every 6 h. (See Tables 1 and 2 and Fig. 2 for additional data.)
subjected to the Tukey studentized range test for determination of significant differences. In vivo measurements of coagulation time, inhibition of platelet aggregation, and bleeding time were subjected to multivariate analysis for the repeated measurement design, paired t test, and Wilcoxon signed-rank test.

RESULTS

In vitro aggregation studies. In vitro platelet aggregation responses to ADP, collagen, and epinephrine to various concentrations of aztreonam, moxalactam, cefotaxime, carbencillin, and piperacillin are shown in Table 1.

All beta-lactams tested in vitro produced a dose-dependent inhibition of ADP-induced aggregation, which was essentially linear between the concentrations of 6.25 and 25 mM. Of those tested, aztreonam was associated with the lowest inhibition (P < 0.05).

Platelet aggregation responses to collagen varied. At the highest collagen concentrations used (190 µg/ml), minimal inhibition of aggregation occurred with all test concentrations of aztreonam, moxalactam, and piperacillin. The highest antibiotic concentration (25 mM) produced mean inhibitions of <18%. At the lowest collagen concentration used (76 µg/ml), 25 mM concentrations of cefotaxime and carbencillin produced 94.9 ± 11.3 and 47.9 ± 32.3% inhibition, respectively. Concentrations of <12.5 mM for all antibiotics tested had little effect on collagen-induced platelet aggregation.

Inhibition of epinephrine-induced platelet aggregation was also dose dependent. However, no statistically significant differences in percent inhibition were apparent between the antibiotics tested at each concentration. Aztreonam and cefotaxime were associated with the lowest epinephrine-induced inhibition at all concentrations of antibiotics tested.

In vivo studies. All subjects in the placebo and aztreonam groups completed the study without evidence of abnormal bleeding or easy bruising. Mean increases (increments) in bleeding times between control (placebo) and aztreonam-treated groups over the 6-day period and on day 6 were 0.9 and 1.4 min, respectively, which were significant at P values of <0.01 and <0.05, respectively (by both paired t and Wilcoxon signed-rank tests). However, mean values for either group were well within the normal range (Fig. 1 and Table 2). By multivariate analysis for the repeated measurement design, no significant increase in bleeding time was noted over the 6-day period.

On day 6 of aztreonam treatment, subject no. 6 (Table 2) exhibited a mean bleeding time of 7.3 min. Although this value exceeded the 95% confidence limits of the test for normal template bleeding time (2 to 7 min), it did not exceed the limits of the known range (2 to 10 min). On day 6 after completing aztreonam, it fell to 2.3 min.

Coagulation tests. All plasma coagulation tests, including prothrombin time, partial thromboplastin time, thrombin time, plasma fibrinogen, and fibrin split products, remained unchanged in all subjects while receiving aztreonam or saline placebo (Table 2). In addition, no abnormalities of platelet count, platelet adhesion, or platelet morphology were observed.

Platelet aggregation. Mean inhibition of platelet aggregation responses to ADP, collagen, and epinephrine on days 1, 2, 3, and 6 during control (placebo) and aztreonam treatment were shown in Fig. 2. The percent inhibition of ADP-induced aggregation significantly increased between days 1 and 3 (P < 0.0001, paired t test) and between days 1 and 6 (P < 0.0001), although no difference in inhibition was apparent between days 3 and 6. The mean percent inhibition of collagen- and epinephrine-induced platelet aggregation did not change significantly during the study.

Aztreonam concentrations in serum. Serum levels of aztreonam did not accumulate during the treatment period (Table 2), and steady states were achieved. Mean differences between aztreonam concentrations were not statistically significant (P < 0.05, paired t test). Mean serum aztreonam peak concentrations on days 1 and 6 were 90.1 ± 16.7 and 95.9 ± 13.7 µg/ml, respectively; the mean trough value on day 6 was 10 ± 3.0 µg/ml.

Complications. One subject developed mild, nonwatery diarrhea on day 2 of aztreonam treatment, which resolved on day 6, 24 h after completing the treatment. No therapy was required for this complication. One subject complained of headaches and a mild sore throat after entering the study. By day 2 of aztreonam treatment, he had a fever of 101°F (38.3°C). Physical examination revealed tender, enlarged nodes associated with a white patchy exudate on the tonsils and pharynx. Throat cultures were negative for group A streptococci. On day 4 of aztreonam administration, erythromycin treatment (250 mg every 6 h) was begun after obtaining a second throat culture. Within 48 h, his fever and sore throat resolved. He was fully recovered 1 week after completion of aztreonam treatment. The second throat culture was also negative for group A streptococci. The etiology

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**TABLE 2. Platelet function and coagulation studies during aztreonam treatment***

<table>
<thead>
<tr>
<th>Patient</th>
<th>Platelet count (×10³)</th>
<th>Platelet adhesion (% retention)</th>
<th>Bleeding time (min)</th>
<th>Peak aztreonam concn (µg/ml) after dose:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base line</td>
<td>Final</td>
<td>Base line</td>
<td>Final</td>
</tr>
<tr>
<td>1</td>
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<td>177</td>
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<td>89.9</td>
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<td>159</td>
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<td>215</td>
<td>92.2</td>
<td>92.0</td>
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<td>6</td>
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<td>7</td>
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<td>80.7</td>
<td>76.0</td>
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<td>8</td>
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<td>175</td>
<td>92.0</td>
<td>88.7</td>
</tr>
<tr>
<td>9</td>
<td>273</td>
<td>244</td>
<td>92.6</td>
<td>84.8</td>
</tr>
<tr>
<td>10</td>
<td>239</td>
<td>182</td>
<td>87.3</td>
<td>77.0</td>
</tr>
</tbody>
</table>

Mean (± SD) 221.7 (49.2) 198.9 (44.7) 87.8 (7.0) 85.4 (7.5) 3.4 (1.4) 5.0 (1.4) 90.1 (16.7) 95.9 (13.7)

* Normal values: platelet count, 150 × 10³ to 250 × 10³/mm³; platelet adhesion, 75 to 97% retention; bleeding time, 2 to 7 min with 95% confidence limits (range, 2 to 10 min).

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of his disease was unknown, but it was not thought to be drug related.

**DISCUSSION**

Defects in hemostasis may occur after the administration of many beta-lactam antibiotics. Usually, these defects are apparent 4 to 6 days after starting therapy. Hemorrhagic episodes and increased bleeding times have been reported in uncontrolled studies of the administration of penicillin G and several antipseudomonal, broad-spectrum penicillins, but not mezlocillin (3–5, 10–12, 14–16, 22). However, few well-controlled studies have assessed the in vivo effects of beta-lactam antibiotics on platelet function.

Aztreonam, the first of a new class of monobactam antibiotics, is excreted primarily by glomerular filtration (23). Its clinical use is intended primarily for the treatment of serious, gram-negative, bacillary infections. Recommended doses range from 0.5 to a maximum of 2.0 g with recommended intervals of 4 to 6 h. It has little or no activity against gram-positive and anaerobic organisms. Since it does not alter bowel flora drastically, interference with vitamin K production should be minimal (M. Barza, M. Giuliano, and S. L. Gorbach, Proc. 14th Int. Congr. Chemother., abstr. no. S-34-5, 1985).

In our in vivo study, no volunteer exhibited bleeding or was observed to bruise easily during or after i.v. infusions of aztreonam given in maximum recommended daily doses (2 g every 6 h) for up to 6 days. Although the mean bleeding time increased significantly (by paired t and Wilcoxon signed-rank tests) over the 6-day period, it did not increase when the data were subjected to multivariate analysis for the repeated measurement design. (However, since the sample size was relatively small, i.e., 10 subjects, the power of multivariate analysis may have been low.) In addition, no defects in platelet function or significant abnormalities in coagulation tests were observed; and template bleeding times exceeded the normal range (2 to 7 min at 95% confidence limits) in only one instance, implying a lack of clinically significant in vivo platelet dysfunction. Although mean ADP-induced platelet aggregation decreased significantly on day 3 and was still evident on day 6 of aztreonam, inhibition did not exceed 40% and therefore also did not appear to be clinically significant.

Data from our in vitro studies also suggested that aztreonam did not significantly interfere with platelet function, although we did not test its metabolite, SQ26,992. Aztreonam in the highest concentration tested (25 mM or 10.9 mg/ml), which far exceeds expected in vivo peak serum concentrations employing maximum recommended dosages, only moderately inhibited (41 ± 17%) ADP-induced platelet aggregation. These in vitro results were one-half of those observed for the same molar concentrations of moxalactam and carbenicillin.

Aggregation by ADP and collagen were relatively uninhibited by 6.25 mM (2.7 mg/ml) aztreonam, the lowest concentration tested. Since this concentration was 20 times greater than the expected maximal peak serum concentrations in humans after a 2-g dose, inhibition of platelet aggregation in therapeutic situations should not occur, except possibly in special situations in which antibiotic levels become inordinately high (e.g., renal failure).

Somani and colleagues demonstrated that mezlocillin produced no defects in hemostasis, including platelet aggregation, whereas ticarcillin in therapeutic doses often caused significant increases in bleeding times in normal volunteers (22). Ballard et al. observed significantly greater platelet dysfunction (e.g., elevated bleeding times) in normal volunteers after therapeutic doses of carbenicillin in contrast to mezlocillin or placebo (5).

Moxalactam, a beta-lactam oxacephem, was shown by Andrassy and colleagues to cause abnormally elevated bleeding times in five subjects with renal insufficiency; only minimal changes were observed in patients with normal kidney function (2). Decreased ADP-induced platelet aggregation was found in renal insufficiency, although no alterations in platelet counts or coagulation tests were observed. In the same study, in 10 patients receiving cefotaxime, no prolongation in bleeding times in patients with normal renal function were noted, but cefotaxime did produce erratic increases in bleeding times in patients with impaired renal function. Like moxalactam, in vitro inhibition of ADP-induced platelet aggregation was increased in the latter group. Weitkamp and Aber evaluated six patients receiving moxalactam for 3 days or more and observed that five of the six patients had prolonged bleeding times (24). A bleeding diathesis was evident in all five patients. Bang et al. administered moxalactam (12 g/day) to five normal volunteers and observed a significant reduction in in vitro ADP-induced platelet aggregation on day 7 of therapy (7). Bleeding times were not reported, and the clinical implications of these findings were unclear. Hemorrhagic episodes have also been observed after moxalactam therapy (6, 19, 24).

The exact mechanism of inhibition of platelet aggregation by beta-lactam antibiotics is not known. Several researchers have proposed that they exert their effect through nonspecific binding to platelet membrane receptors, impeding the effects of aggregating agents (6, 21). If so, different chemical configurations of different beta-lactams may differ in their
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capacity to inhibit platelet aggregation. Chemically, aztreonam differs considerably from other β-lactams, which may explain in part its comparative lack of significant in vitro inhibition of ADP-, epinephrine-, and collagen-induced aggregation.

In conclusion, aztreonam appears to be free of significant interference with coagulation following maximal recommended therapeutic doses in normal volunteers who received 21 consecutive 2-g i.v. doses. In addition, platelet aggregation is only minimally affected in vitro and only at inordinately high concentrations. In vivo, aztreonam at maximum recommended dosages does not appear to produce abnormalities in hemostasis in normal male volunteers, as demonstrated by template bleeding times remaining essentially within acceptable limits and lack of demonstrable clinical evidence of bleeding or easy bruising.

ACKNOWLEDGMENT

This study was supported by a grant from E. R. Squibb & Sons.

LITERATURE CITED