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Effects of Sodium Piperacillin on Platelet Function in Normal Volunteers

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Piperacillin is a new semisynthetic penicillin which is similar in structure to carbenicillin and ticarcillin. Since the latter antibiotics have been shown to cause abnormalities in hemostasis, we studied the effects of piperacillin on blood coagulation and platelet function. Fifteen healthy volunteers received the drug in doses of either 100, 200, or 300 mg/kg per day for a period of 7 days. Serial studies showed no abnormalities in blood coagulation in any subject. Decreased platelet aggregation responses to adenosine diphosphate, epinephrine, collagen, and arachidonic acid were commonly noted, but prolongation of the bleeding time occurred in only 3 of 15 subjects after 7 days of piperacillin administration. These results suggest that although piperacillin also induces platelet dysfunction, these effects may be less than those caused by ticarcillin or carbenicillin at an equivalent dosage.

The administration of penicillin and penicillin-related compounds such as carbenicillin and ticarcillin to normal volunteers causes a defect in hemostasis by inducing platelet dysfunction (1-6). These antibiotics produce a dose- and time-related platelet function abnormality (4, 6). When given intravenously at 300, 400, or 600 mg/kg per day, carbenicillin produces consistent defects in platelet aggregation and a prolonged bleeding time, whereas ticarcillin, a more recently marketed compound with enhanced activity against *Pseudomonas* species, produced similar results at a dose of 200 to 300 mg/kg per day (2, 3, 6).

Piperacillin sodium is a new semisynthetic penicillin which has a broader in vitro antibacterial spectrum than either carbenicillin or ticarcillin (7). Since the molecular structure, pharmacokinetics, and side effects of piperacillin appear to be similar to other semisynthetic penicillin compounds, we studied the potential for hemostatic defects produced by therapeutic doses of this antibiotic in normal subjects.

MATERIALS AND METHODS

Subjects. Fifteen male human volunteers entered the General Clinical Research Center of The Methodist Hospital in Houston, Tex., where the study was performed. After the history and physical examination had excluded any evidence of peptic ulcer disease, gastrointestinal bleeding, renal disease, or penicillin allergy, a laboratory screen was accomplished which included complete blood count, blood chemistries, urinalysis, electrocardiogram, and stool examination for occult blood. Each volunteer gave signed informed consent.

Drug administration. Piperacillin was reconstituted to the desired concentration, then diluted in 100 ml of 5% dextrose and water and infused intravenously every 6 h. The volunteers were divided into three groups of five, with those in each group receiving either 100, 200, or 300 mg/kg of the drug for a 7-day period. Serum piperacillin concentrations were obtained between 30 and 125 min after infusion by a bioassay technique.

Coagulation studies. Blood coagulation and platelet function were studied at base line and on days 4, 7, and 14 after initiation of antibiotic infusion. Platelet count, prothrombin time, activated partial thromboplastin time, thrombin time, and template bleeding time (Stimplate, General Diagnostics) followed standard methodology (2, 3). Platelet aggregation was measured in a PAP-3 aggregometer (Bio/Data Corp., Horsham, Pa.). Aggregation was induced in platelet-rich plasma by epinephrine (Parke-Davis; final concentration, 45 μM), adenosine diphosphate (Sigma; final concentration, 2.5 μM), and collagen (General Diagnostics; final concentration, 0.6 μg/ml) in all studies. In addition, platelet aggregation responses to arachidonic acid (Nu Chek-Prep, Elysian, Minn.; final concentration, 0.5 μM) were also recorded in 4 of the 15 serial studies. Total platelet aggregation was a function of the final change in light transmission after aggregation in platelet-rich plasma (2). Aggregation was considered weak if it measured less than 75% of the base-line value in subsequent studies.

RESULTS

The prothrombin time, activated partial thromboplastin time, thrombin time, and plate-

let count were not significantly altered by a 7-day infusion or piperacillin at any dose level. No subject had an abnormal bleeding time on day 4 of the piperacillin infusion. On day 7, however, one subject receiving 100 mg/kg and two subjects receiving 300 mg/kg showed bleeding times in excess of our 5.5-min upper limit of normal for this test. The longest recorded bleeding time was 6.5 min, measured in two subjects receiving 300 mg/kg. All prolonged bleeding times noted at the end of drug infusion had returned to normal by day 14 of the study.

Platelet aggregation in response to epinephrine stimulation became abnormal with loss of the secondary wave in 13 of 15 subjects after 4 days of therapy. Only 6 of 15 subjects manifested abnormal aggregation patterns to adenosine diphosphate by day 4, but 13 of 15 did so by day 7. Such abnormalities included weak primary aggregation, deaggregation, and loss of the secondary wave. Collagen-induced aggregation became abnormal in 6 of 15 by day 4 and in 7 of 15 by day 7. Arachidonic acid-induced aggregation remained normal in four of four tests by day 4, but became abnormal in each of these plasmas by day 7.

DISCUSSION

This study confirms that piperacillin, like carbenicillin and ticarcillin, can also cause platelet dysfunction by inducing abnormalities in platelet aggregation. As in our previous studies with semisynthetic penicillins, individual variation in the extent of bleeding time prolongation was a significant finding (6). Unlike the studies with carbenicillin and ticarcillin in which adenosine diphosphate aggregation was the most sensitive indicator of abnormal platelet function after piperacillin, epinephrine-induced aggregation became abnormal first. Moreover, collagen-induced aggregation remained normal in many of the subjects. Impaired arachidonic acid-induced aggregation, a sensitive and early indicator of aspirin-induced platelet dysfunction, appeared only after several days of piperacillin administration.

In humans, prolongation of the bleeding time may be the most predictive index of the bleeding tendency induced by semisynthetic penicillins (6). None of the five subjects presented here who received 300 mg/kg per day of piperacillin experienced a bleeding time of 7 min or longer after 1 week of continuous drug infusion. By contrast, in two previous studies, 8 of 17 volunteers receiving a similar dose of ticarcillin for 1 week experienced a prolongation of the bleeding time above 7 min (2, 6). Bleeding times in excess of 7 min may occur after only 3 days of carbenicillin therapy (3). This observation may suggest a lesser effect of piperacillin on platelet function than that induced by ticarcillin or carbenicillin.

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