Impaired Platelet Function Associated with Parenteral Nafcillin*

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ABSTRACT

A 44-year-old Caucasian female was admitted with a subarachnoid hemorrhage owing to a multilobular tubular anterior communicating artery aneurysm. Eleven days after the original craniotomy, an epidural hematoma was evacuated. The patient was placed on empiric nafcillin antimicrobial coverage (two g every six hours). Within 24 hours, the onset of epistaxis and oozing of blood from the endotracheal tube and craniotomy site was noted. Recurrent subdural and epidural hematomas necessitated a third emergent craniotomy. The development of an acquired qualitative platelet defect was suggested by the findings of a prolonged template bleeding time and markedly abnormal platelet aggregation/ATP release studies despite a normal platelet count. Nafcillin therapy was immediately discontinued. Clinical bleeding resolved. Subsequent bleeding times and platelet aggregation studies confirmed the nafcillin-induced platelet dysfunction.

Introduction

Beta-lactam antibiotics, penicillins and cephalosporins, are commonly used pharmacologic agents which have a wide range of antimicrobial activity. A number of the semisynthetic penicillins and cephalosporins have been reported to cause impaired hemostasis with bleeding diatheses in hospitalized patients as well as in healthy volunteers.\textsuperscript{7,8,9,13,16,17} In general, the mechanisms responsible for hematologic defects differ between the penicillins and cephalosporins, and, to date, have not been completely elucidated. It appears that penicillin-mediated hemostatic defects are produced by platelet dysfunction as demonstrated by \textit{in vivo}, as well as, \textit{in vitro} platelet studies.\textsuperscript{9,14}

A case is reported of nafcillin-induced platelet dysfunction with bleeding in a post-operative patient treated with parenteral nafcillin. Template bleeding times and platelet aggregation studies were performed during nafcillin therapy and twice after the antibiotic was discontinued.

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Case Report

A 44-year-old white female experienced sudden onset of global headache with nausea, vomiting, and urinary incontinence. She presented to a local hospital on August 30, 1988 where a lumbar puncture was performed and grossly bloody cerebrospinal fluid (CSF) was obtained. A diagnosis of subarachnoid hemorrhage was made, and the patient was transferred to this Medical Center for further evaluation and treatment. Subarachnoid hemorrhage was confirmed by a computerized axial tomographic scan. Angiography revealed a large multilobular tubular anterior communicating artery aneurysm. There was no history of a bleeding tendency.

Preoperative evaluation included hemoglobin of 13.3 g per dL, hematocrit of 40.0 percent, platelet count of $297 \times 10^9$ per L, prothrombin time (PT) of 11.9 seconds (normal reference range 11 to 13.2 seconds) and activated partial thromboplastin time (aPTT) of 24.0 seconds (normal reference range 21 to 30 seconds). On the day after admission, a left temporal craniotomy was performed, and a complex anterior communicating artery aneurysm was dissected and clipped. Estimated blood loss was 800 cc. The patient received two units of packed red blood cells during surgery. During the first postoperative day (POD 1), the patient remained stable, alert, and was able to follow commands. However, during the next two weeks she experienced several complications. On POD 2, a small left anterior-medial basal ganglia infarct occurred. Neurologic status deteriorated but ultimately resolved by POD 9. During the postoperative course, hematologic parameters remained within normal limits except for a gradual iatrogenically induced decline in the hemoglobin and hematocrit values. Medications during the postoperative period consisted of Decadron (Dexamethasone), Zantac (Ranitidine hydrochloride), mannitol, and morphine.

On POD 11, a second intracranial bleed occurred into the left middle fossa as well as a subacutep dural hematoma in the left frontotemporal region. Re-entry of the craniotomy and evacuation of the extracerebral blood clot (100 cc) was performed. Intraoperative estimated blood loss was 100 cc, and two units of packed red blood cells were transfused intraoperatively.

Postoperatively, nafcillin (two grams every six hours, intravenously) was added for empiric antimicrobial coverage for possible CSF leakage associated with surgical manipulation. Within 24 hours after the second surgery, epistaxis developed with onset of blood oozing from the craniotomy site and around the endotracheal tube. Petechia and ecchymosis were not present. A prolonged template bleeding time of 9.5 minutes (normal reference range 2 to 8 minutes) was obtained. The PT and PTT were normal. The platelet count had decreased from $284 \times 10^9$ per L the previous day to $175 \times 10^9$ per L.

A third emergent craniotomy was performed and left frontotemporal subdural and epidural hemorrhages were evacuated. Oozing from the surgical site continued postoperatively. A repeat template bleeding time was 14.5 minutes with a platelet count of $142 \times 10^9$ per L. The patient had received a total of 16 grams of nafcillin during the previous 48 hours. The next day, platelet aggregation studies were performed and were abnormal. Nafcillin was discontinued and apheresis platelets were administered. Within 24 hours of discontinuation of nafcillin, the template bleeding time normalized at 7.0 minutes and the patient was hemostatically stable without any source of bleeding.

Materials and Methods

Hemoglobin, hematocrit, and platelet counts were obtained from whole blood collected in ethylenediamine tetraacetic acid (EDTA) with an electronic particle counter.* Bleeding times were performed by the template method.4 The prothrombin time (PT) was determined using thromboplastin C.† Activated thromboplastin time was determined using Actin. † Platelet aggregation studies were performed by a turbidimetric method.10‡ Simultaneous measurement of adenosine triphosphate (ATP) was detected using the firefly luciferase-luciferin system with a highly sensitive photomultiplier tube.‡ Values are expressed as $\mu$M ATP per $10^9$ platelets.

Results

Three in vitro platelet aggregation studies were performed. The initial platelet aggregation study was conducted while the patient was on nafcillin and had received a total cumulative dose of 16 grams. Platelet aggregation abnormalities were observed with all aggregating reagents and with all concentrations employed (table I). Abnormalities in ADP-induced aggregation occurred with both high and low concentrations (1 ×
PLATELET DYSFUNCTION WITH NAFCILLIN

Table I
Platelet Aggregation Studies - During Naftcillin Therapy (16 Grams Total)

<table>
<thead>
<tr>
<th>Aggregating Reagent</th>
<th>Control*</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concentration</td>
<td>Aggregation</td>
</tr>
<tr>
<td>ADP‡</td>
<td>5 x 10⁻⁶ 1 x 10⁻⁵</td>
<td>108</td>
</tr>
<tr>
<td>Collagen§</td>
<td>0.038 0.095</td>
<td>92</td>
</tr>
<tr>
<td>Epinephrine‡</td>
<td>5 x 10⁻⁶ 1 x 10⁻⁵</td>
<td>103</td>
</tr>
<tr>
<td>Arachidonic acid§</td>
<td>7.5 x 10⁻⁴</td>
<td>100</td>
</tr>
<tr>
<td>Ristocetin§</td>
<td>1.50</td>
<td>118</td>
</tr>
</tbody>
</table>

*Control platelets were from a healthy donor with reproducible aggregation responses.
†Adenosine triphosphate (ATP) release is expressed in μM ATP per 10⁶ platelets.
‡Concentrations expressed in M.
§Concentrations expressed in g per L.

10⁻⁵M and 5 x 10⁻⁶M). Addition of adenosine diphosphate (ADP) produced a primary wave of aggregation but failed to elicit the secondary irreversible wave (disaggregation phenomenon). The platelet response to high dose epinephrine (1 x 10⁻⁵M) was characterized by diminished aggregation without release. Defects in high dose (9.5 g per L) collagen-induced aggregation consisted of the expected single wave of aggregation followed by a markedly depressed release response. High dose ristocetin produced agglutination without ATP release. There was no aggregation or release with low dose collagen (3.8 g per L), low dose epinephrine (5 x 10⁻⁶M), or arachidonic acid (7.5 x 10⁻⁴M).

The second platelet aggregation studies were performed six days after naftcillin had been discontinued. The patient was hemodynamically stable. Normal aggregation responses were observed with ADP, collagen, and arachidonic acid, but ATP release was diminished or absent with each agonist. Both low and high concentrations of epinephrine produced diminished aggregation and failed to release ATP. Ristocetin produced normal agglutination with abnormal ATP release (table II).

The third and final platelet aggregation study was performed approximately two weeks after naftcillin was discontinued (data not shown). Normal aggregation and release responses were elicited with all of the agonists tested (ADP, collagen, epinephrine, arachidonic acid, and ristocetin).

The template bleeding time was prolonged at 14.5 minutes during naftcillin therapy and normal on day 6 and 17.

Discussion

To date, there has been a single report of two cases of naftcillin-induced platelet dysfunction with associated bleeding diathesis.¹ In one of their patients, Alexander and coworkers performed platelet aggregation studies during naftcillin therapy and after naftcillin rechallenge. Studies performed at both times showed abnormal platelet response to ADP, epi-
nephrine, and collagen. Three concentrations of ADP produced depression of the primary wave of aggregation and absence of the secondary wave with platelet disaggregation. Abnormal platelet aggregation was also produced with low doses of collagen and epinephrine. Bleeding times during both studies were markedly prolonged.

In our initial platelet aggregation study, severe defects in aggregation were noted with all agonists except ristocetin and high-dose collagen. Although previously unreported, the present authors have shown complete absence of ATP release with all agonists except high-dose collagen which had markedly impaired release. Additionally, at six days after nafcillin therapy, documentation by us has shown that aggregation with all agonists was normal, and that ATP release, a response to the irreversible second wave of aggregation, remained markedly abnormal. It has also been indicated that aggregation and ATP release at 17 days post nafcillin therapy was normal. Our patient was not rechallenged with nafcillin, owing to her poor clinical status.

Defects in hemostasis may be caused by therapeutic doses of beta-lactam antibiotics and have been observed in patients treated with natural and semisynthetic penicillin or cephalosporin agents. The penicillins inhibit platelet aggregation by interfering with platelet membrane receptors and their responsiveness to physiologic agonists. In contrast, the cephalosporin antibiotics adversely affect vitamin K-dependent coagulation factors. Moxalactam, a cephalosporin, is unique in so far as it produces both platelet dysfunction and coagulopathy.

The mechanism of penicillin-induced platelet dysfunction has been investigated by in vitro platelet aggregation studies. Normal platelets exposed to physiologic concentrations of penicillin G and carbenicillin demonstrate impairment in the interaction of radiolabeled platelet agonists (epinephrine and ADP) with platelet surface receptors, inhibiting platelet aggregation and serotonin release. Decreased ristocetin-induced platelet agglutination was also observed. Other in vitro studies employing therapeutic doses of apalcillin, ampicillin, methicillin, piperacillin, carbenicillin, and ticarcillin have produced similar results with defective ADP, epinephrine, and collagen-induced primary aggregation. These studies suggest that penicillins produce platelet dysfunction by global interaction with membrane surface receptors. It has been postulated that this may be due to the strong affinity of the penicillins for membrane proteins and lipids.

The frequency and severity of penicillin-induced platelet abnormalities are related to dose and duration of administration of the drug. Studies show that in volunteers, the longest bleeding times occurred in those individuals receiving the largest dose of ticarcillin and returned to normal approximately four days after the drug was stopped.
vitrō platelet aggregation with multiple agonists in these volunteers were all abnormal by day three of drug administration. They reported abnormalities in ADP-induced aggregation, the most sensitive platelet agonist, within 24 hours after drug administration. Recovery of ADP-induced aggregation occurred in most volunteers by seven to 10 days after drug therapy was terminated. Platelet ADP-induced aggregation occurred in most volunteers by seven to 10 days after drug administration. Recovery of ADP-induced aggregation, the most sensitive phase of aggregation, supports the hypothesis for an additional mechanism of penicillin-induced platelet dysfunction.

Risk factors that potentiate hemostatic problems and bleeding in patients receiving penicillins have been identified. Significant co-variables associated with increased template bleeding time and/or clinical bleeding include: thrombocytopenia, dose ≥ 12 g per day, primary bone marrow disorders affecting platelet function, impaired renal function, postoperative status, chemotherapy, and age of ≥60 years. The only factor associated with increased risk of bleeding in our patient was the postoperative status.

Since the incidence of beta-lactam-induced qualitative platelet defects is not known, acquired platelet dysfunction must be considered with the onset of clinically significant new bleeding (epistaxis, petechiae, mucosal hemorrhage or oozing around surgical, ostomy or IV sites) in patients receiving natural or semisynthetic penicillins. Hemostasis evaluation should include a template bleeding time, platelet count and routine coagulation studies. A prolonged template bleeding time with normal platelet count, PT and aPTT (as was seen in our case) indicates a qualitative platelet defect, characteristic of the penicillins. In vitro platelet aggregation studies help to confirm the platelet dysfunction. The offending penicillin must be discontinued and an alternative antibiotic selected for therapy. The template bleeding time will return to normal within two to four days of drug discontinuation, although platelet aggregation studies may remain abnormal for more than 10 to 14 days as previously noted. Platelet transfusions may be indicated in patients at risk of significant bleeding or life-saving in patients actively bleeding.

References


