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Nafcillin-Induced Platelet Dysfunction and Bleeding

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This paper describes two cases of nafcillin-induced platelet dysfunction, with positive rechallenge data for one patient. Nafcillin resulted in abnormal bleeding times in both patients and a clinically apparent bleeding episode in one of the cases. Platelet function tests were performed on one patient during the initial therapy and after rechallenge with nafcillin. Platelet aggregation showed abnormal responses to ADP, collagen, and epinephrine. Platelet count and morphology were normal. Nafcillin should be recognized as another antibiotic which causes platelet function abnormalities and clinical bleeding episodes.

Antibiotic-induced platelet dysfunction has been demonstrated with several penicillins and cephalosporins. Although in vitro abnormalities of platelet aggregation are reported most often, clinical bleeding episodes have also occurred (4, 9, 14). In some the cases, other drugs known to induce platelet dysfunction were administered simultaneously. In other instances, the underlying disease may have contributed to the bleeding diathesis. However, normal, healthy volunteers have exhibited bleeding when challenged with usual dosages of a penicillin, such as carbenicillin (5).

The following cases demonstrate that nafcillin can also induce platelet dysfunction and bleeding, a phenomenon not previously reported. The effects on platelet function studies of one of the patients, who was rechallenged with nafcillin, are also presented.

Report of two cases. (i) Case 1. Case 1 was a 71-year-old female with an 11-year history of rheumatoid arthritis which had been treated for many years with prednisone. On 21 September 1979 she was admitted to the University of Utah hospital for grafting of chronic leg ulcers. Two days after admission, the patient exhibited a temperature of 39.3°C and was found to have an infected wrist. Blood cultures were obtained, and gentamicin and nafcillin therapy was begun. Blood and synovial fluid cultures subsequently yielded *Staphylococcus aureus*. Gentamicin was discontinued, and nafcillin was administered at 14 g/day by constant intravenous infusion. The patient gradually improved over 5 weeks, although oozing was noted from her intravenous sites. Ecchymotic areas developed around these sites, but the hematocrit did not decrease. At this time, debridement with possible grafting was planned for the leg ulcers. The preoperative laboratory screen revealed a template bleeding time of greater than 25 min (normal, 6 to 9 min), and the procedure was cancelled. The partial thromboplastin time and platelet count were normal. Platelet morphology was also normal. The prothrombin time was 15.6 s with a control of 13.6 s and was corrected with normal plasma. Liver function tests were normal, although 1 week earlier mild elevations of serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase had been present. The patient's medications included prednisone (40 mg daily), double-strength trimethoprim-sulfamethoxazole (twice daily), sulindac (Clinoril; 200 mg twice daily), amitriptyline (50 mg at bedtime), and nafcillin as described above. All medications except prednisone and nafcillin were discontinued, and the bleeding time was repeated at 48 and 72 h. Platelet function tests revealed abnormal aggregation (see Table 1). Surgery was deferred, nafcillin was discontinued, and the patient was discharged. A bleeding time repeated 9 days later was normal (6.5 min).

The patient was readmitted 1 month later for surgical repair of the extensor tendons on the right hand. The only medication at that time was prednisone (30 mg daily). The platelet count, prothrombin time, and partial thromboplastin time were normal, and the bleeding time was 6.5 min. The tendon repair was accomplished without excessive bleeding, and consent of the patient to rechallenge her with nafcillin was obtained. During this period, fat-containing foods were not allowed after 10 p.m., to prevent lipemic blood samples. No blood samples were drawn other than those done for coagulation

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purposes in the morning. Base-line studies of bleeding time and platelet aggregation were performed. Nafcillin was started at a dose of 250 mg intravenously over 30 min every 6 h for four doses before the platelet studies were repeated. Nafcillin was then given as it had been previously prescribed (14 g/24 h as a constant infusion). After 17 h, the intravenous line through which the patient was receiving the nafcillin infiltrated and was discontinued. Platelet aggregation studies and a bleeding time were again performed. No adverse clinical effect resulting from the rechallenge was observed. (See Tables 2 and 3 for the results of the rechallenge).

(ii) Case 2. Case 2 was a 16-year-old female admitted to the University of Utah hospital on 19 February 1980 for an evaluation of a nonhealing left-knee wound and to rule out osteomyelitis. She had previously undergone retinacular release of the left knee without excess bleeding. One week after the procedure she fell, causing dehiscence of the wound and bleeding. Because of increased pain, swelling, and persistent oozing of serosanguineous fluid, her knee was surgically debrided. Cultures grew out *S. aureus*. Her vital signs at this time were as follows: blood pressure, 112/60; heart rate, 64; respiration rate, 16; and temperature, 38.2°C. A physical examination was remarkable for a palpable left femoral node and a 3-cm, oozing, erythematous, ulcerated lesion on the left knee which was draining serosanguineous fluid. The joint and proximal tibial areas were painful and tender to mild palpation, with a decreased range of motion. The complete blood count with leukocyte differential and the platelet count were normal, the erythrocyte sedimentation rate (Westergren) was 5 mm/h, and blood cultures were negative. Antibiotics were stopped for 2 days, and cultures were repeated. A surgical exploration of the area showed a normal bone, no joint pus, and a synovial sinus tract which was resected. A Gram stain revealed no organisms and a few polymorphonuclear leukocytes. A bone biopsy culture was negative, but the joint fluid culture was positive for *S. aureus*. The fluid was drained, and the patient was started on nafcillin (12 g/day intravenously). She did well for the next 4 weeks. At that time there was some oozing and weeping from the surgical site, although the wound did not dehisce. During the following week, the oozing increased from about 30 ml of serosanguineous fluid to approximately 1,500 ml of bloody drainage, and the hematocrit dropped from 45 to 31%. At this time, a bleeding time was greater than 25 min. The nafcillin was stopped. No other medications were being administered during this time period. Two days later the bleeding markedly decreased, and a bleeding time was within normal limits (9 min).

TABLE 1. Initial platelet aggregation studies of case 1

Reagent	Concn[a] or dilution	% Response	
		Control[b]	Patient
ADP	1×10^{-4}	82	50[c]
	1×10^{-5}	80	45[c]
	3×10^{-6}	79	38[c]
Collagen	1:16	87	75
	1:32	85	67[c]
	1:64	80	44[c]
Epinephrine	1×10^{-4}	80	80
	1×10^{-5}	77	79
	1×10^{-6}	80	54[c]

[a] Concentrations for ADP and epinephrine are expressed as molarities.

[b] Control platelets were from a normal, healthy person with known and reproducible aggregation responses.

[c] Stimulated platelets which disaggregated.

Four days after nafcillin was stopped, the bleeding time was 6 min.

MATERIALS AND METHODS

Tests of blood coagulation and function included platelet count with an electronic particle counter (Coulter Counter) by the method of Bull et al. (5), one-stage prothrombin time determined by a modified method of Quick (16), activated partial thromboplastin time (15), and bleeding time determined by a modification of the template method of Mielke et al. (12).

Blood was drawn by venipuncture, collected in plastic collection tubes, and immediately mixed with an appropriate anticoagulant (nine parts venous blood and one part 3.8% sodium citrate). Platelet-rich plasma was obtained by centrifugation of whole blood at 205 $\times$ *g* for 12 min. This was pipetted into a second plastic container. The platelet count of platelet-rich plasma was standardized to a count of 250,000/mm^3 by dilution with platelet-poor plasma. Blood drawn by venipuncture from human volunteers who had not ingested aspirin or any other drugs for at least 10 days was used for control samples.

Platelet aggregation studies were performed by a turbidimetric method (7) with dual aggregometers (Chronolog Corp.). Platelet-poor plasma was used to define the maximum change in optical density obtainable for each sample. Platelet aggregation was measured as a percentage of the maximum change in optical density by using the following formula: percent aggregation = (sample optical density change/total optical density change) $\times$ 100.

Reagents used in the aggregation studies were ADP in final concentrations of 10^{-4}, 10^{-5}, and 3×10^{-6} M; epinephrine in final concentrations of 10^{-4}, 10^{-5}, and 10^{-6} M; and collagen prepared by the method of Day and Holmsen (7) and stored at -20°C until used. Immediately before use the collagen solution was thawed, rehomogenized, and diluted with acetic acid. A standard response curve was prepared by addition

TABLE 2. Patient hemostatic parameters during rechallenge with nafcillin

Nafcillin dose	Bleeding time (min)[a]	Platelet count (no./mm³)[b]	Morphology
Base line[c]	6.5	414,000	Normal
Low[d]	6.0	464,000	Normal
High[e]	>25	388,000	Normal

[a] Normal, 6 to 9 min.
[b] Normal, 140,000 to 440,000/mm³.
[c] Before administration of nafcillin.
[d] Four 250-mg intravenous doses, 6 h apart.
[e] Intravenous infusion of 10 g over 17 h.

of diluted collagen to platelet-rich plasma until an adequate aggregation-response curve was demonstrated. Dilutions of this solution (1:8, 1:16, 1:32, 1:64, and 1:128) were then used.

RESULTS

Platelet count and morphology were within normal limits in all sets of aggregation studies. Initial platelet aggregation in case 1 demonstrated abnormal responses to ADP, collagen, and epinephrine (Table 1). The loss of the secondary aggregation response and depression of primary aggregation occurred with all concentrations of ADP. The abnormal aggregation response resulted in platelet disaggregation. The platelet responses to collagen and epinephrine were also abnormal at low concentrations. The responses of the control platelets demonstrated good reactivity. A bleeding time determined concurrently was greater than 25 min.

One month later, several days after the surgery, blood was drawn for base-line platelet aggregation studies. The bleeding time was within normal limits (Table 2). The results of platelet aggregation studies demonstrated mildly abnormal responses only to low concentrations of the three aggregating agents (Table 3). The responses of the control platelets demonstrated good reactivity. The reasons for the abnormal findings at low concentrations of the aggregating agents are unclear at this time, but possibilities include platelet pool selection, sampling error, or some condition which could have damaged the platelet sample.

At 24 h after a low dose of nafcillin was begun, the bleeding time was 6.0 min (Table 2), and the platelet aggregation studies showed good reactivity (Table 3). The responses of the control platelets also showed good reactivity.

Approximately 17 h after the start of a 14-g infusion of nafcillin, the bleeding time was greater than 25 min (Table 2). Platelet aggregation studies showed markedly abnormal responses to ADP and collagen (Table 3). Loss of the secondary aggregation response and depression of primary aggregation occurred at all concentrations of ADP. Platelet responses to weak collagen dilutions were also abnormal. All abnormal responses resulted in platelet disaggregation.

DISCUSSION

Antibiotic-induced platelet dysfunction has been reported most frequently with carbenicillin and penicillin (2, 4). However, other penicillins and some cephalosporins, including a few of the newer agents (e.g., piperacillin and moxalactam), have been shown to produce platelet dys-

TABLE 3. In vitro platelet aggregation studies for nafcillin rechallenge in case 1

Reagent	Concn[a] or dilution	% Response at the following nafcillin dose:					
		Base line[b]		Low[c]		High[d]	
		Control	Patient	Control	Patient	Control	Patient
ADP	1×10^{-4}	85	78	83	88	85	62[e]
	1×10^{-5}	85	64	84	84	83	46[e]
	3×10^{-6}	81	55[e]	81	81	80	42[e]
Collagen	1:8	88	81	85	91	87	85
	1:16	85	74	85	83	83	80
	1:32	86	64[e]	85	89	80	78
	1:64	ND[f]	ND	84	78	81	58[e]
	1:128	ND	ND	ND	ND	76	52[e]
Epinephrine	1×10^{-4}	88	78	83	90	87	70
	1×10^{-5}	88	78	83	91	83	76
	1×10^{-6}	83	30[e]	81	88	85	76

[a] Concentrations for ADP and epinephrine are expressed as molarities.
[b] Before administration of nafcillin.
[c] Four 250-mg intravenous doses, 6 h apart.
[d] Intravenous infusion of 10 g over 17 h.
[e] Stimulated platelets which disaggregated.
[f] ND, Not done.

function at various concentrations (3, 6, 8, 13, 14). The cases presented here suggest that nafcillin can also induce a hemostatic defect attributable to platelet dysfunction.

The pattern of defective platelet aggregation produced by nafcillin is similar to the effect seen with other penicillin derivatives. The platelet defect consists primarily of the loss of the secondary wave of aggregation and a depressed primary aggregation response to an ADP stimulus. Altered platelet responsiveness to epinephrine and collagen stimuli was demonstrated with larger dilutions of these aggregating stimuli, but these effects have not been consistently demonstrated with other penicillins. As evidenced by the case rechallenged with nafcillin, the alteration of platelet function may be dependent upon the administered dose or upon time-related exposure of the platelets to the antibiotic. If these platelet effects are results of antibiotic concentration and exposure time, then the dysfunction may also be produced at the lower dose of nafcillin with prolonged antibiotic administration, but this was not investigated in this case.

The duration of the platelet dysfunction may be as long as 3 to 21 days after treatment is discontinued (1–4, 13). In our first case, the bleeding time became normal and the percent aggregation was close to control values within 9 days of discontinuation of nafcillin therapy. In the second case, the bleeding time was within the normal range after only 2 days.

It is apparent that a variety of penicillins and cephalosporins can cause in vivo and in vitro platelet dysfunction and can alter coagulation. The specific mechanism for these effects and their clinical significance are uncertain. These defects, however, can result in clinically evident bleeding episodes that may be accentuated by the underlying disease of the patients or by other administered drugs. The time course for the appearance of abnormalities in platelet function and of prolonged bleeding time is from 30 min to 3 days after therapy is started (4, 11, 13), with the maximum defect in platelet function occurring between 1 and 10 days (3, 10). The duration of the platelet function abnormalities is variable but may be prolonged in certain individuals. The cases presented in this paper demonstrate that nafcillin should be recognized as an antibiotic which causes platelet function abnormalities and that clinical bleeding episodes can occur in patients being treated with this drug. In patients who exhibit bleeding abnormalities, an alternative regimen might be considered.

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