

## Influence of Cephalosporin Antibiotics on Blood Coagulation and Platelet Function

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Administration of cephalothin to normal volunteers in maximal doses of 300 mg/kg per day resulted in a combined defect of platelet function and blood coagulation. No such abnormalities were evident after infusion of cefazolin or cephapirin at a maximal dosage of 200 mg/kg per day. The observed thrombocytopenia was similar to but less severe than that induced by carbenicillin or ticarcillin and was not reflected by a prolonged bleeding time test or impaired prothrombin consumption. Moreover, it was not a consistent finding in those persons receiving cephalothin. A separate defect involving blood coagulation appeared to result from delayed fibrinogen-fibrin polymerization and was evidenced by extended values of the activated partial thromboplastin and thrombin time tests. It remains uncertain whether the abnormalities described may constitute clinically important hemostatic disorders in patients with normal renal function receiving large doses of cephalosporin antibiotics.

Recent studies have confirmed that a specific hemostatic defect may be induced by administration of certain penicillin derivatives (2, 3). Cephalosporins are closely related in chemical structure to penicillin and have also been implicated as causative of coagulation abnormalities (6). To further investigate this phenomenon, we have studied the effect of three cephalosporin compounds on blood coagulation and platelet function in 15 normal volunteers.

The specific drugs chosen for this study, in addition to cephalothin (Keflin), were two new semisynthetic cephalosporin antibiotics, cefazolin (Kefzol) and cephapirin (Cephadyl). These products appear equivalent in antibacterial spectrum to cephalothin but afford greater and more prolonged serum levels after parenteral injection of an identical dose. They may also offer a lower incidence of thrombophlebitis when given by intravenous injection (1, 4).

### MATERIALS AND METHODS

**Subjects.** Human volunteers participating in this study with permission from the Texas Department of Corrections entered the General Clinical Research Center of The Methodist Hospital where each underwent complete physical examination, routine blood analysis, stool tests for occult blood, electrocardiogram, and roentgenographic evaluation of the upper gastrointestinal tract. Eligible subjects were

those judged normal by the above studies and who denied a history of either allergy to penicillins and cephalosporins, peptic ulcer disease, a bleeding tendency, or thrombophlebitis. All volunteers gave informed consent before receiving any investigational drug and received no other medications for at least 14 days before activation of our protocol and during the periods of antibiotic infusion.

**Cephalosporin administration.** Fifteen subjects received either cephalothin, cephapirin, or cefazolin administered every 6 h by intravenous infusion over a 20-min period. The initial dose level for cephapirin and cefazolin was 25 mg/kg per day with the amount of antibiotic doubled every 3 days until they had received 200 mg/kg per day for 3 days, ending the infusion. Those volunteers given cephalothin received the same dose increments but with the final infusion increased to 300 mg/kg per day. Drug schedules were selected to approximate maximal doses recommended for treatment of overwhelming infection with susceptible organisms.

**Blood coagulation and platelet function tests.** We performed blood coagulation and platelet function studies by previously outlined methods (2, 3, 7, 8) using a semiautomated, optical clot timing system and dual-beam platelet aggregometer (Bio/Data Coagulation Systems, Willow Grove, Pa.). Those tests done before, during, and after drug administration were platelet count, template bleeding time, prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrin-split products, prothrombin consumption, kaolin-induced platelet factor 3 availability, and platelet aggregation response to adenosine 5'-diphosphate (ADP), collagen, and epinephrine. Meas-

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urements of plasma fibrinogen concentration were performed both by measuring the rate of change in optical density ( $V_{max}\Delta OD$ ) of clotting plasma (7, 8) and by biuret digestion of a fibrin clot.

### RESULTS

Five subjects received cephalothin, but in one the study terminated prematurely (day 6) because of difficulty in maintaining an infusion through unsuitable peripheral veins. Another manifested clinical evidence of mild phlebitis (day 9), and we discontinued the drug. None of the subjects experienced a bleeding tendency while under observation.

During the period of cephalothin administration, all tests of blood coagulation and platelet function remained normal and unchanged from base-line values with the exception of platelet aggregation, PT, APTT, TT, and estimation of plasma fibrinogen concentration by the photometric method. Three of the five volunteers demonstrated loss of the second wave of aggregation in response to epinephrine and reduced total aggregation to an ADP stimulus (Fig. 1). When present, these abnormalities were evident by day 3; they disappeared 6 to 9 days after discontinuation of drug. In two subjects all aggregation responses remained entirely normal.

All three subjects receiving cephalothin for at least 10 days manifested prolongation of TT (up to 3 s) and APTT (up to 25 s) above base-line

values (Fig. 2). In these subjects the rapidly clottable fibrinogen concentration as measured by maximal optical density changes ( $V_{max}\Delta OD$ ) in the TT test became 50 to 115 mg/100 ml lower than total plasma fibrinogen (biuret), suggesting an alteration in the initial rate of fibrinogen-fibrin polymerization (7, 8).

All five subjects who received cefazolin tolerated the drug without incident and none experienced phlebitis. In this group all tests of platelet function and blood coagulation remained normal and unchanged from base-line values throughout the study period.

Among the five subjects given cephalothin, one experienced an allergic reaction at day 7 consisting of fever and urticarial rash, and he received no further drug. None of the remaining group evidenced an untoward reaction. Tests of hemostasis and platelet function remained normal in all five subjects during drug infusion.

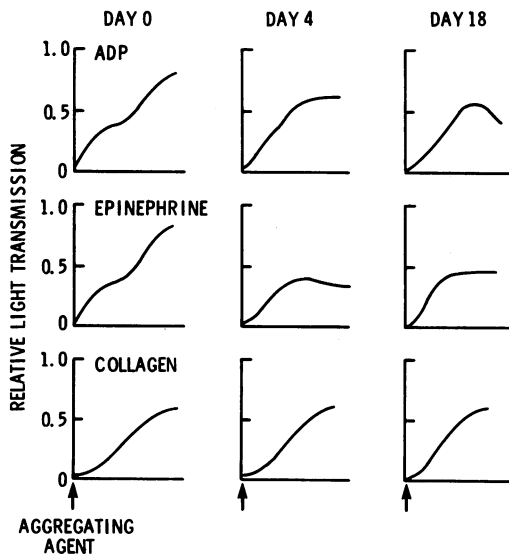


FIG. 1. Platelet aggregation patterns in a volunteer receiving cephalothin. On day 18 (6 days after final drug infusion) aggregation responses to ADP and epinephrine remain abnormal. They returned to base-line values within 3 additional days.

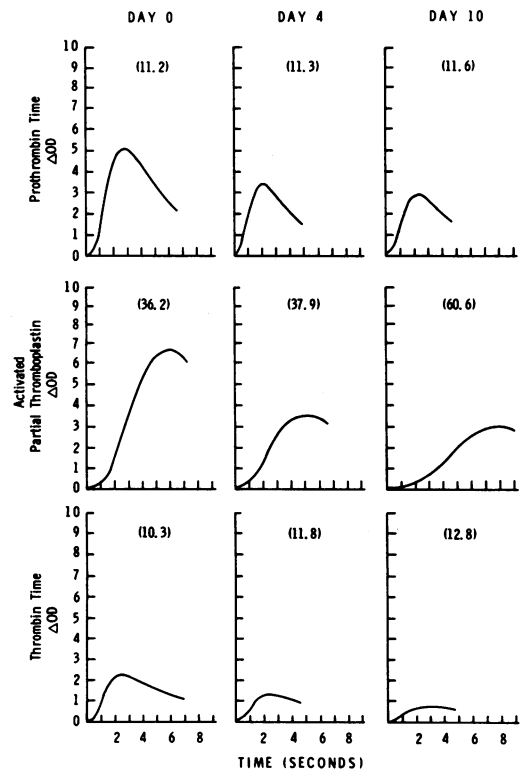


FIG. 2. Graphic representation of plasma coagulation in the PT, APTT, and TT for a subject given cephalothin. The clotting time (in seconds) is shown for each test. A depressed peak amplitude ( $V_{max}\Delta OD$ ) in all studies on days 4 and 10 suggests progressively delayed fibrinogen-to-fibrin polymerization. Results of all three tests returned to base-line values within 24 h of final drug infusion.

## DISCUSSION

The pathogenesis and clinical significance of the abnormality in platelet function described here after infusion of cephalothin into normal volunteers remain uncertain. The pattern of defective platelet aggregation is similar to that induced by semisynthetic penicillins and comprises loss of the secondary wave in response to an epinephrine or ADP stimulus. With both classes of antibiotic, continued presence of the defect long after cessation of drug suggests a permanent alteration in platelet membrane receptors (2, 3). Unlike the carbenicillin- and ticarcillin-induced thrombocytopenia, however, we did not observe changes in bleeding time, prothrombin consumption, or clot retraction after cephalothin. Moreover, abnormalities in platelet function were not present in all subjects receiving cephalothin and were not evident in those given cefazolin or cephapirin.

An unexpected finding in three volunteers receiving cephalothin was prolongation of the APTT and TT. Reduced maximal rate of change in optical density ( $V_{max}\Delta OD$ ) during plasma coagulation in both these tests and the PT (Fig. 2) suggested retarded fibrinogen-fibrin polymerization (7, 8). A similar process has been described in vitro in the presence of large concentrations of penicillin (5) but was not present in vivo in normal subjects after sustained intensive treatment with carbenicillin or ticarcillin (2, 3). Although we did not observe any change in plasma coagulation in those subjects given cefazolin or cephapirin, presence of this defect may be dose related. Such a coagulopathy has been reported in a patient with renal failure who received cefazolin and achieved massive blood levels of the drug (6).

Our findings suggest that patients with normal renal function are unlikely to manifest clinically important hemostatic abnormalities consequent to cephalosporins alone, even when given in maximally recommended dosage.

Certainly in patients with compromised renal function and those in whom the antibiotic is used in combination with carbenicillin or ticarcillin careful attention should be given to the dosage regimen to avoid the potential hazard of a bleeding diathesis (2, 4).

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