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Effect of Cefamandole Nafate on Blood Coagulation and Platelet Function

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Platelet function and coagulation were tested after brief in vivo exposure to cefamandole nafate and in the presence of various concentrations of the drug in vitro. Alterations in hemostatic function were observed only with exposure to drug concentrations severalfold higher than those expected to prevail clinically.

Several cephalosporin antibiotics have been shown to induce defects in hemostasis (1, 2, 10, 12). We therefore examined the effect of the new cephalosporin, cefamandole nafate (Mandol), on platelet function and coagulation. It has been shown that peak serum levels of 100 to 500 μg/ml are reached within 10 min when 2 g of cefamandole nafate are given intravenously over 10 min (3, 5). Such levels prevail, however, only momentarily in intervals between repetitive treatments. Excretion is mainly by renal tubular secretion, and it is recommended that doses be adjusted in the presence of renal impairment (13).

In the following study, we evaluated the effect of cefamandole nafate on hemostatic function under the following circumstances: (i) in vivo, after a single 2-g intravenous (i.v.) infusion in six normal volunteers and after eight repetitive i.v. infusions (2 g every 6 h) in two patients; (ii) in vitro, after exposure of platelets and plasma from three normal volunteers and three uremic volunteers to a wide range of drug concentrations; and (iii) in vitro, after simultaneous exposure to high levels of both penicillin G and cefamandole nafate to test for possible synergism. Although application of in vitro data and findings after a single infusion to the usual clinical situation may be somewhat artificial, our results indicate no adverse effect of cefamandole nafate on coagulation. Alterations in hemostatic parameters were seen only in the presence of concentrations severalfold higher than those which might realistically be attained clinically.

Two-gram i.v. infusions of cefamandole nafate were administered to six normal volunteers over 15 min and two patients with pneumonia over 30 min. Ten to 15 min after completion of the infusion, blood was obtained for platelet function evaluation. Normal subjects were tested after single infusions, while both patients received eight doses each over 48 h. Cefamandole nafate serum levels were not measured.

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Blood coagulation and platelet function studies were performed by previously described methods (4, 6-8, 11, 14-16) using a semiautomated, optical clot timing system and dual channel aggregometer (Payton Assoc., Inc., Buffalo, N.Y.). Tests done after drug administration included platelet count, bleeding time, and platelet aggregation induced by adenosine 5'diphosphate (ADP), epinephrine, collagen, and ristocetin. Results were compared with base-line studies done at a time remote from the cefamandole nafate infusion.

Blood samples were obtained from three normal and three uremic subjects that had not taken platelet-inhibiting drugs for at least 10 days for the determination of the one-stage prothrombin time (PT), activated partial thromboplastin time (APTT), reptilase time, thrombin time, fibrinolytic activity, fibrinogen titers, platelet factor 3 availability, and platelet aggregation. The blood urea nitrogen determinations and serum creatinine levels of the uremic patients ranged from 61 to 88 mg/dl and from 13.1 to 18.0 mg/dl, respectively. Values were determined in plasma samples and platelet-rich plasma (PRP) after 15 min of incubation with or without incremental concentrations of cefamandole nafate at 200, 400, 1,000, 2,000, 4,000, and 8,000 μg/ml.

In addition, PRP from three normal subjects was incubated with inhibiting concentrations of either cefamandole nafate alone (1,000 μg/ml), penicillin G alone (2,000 μg/ml), or both drugs simultaneously. They were aggregated with incremental doses of either ADP or collagen to determine the reversibility of inhibition.

All experiments were done in duplicate with simultaneous controls using volumes of normal saline equal to the volume of antibiotic solution added to the test samples included. All tests were highly reproducible.

Bleeding time, platelet retention, and platelet aggregation in response to collagen, ADP, epinephrine, and ristocetin were determined in six volunteers after a single 2-g i.v. infusion. In two cases, a slightly decreased maximum response to collagen was observed and there was an increased response to epinephrine in one case. Otherwise, no abnormality in platelet function was seen after this brief exposure to the drug. In all but one case, remote base-line determinations were made at a later date which confirmed normal platelet function in the absence of any medication (although one subject did have abnormal base-line responses to collagen and epinephrine).

In addition, the above-noted tests of platelet function were performed on two infected patients after receiving eight repetitive doses of cefamandole nafate. No deviation from the normal range was observed in any instance.

Plasma and PRP samples from three normal volunteers and three uremic volunteers were tested after incubation in vitro with concentrations of cefamandole nafate ranging from 0 to 8,000 μg/ml. In all cases, thrombin time, reptilase time, fibrinogen titers, fibrinolytic activity, and platelet factor 3 availability remained unchanged throughout. PT and APTT also were normal at concentrations up to 2,000 μg/ml. Incubation with concentrations greater than 2,000 μg/ml resulted in abnormal responses in all cases except in one of the uremic subjects who showed no change even in the presence of 4,000 μg of cefamandole nafate per ml (Table 1). That these observed changes did not result from simple plasma dilution was confirmed by demonstrating normal activity of all plasma factors in one plasma sample which had been incubated with 8,000 μg of the drug per ml.

ADP, collagen, and ristocetin-induced platelet aggregations were also normal when incubated with all but the highest concentrations of cefamandole nafate. Only one uremic subject's platelets showed decreased maximum percent ADP-induced aggregation and increased rate of disaggregation after incubation with 400 μg/ml; one other showed decreased maximum percent collagen-induced aggregation after incubation with 200 μg/ml. Otherwise, these changes in aggregation were seen only after incubation with >2,000 μg of the drug per ml. At these very high concentrations, changes in aggregation were dose related (Fig. 1).

TABLE 1. *Effect of cefamandole nafate on PT and APTT*

Subject	Cefamandole nafate (μg/ml)	PT	APTT
1	0	9.5	29.3
	800	9.5	29.3
	4,000	10.7	31.8
	8,000	13.8	37.8
2	0	10.6	32.3
	800	10.9	32.5
	4,000	11.4	33.1
	8,000	15.5	45.5
3	0	9.0	32.9
	800	13.1	33.0
	4,000	15.8	36.5
	8,000	20.1	40.1
4[a]	0	10.0	30.1
	800	10.4	31.2
	4,000	11.7	33.8
	8,000	12.6	36.3
5[a]	0	11.2	29.7
	800	12.6	32.2
	4,000	12.9	32.0
	8,000	14.1	36.3
6[a]	0	10.1	31.2
	800	9.9	30.9
	4,000	10.4	31.0
	8,000	—[b]	—

[a] Uremic patient.
[b] —, Not done.

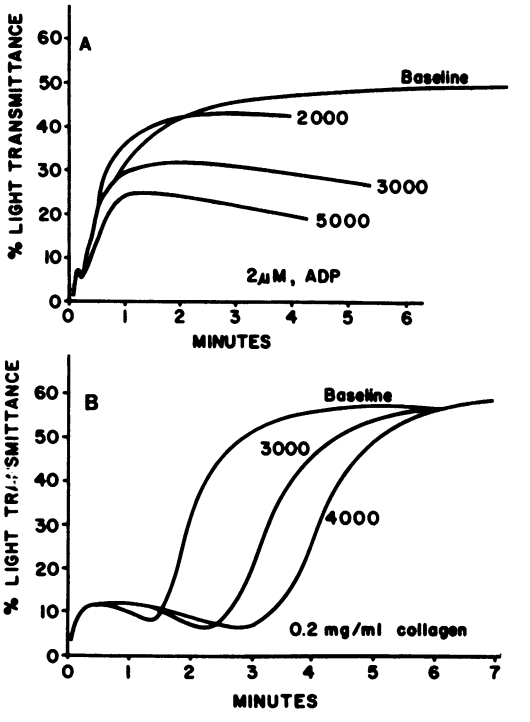

FIG. 1. *Representative platelet aggregation response curves with and without preincubation with cefamandole nafate. (A) Aggregation induction by 2 uM ADP showing base-line response curve (in the absence of the drug) and those after incubation with 2,000, 3,000, and 5,000 μg of cefamandole nafate per ml. (B) Aggregation induction by 0.2 mg collagen showing base-line response curve and those after incubation with 3,000 and 4,000 μg of cefamandole nafate per ml.*

In separate experiments, to test for possible synergistic effects, platelets were exposed to high doses of cefamandole nafate, penicillin G (known to inhibit aggregation), or both simultaneously. Each drug individually caused decreased maximum percent ADP-induced aggregation and collagen-induced aggregation characterized by lag-phase prolongation with relative preservation of maximum percent aggregation (Fig. 2). These changes were accentuated by incubation with both drugs simultaneously. By inducing aggregation with increased amounts of aggregating agents, it was possible to at least partially correct the altered aggregation patterns.

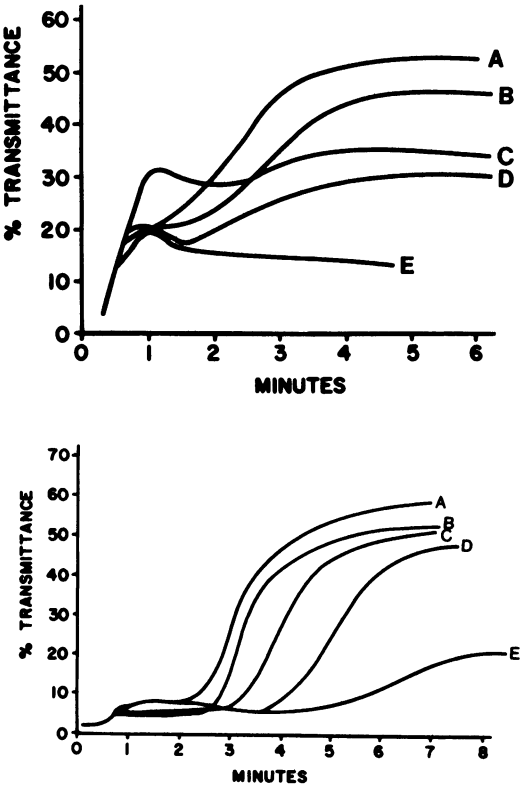

FIG. 2. *Representative platelet aggregation response curves with and without preincubation with cefamandole nafate, penicillin G, or both. (top panel) (A) Aggregation induction by 1 uM ADP showing base-line response curve and those after incubation with (B) cefamandole nafate (1,000 μg/ml) alone, (D) penicillin G (2,000 μg/ml) alone, and (E) both cefamandole nafate and penicillin G. Also shown is (C) the effect of doubling the amount of ADP (2 uM) used for induction of aggregation after incubation with both drugs. (bottom panel) (A) Aggregation induction by 0.2 mg of collagen showing base-line response curve and those after incubation with (B) cefamandole nafate, (D) penicillin G, and (E) both drugs. Also shown is (C) the effect of doubling the amount of collagen (0.4 mg) used for induction of aggregation after incubation with both drugs.*

These data indicate the lack of hemostatic effect following brief in vivo exposure to cefamandole nafate. Also, while in vitro drug exposure may not be strictly comparable to clinical usage, our findings suggest that clotting function is preserved even in the presence of quite high drug concentrations. Alterations in clotting function (prolongation of PT and APTT and aggregation changes) were observed only in the presence of concentrations severalfold higher than expected peak serum levels. The mechanism of these changes is not revealed by our results. That thrombin times and fibrinolytic activity remained normal, however, mitigates against retarded fibrinogen-fibrin polymerization as a basis for PT and APTT prolongation, contrary to previous reports (2, 12). The observed changes in ADP and collagen-induced aggregation patterns and reversal of these changes by induction with increased amounts of ADP suggests that at the nonphysiological concentrations of cefamandole nafate used, it may interfere with ADP-platelet receptor reactivity.

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