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Coagulopathy Associated with Extended-Spectrum Cephalosporins in Patients with Serious Infections

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Patients enrolled in two double-blind multicenter studies were evaluated for the development of hypoprothrombinemia during treatment with cephalosporins. Patients with pneumonia or peritonitis received ceftizoxime, cefotaxime, or moxalactam. The incidence of hypoprothrombinemia was greater in patients with peritonitis (12 of 49) than in those with pneumonia (5 of 96; $P < 0.05$). Overall, moxalactam was associated with a higher incidence of hypoprothrombinemia (13 of 52) than either ceftizoxime (1 of 43; $P < 0.05$) or cefotaxime (3 of 50; $P < 0.05$), and moxalactam patients incurred the highest average increase in prothrombin time (3.7 s) as compared with either ceftizoxime (0.5 s; $P < 0.05$) or cefotaxime (0.9 s; $P < 0.05$) patients. The occurrence of hypoprothrombinemia in moxalactam patients with peritonitis was not related to dosage, duration of therapy, age, sex, race, or renal or hepatic function. The degree of ileus was, however, strongly related to the development of coagulopathy in moxalactam-treated patients only.

In the three decades since their introduction, the cephalosporin group of antibiotics has become the most widely prescribed class of parenteral antimicrobial agents in the United States (15). Although allergic reactions have been recorded with these agents, the drugs have been remarkably free of serious toxicities (25). Cephalosporins introduced since the late 1970s have, in general, been characterized by increased spectrum and potency against gram-negative members of the family *Enterobacteriaceae* and longer serum half-lives as compared with earlier agents (16). Concurrent with the introduction of these newer cephalosporins has been a growing number of reports of prolonged prothrombin time and bleeding diathesis associated with their use (4, 8, 10, 20, 23, 24; C. D. Schwigon and D. Barckow, Program Abstr. 22nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 819, 1982).

To date, moxalactam, cefoperazone, and cefamandole have been the antibiotics most commonly associated with hypoprothrombinemia. The mechanisms whereby these agents cause this reaction and the actual incidence of hypoprothrombinemia associated with their therapeutic use are controversial (2, 12, 14; N. V. Bang, A. Dwyer, S. S. Campbell, C. A. Marks, and R. O. Heidenreich, 20th ICAAC, abstr. no. 128, 1980). Other cephalosporins (e.g., cefotaxime and ceftizoxime) with antimicrobial spectra similar to those of moxalactam and cefoperazone have not been associated with this disorder. Although these issues have been addressed in several recent studies, the definition of hypoprothrombinemia has varied, and certain comparative assessments of clotting function have been made in normal, healthy volunteers rather than the diseased patients that these agents are intended to treat (2; Bang et al., 20th ICAAC).

We conducted two separate multicentered studies to determine the clinical efficacy of moxalactam, cefotaxime, and ceftizoxime and the relative incidence of hypoprothrombinemia associated with the therapeutic use of these agents. The results of these trials with respect to the comparative efficacy and safety of these agents have been presented separately (18; B. Yangco, I. Baird, R. Bermudez, B. Lorber, R. Noble, F. Silverblatt, G. Vasquez, G. Moonsammy, M. Wikler, and A. Lentnek, 24th ICAAC, abstr. no. 958, 1984). We report here an analysis of the clinical features associated with the development of hypoprothrombinemia in the study populations.

MATERIALS AND METHODS

The incidence of hypoprothrombinemia associated with moxalactam, cefotaxime, and ceftizoxime treatment was evaluated in two prospective, randomized, double-blind multicenter trials. One of these trials was conducted at five centers with patients who had intra-abdominal infections. Patients were eligible for this study if they had clinical and bacteriologic evidence of peritonitis or a surgically demonstrable large bowel perforation. The second study was conducted at seven different institutions with patients who had clinical and microbiologic evidence of bacterial pneumonia and at least one of the following risk factors predictive of poor outcome: nosocomially acquired infection, age >70 years, alcoholism, chronic obstructive pulmonary disease, underlying malignancy, severe malnutrition, or use of immunosuppressive drugs.

In both trials, all patients were randomly assigned to one of the following drug regimens: moxalactam, 2 to 4 g every 8 h; cefotaxime, 1 to 2 g every 4 to 6 h; ceftizoxime, 2 to 4 g every 8 h. Drugs were dispensed from the pharmacy so as to conceal their identity from the investigator. Dosage adjustments for renal impairment were made according to respective product labeling.

For all patients a complete history and physical examination were done upon admission to the study. For each patient in the intra-abdominal infection trial, investigators evaluated the following clinical signs and symptoms of

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TABLE 1. Summary of dosing and demographics in peritonitis and pneumonia studies

Disease and drug	Total no. of evaluable patients	No. of males/no. of females	Mean age in yr (range)	Mean daily dose in g (range)	Mean duration of treatment in days (range)
Peritonitis					
Ceftizoxime	15	12/3	33 (18–76)	6.4 (6–12)	6.6 (4–13)
Cefotaxime	16	10/6	45 (18–84)	8.1 (2–12)	8.8 (4–13)
Moxalactam	18	12/6	39 (18–76)	6.1 (4–9)	8.5 (3–19)
Pneumonia					
Ceftizoxime	28	18/10	63 (23–91)	7.2 (1–12)	9.1 (3–15)
Cefotaxime	34	30/4	63 (20–92)	7.4 (1–12)	8.7 (3–15)
Moxalactam	34	30/4	61 (25–90)	7.5 (2–12)	8.3 (3–15)

peritonitis: fever, abdominal tenderness (either direct or rebound), guarding, bowel sounds, abdominal distention, and drainage. These parameters were subjectively graded and scored according to severity on a scale of 0 to 2 (from normal [0] to most abnormal [2]) at the time of each examination. A similar grading scale was used in the pneumonia study to assess cough, chest pain, sputum production, and physical evidence of pulmonary infiltrate. In addition, in both studies clinical laboratory values, including complete blood count, blood urea nitrogen, creatinine, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, total bilirubin, urinalysis, prothrombin time, and activated partial thromboplastin time, were obtained immediately prior to and every 3 to 5 days after the initiation of study medication.

Patients were included for analysis of hypoprothrombinemia provided that they received treatment with the study drug for at least 48 h, did not receive prophylactic vitamin K or any anticoagulant therapy, and had pretherapy base-line prothrombin time values which were within the "normal range" for the respective investigator's site.

Hypoprothrombinemia was defined as an increase in prothrombin time which was associated with the study medication and was at least 2 s greater than the pretherapy base-line prothrombin time value as well as at least 2 s greater than the upper limit of the laboratory's normal range.

The statistical analysis of these data followed the model for a replicated study by using infections as replications. The data were organized in a two-way table showing incidence rates for each drug across each infection. A categorical datum analysis (5, 11) that accounted for sample sizes and incidence rates within drugs and within infections was carried out. The results were presented as chi-square comparisons for the difference between infection sites and the difference between overall ceftizoxime and cefotaxime rates versus the rate for moxalactam.

RESULTS

A total of 241 patients from 12 clinical centers were entered. Of these, 106 were enrolled in the peritonitis study, and 135 were enrolled in the pneumonia study. A total of 145 patients were evaluable for the development of hypoprothrombinemia (49 patients with peritonitis and 96 patients with pneumonia). A total of 25 patients were unevaluable because they were given prophylactic vitamin K. Of the remaining unevaluable patients, 62 had insufficient prothrombin time data to permit assessment, and 7 had increases in prothrombin time possibly due to concomitant medication or underlying disease state. The reasons for lack of evaluability were similar across study medication groups as well as sites of infection.

The demographic characteristics of evaluable patients are presented in Table 1. Within each trial, no major differences were noted between drug treatment groups. The evaluable patients in the pneumonia study, however, were significantly older ($P < 0.05$) than those in the peritonitis study, and there was a predominance of males in both studies.

As might be anticipated, there were marked differences in concomitant medication usage between patients with pneumonia and patients with peritonitis. Aminophylline and prednisone were used more frequently in patients with pneumonia, whereas morphine, meperidine, and hydroxyzine were used more frequently in peritonitis patients. Within the pneumonia and peritonitis study groups, however, no differences in concomitant medication usage were noted between drug regimens.

The average daily dose of drug and duration of therapy for each treatment group are also shown in Table 1. There were no significant differences between treatment groups for patients in the pneumonia study. For those in the peritonitis study, however, cefotaxime was administered at a higher does than either ceftizoxime or moxalactam. Ceftizoxime was administered for a shorter period than both cefotaxime and moxalactam. None of these differences was statistically significant.

In both trials, the most frequent underlying conditions noted were age >65 years, alcoholism, diabetes mellitus, and use of corticosteroids. The incidences of these factors in the pneumonia trial were 25.5, 20, 12, and 7%, respectively. Their respective incidences in the intra-abdominal infection trial were 16, 18, 6, and 6%. Within each study the distribu-

TABLE 2. Hypoprothrombinemia incidence

Drug	Incidence[a] (%) of hypoprothrombinemia in indicated patients		
	Peritonitis	Pneumonia	Total
Ceftizoxime	1/15 (6.7)	0/28 (0)	1/43 (2.3)
Cefotaxime	3/16 (18.7)	0/34 (0)	3/50 (6.6)
Moxalactam	8/18[b,c] (44.4)	5/34 (14.7)	13/52[d] (25.0)
Total	12/49[c] (24.5)	5/96 (5.2)	

[a] Number of patients with hypoprothrombinemia/total number evaluable.
[b] $P < 0.05$ for moxalactam versus ceftizoxime.
[c] $P < 0.05$ for peritonitis versus pneumonia.
[d] $P < 0.05$ for moxalactam versus ceftizoxime or cefotaxime.

tion of these risk factors was similar among all treatment groups.

The incidence of drug-related hypoprothrombinemia varied widely between both drugs and infection types (Table 2). Drug-related hypoprothrombinemia occurred in 24.5% (12 of 49) of patients with peritonitis and 5.2% (5 of 96) of patients with pneumonia. Based on a chi-square analysis, this represented a statistically significant ($P < 0.05$) difference. The overall incidences of drug-related hypoprothrombinemia among treatment groups were 25% for moxalactam, 6.6% for cefotaxime, and 2.3% for ceftizoxime. The incidence of hypoprothrombinemia was significantly greater for moxalactam-treated patients than for those treated with ceftizoxime ($P < 0.05$) or cefotaxime ($P < 0.05$). The highest incidence of hypoprothrombinemia (44.4%) was observed in peritonitis patients who received moxalactam. There was a statistically significant difference ($P < 0.05$) between the number of moxalactam-treated patients with peritonitis who developed hypoprothrombinemia and the number of ceftizoxime-treated patients who developed hypoprothrombinemia in the same trial. With the exception of one moxalactam patient who experienced a gastrointestinal bleeding problem, no other bleeding was reported.

The average maximum increases in prothrombin time and respective ranges are presented for evaluable patients in Table 3. Corresponding to the results presented in Table 2, these results indicated that the average maximum increase in prothrombin time with moxalactam was significantly (Student's t test, $P < 0.05$) higher than that incurred with either ceftizoxime or cefotaxime.

For the 17 patients who developed hypoprothrombinemia, the average time from the initiation of antibiotic therapy to the identification of hypoprothrombinemia was 5.7 days (range, 2 to 15 days). With the exception of one peritonitis patient who received moxalactam, all of these patients had normal tests of renal and liver function prior to as well as during therapy. In all cases, elevated prothrombin times returned to normal within 1 to 3 days following the administration of vitamin K.

A comparison of demographic characteristics, concomitant medications, risk factors, dosage, duration of therapy, clinical laboratory parameters, and pretherapy signs and symptoms of peritonitis was made for evaluable patients in the group with the highest incidence of hypoprothrombinemia, those with peritonitis who received moxalactam therapy. No differences between those developing and those not developing hypoprothrombinemia were observed in this group with respect to demographic characteristics, total daily dosage of moxalactam (total mean grams or milligrams per kilogram), pretherapy laboratory indices of renal or hepatic function, platelet count, or prothrombin time. The predominant concomitant medications, meperidine, morphine, cimetidine, hydroxyzine (Vistaril; Pfizer Inc.), furosemide, and potassium chloride, were used with equal frequency and in similar dosages in those patients who developed hypoprothrombinemia and in those who remained normal. Owing to the relatively low incidence of hypoprothrombinemia in the cefotaxime and ceftizoxime groups, a similar comparison within these groups was not undertaken.

An analysis of the mean pretherapy scores for signs and symptoms of peritonitis indicated that there was significantly more abdominal distention ($P < 0.01$) and diminution or absence of bowel sounds ($P < 0.05$) in moxalactam-treated patients developing hypoprothrombinemia (mean ± standard error [SE] bowel sound score = 1.8 ± 0.16; mean ± SE abdominal distention score = 1.6 ± 0.26) than in those not developing hypoprothrombinemia (mean ± SE bowel sound score = 0.9 ± 0.28; mean ± SE abdominal distention score = 0.4 ± 0.27). Abdominal distention was noted in 7 of 8 moxalactam patients who subsequently developed hypoprothrombinemia but in only 2 of 10 moxalactam patients who maintained normal prothrombin times. Similarly, 6 of the 8 patients developing hypoprothrombinemia had no bowel sounds, whereas only 3 of the 10 moxalactam patients not developing this side effect had no bowel sounds. These indices of ileus were, in each case, noted prior to the development of hypoprothrombinemia and did not develop concurrently with this side effect. The mean scores and distribution of scores for the other signs and symptoms of peritonitis (i.e., fever, drainage, guarding, and tenderness) did not indicate any difference between patients who developed hypoprothrombinemia and those who remained normal.

TABLE 3. Maximum increase in prothrombin time from the base line

Disease	Avg increase in prothrombin time in s (range) [no. tested] with[a]:		
	Ceftizoxime	Cefotaxime	Moxalactam
Peritonitis	0.9 (0–9.9) [15]	1.7 (0–16.7) [16]	4.0 (0–16.5) [18]
Pneumonia	0.3 (0–1.1) [28]	0.5 (0–2.5) [34]	3.6 (0–43.5) [34]
Total	0.5 (0–9.9) [43]	0.9 (0–16.70) [50]	3.7 (0–43.5) [52]

[a] Data represent the maximum increase in each patient.

DISCUSSION

Coagulation abnormalities associated with the administration of a cephalosporin antibiotic were first reported in 1974 in patients with severe renal impairment (P. I. Lerner and A. Lubin, Letter, N. Engl. J. Med. **290**:1324, 1974). With the recent introduction of extended-spectrum cephalosporins, reports of drug-related coagulopathy have increased markedly (1, 4, 7, 8, 10, 14, 20, 23, 24; Schwigon and Barckow, 22nd ICAAC).

Several hypotheses have been advanced to explain the relation of cephalosporins to hypoprothrombinemia. Pineo and colleagues have suggested that hypoprothrombinemia is a frequent concomitant condition in the malnourished, often severely debilitated population for whom extended-spectrum cephalosporins are most commonly used and that the apparent increased incidence of coagulopathy reflects the selection bias inherent in the use of these agents in patients with a dietary deficiency of vitamin K (21). Others have proposed a direct inhibition of fibrin formation by β-lactam antibiotics through the inhibition of the final steps of blood coagulation (6, 14). Conly and colleagues have recently proposed that the broad antimicrobial spectrum of the newer cephalosporins eliminates the menaquinone-producing bacteria in the intestinal lumen, thereby facilitating the development of vitamin K deficiency and hypoprothrombinemia in hosts already so predisposed because of pre-existing malnutrition and general debilitation (3, 22).

Another explanation proposed by Lipsky et al. (13) and Neu (17) suggests that a specific structural configuration, namely, the presence of a methylthiotetrazole moiety at the three position on the dihydrothiazolidine ring, directly interferes with the vitamin K-mediated production of prothrombin precursors. Those cephalosporins containing this moiety have been the agents most frequently involved in adverse

reactions related to the prolongation of prothrombin time (9, 19, 26; Z. A. Haubenstock, P. Schmidt, J. Zazgornik, P. Balcke, and H. Kopsa, Letter, Lancet i:1215–1216, 1983; B. C. Jensen, Letter, Clin. Pharm. 2:301–302, 1983; F. M. MacLennan, A. K. Ah-See, A. E. Wong, J. A. Anderson, and B. Bennett, Letter, Lancet i:1215, 1983). Finally, both in vitro and in vivo evidence linking the methylthiotetrazole moiety to the inhibition of vitamin-K dependent carboxylation of prothrombin precursors as well as to the development of hypoprothrombinemia in a murine model has been presented (13, 14).

The results of this study support previous reports regarding the association of moxalactam with vitamin K-dependent coagulopathy. in similar therapeutic groups, differences in the incidence of hypoprothrombinemia and average maximum increases in prothrombin time were noted between patients treated with moxalactam and those treated with either ceftizoxime or cefotaxime. Ceftizoxime and cefotaxime are agents with antimicrobial spectra and therapeutic activity similar to those of moxalactam, but they lack the methylthiotetrazole side chain associated with the moxalactam molecule. Conly et al. demonstrated a significantly higher incidence of coagulopathy in oncologic patients treated with moxalactam-ticarcillin than in those treated with tobramycin-ticarcillin (3). These authors interpreted the observed higher incidence of hypoprothrombinemia in the moxalactam-ticarcillin group to be related to the greater suppression of aerobic and anaerobic gram-negative fecal flora. Stool flora was neither qualitatively nor quantitatively measured in the present study. However, in view of the similarities among these agents in terms of antimicrobial activity and routes of elimination, it is unlikely that moxalactam produced a more profound effect on fecal flora than either cefotaxime or ceftizoxime. In addition, other antibiotics with activity against enteric anaerobic flora, such as clindamycin, cefoxitin, chloramphenicol, and metronidazole, have not been associated with an excess incidence of hypoprothrombinemia despite widespread use.

It has also been suggested that certain easily identifiable risk factors, such as advanced age, renal impairment, and hepatic disease, predispose patients to the development of hypoprothrombinemia. We were unable to confirm such associations. In fact, patients in the group with the highest incidence of coagulopathy, those with intra-abdominal infections, were younger than those being treated for pneumonia. Interestingly, other reports of the development of coagulopathy with moxalactam have often described a disproportionate incidence of intra-abdominal infections. (9, 19; Jensen, Clin. Pharm. 2:301–302).

It is likely that altered bowel motility rather than peritonitis per se predisposes patients to hypoprothrombinemia. We found a strong association between the loss of bowel function, as reflected in the findings of abdominal distension and hypoactive or absent bowel sounds, and the development of prothrombin time prolongation. It is of interest that, although the information was not specifically solicited, of the five moxalactam-treated patients with pneumonia who developed hypoprothrombinemia, two were spontaneously noted by the clinical observers to have developed marked ileus.

These studies indicated that extended-spectrum cephalosporins vary widely in their potential to produce hypoprothrombinemia. It is likely that the development of hypoprothrombinemia by these agents is a multifactor phenomenon. However, we believe that coagulopathy is especially associated with the presence of a methylthiotetrazole side chain and that agents containing this or related structures need to be carefully evaluated for their hypoprothrombinemic potential. Also, our analysis indicated that the incidence of coagulopathy may be higher in patients with altered bowel motility.

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