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Cefotaxime and Cephalosporins: Adverse Reactions in Perspective

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Cefotaxime was used to treat infections in 2,579 patients during phase II and phase III clinical trials. This paper summarizes the adverse reactions reported to Hoechst-Roussel Pharmaceuticals (Somerville, NJ) during the treatment of these infections. Cefotaxime caused adverse reactions that are caused by all other cephalosporins, including pain at the site of injection (31.9%), thrombophlebitis (4.9%), skin rash (1.8%), thrombocytopenia (3.8%), glomerulotubular dysfunction (1.4%), diarrhea (1.2%), and superinfection (1.1%). Compared with cefazolin, cefotaxime caused pain on injection, phlebitis, and diarrhea more commonly ($P < 0.05$) but caused superinfection less commonly ($P < 0.04$). Since these data were obtained from many different sources by diverse methods, further controlled trials are needed to substantiate these differences. However, the adverse reactions caused by cefotaxime appear to be similar in spectrum and severity to those caused by other cephalosporins.

The cephalosporin antibiotics have displayed considerable safety during more than 20 years of clinical use [1-4]. Adverse reactions to the cephalosporins can be classified in four groups by their etiology: (1) the physical and chemical properties of the cephalosporins; (2) hypersensitivity; (3) drug dose; and (4) other diverse or unknown etiologies.

Etiology and Incidence of Various Adverse Reactions

Adverse reactions due to the physical and chemical properties of the cephalosporins are pain on intravenous injection and thrombophlebitis (table 1). In most series studied, these two reactions occur in 5%-40% and 15%-80% of patients, respectively. This wide range in incidence is probably a function of the frequency and care with which the reaction is looked for, the cephalosporin administered, and (in the case of thrombophlebitis) the definition used. Pain on injection is often mild to moderate in severity and seldom requires discontinuation of therapy [1, 5, 6]. Various techniques have been used to study the ability of cephalosporins to produce thrombophlebitis [7-12]. Siebert et al. [7], using a double-blind technique, a water

control, and a 21-gauge scalp-vein needle, found no difference in frequency between phlebitis due to injection of water and that due to injection of cephalothin; most patients in both treatment groups developed phlebitis. This finding attests to the fact that the needle may often be the cause of the phlebitis. However, Siebert et al. did find that injection of cephalothin caused more severe phlebitis.

Adverse reactions due to hypersensitivity include skin rash, fever, eosinophilia, hemolytic anemia, and anaphylaxis [5, 6, 12-16]. Fortunately, all of these reactions, with the possible exception of eosinophilia, are unusual. Two types of skin rash may be noted: urticaria, which usually develops rapidly after the start of therapy, and a maculopapular pruritic rash, which usually develops after three to five days of therapy and is the more common of the two. Other adverse reactions that presumably are due to hypersensitivity include exfoliative dermatitis, interstitial nephritis, and thrombocytopenia [17-20]. The incidence of these reactions is unknown, but they are presumed to be rare. Although the extent of the cross-reactivity between cephalosporins and penicillins is unknown [21, 22], it appears that patients with a history of penicillin allergy have a 10% chance of reacting to either a penicillin or a cephalosporin. However, it is not known whether the same patient will react to both drugs simultaneously.

Dose-dependent adverse reactions to the cepha-

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Table 1. Etiologic classification of adverse reactions noted in patients given cephalosporins.

Etiologic classification	Adverse reaction	Incidence (%)
Physical properties of drug	Pain on injection	5-40
	Thrombophlebitis	15-80
Hypersensitivity to drug	Skin rash	1-5
	Exfoliative dermatitis	Unknown
	Hemolytic anemia	Rare
	Eosinophilia	2-26
	Thrombocytopenia	Unknown
	Fever	0.4-0.6
	Interstitial nephritis	Unknown
Dose of drug	Anaphylaxis	Rare
	Positive Coombs' reaction	0-65
	Glomerulotubular dysfunction	0-5
	Central nervous system dysfunction	Rare
	Platelet dysfunction	Unknown
Other (diverse or unknown)	Leukopenia and agranulocytosis	Rare
	Diarrhea	0.5-30
	Pseudomembranous colitis	Rare
	Prolonged prothrombin time	0-8
	Disulfiram-like reaction	Unknown
	Colonization and superinfection	2-5

losporins include the development of a positive Coombs' reaction, glomerulotubular dysfunction, central nervous system toxicity, platelet dysfunction, leukopenia, and agranulocytosis. As might be expected, these dose-dependent reactions are usually seen in patients receiving high doses or in those with severe renal dysfunction. The positive Coombs' reaction has an interesting etiology in most cases [23-25]. Cephalosporins bind to serum proteins, and the serum protein-cephalosporin complex then binds to the red cell membrane. This complex does not activate complement and does not lead to hemolysis. However, it does contain globulins that react with Coombs' antisera. Consequently, the development of a direct Coombs' reaction usually is not indicative of the immunologic reaction that leads to hemolytic anemia. The serum drug levels at which a positive Coombs' reaction develops are usually >150-300 µg/ml—levels rarely obtained clinically [25]. The sensitivity of the Coombs' antisera used is also a factor in the frequency of this reaction. The reported fre-

quency of a positive direct Coombs' reaction varies from 0 to 65%. The clinical importance of this reaction appears to be limited to the difficulty it produces in typing and cross-matching of blood.

The development of glomerulotubular dysfunction has been most frequently reported with cephaloridine [26]. This drug is taken up into proximal tubular cells by the organic-acid transport system and accumulates within these cells, causing damage to or death of cells. Accumulated levels of cephaloridine are high because the drug is poorly secreted into the tubular lumen [27, 28]. Probenecid can block the uptake of cephaloridine into proximal tubular cells and thus can reduce the nephrotoxicity of this drug. Other cephalosporins that are secreted more readily into the tubular lumen accumulate less markedly and induce glomerulotubular dysfunction less frequently [28]. In most series studied, reduction in the glomerular filtration rate, measured as a rise in levels of either blood urea nitrogen or serum creatinine, has been noted in 0 to 5% of patients [1, 6, 12]. Pickering et al. [29] have suggested that the presence of preexisting renal disease is associated with a higher incidence of nephrotoxicity. Mondorf [30] has measured the elimination of alanine aminopeptidase, an enzyme found in the brush border of proximal tubular cells in eight healthy volunteers receiving 3 g of cefotaxime twice daily. In contrast to gentamicin, which caused a 5- to 10-fold increase in the excretion of this enzyme, cefotaxime did not induce any changes. These data suggest that the intrinsic propensity of cefotaxime to induce changes in proximal tubular function is low. Ninane [31] and Clumeck et al. [32] have found similar results, by measuring either excretion of β -N-acetylglucosaminidase or levels of serum creatinine.

Cephalosporins, like penicillins, can cause mental confusion, myoclonus, and seizures [33]. These reactions are rare except in patients with renal failure who receive high doses. Leukopenia typically develops during the second week of therapy, is seldom severe, and occurs in patients receiving doses of >12 g per day [34-37]. Agranulocytosis has been reported in only a few patients [38, 39]. Both of these dose-dependent reactions are reversible within two to seven days after therapy has been discontinued.

Adverse reactions to the cephalosporins with other etiologies include diarrhea, pseudomem-

branous colitis, prolongation of the prothrombin time, disulfiram-like reactions, and colonization or superinfection. Cephalosporin-associated pseudomembranous colitis is caused by a toxin-producing strain of *Clostridium difficile* that is resistant to these drugs [40-44]. Diarrhea, which occurs in as many as 30% of patients receiving cephalosporins and is much more common than pseudomembranous colitis, may be due to a similar mechanism or to other factors [45]. The diarrhea is occasionally quite severe and may necessitate discontinuation of therapy.

Prothrombin time is prolonged in up to 8% of patients taking cephalosporins, and the prolongation is possibly caused by the elimination of vitamin K-producing bacteria in the gastrointestinal tract [46-49]. This condition usually develops after five to seven days of treatment in nutritionally deficient patients and is reversible by parenteral administration of vitamin K [48]. Although the mechanism of interference by the antibiotic with the synthesis or utilization of vitamin K is unknown, the excretion of the cephalosporin into the bile may be a key factor, as Hooper et al. [48] have suggested. Prolongation of the thrombin time and of the activated partial thromboplastin time has also been reported. Natelson et al. [47] have suggested that cephalothin may retard fibrinogen-fibrin polymerization. However, this reaction occurs only with levels of >200-300 µg/ml and would be expected only in patients with severe renal failure.

The development of a disulfiram-like reaction with the ingestion of alcohol after treatment with cefoperazone was first reported by McMahon [50]. The reaction is a typical disulfiram reaction, with intense flushing, diaphoresis, headache, nausea, vomiting, and diarrhea. Hypotension has also been reported. Subsequently, several additional cases reported in the literature have implicated moxalactam and cefamandole as well [51-54]. The reaction occurred in patients between 16 and 68 years of age who had received treatment ranging from a single 3-g iv dose of a cephalosporin to several days of treatment with individual doses of 750 mg to 2 g. The reaction developed after three to seven days of treatment and within 6-60 hr after the last dose of the cephalosporin. Beer, vodka, and wine have been associated with the reaction, which occurs within 30 min after ingestion of alcohol. Recently it has been shown that

the disulfiram-like reaction is due to inhibition of acetaldehyde dehydrogenase by the methyltetrazolethiol side chain of cefamandole, cefoperazone, and moxalactam [55]. Cefotaxime does not have this side chain.

Colonization and superinfection are serious problems in the use of broad-spectrum antibiotics [56]. It has been assumed that these problems are more frequent with broad-spectrum antibiotics than with drugs whose targets are more specific. However, Petty et al. [12] found that the superinfection rate in patients with pneumococcal pneumonia who were given penicillin did not differ from that in similar patients given cefamandole in a double-blind study. This potentially serious adverse reaction has been noted in only 2%-5% of patients treated with cephalosporins. The organisms causing superinfection are those typically found in nosocomial infections, including multiply resistant aerobic gram-negative bacilli and fungi.

Review Methods

Occurrence of adverse reactions to cefotaxime in 2,379 patients was reported to Hoechst-Roussel Pharmaceuticals by 130 investigators. Two hundred twenty-two patients given a single 1-g im injection of cefotaxime for the treatment of gonorrhea did not experience any significant adverse reactions. Data that could be evaluated for safety were available for all of the remaining 2,157 patients (90.6%), who received multiple doses. All patients and all adverse reactions that were considered by the investigators to be possibly or probably related to cefotaxime therapy were included in this analysis. Standard definitions were employed to determine changes in laboratory measurements. Measurements from patients who had pretreatment values within the normal range and who had follow-up determinations were included. The following criteria were used to indicate a significant change: platelets, decrease of >100,000/mm; neutrophils, decrease of >40%; eosinophils, increase of ≥9%; serum aspartate aminotransferase (otherwise known as serum glutamic oxalacetic transaminase [SGOT]), increase of ≥50 IU/liter; alkaline phosphatase, increase of ≥30 IU/liter; total bilirubin, increase of ≥0.5 mg/dl; serum creatinine, increase of ≥0.5 mg/dl; and

Table 2. Demographic characteristics of patients given cefotaxime, by site of infection.

Site of infection (no. of patients)	Mean duration of treatment (days)	Mean daily dose (g)	Mean age (years)	Percentage male	Percentage seriously or critically ill
Lower respiratory tract (530)	8.3	4.4	57.4	64.9	33
Urinary tract (872)	7.4	3.0	57.3	58.6	16
Skin/soft tissue (408)	11.1	5.2	50.9	69.7	16
Bone (55)	25	6.7	50.9	80.0	11
Blood (129)	11.6	5.9	57.7	58.9	62
Gynecologic tract (134)	5.5	3.0	24.1	0	56
Intraabdominal region (59)	9.3	5.2	53.8	42.3	29

serum creatine kinase, increase of ≥ 25 IU/liter. Comparisons were made by either χ^2 analysis or Student's *t* test.

Results

Of the 2,157 patients given multiple doses of cefotaxime, 1,483 were enrolled in an open prospective trial, and 674 were studied in prospective, randomized, controlled trials of cefazolin as standard therapy. Cefazolin was given to a total of 422 patients.

The demographic data on patients given cefotaxime are shown in table 2, and the adverse reactions are listed in table 3. Pain on injection was noted in 31.9% of the 889 patients who received cefotaxime im. Mild pain was noted in 27%, moderate pain in 4.5%, and severe pain in only 0.4% of these patients. Thrombophlebitis was found in 4.9% of the 1,641 patients who received cefotaxime iv.

Skin rash was noted in 1.8% of the 2,157 patients evaluated. Of the 38 rashes reported, two were urticarial and 36 were maculopapular. Skin rash developed an average of 10.6 days after initiation of therapy (range, 2–36 days) and lasted 5.8 days (range, 8 hr to 36 days). None of the rashes was severe, and exfoliative dermatitis was not reported. Eosinophilia occurred in 1.3% of the 1,197 patients evaluated. Fever developed in 0.4% of the entire group of 2,157 patients. Thrombocytopenia was noted in 3.8% of the 764

patients evaluated. Hemolytic anemia, interstitial nephritis, and anaphylaxis were not observed in any patients. Since a previous history of hypersensitivity to penicillin was a reason for exclusion from entry into the protocols, cross-sensitivity between penicillin and cefotaxime could not be assessed.

A positive direct Coombs' reaction was noted in 6.4% of the 329 patients for whom serial measurements were taken. Glomerulotubular dysfunction occurred in 1.4% of the 1,249 patients with a normal base line value. Central nervous system toxic-

Table 3. Adverse reactions noted in patients given cefotaxime.

Adverse reaction	No. of patients at risk	Incidence (%)
Pain on injection	889	31.9
Mild	...	27.0
Moderate	...	4.5
Severe	...	0.4
Thrombophlebitis	1,641	4.9
Skin rash	2,157	1.8
Eosinophilia	1,197	1.3
Fever	2,157	0.4
Thrombocytopenia	764	3.8
Positive Coombs' reaction	329	6.4
Glomerulotubular dysfunction	1,249	1.4
Central nervous system dysfunction	2,157	0.3
Leukopenia	772	0.5
Diarrhea	2,157	1.2
Superinfection	2,091	1.1

ty (hallucinations, vertigo, or disorientation) occurred in 0.3% of all 2,157 patients. No instances of seizures or myoclonus were noted. Leukopenia occurred in 0.5% of the 772 patients evaluated for this reaction. One case of reversible agranulocytosis was reported.

Diarrhea developed in 1.2% of the 2,157 patients an average of 7.4 days after initiation of therapy (range, 1–26 days) and lasted for 5.4 days (range, 1–15 days). Twelve cases (71%) were thought to be mild; only one case was thought to be severe. Colitis was reported in two patients, one of whom had *C. difficile* and its toxin isolated from stool. One case of pseudomembranous colitis was reported but was discovered only at autopsy. The patient had undergone chemotherapy for cancer and had received antibiotics other than cephalosporins; these factors may have led to this problem.

Serial determinations of prothrombin time have been made so far for only 26 patients. No patient developed a prolongation of prothrombin time.

The disulfiram-like reaction was evaluated prospectively in 22 healthy male volunteers. Patients were given a 1-g iv dose of cefotaxime and 6 hr later were given 0.2 g of alcohol (e.g., vodka)/kg. They were then observed for 48 hr. None of the patients developed a disulfiram-like reaction.

Superinfections, defined as culture of a new organism associated with clinical manifestations of infection during treatment, occurred in only 1.1%

of the 2,091 patients described on case report forms that supplied this information. Superinfections most commonly involved the skin and skin structures (table 4). The most common infecting organisms were *Pseudomonas* species (11 cases), *Enterobacter* species (five), *Candida* species (three), and enterococci (two).

No changes attributable to cefotaxime were noted in levels of hemoglobin, hematocrit, total serum protein, serum albumin, blood glucose, serum lactate dehydrogenase, total bilirubin, uric acid, inorganic phosphorus, or serum calcium.

Of the 2,157 patients, therapy was discontinued in 47 (2.2%) because of an adverse reaction (table 5). Hypersensitivity reactions, such as skin rash and fever, were the most frequent reasons for discontinuation of therapy.

Adverse reactions to cefotaxime and cefazolin were compared in a prospective, observer-blind protocol in several medical centers (table 6). Pain on injection, phlebitis, diarrhea, and elevation of alkaline phosphatase were significantly more common with cefotaxime. In contrast, superinfections were significantly more common with cefazolin. Of the 13 superinfections during cefazolin treatment, 11 occurred in the urinary tract and were often associated with catheters or anatomical abnormalities of the urinary tract. The organisms causing superinfections during cefazolin therapy were *Pseudomonas aeruginosa* (seven cases), *Proteus* species (two), *Serratia marcescens* (two), *Enterobacter* (one), and enterococci (one).

Table 4. Superinfections in 2,157 patients given cefotaxime, by site.

Body site	No. of infections	No. of superinfections	Frequency of superinfection (%)
Gynecologic tract	134	0	0
Intraabdominal region	59	1	1.7
Lower respiratory tract	530	5	0.9
Urinary tract	872	8	0.9
Skin and skin structures	408	9	2.2
Bones and joints	55	0	0
Blood	129	1	0.8
Total	2,187*	24	...

* The number of infections is >2,157 because some patients had infections at more than one site.

Table 5. Adverse reactions resulting in discontinuation of cefotaxime therapy in 47 of 2,157 patients.

Adverse reaction	No. of patients with therapy discontinued
Skin rash	21
Fever	6
Diarrhea	5
Phlebitis	4
Colitis	3
Pain on injection	2
Cellulitis	1
Thrombocytopenia	1
Disorientation	1
Vertigo	1
Leukopenia	1
Chills	1
Total	47 (2.2%)

Table 6. Comparison of adverse reactions to cefotaxime and cefazolin.

Adverse reaction	Incidence with indicated drug*		P
	Cefotaxime	Cefazolin	
Pain on injection (total)	284/889 (31.9)	64/249 (25.7)	0.05
Pain on injection (moderate/severe)	44/889 (4.9)	6/249 (2.4)	NS†
Creatine kinase increase	45/226 (19.9)	8/51 (15.7)	NS
Phlebitis	80/1,641 (4.9)	2/230 (0.9)	<0.001
Skin rash	38/2,157 (1.8)	3/422 (0.7)	NS
Diarrhea	26/2,157 (1.2)	0/422 (0.0)	<0.03
Fever	8/2,157 (0.4)	2/422 (0.5)	NS
SGOT increase‡	17/1,237 (1.4)	4/252 (1.6)	NS
Alkaline phosphatase increase	77/980 (7.9)	7/202 (3.5)	<0.03
Bilirubin increase	31/1,424 (2.2)	6/282 (2.1)	NS
Thrombocytopenia	29/764 (3.8)	6/182 (3.3)	NS
Leukopenia	2/772 (0.3)	2/149 (1.3)	NS
Eosinophilia	15/1,197 (1.3)	1/206 (0.5)	NS
Creatinine increase	17/1,249 (1.4)	4/237 (1.7)	NS
Superinfection	24/2,091 (1.1)	13/422 (3.1)	<0.004

* Findings are expressed as the number of patients with the reaction/number at risk (percentage with the reaction).

† NS = not statistically significant.

‡ SGOT = serum glutamic oxalacetic transaminase.

Discussion

Assessment of the frequency and severity of adverse reactions is an important aspect of the development of a new drug. Data collected by the pharmaceutical industry during phase II and phase III clinical trials provide useful information about these reactions. However, the utility of this information is limited by the bias inherent in the methodology used for collection of data. In these studies, patients are often selected for treatment without well-defined criteria, and different centers use different doses, measurement techniques, and definitions of adverse effects. In comparative trials, drug assignment may not be random and a double-blind technique is rarely used. Therefore, patients may not be equally predisposed to develop adverse reactions or equally likely to be monitored for such reactions. Often, so many differences are sought that some turn out to be statistically significant by chance alone. Also, because large numbers of patients often are studied, some small differences may be statistically significant but clinically unimportant. Despite these problems, useful information may be gathered because of the large number of patients treated in different clinical settings.

The frequency and severity of adverse reactions to cefotaxime appear to be similar to those

reported for other cephalosporins. However, pain on injection, phlebitis, diarrhea, and increase in alkaline phosphatase were found to be more common with cefotaxime than with cefazolin, and superinfection was more common with cefazolin. The difference in the incidence of pain on injection was small (32% vs. 26%) and was noted only among patients reporting mild pain. The incidence of phlebitis was fivefold greater with cefotaxime (5% vs. 1%). However, the absolute incidence of phlebitis reported for both drugs is lower than that reported for other cephalosporins, which varies from 15% to 80%. (We do not have any data on the severity of these episodes except that therapy was discontinued in only 4 of 80 patients (5%) with cefotaxime-associated phlebitis.) The low reported incidence of phlebitis probably reflects differing definitions and differing degrees of care with which this adverse reaction was sought. Because of the limitations of the methodology used for collection of the data, we must be cautious about the interpretation of this difference.

The difference in the incidence of diarrhea is also small (1% with cefotaxime vs. 0 with cefazolin) and is statistically significant only because diarrhea was not reported at all in the cefazolin group. Diarrhea has been reported with cefazolin therapy in other studies. Three cases of colitis

were reported in patients treated with cefotaxime, but this result was expected in view of the inactivity of the drug against *C. difficile*.

The difference in the incidence of increase in alkaline phosphatase is difficult to interpret. No cases of drug-induced hepatitis were reported. It seems probable that this difference is due to differences among patients rather than between cefotaxime and cefazolin. Even if the difference is real, it appears to be clinically unimportant.

The lower incidence of superinfection with cefotaxime was unexpected. When examined more closely, the difference may be attributable to indwelling catheters and other predisposing factors rather than to differences in drug therapy. The spectrum of organisms causing superinfection was similar with cefotaxime and cefazolin.

This review has demonstrated that cefotaxime is safe and well tolerated in most patients. Focused clinical trials need to be conducted to determine whether phlebitis and diarrhea are more frequent with cefotaxime than with other cephalosporins. More information is needed on the frequency of colonization and superinfection and the frequency of adverse reactions in patients with severe renal and hepatic disease. Finally, adverse reactions to cefotaxime should be compared with those to the antibiotics or antibiotic combinations it may replace.

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