

Comparative Incidence of Phlebitis Due to Buffered Cephalothin, Cephapirin, and Cefamandole

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Received for publication 30 December 1975

Buffered cephalothin, cefamandole, and cephapirin were compared with respect to their tendency to produce phlebitis. Two grams of each agent was administered every 6 h for 4 days to 12 healthy volunteers in a double-blind crossover fashion. Approximately 50% of intravenous sites developed mild (grade 1) phlebitis and 25% developed moderate (grade 2) phlebitis. The frequency of grade 1 inflammation did not differ significantly among the three cephalosporins. The proportion of individuals eventually exhibiting grade 2 phlebitis was highest with cefamandole, lowest with cephalothin ($P = 0.07$), and intermediate with cephapirin; however, cephapirin required a substantially greater number of doses to produce grade 2 phlebitis than did the other two drugs. These findings, together with the results of other reports, suggest that interpretation of the phlebitogenic potential of these antibiotics must be made with caution.

Phlebitis is a troublesome accompaniment of the intravenous administration of cephalosporins, occurring in 30 to 50% of recipients of cephalothin (4, 7). Neutralization of the acidity of cephalothin has been found in one study to reduce the incidence of phlebitis significantly (1), whereas no such effect was noted in two other investigations (4, 7). Cephapirin, a congener with activity and pharmacological characteristics similar to those of cephalothin, has been stated to be less phlebitogenic than cephalothin (2, 6); however, conflicting results have been reported (3). Cefamandole is a newly synthesized cephalosporin with an expanded spectrum against gram-negative bacilli (8); its propensity to produce phlebitis is not yet known.

The purpose of the present investigation was to compare, in a randomized double-blind fashion, the capacity of these three cephalosporins to cause phlebitis in healthy subjects.

MATERIALS AND METHODS

Twelve healthy men between the ages of 18 and 40 years were admitted to the Clinical Study Unit of the New England Medical Center Hospital. None had ingested drugs or alcohol recently, and all denied allergy to penicillins or cephalosporins. A hemogram, urinalysis, and measurements of serum elec-

trolytes, creatinine, blood urea nitrogen, glutamic-oxalacetic transaminase, bilirubin, and Coombs' test were within normal limits in all volunteers. After informed consent had been obtained, each individual was assigned one of 12 randomized sequences of antibiotics.

The following drugs were administered to each subject: sodium cephalothin, buffered with sodium bicarbonate (Keflin, Neutral, Eli Lilly and Co.); cefamandole nafate (Eli Lilly and Co.); and sodium cephapirin (Cefadyl, Bristol Laboratories). Two grams of antibiotic diluted in 50 ml of 5% dextrose in water was administered intravenously every 6 h for 4 days (16 doses). After an interval of 24 h, the next regimen was begun according to the sequence assigned to the individual.

Each dose was administered by infusion pump over 30 min, through a 21-gauge scalp-vein needle placed in the dorsum of the hand or the distal forearm. A "heparin lock" (500 U of heparin per ml of saline) prevented clotting between doses. Administration sets were covered during the infusion to prevent identification of the particular drug by the subjects or observers.

Twice daily, each volunteer was examined by two physicians who independently recorded the condition of the needle site and any adverse effects. The presence of phlebitis was characterized as follows: (i) grade 1, erythema and/or swelling with tenderness extending ≤ 2.5 cm from the site of insertion of the needle; (ii) grade 2, similar findings extending > 2.5 cm from the point of insertion of the needle. Upon the recognition by either observer of grade 2 phlebitis or extravasation of fluid, the needle was relocated in the opposite extremity remote from any site of recent infusions or phlebitis. If a subject

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sustained two episodes of grade 2 phlebitis with a drug, the antibiotic was stopped and the next regimen was begun after 24 h. After the completion of each course of antibiotic, the laboratory tests performed on admission were repeated.

Analysis of data. Courses of therapy during which one observer recognized no phlebitis and the other recorded a grade 1 phlebitis were counted as 0.5 episode of grade 1 phlebitis. Where grade 1 phlebitis was noted by both physicians, but after a differing number of infusions, the time of onset of phlebitis was considered to lie midway between the two observations. Episodes of grade 2 phlebitis noted by either observer were accepted by both, and the needle was promptly removed. Statistical comparisons were performed by chi-square test with Yates correction and the Fisher exact probability test (6).

The mean (and range) of pH values of the various solutions, determined at 22 C (Radiometer/Copenhagen pH 26, The London Co., Cleveland, Ohio), were: buffered cephalothin, 7.06 (6.9 to 7.4); cefamandole, 7.08 (6.8 to 7.2); and cephalirin, 7.03 (6.8 to 7.2).

RESULTS

Two of 12 subjects did not receive all three antibiotic regimens. One developed nausea during administration of the third drug and another experienced generalized urticaria while receiving the second agent (buffered cephalothin in both instances). No renal, hepatic, or hematologic abnormalities were observed among any of the volunteers during the course of the studies.

A total of 530 doses of antibiotics (1,060 g) were administered through 56 intravenous sites (Table 1). The number of infusions started was similar for each of the three agents; however, for reasons that were not apparent a lesser number of infiltrations occurred with cephalirin than with the other drugs. This circumstance contributed to the fact that more infu-

TABLE 1. Characteristics of infusion sites

Determination	Antibiotic		
	Cephalothin	Cefamandole	Cephalirin
No. of recipients	12	11 ^a	12
No. of infusions started	19	20	17
No. of doses	166	173	191
Episodes of infiltration	6	6	2

^a One individual had experienced an allergic reaction during the preceding trial (cephalothin).

sions of cephalirin than of the other agents were given through a single intravenous site (Table 2). Despite this, the number of instances in which at least six, or at least eight, doses of drug could be given through the same needle did not differ among the three cephalosporins, indicating that the "opportunity" to develop phlebitis was not grossly disparate.

When averaged between the two observers, there were 28.5 instances of grade 1 and 14 of grade 2 phlebitis, involving 51 and 25% of intravenous sites, respectively (Tables 3 and 4). Grade 1 phlebitis occurred in a higher proportion of subjects receiving cefamandole than the other two drugs; the differences, however, were not significant (cefamandole versus cephalirin: chi-square = 1.50, $P = 0.2$ to 0.3 ; Fisher exact probability test, $P_F = 0.26$). Similarly, the number of instances of grade 1 phlebitis per 100 infusions did not differ significantly among the three agents. The mean and median number of doses given before the appearance of phlebitis was greatest with cephalirin.

A greater proportion of patients receiving cefamandole than those receiving cephalothin experienced grade 2 phlebitis (Table 4); this difference was of borderline significance (chi-square = 2.15, $P = 0.1$ to 0.2 ; Fisher exact probability

TABLE 2. Opportunities to develop phlebitis

Parameter	Antibiotic		
	Cephalothin	Cefamandole	Cephalirin
Median (mean) no. of doses through a single intravenous site	7 (8.3)	8 (8.7)	12 (11.2)
No. of courses in which ≥ 6 doses were given through a single intravenous site ^a	14	14	14
No. of courses in which ≥ 8 doses were given through a single intravenous site ^a	10	11	12

^a Including those interrupted by grade 2 phlebitis.

TABLE 3. *Development of grade 1 phlebitis*

Determination	Antibiotic		
	Cephalo- thin	Cefaman- dole	Cephapi- rin
No. of sub- jects with phlebitis/no. of recipients ^a	7.5/12	9.5/11	6.5/12
No. of epi- sodes ^a	9.5	12	11
Episodes per 100 doses	5.7	6.9	3.6
Time to ap- pearance of phlebitis: median (mean) no. of doses	6 (6.7)	8 (7.8)	9.5 (9.3)

^a Average between two observers (see text).

TABLE 4. *Development of grade 2 phlebitis*

Determination	Antibiotic		
	Cephalo- thin	Cefa- mandole	Cephapi- rin
No. of subjects with phlebitis/no. of recipients	2/12	6/11	5/12
No. of episodes	3	6	5
Episodes per 100 infusions	1.8	3.4	2.6
Time to appear- ance of phlebi- tis: median (mean) no. of doses	7 (8.3)	8 (8.7)	12 (11.2)

test, $P_F = 0.07$). The number of episodes per 100 infusions did not differ significantly among the drugs. As with grade 1 phlebitis, the time to appearance of grade 2 phlebitis was greater with cephapirin than with the other agents.

With all three antibiotics, approximately half (43 to 58%) of the instances of grade 1 phlebitis were evident by dose 6 and two-thirds (58 to 71%) were evident by dose 8. Grade 2 phlebitis, however, was noted only after eight doses of drug in 33% of episodes occurring with cephalothin, 67% with cefamandole, and 80% with cephapirin.

DISCUSSION

The results of this study support the notion that phlebitis is a common occurrence during the intravenous administration of cephalosporins (4, 7). There was an overall frequency of phlebitis, in the present investigation, of 5.7 episodes per 100 doses, involving 51% of needle sites. There was no significant difference among buffered cephalothin, cefamandole, and cephapirin in the proportion of subjects sustaining grade 1 phlebitis or in the incidence of this reaction per 100 infusions. In contrast, grade 2 phlebitis occurred most frequently with cefamandole and least often with buffered cephalothin; the difference was of borderline significance ($P = 0.07$).

The analysis of these data was made difficult by the fact that more infusions of cephapirin than of the other agents were given through a single intravenous site. This outcome arose from the combination of a lesser number of extravasations with this antibiotic and a longer time to appearance of grade 2 phlebitis, each of which necessitated a change in the needle site. To the extent that phlebitis is time related, therefore, cephapirin had a greater "opportunity" to produce inflammation. The fact that phlebitis, especially of grade 2 severity, took longer to appear with cephapirin than with the other agents may be considered to compensate for this increased "opportunity"; alternatively, it could be interpreted to suggest that frequent changes of intravenous sites might result in a lower frequency of severe phlebitis with cephapirin than with cephalothin or cefamandole.

The results of the present and of eight other controlled studies of the incidence of phlebitis with various cephalosporins are summarized in Table 5. The results are markedly divergent with respect to the effects of buffering on the phlebitogenic potential of cephalothin (1, 4, 7) and the relative phlebitogenicity of cephalothin and cephapirin (2, 3, 5, 6). It appears likely that many of these discrepancies are related to the small numbers of subjects studied as well as to differences in the design of the investigations.

In view of these factors, our interpretation of the data in the present study is a cautious one. The frequency of grade 2 phlebitis appears to be greatest with cefamandole, least with cephalothin, and intermediate with cephapirin; however, the time to appearance of moderate phlebitis is longer with cephapirin than with the other two agents. The propensity to produce mild (grade 1) phlebitis does not appear to differ substantially among the three cephalosporins.

TABLE 5. *Controlled studies of the comparative incidence of phlebitis with various cephalosporins*

Reference	Study population	Regimen	Results
Carrizosa et al. (4)	13 patients	Cephalothin vs. buffered cephalothin, 2 g every 6 h × 2 days	No difference in incidence or severity of phlebitis
Lipman (7)	32 patients	Cephalothin vs. buffered cephalothin, 1 g every 4-6 h	No difference in incidence of phlebitis
Bergeron et al. (1)	12 volunteers	Cephalothin vs. buffered cephalothin, 1 g every 2 h × 4 days	Buffered cephalothin produced significantly less phlebitis than unbuffered drug ($P < 0.01$)
Shemonsky et al. (11)	20 patients	Cephalothin, 2 g every 6 h, vs. cefazolin, 1 g every 6 h × 2 days	Cephalothin produced more severe phlebitis ($P < 0.05$) but no significant difference in incidence or time of onset
Lane et al. (6)	20 volunteers	Cephalothin vs. cephapirin, 1 g every 6 h × 5 days (continuous infusion)	Cephalothin produced significantly higher incidence of phlebitis ($P < 0.05$), more quickly and of greater severity than cephapirin
Carrizosa et al. (3)	20 patients	Cephalothin vs. cephapirin, 2 g every 6 h × 2 days	No difference in incidence, severity, or rapidity of onset of phlebitis
Bran et al. (2)	4 patients	Cephalothin vs. cephapirin, 1-2 g every 4-6 h × 2 days	Cephalothin produced more phlebitis than cephapirin; no statistical analysis
Inagaki and Bodey (5)	214 patients	Cephalothin vs. cephapirin, 3 g every 6 h × 1-2 weeks	No difference in overall incidence of phlebitis; cephalothin produced severe phlebitis more frequently (23 vs. 11% of patients, $P < 0.05$) than cephapirin
Present study	12 volunteers	Buffered cephalothin vs. cephapirin vs. cefamandole, 2 g every 6 h × 4 days	No difference in incidence of grade 1 phlebitis; cefamandole produces grade 2 phlebitis more frequently than does cephalothin ($P = 0.07$); cephapirin produces grade 2 phlebitis more slowly than the other agents

ACKNOWLEDGMENTS

This investigation was supported by a grant from Eli Lilly and Company, Indianapolis, Ind.

Cephapirin was provided through the courtesy of Bristol Laboratories, Syracuse, N.Y. We thank R. Ernst Clark for help in the statistical analysis of the data.

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