Comparison of Thrombophlebitis Associated with Three Cephalosporin Antibiotics

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A double-blind study with volunteers was performed to determine the incidence and severity of thrombophlebitis associated with cephalothin, cephapirin, cefamandole, and a water control. Although there were no statistical differences in the incidence of thrombophlebitis, cephalothin resulted in significantly more severe thrombophlebitis compared with the other agents.

The intravenous administration of cephalothin is associated with a high incidence of thrombophlebitis (7, 8). Cephapirin is a newer cephalosporin similar in bacterial spectrum to cephalothin (1). In single-blind studies, investigators found that cephapirin caused less thrombophlebitis than that reported for cephalothin (2, 5). In two reported double-blind studies, Inagaki and Bodey found a significant reduction in thrombophlebitis with cephapirin; however, this could not be substantiated by Carrizosa et al. (3, 4). The inability to perform a truly controlled study in patients because of the need for other intravenous medications perhaps contributed to these conflicting data. Cefamandole is a new cephalosporin with a somewhat broader gram-negative spectrum than that of cephalothin (6). There are no studies comparing the incidence of thrombophlebitis with cefamandole to other cephalosporin antibiotics. We undertook a double-blind study in normal volunteers to determine the incidence and severity of thrombophlebitis associated with the administration of cephalothin, cephapirin, cefamandole, and a vehicle control.

MATERIALS AND METHODS

Prior to performance, the study was reviewed and approved by four experimentation committees. After a detailed explanation, informed consent was obtained from 16 male volunteers with a negative history of penicillin and cephalosporin hypersensitivity. A continuous infusion of 5% dextrose and 0.2% sodium chloride at 1,000 ml/day was started in each volunteer via a 21-gauge "scalp vein" needle. Each volunteer served as his own control and received three cephalosporin antibiotics and a control vehicle in a sequential, randomized manner. The medications and dosages administered were: (i)

cephalothin, 2 g every 6 h; (ii) cephapirin, 2 g every 6 h; (iii) cefamandole, 2 g every 6 h; and (iv) sterile water control, 20 ml every 6 h. The medications were given intravenously via Soluset in a total volume of 100 ml over a 30-min period. A 2-day rest period separated each 5-day infusion period.

The infusion site was examined and scored twice daily by two independent observers without knowledge of the medication received or the other observers' score. Thrombophlebitis was graded from 0 to +4 according to the following scale: 0, no evidence of thrombophlebitis; +1, erythema and tenderness along the vein less than 2.5 cm above the infusion site; +2, erythema and mild tenderness along the vein more than 2.5 cm above the infusion site; +3, erythema and moderate discomfort along the vein more than 2.5 cm above the infusion site; and +4, erythema and severe discomfort along the vein more than 2.5 cm above the infusion site. When a +4 score was rendered, the intravenous infusion was stopped, and hot soaks and elevation were applied to the affected arm. In all cases, the discomfort and inflammation abated within 24 h. If infiltration of fluids into subcutaneous tissue occurred, the infusion site was changed to the opposite arm.

RESULTS

Each volunteer received a morning and evening thrombophlebitis score for a total of 5 days. If +4 thrombophlebitis was graded, a +4 score was given for all subsequent grades. Only 3 of 16 volunteers receiving cephapirin and water, 1 of 16 receiving cephalothin, and 0 of 16 receiving cefamandole had no thrombophlebitis. Table 1 shows the mean thrombophlebitis score for the three cephalosporins and water for each day of the study. The results were analyzed by the Friedman descriptive two-way analysis of variance by ranks. There were no statistical differences in the first 3 days of therapy, but by day 4 cephalothin reached a significantly higher mean of thrombophlebitis ($P < 0.01$),

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TABLE 1. Descriptive statistics and results of the Friedman two-way analysis of variance by ranks

Treatment	Severity score on day:									High ^a	Count ^b
	1 (p.m.)	2 (a.m.)	2 (p.m.)	3 (a.m.)	3 (p.m.)	4 (a.m.)	4 (p.m.)	5 (a.m.)	5 (p.m.)		
Cefamandole											
Mean	0.13	0.31	0.31	0.69	0.19	0.56	0.31	0.25	0.31	1.69	2.13
SD ^c	0.50	0.60	0.60	1.14	0.40	0.89	0.60	0.58	0.60	0.79	1.31
n	16	16	16	16	16	16	16	16	16	16	16
Cephapirin											
Mean	0.06	0.31	0.50	0.31	0.69	0.63	0.81	0.69	1.13	1.56	3.06
SD	0.25	0.60	0.73	0.60	0.95	1.09	1.17	1.20	1.54	1.36	2.84
n	16	16	16	16	16	16	16	16	16	16	16
Cephalothin											
Mean	0.06	0.44	0.88	1.38	1.25	2.06	2.44	2.56	2.63	2.94	5.19
SD	0.25	0.81	1.02	1.41	1.44	1.69	1.63	1.67	1.59	1.29	2.48
n	16	16	16	16	16	16	16	16	16	16	16
"Water"											
Mean	0.00	0.63	0.25	0.56	0.50	0.38	0.44	0.38	0.31	1.31	2.69
SD	0.00	0.81	0.58	0.81	0.63	0.62	0.73	0.50	0.60	0.79	2.21
n	16	16	16	16	16	16	16	16	16	16	16
Friedman two-way ANOVA ^d											
Result	0.11	0.69	2.87	5.31	4.86	5.32	12.94	10.99	13.63	8.23	9.81
Significance	0.99	0.87	0.41	0.15	0.18	0.15	<0.01	0.01	<0.01	0.04	0.02

^a High, The highest score each patient received during a treatment period.^b Count, The number of non-zero severity score periods; total of +1 → +4 scores.^c SD, Standard deviation.^d ANOVA, Analysis of variance.

which was maintained throughout the duration of the study.

Infiltration of intravenous fluid was not a significant problem. Of the infusions that needed to be restarted, equal numbers appeared in the cephalothin, cephapirin, cefamandole, and water groups.

DISCUSSION

Although there were no significant differences in the incidence of thrombophlebitis resulting from infusion of water, cephapirin, cefamandole, and cephalothin, there was a statistically significant difference in the severity of thrombophlebitis. Cephalothin produced more severe thrombophlebitis than cephapirin, cefamandole, or water. There were no statistical differences in the severity of thrombophlebitis caused by cephapirin, cefamandole, and water.

Disadvantages of previously reported thrombophlebitis studies have been lack of control to assess incidence and severity of thrombophlebitis from the infusion vehicle alone (3-5) and inability to use each patient as his own control (4). The administration of water and each cephalosporin to all volunteers in the study circum-

vented these difficulties. The almost uniform need for other intravenous medications, the presence of other diseases, and the inability to assess the contribution of the vehicle alone restrict a controlled study to a volunteer population.

Our results are in agreement with those of Lane et al. (5) and Inagaki and Bodey (4) but in contrast with those of Carrizosa et al. (3). The most likely explanation for the difference is the duration of the study. Following the example of Lane et al. (5), we used a 5-day infusion period. In our experience, significant cephalothin thrombophlebitis occurred only at 72 h or later. Since Carrizosa stopped his study at 48 h, this may have been too short a time for the development of full cephalothin thrombophlebitis. There do not appear to be any major differences in the severity of thrombophlebitis caused by water, cephapirin, and cefamandole.

Our current study demonstrates that cephapirin and cefamandole produce less severe inflammation than cephalothin when evaluated in a 5-day infusion period. If pharmacological and microbiological parameters prove to be equal, it would appear that cephapirin and cef-

amandole are more desirable intravenous cephalosporins than cephalothin.

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