

Relative Incidence of Phlebitis Caused by Continuous Intravenous Infusion of Cephapirin and Cephalothin

A. Z. LANE, J. G. TAGGART, AND R. L. ILES

Bristol Laboratories, Division of Bristol-Myers Co., Syracuse, New York 13201

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In a single-blinded study, two groups of 10 healthy subjects were given cephapirin or cephalothin by continuous intravenous infusion for 5 days, 0.5 g every 6 hr for the first day and then 1.0 g every 6 hr for 4 days. Eight of the cephalothin subjects and two of the cephapirin subjects developed phlebitis. Phlebitis was more severe in the cephalothin group and developed more rapidly, necessitating vein changes six times more often than in the cephapirin group. The less irritating properties of cephapirin demonstrated in this study indicate it may be the more useful cephalosporin analogue for intravenous therapy.

Of the two parenteral cephalosporins available, cephalothin is usually preferred for the treatment of infections requiring high intravenous doses because cephaloridine in doses over 2 g daily may be nephrotoxic (Loridine® package insert, Eli Lilly & Co.). The incidence of phlebitis with cephalothin, however, has been reported to be as high as 50%, depending on dosage and technique (5-8). The manufacturer's package insert recommends alternating veins or adding hydrocortisone to solutions containing more than 4 g of cephalothin to reduce the incidence of thrombophlebitis.

Cephapirin sodium, a new cephalosporanic acid derivative, shows evidence of being perhaps less chemically irritating than cephalothin (1a, 2, 4) while having essentially the same spectrum and level of antibacterial activity (1-3). In the course of studying systemic tolerance to cephapirin, we took the opportunity to determine also the local tolerance of this drug relative to that of cephalothin by giving the drugs in identical fashion by continuous intravenous infusion.

MATERIALS AND METHODS

Twenty healthy male subjects, 21 to 50 years of age, were selected from volunteers given complete physical examinations. Only the following reasons were used for exclusion: history of hypersensitivity to cephalosporins or penicillins; history of inflammatory venous disease; hepatic, renal, or gastrointestinal disease; flexor arm veins of a type making venipuncture difficult; or having had any medication within 2 weeks previous to the study. Two groups of 10 subjects each were obtained by listing the 20 surnames in alphabetical order, numbering them, and then assigning even numbers to cephapirin and odd numbers to cephalothin.

For the first 24 hr, 0.5-g amounts of the drugs in 250 ml of normal saline were infused over each 6-hr period; then the dosage was raised to 1.0 g in 250 ml every 6 hr for the remaining 4 days. During each 6-hr period, flow rates were kept as uniform as possible. To simulate the clinical situation, 21-gauge needles and an intravenous infusion apparatus commonly used in hospitals (Metriset) were employed.

The physician in residence at the institution started all infusions and kept them going at a constant rate around the clock for 5 days with the aid of technicians. He examined infusion sites at least once every day and graded phlebitis as absent, mild, moderate, or severe, depending on the degree of any swelling, redness, tenderness, discoloration, induration, or sclerosing of veins. The subject's comments regarding pain or discomfort were elicited without the use of leading questions. The physician decided when infusion sites should be changed.

Because cephapirin went into solution more rapidly on reconstitution and was usually a darker color than cephalothin, it was not possible to blind the physician and paramedical staff as to drug identity. Subjects, however, were kept unaware of which drug they were receiving, and care was taken not to influence their subjective reactions during the study.

RESULTS

The incidence and severity of phlebitis were greater with cephalothin and irritation developed more rapidly. Eight of 10 subjects given cephalothin and 2 of 10 subjects given cephapirin developed phlebitis, necessitating 13 vein changes in the cephalothin group compared to 2 in the cephapirin group (Tables 1 and 2). The difference in the number of patients who developed phlebitis in the two groups is statistically significant at the 0.05 level of confidence (chi-square test).

One subject in the cephalothin group had thrombophlebitis, distinguished from phlebitis

TABLE 1. Incidence of phlebitis

Drug	No. of subjects			
	No phlebitis	Mild phlebitis	Moderate phlebitis	Severe phlebitis
Cephapirin.....	8	2	0	0
Cephalothin.....	2	5	2	1 ^a

^a Dropped out on day 4.

TABLE 2. Vein changes made because of phlebitis

Drug	Subject No.	No. of vein changes	Day of vein changes
Cephapirin	01	0	—
	03	1	3
	05	1	3
	07	0	—
	09	0	—
	11	0	—
	13	0	—
	15	0	—
	17	0	—
	19	0	—
Total		2(2) ^a	
Cephalothin	02	1	4
	04	2	1, 3
	06	4	1, 4, 4, 5
	08	1	1
	10	2	4, 5
	12	0	—
	14	1	4
	16	1	3
	18	0	—
	20	1	4
Total		13(8) ^a	

^a Number of patients in whom the indicated number of vein changes were made.

by the presence of fever. He had required vein changes at 11 and 48 hr, and had to be dropped from the study at 86 hr. The symptoms of fever, pain, tenderness, gross edema, and discoloration at the infusion site persisted for 1 week.

To demonstrate the presence of active compounds, drug concentrations in serum were determined at frequent, regular intervals throughout the study. Mean serum concentrations of both drugs were approximately 2.50 µg/ml at 6 hr and approximately 4.5 µg/ml at 120 hr (end of day 5).

DISCUSSION

Intravenous cephalothin has caused varying incidences and severities of venous irritation in clinical use. Storey (7) reported that 50% of 60 patients treated with 3 g daily for an average of 7 days developed phlebitis. Perkins and Saslaw (5) reported phlebitis in 5 of 18 (27%) patients given 6 g or more daily. Rahal et al. (6) found thrombo-

phlebitis in 2 of 12 patients given 4 to 12 g daily over extended periods.

Such reports have led to an interest in developing a better-tolerated intravenous cephalosporin, and clinical trials with cephapirin have thus far been encouraging. Jameson et al. (4) gave 3 to 12 g of cephapirin daily to 22 patients for an average of 16 days and had one case of thrombophlebitis. Bodner and Koenig (1a) gave 2 to 12 g daily to seven patients for up to 50 days, encountering only one case of mild phlebitis. Three of their other patients who were given several hundred grams over 4 weeks or more had only mild redness within 2 cm of the infusion site during the last week. Bran et al. (2) treated 27 patients with 2 to 8 g daily for 2 to 15 days without finding evidence of phlebitis. They then studied an additional four patients who served as their own controls in a comparison of cephalothin and cephapirin. One drug was infused for 48 hr into one arm, and then the other drug was given for 48 hr into the other arm. Cephalothin caused moderate to marked phlebitis in all four cases but cephapirin caused none.

The present study in healthy volunteers demonstrates better tolerance to cephapirin than to cephalothin when the two are given by continuous intravenous infusion. Incidence, severity, and the speed with which phlebitis developed were greater with cephalothin, indicating that cephapirin may be the more useful analogue for intravenous cephalosporin therapy.

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