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A COMPARATIVE STUDY ON PHLEBITIS ASSOCIATED WITH CEPHAPIRIN AND CEPHALOTHIN

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A series of comparative studies on the incidence and severity of phlebitis was made on 278 patients with urologic disease who received Cephalothin (CET) or Cephapirin (CEPR). Each patient received a dose of 2 g, twice daily, administered by a one-hour intravenous infusion for 5 to 7 days. However, the dosages were modified as necessary.

The incidence of phlebitis was more frequent among 140 patients receiving CET than among 138 receiving CEPR, but the difference was not statistically significant. All of the cases of phlebitis were below grade 3+. Both in the groups receiving CEPR and CET, increased daily dosages caused a higher incidence of phlebitis, but increase in the group receiving CEPR was not statistically significant. In the CET group, a higher incidence was noted among the patients receiving 5 g or more daily. Accordingly, the patients receiving 5 g or more of CET developed phlebitis more frequently than those receiving CEPR.

The patients who were administered the drug through long-dwell plastic catheters developed a significantly higher rate of phlebitis than those without catheter retention. The incidence of phlebitis was higher in the patients receiving 6 g per day CET through long-dwell plastic catheters.

INTRODUCTION

Much attention has been paid to side-effects of drugs in Japan. However, post-infusion phlebitis which is occasionally induced by such drugs has rarely been discussed as a medical problem.

It is well known that phlebitis is caused by

intravenous infusion of cephalosporin antibiotics. Based on these clinical experiences, various studies have been made to compare the phlebitogenic effect of several cephalosporin antibiotics in the United States. As a result, it has been confirmed that cephalothin (CET) causes phlebitis more frequently than cephapirin (CEPR) or cefazolin (CEZ). This finding has helped us establish a certain criterion for selecting the cephalosporins having almost equal effects in the antibacterial spectrum and in clinical practice.

We have studied to what degree CET and CEPR cause phlebitis in Japanese people and whether there is any difference between the two drugs in producing phlebitis.

MATERIALS AND METHODS

The study population consisted of 278 patients, admitted to the Department of Urology, Kyoto University Hospital, or to affiliated hospitals between 1980 and 1981, and who received CET or CEPR for 5 to 7 days. When the patient developed phlebitis, administration of these drugs was discontinued within 4 days, and other antibiotics were used. CEPR was administered to 138 patients and CET to 140 patients. The diseases and age distribution of these patients are given in Table 1, 2.

The patients received a dose of 2 g of the antibiotic diluted in 300 ml of the intravenous fluid twice a day (a total of 4 g daily) by one-hour intravenous drip. However, the administration method was varied according to the patient's general condition and severity of infection. Some patients received a 1 g dose, once a day, and others 2 g doses three times a day (t.i.d.), a total of 6 g daily. Some patients received 4 g of CET t.i.d., a total of 12 g daily, or 4 g of CET five times a day, a total of 20 g daily. The infusion site was always the same vein,

Table 1. Primary diseases

Drugs	No. of Cases	Urolithiasis			BPH	Tumor				Others
		Kidney	Ureter	Bladder		Kidney	Ureter	Bladder	Others	
CEPR	Total 138	10	27	4	36	6	3	16	4	32
	Catheter[a] 32	2	8	1	15	2	0	2	0	2
CET	Total 140	11	25	5	34	5	3	21	7	29
	Catheter[a] 29	2	1	1	6	2	2	7	3	5

[a] Long-dwell plastic catheter used

Table 2. Average ages

	Average age (standard deviation)				Remarks
	CEPR		CET		
Total	138	58.06 (17.59)	138[a]	57.24 (17.71)	
Plastic catheter	32	55.59 (15.69)	29	58.97 (16.58)	No significant difference in distributions
Plastic catheter 6g/day group	23	54.91 (14.66)	22	57.68 (16.13)	

[a] Excluding 2 patients whose ages unknown

Table 3. Criteria for judging phlebitis (Maddox et al.[12])

Severity	Criteria
0	No pain at intravenous site, no erythema, no swelling, no induration, no palpable venous cord
1+	Painful intravenous site, no erythema, no swelling, no induration, no palpable venous cord
2+	Painful intravenous site with erythema or some degree of swelling, or both, no induration, no palpable venous cord
3+	Painful intravenous site with erythema and swelling and with induration or palpable venous cord less than 3 inches above intravenous site
4+	Painful intravenous site, erythema, swelling, induration and palpable venous cord greater than 3 inches above intravenous site
5+	Frank venous thrombosis along with all signs of 4+; intravenous running may have stopped due to thrombosis

and the 21-G needle was used in most cases. In some cases, a long-dwell plastic catheter was retained in the vein during the study period. Phlebitis was graded according to the criteria of Maddox et al.[12] (Table 3). The study was conducted according to the same protocol.

RESULTS

Of the 138 patients receiving CEPR, 16 patients (12%) developed 1+phlebitis, and 4 patients (3%) developed 2+ phlebitis. Of the 140 patients receiving CET, 23 patients (16%) developed 1+ phlebitis, and 7 patients (5%) developed 2+ phlebitis. More patients receiving CET had phlebitis but the difference was not statistically significant (Table 4). Phlebitis of grade 3+ or more did not occur.

To study the relationship between the daily dosage and the incidence of phlebitis, the patients were divided into three groups according to daily dosage: One group received less than 4 g, one received 4 g and one received 5 g or more.

Nine (10%) out of 86 patients receiving 4 g dosages of CEPR developed 1+phlebitis and 2 patients (2%) developed 2+phlebitis. Seven (12%) out of 59 patients receiving 4 g dosages of CET developed 1+phlebitis and 2 patients (3%) developed 2+phlebitis.

Six (18%) out of 33 patients receiving 5 g or more of CEPR developed 1+phlebitis, and 2 patients (6%) developed 2+phlebitis. Sixteen (32%) out of 50 patients receiving 5 g or more of CET developed 1+phlebitis and 5 (10%) developed 2+. Among the patients receiving dosages of less than 4 g, 1+phlebitis developed in one patient receiving CEPR.

In both the CEPR and CET groups, phlebitis occurred more frequently in proportion to larger dosage. Although there was no significant difference between the groups receiving dosages of 4 g and 5 g or more of CEPR, there was a significant difference ($p<0.01$) between the groups receiving the same dosage of CET. The incidence of phlebitis was high ($p>0.50$) in the group receiving 4 g of CET and higher ($p>0.05$) in

Table 4. Incidence of phlebitis by daily dosage

Daily dosage	CEPR No. of Cases	CEPR Phlebitis 1+	CEPR Phlebitis 2+	CEPR Phlebitis Total	CEPR χ^2 Test	CET No. of Cases	CET Phlebitis 1+	CET Phlebitis 2+	CET Phlebitis Total	CET χ^2 Test	χ^2 Test (between CEPR & CET)
Less than 4g	19	1 (5%)	0	1 (5%)		31	0	0	0		p>0.10
4g	86	9 (10%)	2 (2%)	11 (13%)	p>0.10	59	7 (12%)	2 (3%)	9 (15%)	Significant (p<0.01)	p>0.50
5g or more	33	6 (18%)	2 (6%)	8 (24%)		50	16 (32%)	5 (10%)	21 (42%)		p>0.05
Total	138	16 (12%)	4 (3%)	20 (14%)		140	23 (16%)	7 (5%)	30 (21%)		p>0.10

Table 5. Comparison between the cases with and without plastic catheter

	CEPR No. of Cases	CEPR Phlebitis 1+	CEPR Phlebitis 2+	CEPR Phlebitis Total	CEPR χ^2 Test	CET No. of Cases	CET Phlebitis 1+	CET Phlebitis 2+	CET Phlebitis Total	CET χ^2 Test	χ^2 Test (betweem CEPR & CET)
With catheter	32	5 (16%)	3 (9%)	8 (25%)	p<0.05	29[a]	14 (48%)	4 (14%)	18 (62%)	Singificant (p<0.001)	Significant (p<0.01)
Without catheter	106	11 (10%)	1 (1%)	12 (11%)		109	7 (6%)	3 (3%)	10 (9%)		p>0.50

[a] Excluding 2 patients who did not develope phlebitis with long-dwell plastic catheter, but developed 1+ phlebitis after the needle was changed

the group receiving 5 g or more of CET (Table 4).

As to the incidence of phlebitis related to the plastic catheter, 26 (43%) out of 61 patients receiving the antibiotic through the long-dwell plastic catheter developed phlebitis, while among those without plastic catheter retention 22 (10%) out of 215 patients developed it significantly ($p<0.001$). In a comparative study between CEPR and CET administration through the long-dwell plastic catheter, phlebitis develloped in 8 (25%) out of 32 patients receiving CEPR, and in 18 (62%) out of 29 patients receiving CET, the difference between the two being significant ($p<0.01$) (Table 5).

Since the reaction of the veins to plastic catheter retention has been shown to be a factor in the development of phlebitis, we made a comparative study on phlebitis caused by CEPR and CET administration excluding the cases in which plastic catheters were used (Table 6). Phlebitis developed in 8 (8%) out of 96 patients receiving dosages of up to 4 g of CEPR and in 4 (40%) out of 10 patients receiving dosages of 5 g or more. In the CET group, phlebitis developed in 4 (5%) out of 82 patients receiving dosages of up to 4 g, and in 6 (22%) out of 27 patients receiving dosages of 5 g or more.

The above results show that phlebitis is exhibited significantly in both the groups administered CEPR and CET as the daily dosage is increased to 5 g or more. However, there was no significant difference in the frequency between the two groups.

As for the 61 cases administered the drug through plastic catheters (Table 7), there was no significant difference in the frequency of phlebitis between the groups receiving dosages of 4 g and 6 g of CEPR or CET. There was no significant difference between the CET and CEPR groups receiving 4 g dosages, but phlebitis developed in 4 (17%) out of 23 patients receiving 6 g dosages of CEPR and in 14 (64%) out of 22 patients receiving CET, there being a significant difference between the two drugs in the incidence of phlebitis.

DISCUSSION

Postinfusion phlebitis is considered to be due to the antibiotics administered as well as to the pH of the intravenous solution, intravenous cannulas, and bacterial contamination. Among the antibiotics administered, cephalosporin has proved to have phlebitogenic factors. In 1960, Perkins and Saslaw[14] reported that CET was more phlebitogenic. As clinical studies on CEPR were begun, Gordon et al.[8] and Bran et al.[3] pointed out that postinfusion phlebitis was caused less frequently by CEPR than by CET.

Further studies have been conducted on clinical cases[4,7,9,13,18] and on healthy volunteers[2,10] to investigate whether CET is more phlebitogenic than CEPR. One of these studies was made using the double-blind crossover method[2]. However, the reports have been conflicting: Some suggest that CET causes a significantly higher incidence of phlebitis than CEPR, earlier development of phlebitis, and more severe phlebitis[10] while others showed no significant difference between CET and CEPR as to incidence, severity or duration[4,15] Other reports are located between these two extremes. Although there was no difference in frequency of phlebitis between the two drugs, the phlebitis caused by CET tended to be more severe[7,9,13]. Phlebitis developed earlier with CET than with CEPR, most of the cases being identified within 4 days after the start of drug administration. But, on the whole, there was no significant difference in the incidence of phlebitis[18].

The phlebitis caused by the intravenous administration of CET is considered to be due to the acidity of the CET solution which had a pH of 4.2 to 5.2. The difference in the incidence of phlebitis has been studied on hospitalized patients and healthy volunteers with buffered and unbuffered CET in a double-blind study. There are various reports, some stating no significant difference in incidence or severity[5,11] and others showing a significant difference[2]. The phlebitogenic factors of CET can be de-

Table 6. Incidence of phlebitis excluding cases with plastic catheter

Daily dosage	CEPR No. of Cases	CEPR Phlebitis 1+	CEPR Phlebitis 2+	CEPR Phlebitis Total	CEPR χ^2 Test	CET No. of Cases	CET Phlebitis 1+	CET Phlebitis 2+	CET Phlebitis Total	CET χ^2 Test	χ^2 Test (between CEPR & CET)
Up to 4g	96	8 (8%)	0	8 (8%)	Significant ($p<0.02$)	82	2 (2%)	2 (2%)	4 (5%)	Significant ($p<0.05$)	$p>0.50$
5g or more	10	3 (30%)	1 (10%)	4 (40%)		27	5 (19%)	1 (4%)	6 (22%)		$p>0.50$

Table 7. Incidence of phlebitis in the cases in which plastic catheters were used

Daily dosage	CEPR No. of Cases	CEPR Phlebitis 1+	CEPR Phlebitis 2+	CEPR Phlebitis Total	CEPR χ^2 Test	CET No. of Cases	CET Phlebitis 1+	CET Phlebitis 2+	CET Phlebitis Total	CET χ^2 Test	χ^2 Test (between CEPR & CET)
4g 2g×2	2	0	2	2		5	4	0	4		$p>0.50$
4g×1	7	2	0	2		2	0	0	0		$p>0.90$
Subtotal	9	2	2	4		7	4	0	4		$p>0.99$
		(22%)	(22%)	(44%)	$p>0.20$		(57%)		(57%)	$p>0.70$	
6g 3g×2	23	3	1	4		22	10	4	14		Significant
		(13%)	(4%)	(17%)			(45%)	(18%)	(64%)		($p<0.01$)
Total	32	5	3	8		29[a]	14	4	18		Significant
		(16%)	(9%)	(25%)			(48%)	(14%)	(62%)		($p<0.01$)

[a] Excluding 2 cases who did not develope phlebitis with a long-dwell plastic catheter, but did (1+) after the needle was changed

creased by increasing the solubility of CET by neutralizing it and by reducing the number of particulate matters by improved filtration. It is also reported[12] that a higher pH does not lessen the incidence of phlebitis. Such difference in results may be due to difference in drug dosage, administration method, the period of administration, use of cannulas, and so on. Our studies show that the incidence of phlebitis is more significantly increased by an increased dosage of CET. The use of long-dwell plastic catheters significantly intensifies the phlebitogenic factors of CET. This is quite similar to the results reported by Cross et al.[7].

Further comparative studies have been made on the incidence of phlebitis between CET and CEZ, and between CET and CEPR. They have shown that the incidence of phlebitis by CET is significantly higher and the severity is greater[6,16]. Besides these, similar comparative studies have been made on the three different antibiotics, CET, CEPR and cefamandole[17] as well as with buffered CET, CEPR and cefamandole[1]. The results obtained through these studies are not in good accordance. In the former, there was no significant difference in the frequency of incidence, but CET developed a higher severity. While, in the latter the incidence of grade 2 phlebitis was higher in the order of cefamadole, CEPR and CET without any significant difference between any of the drugs. Compared to the other two antibiotics, CEPR develops phlebitis at a larger dosage.

According to Maddox et al.[12], the concomitant use of heparin and hydrocortisone with the drug or the use of an inline 0.22-μm final filter helps prevent the development of CET-induced phlebitis.

In Japan, clinicians have not been aware of these side-effects as being related to the usual postinfusion phlebitis. At present, a variety of antibiotics having similar antibacterial potentiality, pharmacodynamics, and clinical effects are available for use by the clinician, and they may have to be studied for their antibiotic utility concerning the potential hazard of phlebitis.

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和文抄録

Cephapirin および Cephalothin の静脈注射による静脈炎について

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泌尿器科的疾患患者278例に，Cephalothin（CET）および Cephapirin（CEPR）を経静脈的に投与したときの，静脈炎の発生について比較検討した．CET または CEPR 2 g を1日2回，5～7日間点滴静注にて投与した．CET 投与群140例と CEPR 投与群138例では，CET 群21%，CEPR 群14%に静脈炎発生が認められた．

CEPR および CET ともに1日投与量を増加すると，静脈炎の発生頻度も増加する傾向があった．1日5 g 以上投与群では CET 群の方が静脈炎の発生頻度は高かった．

静脈用カテーテル留置により投与した群では静脈炎の発生頻度は高く，とくに CET 1日6 g を投与した群では CEPR にくらべ有意に高い頻度で静脈炎が発生した．

経静脈的抗生物質投与時の静脈炎の発生は患者にとって大きな苦痛である．充分に注意しなければならない．