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Cefotaxime and Desacetyl Cefotaxime in Human Bile

Summary: Ten patients were injected with 2 g cefotaxime i. v. The antibacterial activity in the bile was measured by the agar diffusion test and the concentrations of cefotaxime and desacetyl cefotaxime were determined by high performance liquid chromatography. The values found allow the use of cefotaxime in infectious biliary diseases.

Zusammenfassung: *Cefotaxim und Desacetyl-Cefotaxim in der Galle des Menschen.* Zehn Patienten wurden je 2 g Cefotaxim i. v. injiziert. In der Galleflüssigkeit wurden die antibakterielle Aktivität mittels Agardiffusionstest und die Konzentrationen von Cefotaxim und Desacetyl-Cefotaxim mit Hochdruckflüssigkeitschromatographie bestimmt. Die gefundenen Werte erlauben den Einsatz von Cefotaxim bei infektiösen Gallenwegserkrankungen.

Introduction

In a previous paper we reported on the determination of cefotaxime and desacetyl cefotaxime in human and rat serum after an i.v. injection of this cephalosporin (1); the concentrations of the parent compound and its metabolite in human bile were also briefly described.

It has been shown that older cephalosporins with a 3-acetoxymethyl substituent, e. g. cephalothin, are metabolised to the respective desacetyl compounds (2). The degradation of cefotaxime to desacetyl cefotaxime has also been observed in man and was simultaneously reported from other laboratories (3, 4).

The purpose of this paper is to report in detail on the concentrations of cefotaxime and its antimicrobially active metabolite in human bile, measured both by high performance liquid chromatography (HPLC) and by bioassay with a selective test organism after an i.v. injection of 2 g.

Patients and Methods

Ten patients, three men and seven women aged between 32 and 82 years, were given a loading dose of 2 g cefotaxime administered i.v. over 3 min. The patients were selected for the study if physical examination suggested an infection of the gall bladder. None of the patients had received any antibacterial drugs beforehand. Informed written consent was obtained from each patient.

Bile was collected through a catheter inserted into the bile duct as for ERCP and collected in nine fractions: before the injection of cefotaxime and 5, 10, 30, 60, 90, 120, 240 and 360 min after the injection. The samples were frozen and stored at −20° C until assayed.

The assay of cefotaxime and desacetyl cefotaxime by HPLC or bioassay with *Escherichia coli* V 6311/65 were described in detail in our previous paper (1).

Results

Figure 1 shows the average time-concentration curves of cefotaxime and desacetyl cefotaxime in the bile of eight patients following an i.v. injection of 2 g. Because the test organism is slightly susceptible to desacetyl cefotaxime, the concentrations of the parent compound are overestimated by the microbiological method. 1.5 h after the

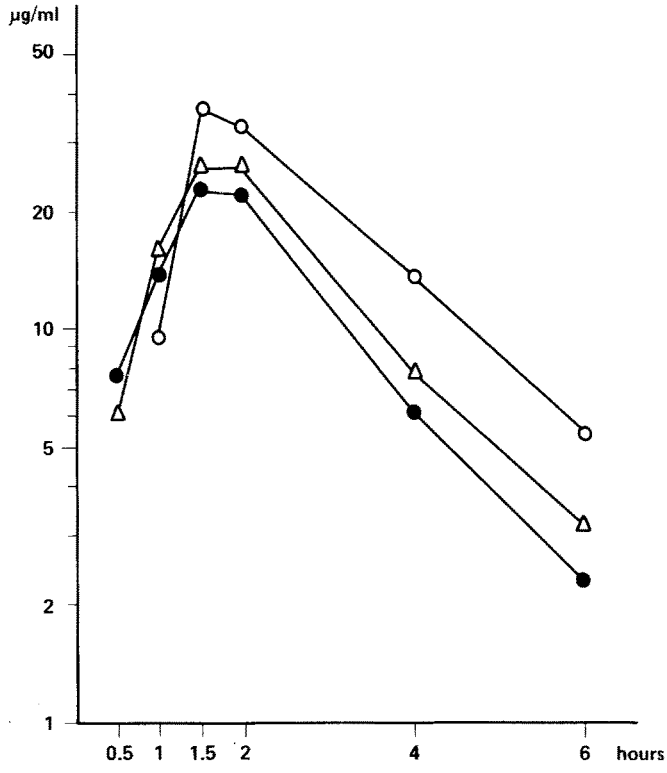

Figure 1: Concentrations of cefotaxime (●, △) and desacetyl cefotaxime (○) in human bile after an i.v. injection of 2 g. ●——●, ○——○ = high performance liquid chromatography; △——△ = bioassay.

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Infection 11 (1983) Nr. 2

injection, the desacetyl cefotaxime concentration exceeded the concentration of the parent drug and remained higher during the period of investigation. Because the values found in Patients 3 and 10 differed so widely from those of the other patients, individual values of the concentrations of the parent compound and its metabolite assayed in the bile of all patients are given in Table 1.

Discussion

After an i.v. injection of 2 g cefotaxime, the parent compound and its microbiologically active desacetyl metabolite were demonstrated in the bile of all patients investigated. The concentrations of both cefotaxime and desacetyl cefotaxime were 2–3 fold higher in the bile of younger patients (Patient 3, 44 years and Patient 10, 32 years) than in the eight patients aged 58–82 (Table 1). Moreover, the formation of desacetyl cefotaxime seemed to be impaired in Patient 2 (Table 1), possibly due to insufficiency of liver function (5).

The biliary concentrations of cefotaxime are about ten times lower than cefoperazone concentrations following i.v. administration (6). Nevertheless, the concentrations of cefotaxime assayed in the bile are higher than most of the minimal inhibitory concentrations tested with a variety of strains, e. g. *Proteus mirabilis* ATCC 14273,

Table 1: Individual concentrations of cefotaxime and desacetyl cefotaxime in the bile of ten patients following an i.v. injection of 2 g.

Patient	Age (years)	Sex	Height (cm)	Weight (kg)	Assay	Compound	Bile concentrations (µg/ml) after an i.v. injection of 2 g cefotaxime							
							5	10	30	60	90	120	240	360 (min)
1	81	F	165	75	BA	CTX	n.d.	0.6	5.6	21.2	27.6	27.6	14.4	7.9
					HPLC	CTX	n.d.	n.d.	4.0	15.3	22.1	21.3	12.2	6.3
					HPLC	dCTX	n.d.	n.d.	1.2	6.4	20.5	28.7	25.9	17.1
2	74	M	179	68	BA	CTX	n.d.	n.d.	8.5	8.5	10.8	8.5	4.4	3.2
					HPLC	CTX	n.d.	n.d.	8.1	7.2	9.6	7.8	3.5	2.1
					HPLC	dCTX	n.d.	n.d.	0.9	1.7	3.1	3.2	2.7	2.2
4	68	M	172	76	BA	CTX	0.3	0.8	2.2	12.5	14.2	11.1	6.2	4.0
					HPLC	CTX	2.9	2.1	5.4	11.5	12.0	13.1	5.9	2.6
					HPLC	dCTX	1.1	n.d.	0.4	8.0	12.7	14.7	6.8	2.5
5	82	F	175	55	BA	CTX	0.7	1.0	2.1	4.9	9.9	12.7	2.1	1.7
					HPLC	CTX	n.d.	1.0	3.2	6.5	11.2	15.1	1.9	1.1
					HPLC	dCTX	n.d.	n.d.	n.d.	3.1	9.1	19.1	3.7	2.1
6	78	M	165	48	BA	CTX	7.5	2.3	15.5	10.7	13.7	25.9	4.8	3.9
					HPLC	CTX	11.0	2.5	31.0	22.8	36.9	46.6	5.1	2.1
					HPLC	dCTX	n.d.	n.d.	11.3	15.7	44.7	61.3	12.1	9.0
7	75	F	153	57	BA	CTX	1.0	2.8	4.3	8.6	35.7	27.1	10.9	2.3
					HPLC	CTX	0.7	2.3	2.6	5.5	20.1	17.6	6.2	2.0
					HPLC	dCTX	n.d.	n.d.	n.d.	1.8	22.5	23.0	11.8	4.0
8	58	F	163	51	BA	CTX	n.d.	n.d.	1.1	13.8	70.5	61.0	12.2	0.7
					HPLC	CTX	n.d.	n.d.	1.1	13.4	47.2	32.5	8.7	0.7
					HPLC	dCTX	n.d.	n.d.	n.d.	3.1	93.1	54.1	19.6	2.1
9	76	F	165	89	BA	CTX	n.d.	1.9	9.7	48.3	27.5	36.3	7.6	2.1
					HPLC	CTX	n.d.	1.3	6.4	28.5	22.2	22.0	5.4	1.3
					HPLC	dCTX	n.d.	1.5	5.6	37.3	90.9	64.4	26.8	4.5
mean ± SD					BA	CTX			6.1±1.7	16.1±4.9	26.2± 7.2	26.3±6.0	7.8±1.5	3.2±0.8
					HPLC	CTX			7.7±3.4	13.8±2.9	22.7± 4.7	22.0±4.4	6.1±1.1	2.3±0.6
					HPLC	dCTX				9.6±4.3	37.1±12.8	33.6±8.2	13.7±3.4	5.4±1.9
3	44	F	163	66	BA	CTX	2.0	17.6	70.6	52.8	22.9	15.5	8.3	1.2
					HPLC	CTX	1.8	22.0	105.2	68.9	27.3	18.4	12.0	0.8
					HPLC	dCTX	n.d.	5.2	108.0	128.7	54.1	46.8	21.9	2.3
10	32	F	164	61	BA	CTX	17.7	23.1	217.5	112.1	34.8	34.8	12.0	2.7
					HPLC	CTX	11.3	16.2	158.7	64.4	27.6	22.1	7.7	3.0

BA = biossay; HPLC = high performance liquid chromatography; n. d. = not detected; CTX = cefotaxime; dCTX = desacetyl cefotaxime.

Pseudomonas aeruginosa K 1118 and *E. coli* V 6311/65 (1, 7–9). On the other hand, high antibiotic concentrations in serum seem to be more important than bile levels of antibiotics in reducing the risk of infectious complications following gall bladder extirpation (10, 11).

Cephalosporins usually achieve high concentrations in the bile (12–16) and are generally highly effective against those organisms most commonly isolated from the biliary tract (17).

Therefore, preoperative administration of cephalosporins such as cefotaxime should reduce the risk of infectious complications during complicated cholecystectomy when anti-infective prophylaxis is indicated (18).

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