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Human pharmacokinetics of ceftazidime in comparison to moxalactam and cefotaxime—abstract

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The present study (Lüthy *et al.*, 1981) was conducted to compare the pharmacokinetics of three different doses of cefotaxime (CTAX), moxalactam (MOXA) and ceftazidime (CTAZ) and to evaluate the influence of probenecid on the pharmacokinetic behaviour of these three compounds. Six male volunteers received in a cross-over fashion doses of 0·5, 1·0 and 2·0 g of each drug by a 5-min infusion. Doses of 1·0 g were repeated after administration of probenecid. During each study 17 blood samples were drawn to document the distribution and elimination phases. The urinary excretion was determined from five quantitative urine collections which were made over the 24 h of the study. Serum and urine concentrations were assayed by an agar diffusion method, the assay strain for CTAX being resistant to its desacetyl metabolite. The coefficient of variation for interassay precision averaged $4{\cdot}6 \pm 0{\cdot}9\%$. Serum samples of the 0·5 and 2·0 g doses of CTAX and MOXA were also analysed by a high pressure liquid chromatography method which provided information on the behaviour of the desacetyl metabolite of CTAX and the two naturally occurring epimers of MOXA. The pharmacokinetic parameters of a two-compartment open model were adapted to the experimental data with a non-linear fitting program. For all statistical evaluations the Wilcoxon matched pairs signed rank test was used. Probabilities $2\alpha \leq 0{\cdot}05$ were considered significant.

The 10 min, 6, 8 and 12 h mean serum concentrations of CTAX, MOXA and CTAZ are presented in Table I. Serum concentrations of MOXA exceeded those of CTAZ at all times and were distinctly higher than those of CTAX. To facilitate the comparison between the various doses and drugs, the areas under the serum concentration time curves (AUC) were normalized by dividing through the individual doses. Compared with CTAX the normalized AUC of MOXA was three to four times, and of CTAZ two to three times, higher. Linear regression analysis of the dose (x in [g]) versus normalized AUC (y in [mg/h//l]) yielded a slope for CTAX($y = 13{\cdot}4x + 45{\cdot}12$) which was significantly different from zero ($P < 0.001$) indicating a non-linear increment in AUC for increasing doses. In contrast, slopes of MOXA ($y = -19{\cdot}36x + 240{\cdot}09$) and CTAZ ($y = -14{\cdot}59x + 168{\cdot}51$) did not differ significantly from zero. The pharmacokinetic parameters of CTAX, MOXA and CTAZ are summarized in Table II. Significant differences between the three compounds in the total volume of distribution were observed for the 0·5 g dose, but not for the 1·0 and 2·0 g dose. Intraindividual

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comparisons of the elimination half lives, total body and renal clearances demonstrated significant differences between these antibiotics. The half-lives calculated from the 0·5, 1·0 and 2·0 g doses averaged 2·34, 1·95 and 1·16 h for MOXA, CTAZ and CTAX, respectively. The 24 h urinary recovery was highest for MOXA (75 ± 4%), followed by CTAZ (68 ± 11%) and CTAX (53 ± 6%). Total body and renal clearance of CTAX decreased significantly with increasing doses. In contrast to MOXA and CTAZ, the ratio of renal to creatinine clearance indicated that considerable tubular secretion of CTAX occurred.

The influence of probenecid on serum concentrations, half-life, AUC, volume of distribution and clearance was most obvious with CTAX. Saturation of tubular secretion led to serum concentrations with the 1·0 g dose of CTAX which already at 2 h were higher than those achieved with the 2·0 g dose. The renal clearance of this drug was decreased by almost 50% and the AUC doubled when probenecid was administered. This is in contrast to MOXA and CTAZ where the marginal influence of this agent is of no practical significance.

The desacetyl metabolite of CTAX, determined by high pressure liquid chromatography, reached its peak 45 min after administration. It averaged 2·7 ± 1·0 and 9·8 ± 1·8 mg/l for the 0·5 and 2·0 g dose, respectively. Compared to CTAX, its half-life was approximately twice as long (1·9 ± 0·7 h and 1·4 ± 0·4 h). Following the 0·5 g dose the AUC for the desacetyl metabolite was 31 ± 12% of the total area of CTAX, whereas for the 2·0 g dose this proportion decreased to 18 ± 2%, suggesting that desacetylation may not follow first-order kinetics.

Freshly prepared solutions of MOXA contain two epimers, designated R (−) and S (−), in approximately equal amounts. The serum protein binding of the R (−) epimer averages 53%, that of the S (−) epimer 67% (Yamada *et al.*, 1981). The antimicrobial

Table I. Mean serum concentrations (mg/l) of cefotaxime (CTAX), moxalactam (MOXA) and ceftazidime (CTAZ) in six volunteers

Drug/dose level (g)	Actual dose (g)*	Time (h) 0·17	6	8	12
CTAX/0·5	0·58	37·8 ± 7.1†	0·3 ± 0·1 (n=3) <0·1 (n=3)	<0·1	<0·1
MOXA/0·5	0·47	63·3 ± 6·0	4·2 ± 1·7	2·2 ± 0·6	0·7 ± 0·2
CTAZ/0·5	0·48	49·9 ± 8·0	2·1 ± 0·5	1·0 ± 0·3	0·3 ± 0·1
CTAX/1·0	1·06	80·8 ± 14·1	0·4 ± 0·1	<0·1	<0·1
MOXA/1·0	0·99	120 ± 12·4	8·2 ± 2·0	4·7 ± 1·0	1·4 ± 0·5
CTAZ/1·0	0·96	107 ± 18·0	4·4 ± 1·4	2·1 ± 0·7	0·5 ± 0·3
CTAX/2·0	2·02	174 ± 36·7	0·9 ± 0·5	0·5 ± 0·4 (n=3) <0·1 (n=3)	<0·1
MOXA/2·0	1·87	210 ± 30·8	14·2 ± 2·4	8·0 ± 1·8	2·6 ± 0·8
CTAZ/2·0	1·94	181 ± 23·2	6·6 ± 1·5	3·8 ± 0·9	1·1 ± 0·5
CTAX/1·0 + P‡	0·96	109 ± 12·3	1·4 ± 0·7	0·6 ± 0·4 (n=5) <0·1 (n=1)	<0·1
MOXA/1·0 + P	1·10	111 ± 10·8	10·0 ± 1·7	6·2 ± 1·2	2·7 ± 0·8
CTAZ/1·0 + P	0·97	98·9 ± 12·5	4·2 ± 0·6	2·1 ± 0·5	0·5 ± 0·2

*Mean value of six administered doses

† ± S. D.

‡Probenecid (0·5 g every 6 h on day before study and 1·0 g 30 min pre dose).

Table II. Synopsis of pharmacokinetic parameters of cefotaxime (CTAX), moxalactam (MOXA) and ceftazidime (CTAZ). Mean values ± S.D. of six volunteers

Dose (g)	V_1 (l/kg)	V_d (l/kg)	k_{12} ($\times 10^4 h^{-1}$)	k_{21} ($\times 10^4 h^{-1}$)	$T\frac{1}{2}$ (h)	C_b (ml/min)	feU (%)	C_r (ml/min)	C_{cr} (ml/min)	C_r/C_{cr}
CTAX 0·5	0·17 ± 0·04	0·29 ± 0·05	2·30 ± 1·10	3·05 ± 1·12	1·10 ± 0·38	391 ± 97	58 ± 12	217 ± 31	129 ± 18	1·69 ± 0·11
1·0	0·14 ± 0·03	0·24 ± 0·04	2·10 ± 0·72	2·98 ± 0·85	1·08 ± 0·27	326 ± 48	47 ± 7·9	154 ± 38	132 ± 16	1·16 ± 0·22
2·0	0·15 ± 0·02	0·21 ± 0·04	1·00 ± 0·43	2·13 ± 0·73	1·31 ± 0·32	267 ± 49	56 ± 18	145 ± 48	141 ± 18	1·03 ± 0·29
1·0 + P[1]	0·10 ± 0·01	0·18 ± 0·02	3·40 ± 0·82	3·97 ± 0·55	1·15 ± 0·03	169 ± 16	51 ± 3·6	85 ± 8·8	124 ± 10	0·69 ± 0·10
MOXA 0·5	0·09 ± 0·01	0·18 ± 0·01	2·45 ± 0·60	2·63 ± 0·73	2·35 ± 0·32	77·8 ± 9·4	79 ± 4·8	61·7 ± 9·0	135 ± 18	0·46 ± 0·06
0·1	0·10 ± 0·01	0·19 ± 0·01	3·35 ± 1·18	3·47 ± 1·03	2·25 ± 0·21	81·2 ± 10·6	71 ± 7·3	58·0 ± 9·2	140 ± 17	0·41 ± 0·05
2·0	0·12 ± 0·02	0·23 ± 0·03	2·33 ± 0·97	2·48 ± 0·47	2·42 ± 0·13	94·4 ± 15·7	73 ± 5·2	69·4 ± 14·6	141 ± 10	0·49 ± 0·08
1·0 + P[1]	0·13 ± 0·02	0·24 ± 0·02	2·38 ± 0·67	2·53 ± 0·47	2·79 ± 0·24	83·2 ± 9·6	67 ± 6·9	55·7 ± 11·6	130 ± 16	0·43 ± 0·10
CTAZ 0·5	0·14 ± 0·01	0·22 ± 0·02	1·05 ± 0·18	1·97 ± 0·33	2·01 ± 0·16	144 ± 16	66 ± 2·8	75·1 ± 11·6	131 ± 24	0·58 ± 0·09
1·0	0·13 ± 0·02	0·21 ± 0·02	1·48 ± 0·53	2·18 ± 0·33	1·87 ± 0·15	116 ± 18	75 ± 3·3	87·6 ± 16·1	143 ± 24	0·61 ± 0·05
2·0	0·14 ± 0·01	0·25 ± 0·02	1·78 ± 0·65	2·37 ± 0·65	1·96 ± 0·18	133 ± 20	60 ± 9·1	81·1 ± 17·6	121 ± 12	0·67 ± 0·12
1·0 + P[1]	0·13 ± 0·01	0·21 ± 0·01	1·32 ± 0·20	2·23 ± 0·35	1·97 ± 0·17	114 ± 13	68 ± 4·2	78·6 ± 9·4	133 ± 44	0·64 ± 0·19

Parameters for CTAX were derived from a two-compartment model fitted to serum data of the first 6 h only, whereas for MOXA and CTAZ all measured data were included.

V_1 volume of distribution of the central compartment; V_d total volume of distribution; k_{12}, k_{21} rate constants of transfer between the two compartments; $T\frac{1}{2}$ terminal half life; C_b total body clearance; feU excreted urinary fraction of the administered dose; C_r renal clearance; C_{cr} creatinine clearance.

activity of the former is approximately doubled compared to S (−) (R. Wise *et al.*, 1981). Analysis of the two epimers revealed that their pharmacokinetic behaviour is different. Ten minutes following the intravenous administration the ratio of the R (−) to the S (−) epimer was 0·84 and fell rapidly to 0·5 at 5 h, indicating the presence of twice as much of the S (−) epimer compared to R (−). At this time the antimicrobial activity determined by the agar diffusion assay is reduced by one-fourth when compared to HPLC analysis.

No side effects were recorded throughout the entire study and chemistry profiles, blood counts, urinalysis and creatinine clearance remained within normal limits.

This study demonstrated that significant differences exist between the pharmacokinetic behaviour of CTAX, MOXA and CTAZ. From this standpoint it appears reasonable to conclude that MOXA and possibly CTAZ could be administered twice daily and CTAX three or even four times daily.

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