PHARMACOKINETICS OF CEPHRADINE GIVEN INTRAVENOUSLY WITH AND WITHOUT PROBENECID

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- 1 In the light of questions raised by an earlier oral study (Welling, Dean, Selen, Kendall & Wise, 1979) the influence of probenecid on the pharmacokinetics of intravenously administered cephadrine has been investigated.
- 2 Intravenous administration of cephadrine resulted in a bi-exponential curve and the level of antibiotic after 15 min was significantly greater when subjects received probenecid than when they did not. The influence of probenecid on urinary excretion of cephadrine was similar to that observed previously.
- 3 The increase in serum of cephadrine due to probenecid could be accounted for by the decrease in the elimination rate of the antibiotic. These results are discussed in the light of other observations.

Introduction

In 1950 Boger, Beatty, Pitts & Flippin reported the increase in penicillin G concentration in the blood, and a decrease in its rate of elimination in the urine, when the antibiotic was administered concurrently with the uricosuric agent probenecid. Probenecid has since been shown to have this effect with many β -lactam antibiotics (Klein & Finland 1963; Mischler, Sugeran, Willard, Brannick & Neiss, 1974). Probenecid also has a similar effect on compounds such as methotrexate (Aherne, Pfall, Marks, Mould & White, 1978) and indomethacin (Skeith, Simkin & Healey, 1968). The decrease in the elimination of all these drugs is thought to involve renal tubular inhibition, probenecid competing with the drug for the active transport site(s) (Weiner, Washington & Mudge, 1960). However, it is uncertain whether this is the only mechanism responsible for the increased plasma levels of drug in the presence of probenecid (Gibaldi & Schwartz 1968). Welling, Dean, Selen, Kendall & Wise (1979) examined the pharmacokinetics of two orally dosed cephalosporins, cephadrine and cefaclor in the absence and presence of probenecid. The study appeared to show that the increase in serum levels of both antibiotics in the presence of probenecid could not be fully explained by the decrease in their apparent elimination rates and might therefore involve a change in the distribution volume of the drug. However, it was not possible to separate the pharmacokinetic parameters for the fraction of the doses

absorbed (F) and the volume of distribution of the drug (V). In the present study, the pharmacokinetics of cephadrine, a broad spectrum antibiotic indicated for acute infective disease (Limson, Siasoco & Dial, 1972), have been examined following intravenous doses to healthy individuals, in the presence and absence of probenecid.

Methods

Eight healthy male volunteers aged between 19–23 years and weighing between 61.5–80.5 kg were used. Each subject underwent a clinical examination after having given informed consent, and blood was taken in order to obtain biochemistry and haematology profiles, which included creatinine, urea, aspartate transaminase, alkaline phosphatase, albumin, globulin and ESR. For all subjects the results were within normal ranges. Subjects were not on any other medication for at least one week before and during the study.

Protocols

Each subject presented after overnight fast on two occasions separated by at least 7 days. Blood samples were obtained from a cannula inserted into a forearm vein attached to a three way tap through which

physiological saline was slowly perfused to prevent clotting. Cephadrine (500 mg, Velosef, E.R. Squibb & Sons Ltd) re-constituted in sterile water (5 ml) immediately prior to injection was administered over a 2 min period into a vein in the opposite arm. Blood specimens were withdrawn at zero time and at 5, 10, 15, 20, 30, 45 and 60 min, and at 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0 and 6.0 h post-dosing. The blood was placed in plain tubes, allowed to clot, spun, and the serum removed and frozen at -20°C until analysis. Quantitative urine collections were made after 2, 4, 6, 8, 10 and 12 h, the total volume voided was recorded and an aliquot stored at -20°C . All specimens were analysed within 48 h of collection. The drugs were given as follows:

Treatment A—500 mg cephadrine was given intravenously over a period of two minutes at 09.00 h.

Treatment B—Probenecid (Benemid, Merck Sharp & Dohme Ltd), 1×500 mg tablet, was taken orally at 08.00 h and 20.00 h for 2 days prior to the study day, and at 08.00 h on the morning of the study. Cephadrine was then administered at 09.00 h as in Treatment A. The treatment order was randomized.

Assay

The serum and urine cephadrine concentrations were determined by a plate diffusion method using Penassay I (Oxoid) antibiotic agar as the medium and *B. subtilis* ATCC 6633 (Dudley Road Hospital, Dudley Road, Birmingham 18) as the test organism. The 95% confidence limits for the assay were routinely less than $\pm 16\%$.

Data analysis

Serum profiles of antibiotic were analysed according to two-compartment model kinetics by the equation

$$C_t = Ae^{-\alpha t} + Be^{-\beta t}$$

where C_t is the drug concentration in serum at time t , and α and β , A and B , are the rate and concentration constants respectively which define the drug concentration curve (with $\alpha > \beta$). Initial estimates of A , B , α and β were determined graphically, and these were used for the nonlinear regression analysis programme NONLIN (Metzler, 1969). From the computer estimates of these parameters, additional pharmacokinetic parameters were calculated. Pharmacokinetic values obtained from the two treatments were compared by paired t -test.

Table 1 Mean concentrations of cephadrine in serum ($\pm$ s.d.) ($n = 8$)

Time (h)	Concentration of cephadrine ($\mu\text{g ml}^{-1}$)	
	Treatment A ^a	Treatment B ^b
0.0	0.00	0.00
0.08	42.7 $\pm$ 13.5	46.6 $\pm$ 6.9
0.16	29.2 $\pm$ 11.4	35.3 $\pm$ 5.8
0.25	22.3 $\pm$ 5.3	30.1 $\pm$ 4.8
0.33	18.5 $\pm$ 3.2	26.7 $\pm$ 4.1
0.50	14.3 $\pm$ 2.4	21.6 $\pm$ 3.2
0.75	10.3 $\pm$ 1.5	18.0 $\pm$ 2.9
1.0	8.0 $\pm$ 1.3	15.7 $\pm$ 1.8
1.5	5.2 $\pm$ 1.1	12.3 $\pm$ 1.5
2.0	3.2 $\pm$ 0.8	9.8 $\pm$ 1.4
2.5	1.8 $\pm$ 0.7	7.7 $\pm$ 1.0
3.0	1.2 $\pm$ 0.4	5.8 $\pm$ 0.8
3.5	0.3 $\pm$ 0.4	4.5 $\pm$ 0.9
4.0	ND	3.5 $\pm$ 1.2
5.0	ND	2.0 $\pm$ 0.6
6.0	ND	0.7 $\pm$ 0.7

a: Treatment A—500 mg cephadrine (Velosef) in 5 ml water injected over a period of 2 min.

b: Treatment B—Probenecid loading, then as above.

Table 2 Urine concentrations ($\mu\text{g ml}^{-1}$) of cephadrine after treatments A and B.

Volunteer	Treatment A			Treatment B			P A v B		
	0–6 h	6–12 h	Clearance (l/h)	0–6 h	6–12 h	Clearance (l/h)	0–6 h	6–12 h	Clearance
1	749.5	24.0	17.0	499.8	18.2	7.1			
2	611.6	2.5	20.7	327.4	9.7	11.8			
3	251.6	20.0	19.7	372.7	93.5	14.4			
4	468.0	5.9	26.6	468.2	58.6	15.7			
5	620.0	3.8	26.5	353.4	16.9	10.0			
6	774.0	5.7	21.1	766.8	41.1	10.9			
7	971.0	15.5	17.5	*	*				
8	958.0	17.8	25.4	601.7	58.0	13.7			
Mean	675.5	11.9	21.8	484.3	42.3	11.9	NS	< 0.05	< 0.01

*Specimens not taken.

Table 3 Summary of mean values of pharmacokinetic parameters for cephadrine in serum ($\pm$ s.d.).

Pharmacokinetic parameter	Treatment A	Treatment B	P
A ($\mu\text{g/ml}$)	38.0 $\pm$ 16.8	29.2 $\pm$ 11.9	NS
B ($\mu\text{g/ml}$)	19.4 $\pm$ 10.0	23.6 $\pm$ 4.0	NS
α (h^{-1})	7.9 $\pm$ 2.6	6.5 $\pm$ 2.0	NS
β (h^{-1})	0.9 $\pm$ 0.1	0.5 $\pm$ 0.06	< 0.01
$T_{1/2} \alpha^a$ (h)	0.1 $\pm$ 0.03	0.1 $\pm$ 0.03	NS
$T_{1/2} \beta^b$ (h)	0.8 $\pm$ 0.1	1.5 $\pm$ 0.2	< 0.01
AUC ^c ($\mu\text{g ml}^{-1} \text{h}$)	24.0 $\pm$ 8.8	57.3 $\pm$ 11.3	< 0.01
k_{21}^d (h^{-1})	3.7 $\pm$ 1.3	3.3 $\pm$ 1.4	NS
k_{10}^e (h^{-1})	2.0 $\pm$ 0.5	1.0 $\pm$ 0.2	< 0.01
k_{12}^f (h^{-1})	3.2 $\pm$ 1.4	2.6 $\pm$ 1.0	NS
V_1^g (l)	9.3 $\pm$ 3.0	10.3 $\pm$ 3.4	NS
$V_d(ss)^h$ (l)	17.4 $\pm$ 5.9	18.1 $\pm$ 3.9	NS
$V_1 k_{10}^i$ (ml/min)	17.2 $\pm$ 4.4	9.4 $\pm$ 2.7	< 0.01

^a Half-life of α distribution phase, $T_{1/2}\alpha = \ln 2/\alpha$

^b Half-life of β distribution phase, $T_{1/2}\beta = \ln 2/\beta$

^c Area under the cephadrine profile in serum.

^d First-order rate constant for transfer of drug from the tissue to the central compartment of the two-compartment model.

^e First-order rate constant for elimination of drug from the central compartment of the two compartment model.

^f First-order rate constant for transfer of the drug from the central compartment to the tissue compartment of the two-compartment model.

^g Apparent volume of the central compartment.

^h Apparent overall distribution volume of cephadrine at equilibrium $V_d(ss) = V_1(1 + k_{12}/k_{21})$.

ⁱ Serum clearance of cephadrine.

Results

The mean serum levels of cephadrine and cumulative urinary excretion are summarised in Tables 1 and 2. Table 3 gives the mean values of pharmacokinetic parameters obtained from the two treatments and the results of statistical analysis.

From Tables 1 and 2 it can be seen that the serum concentration of cephadrine in the presence of probenecid is higher than in its absence as early as 15 min post-dosing, and remains so over the 6 h sampling period. The amount of antibiotic excreted in the urine during the first 6 h, when given with probenecid, is slightly but not significantly reduced from that excreted in its absence. During the subsequent six hours, the concentration of cephadrine in urine is

significantly higher in the presence than in the absence of probenecid.

The areas under the cephadrine serum profiles, given in Table 3, are essentially the same as those reported previously following oral doses of the drug (Welling *et al.*, 1979), and the elimination rate constants, β after intravenous dosing and k_{el} after oral dosing, are also similar for both studies.

Discussion

As the same quantity of drug was administered in the intravenous and oral studies, and similar serum concentrations and area under the curve values were obtained, it may be assumed that cephadrine was absorbed quantitatively from the oral dosage form, both in the absence and presence of probenecid. Thus the observed changes in FD/V values in that study were related to changes in drug distribution characteristics and were independent of any absorption effects.

Comparison of the pharmacokinetic parameters obtained from the two treatments in the present study shows that only the cephadrine elimination rate constant k_{10} , the hybrid rate constant β , and the plasma clearance $V_1 k_{10}$ were significantly affected by co-administration of probenecid. The decrease in these values in the presence of probenecid is consistent with the prolongation of serum levels of antibiotic, presumably due to inhibition of renal tubular secretion by probenecid.

The pharmacokinetic parameters associated with physical distribution of cephadrine in the body, i.e. the volume of central compartment V_1 , the overall steady-state distribution volume $V_d(ss)$, were unchanged in the presence of probenecid.

Under our experimental conditions therefore, probenecid inhibited the renal excretion of cephadrine, but did not significantly alter its distribution characteristics.

The results obtained in this study lead us to conclude that, whereas co-administered probenecid has previously been shown to have a marked influence on the apparent distribution volume of oral cephadrine, no such phenomenon occurs when cephadrine is administered by intravenous injection. The elevation of circulating levels of antibiotic in the presence of probenecid could be accounted for in terms of reduced renal elimination. This data does not rule out the possibility of probenecid-mediated changes in cephadrine distribution in tissues, which may be very complex and finely balanced. These may not be reflected in our only measure of such change, the apparent volume of distribution.

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