EFFECT OF POSTURE ON AMPICILLIN PHARMACOKINETICS, GLOMERULAR FILTRATION RATE AND RENAL PLASMA FLOW IN RESTING SUBJECTS

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- 1 Differences in drug kinetics between supine rest and ambulation have been reported, but the relative contribution of postural changes and changes in the level of physical activity has not been evaluated.
- 2 Ampicillin pharmacokinetics, glomerular filtration rate (GFR) and renal plasma flow (RPF) were studied in six male volunteers at rest in the sitting and lying position with an interval of 1 week.
- 3 After intravenous administration ampicillin kinetics, analyzed according to a two-compartment open model, demonstrated significant changes in drug distribution when the position was changed from lying to sitting: α -increased by 50%, V_1 and V_β increased by 19% and 22% respectively.
- 4 Ampicillin clearance, the fraction of dose recovered from urine, GFR and RPF were, however, not influenced by the change in posture.
- 5 Our data on effects of posture in resting subjects suggest that previously reported differences in drug elimination and RPF between lying and ambulatory subjects are largely due to differences in the level of physical activity.

Keywords posture ampicillin pharmacokinetics GFR renal plasma flow

Introduction

Interest in the effect of posture on pharmacokinetics in man has centred mainly on the difference between supine rest and ambulation (Levy, 1967; Roberts & Denton, 1980; Swartz & Sidell, 1973; Swartz *et al.*, 1974). In these studies postural changes in elimination kinetics were observed with high clearance drugs, and were related to concomitant changes in blood plasma flow of the eliminating organ. Differences in pharmacokinetics between supine rest and ambulation could be due both to the changes in posture and the change of physical activity. The relative contribution of these factors has been evaluated with respect to cardiac output and stroke volume (Reeves *et al.*, 1961; Chapman *et al.*, 1960; Wang *et al.*, 1960), but no data are available on the relative importance of posture and level of exercise for liver and renal blood flow. Furthermore, in resting subjects, the relation between renal blood flow and pharmacokinetics of drugs eliminated via the renal route in the lying, sitting, and standing position is unknown.

The present study was undertaken as a first attempt to establish relationships between renal plasma flow (RPF), glomerular filtration rate (GFR), and drug

kinetics at rest in different positions. Ampicillin was chosen as a probe for drugs eliminated via the kidneys, since 80% is excreted as unchanged ampicillin in the urine after an intravenous dose (Bergan, 1978). In order to obtain distribution as well as elimination kinetics, ampicillin was given to healthy male volunteers as a short time infusion. The same subjects were studied on two occasions, either sitting or lying at rest, in a cross over design.

Methods

Subjects

Six healthy male volunteers, aged 23–29 years, gave their informed consent to participate in the study. None of the subjects had any history of known allergy to penicillins. Before the study a general clinical and haematological investigation was carried out; and liver, kidney and thyroid function were estimated by measurements of serum albumin, NT, ALAT (SGOT), γ GT, creatinine, T_4 , TBG and TSH.

Design

Each subject served as its own control in a two period cross-over design. The interval between the ampicillin infusions was 7 days.

Experiments

The experiments were started when the subjects had been either sitting or lying for 30 min, a period intermediate between the previously used 15 min (Chapman *et al.*, 1960; Wang *et al.*, 1960) and 40 min (Waterfield, 1931; Chapman *et al.*, 1948) and identical to the equilibration period of Radigan & Robinson (1949) and Swartz *et al.* (1973). Changes in posture were not permitted until the end of the experiment. Subjects received ampicillin (Doctacillin Astra AB, Södertälje, Sweden) (10 mg/kg body weight) as a continuous infusion for 2 min via a cannula in the right cubital vein. Blood samples were drawn from the left cubital vein prior to infusion, and at intervals indicated at Figure 1 after the end of infusion. A urine sample was collected prior to the infusion and 4 h after the infusion. Blood samples were immediately centrifuged and serum was stored at -20°C until analysis. Urines were also immediately frozen after sampling.

Sixty minutes after the end of the ampicillin infusion GFR and RPF were measured by constant infusion of $[^{51}\text{Cr}]$ EDTA and $[^{125}\text{I}]$ *o*-iodo-hippurate. Eighty kBq $[^{51}\text{Cr}]$ EDTA and 40 kBq $[^{125}\text{I}]$ *o*-iodo-hippurate in 100 ml of saline were infused via a cannula in the right cubital vein. An initial infusion rate of 2.0 ml/min was maintained for 10 min followed by infusion of 0.3 ml/min for 110 min. Blood samples (3 ml) for determination of $[^{51}\text{Cr}]$ and $[^{125}\text{I}]$ radioactivity were drawn at 10 min intervals during the last 30 min of infusion. The variation in the samples was less than 5%, indicating that constant plasma levels of radioactivity was achieved.

Ampicillin determination

Since ampicillin is unstable even in frozen aqueous solutions (Westerlund *et al.*, 1979), all samples were analyzed after less than 24 h by means of high pressure liquid chromatography (Westerlund *et al.*, 1979). Shortly, 1 ml of serum or urine was precipitated with 100 μl of 70% TCA, whirlimixed and centrifuged. The supernatant (200 μl) was injected on a reverse phase column (LiChrosorb RP₁₈), E. Merck, Darmstadt, GFR. The mobile phase was phosphate buffer pH 8.0 and methanol (7:3 v/v) at a flow of 2 ml/min delivered by a LDC Constametric pump.

Detection was performed by reading the absorption at 254 nm with a Spectromonitor III LDC.

Calculations

The pharmacokinetic data were analyzed according to a two compartment open model with first order elimination kinetics (Gibaldi & Perrier, 1975).

$[^{51}\text{Cr}]$ EDTA clearance and $[^{125}\text{I}]$ *o*-iodo hippurate clearance were calculated as the ratio between the infusion rate and steady state plasma concentrations.

Results

After the short time intravenous infusion of ampicillin the serum concentrations of the drug demonstrated a biexponential decline in all six volunteers as illustrated in Figure 1.

Figure 1 Serum ampicillin concentrations in healthy volunteers measured with the subjects sitting ($\square$ — $\square$) and lying ($\blacktriangle$ — $\blacktriangle$) at complete rest. Values are mean $\pm$ s.d., $n = 6$.

When ampicillin kinetics at rest in the sitting position were compared with the kinetics in the same volunteers in the lying position, there was a statistically significant change in the following variables: α was increased by 50%, V_1 and V_β was decreased by 10% and 22%, respectively (Table 1).

$[^{51}\text{Cr}]$ EDTA clearance, $[^{125}\text{I}]$ hippuran clearance and the fraction of ampicillin excreted as unchanged ampicillin in urine was not significantly different in the sitting compared with the lying position (Table 2).

Discussion

A change in posture from the sitting to the lying position in healthy volunteers at rest caused only changes in pharmacokinetic variables characterizing

Table 1 Ampicillin kinetics in six healthy volunteers at rest in the lying and sitting position. Ampicillin (10 mg/kg) was infused i.v. on two occasions with an interval of 1 week.

Kinetic variable	Lying	Sitting	P
α (10^{-2} min^{-1})	8.6 ± 3.2	12.9 ± 6.8	< 0.05
$t_{1/2}$ (α) (min)	8.0 ± 2.5	5.4 ± 2.5	< 0.05
β (10^{-2} min^{-1})	1.5 ± 0.5	1.8 ± 0.8	NS
$t_{1/2, \beta}$ (min)	46.7 ± 14	37.5 ± 11.3	NS
CL ($\text{ml min}^{-1} \text{ kg}^{-1}$)	4.6 ± 2.4	4.4 ± 1.1	NS
V_1 (ml kg^{-1})	98.5 ± 22.3	79.1 ± 23.8	< 0.05
V_β (ml kg^{-1})	293.0 ± 78.1	226.8 ± 47.5	< 0.05
$V_{d(ss)}$ (ml kg^{-1})	162.5 ± 64.1	143.9 ± 57	NS
k_{12} (10^{-2} min^{-1})	2.7 ± 1.4	4.6 ± 2.8	NS
k_{21} (10^{-2} min^{-1})	3.2 ± 1.4	4.5 ± 1.9	NS
k_{10} (10^{-2} min^{-1})	4.1 ± 1.2	5.9 ± 2.9	NS

NS – not significant (Wilcoxon's test for paired differences)

the distribution of ampicillin. No significant changes were noted in the elimination characteristics, neither was there any change in renal plasma flow and glomerular filtration rate.

Since previous studies have been largely based on intramuscular and oral administration of drugs, distribution kinetics before and after a change in posture are unknown. In a study with antipyrine, a drug which is distributed to total body water and eliminated by slow hepatic metabolism (Soberman *et al.*, 1949; Brodie & Axelrod, 1950), Schwartz *et al.* (1974) showed an increase in α - and decrease in V_1 in healthy volunteers after a change from lying at rest to ambulation and exercise. The same type of changes were noted in this study, which to the best of our knowledge, is the first report of a change in posture only. The effects may be explained in the light of the fact that the upright position leads to an increase of extracellular fluid volume of the lower legs, together with a decrease of about 15% in total plasma volume (Waterfield *et al.*, 1931). Thus, the distribution of several drugs, is changed not only by several types of stress (Swartz & Sidell, 1973; Chapman *et al.*, 1948), but also by a change in posture intermediate between the supine and standing position in resting subjects. Higher initial plasma concentrations and a more rapid initial disappearance rate suggest an altered distribution from a contracted central compartment, to an

expanded peripheral compartment as indicated by studies with amoxycillin given orally (Roberts & Denton, 1980) and benzyl penicillin given intramuscularly (Levy, 1967).

The present study confirms previous data obtained with microbiological methods (Bergan, 1978) with respect to the fraction of ampicillin excreted unchanged in urine. Furthermore, no significant change in the metabolic fate of ampicillin was noted between the sitting and lying position. The data were used to calculate a mean clearance of ampicillin of 212 and 241 ml/min in the lying and sitting position, respectively, in our subjects. These values, intermediate between glomerular filtration rate and renal plasma flow in man, confirms a tubular secretion of ampicillin in man.

Consistent with the finding of no difference in glomerular filtration rate and renal plasma flow in the lying and sitting position, no difference in ampicillin elimination kinetics was observed in our subjects. A significant decrease in renal plasma flow occurs in subjects during graded exercise in the supine (Grimby, 1965), sitting (Sundsford *et al.*, 1975) and erect position (Chapman *et al.*, 1948; Radigan & Robinson, 1949). Since no data have been published in erect subjects at rest, one can only speculate as to the relative contribution of exercise and posture. However, subject 3 in this study has been investigated in the erect position without any physical activity for 3 h. GFR was unchanged from the lying position and only a 15% reduction in RPF was observed (data not shown). These preliminary findings and the results in the sitting position suggest that exercise has been mainly responsible for the previously reported changes in renal plasma flow in ambulatory subjects.

To summarize, this study in healthy male volunteers has shown that ampicillin is distributed more rapidly to peripheral compartments in the sitting position after an intravenous infusion than in the lying position. No significant difference in the elimination characteristics of the drug was seen between the two positions. Since many patients and elderly will receive the drugs while they are sitting during most parts of the day, the present study describes a suitable model for studies of drug kinetics in a relevant posture in such groups as patients with kidney disease, cardiovascular disease, and elderly healthy subjects.

Table 2 [^{51}Cr]-EDTA clearance, [^{125}I]-o-hippuran clearance and renal ampicillin excretion in six healthy volunteers in the sitting and lying position

	Lying	Sitting	P
[^{51}Cr]-EDTA clearance ($\text{ml} \times (\text{min} \times 1.73 \text{ m}^2)^{-1}$)	135.6 ± 11.4	141.5 ± 4.2	NS
[^{125}I]-o-hippuran ($\text{ml} \times (\text{min} \times 1.73 \text{ m}^2)^{-1}$)	541.6 ± 19.7	547.8 ± 27.6	NS
Urinary ampicillin (% of i.v. dose)	77.5 ± 10.6	83.8 ± 9.9	NS

NS – not significant (Wilcoxon's test for paired differences)

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