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The Effects of Posture on the Pharmacokinetics of Intramuscular Benzylpenicillin

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Summary. Previous reports have produced conflicting results as to whether changes in posture affected the pharmacokinetics of the penicillins.

We have studied the pharmacokinetics of intramuscularly administered benzylpenicillin in normal subjects during bedrest and ambulation and compared it with data obtained following intravenous administration of the same dose to the same subjects under the same conditions. The values of area under the curve, total clearance, mean residence time and renal clearance found during ambulation were 1175 ($min \cdot min \cdot l^{-1}$), 488 ($ml \cdot min^{-1}$), 101 (min), and 264 ($ml \cdot min^{-1}$) (means). The corresponding values for bedrest were 1032 ($min \cdot mg \cdot l^{-1}$), 544 ($ml \cdot min^{-1}$), 96.7 (min), and 315 ($ml \cdot min^{-1}$).

There was a significant difference between the areas under the curve with change of posture but not between any of the other pharmacokinetic variables. The differences observed in this study are unlikely to be of clinical relevance.

We suggest that the differences between the results of this study and those of previous studies may be related to the level of exercise undertaken by the subjects in the various studies.

Key words: benzylpenicillin; posture, intramuscular administration, pharmacokinetics

One of the earliest pharmacokinetic evaluations of the effect of posture on drug disposition was carried out by Levy (1967) using the data of Schmidt and Roholt (1966). Schmidt and Roholt (1966) observed that, following *intramuscular administration of benzylpenicillin,* serum levels of the drug were higher during ambulation than during bedrest. Levy (1967) determined that the renal clearance and fraction excreted unchanged were increased and the metabolic rate constant decreased during bedrest. Roberts and Denton (1980) found that the renal clearance of amoxycillin was lower during ambulation than during either bedrest or sleep. However, we recently reported that the pharmacokinetics of intravenously administered benzylpenicillin are not significantly affected by posture (Rumble et al. 1986). We concluded that the findings of previous studies reporting changes in the disposition of the penicillins may have reflected absorption effects.

In order to ascertain whether the earlier reported changes in penicillin disposition with posture were absorption related, the volunteers from our earlier intravenous benzylpenicillin study (Rumble et al. 1986) were given intramuscular benzylpenicillin during bedrest and ambulation. The effect of absorption changes with posture can be ascertained by a comparison of the intramuscular and intravenous data for a particular subject in a particular state of posture.

Method

Seven healthy volunteers (4 male, 3 female) aged 21–23 years who had previously participated in a study of the effects of posture on the pharmacokinetics of i.v. benzylpenicillin (Rumble et al. 1986), were entered into the study. An additional female volunteer was entered into the study to provide a balanced design in relation to possible sex differences. Prior to the investigation, a detailed medical history was taken with particular attention to possi-

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ble penicillin hypersensitivity. Subjects with a history of drug allergy, eczema and hayfever were excluded. No subjects gave a history of liver or renal disease. Physical examination, haematological tests and tests of liver and renal function showed no abnormalities. No other drugs were taken during the two weeks before the study or during the study. Informed consent was obtained from each subject and approval from the Human Ethics Committee of the University of Tasmania was obtained before commencing the study.

Procedure

Each subject was administered benzylpenicillin 600 mg (Commonwealth Serum Laboratories, Parkville, Australia) by intramuscular bolus injection into the gluteus maximus on two separate occasions, during bedrest and during ambulation, with at least 1 week between each study. The investigation was conducted in a randomised cross-over design with each subject acting as his/her own control. The dose was administered after the subject had been either standing or lying for 1 h. Changes in posture were not allowed throughout each phase of the study.

As caffeine appeared to interfere with the assay for benzylpenicillin, subjects refrained from caffeine-containing beverages for several hours (at least eight) before and during each study.

Sample Collection and Analytical Methods

An indwelling catheter was inserted into an antecubetal vein approximately one hour before dosing. Blood samples (5 ml) were drawn at 0, 10, 20, 30, 45, 60, 90, 120, 150, 180, 240 min after dosing. All samples were placed into heparinised tubes and immediately centrifuged and the plasma stored at −20 °C until assayed.

All urine excreted by the subjects 0–8 h and 8–24 h was collected, measured and an aliquot stored at −20 °C until assayed. Plasma and urinary benzylpenicillin were determined by high performance liquid chromatography (Rumble and Roberts 1985) as soon as possible after collection. The reproducibility, detection limits (0.2 mg/l plasma; urine 10 mg/l) and determination limits were the same as those described by Rumble and Roberts (1985).

Pharmacokinetics and Statistical Analysis

The overall elimination rate constant (λ) was determined from the slope of the terminal linear segment of a semi-logarithmic plot of plasma concentration versus time. The elimination half-life ($t_{½}$) was then calculated in the usual manner ($t_{½} = \ln 2/\lambda$).

The area under the plasma benzylpenicillin concentration versus time curve (AUC) was determined using the trapezoidal rule with appropriate correction for the partial area from the final data point to infinity based on the slope of the terminal exponential phase (Gibaldi and Perrier 1982). Since benzylpenicillin was administered intramuscularly in the present study, its apparent volume of distribution could not be estimated directly. The ratio of the apparent volume of distribution for benzylpenicillin (V) to its extent of absorption into the systemic circulation (f) was calculated according to Eq. (1).

$$\frac{V}{f} = \frac{D}{\lambda \cdot AUC} \quad (1)$$

where D is the administered dose and AUC is the area under the plasma benzylpenicillin concentration versus time curve.

For the seven subjects who had participated in the intravenous administration study (Rumble et al. 1986), the area under the plasma benzylpenicillin concentration versus time curve following intramuscular administration ($AUC_{i.m.}$) was compared with the area under the plasma benzylpenicillin concentration versus time curve following intravenous administration of the same dose ($AUC_{i.v.}$). As the dose of benzylpenicillin administered by the intravenous and intramuscular routes was identical, the bioavailability (f) of benzylpenicillin from the intramuscular site is given by the ratio of the $AUC_{i.m.}$ and $AUC_{i.v.}$:

$$f = \frac{AUC_{i.m.}}{AUC_{i.v.}} \quad (2)$$

The apparent volume of distribution for those 7 subjects was determined by substitution of estimated availabilities using Eq. (2) into Eq. (1). For these subjects total body clearance (CL) was determined from the ratio of the fraction of the dose absorbed ($D \cdot f$) to the area under the plasma benzylpenicillin concentration versus time curve (AUC) ($CL = D \cdot f/AUC$).

The renal clearance of benzylpenicillin (CL_R) was estimated from the ratio of amount of unchanged benzylpenicillin excreted in the urine to infinite time $Ae(\infty)$ to the area under the plasma benzylpenicillin concentration versus time curve (AUC) ($CL_R = Ae(\infty)/AUC$). For this calculation it was assumed that urine excreted over 24 h was equivalent to that to infinite time.

The dependence of renal clearance on renal plasma flow was examined using the "well-stirred"

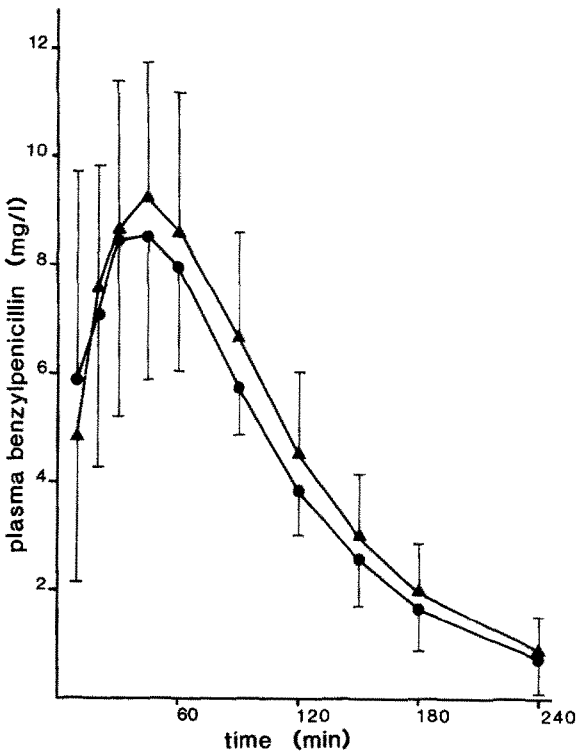

Fig. 1. Mean (±SD) plasma benzylpencillin concentrations in 8 healthy subjects during ambulation and bedrest

Table 1. Comparison of mean estimates (±SD) of pharmacokinetic variables for benzylpenicillin in 8 subjects

Parameter[a]	Ambulation	Bedrest
$t_{½}$(min)	52.5 ± 11.7	50.9 ± 19.3
AUC (min·mg·l^{-1})	1175 ±256	1032 ±204[b]
V/f (l·kg^{-1})	0.63± 0.22	0.64± 0.19
f[c]	0.93± 0.11	0.95± 0.11
V[c] (l·kg^{-1})	0.55± 0.18	0.62± 0.25
CL[c] (ml·min^{-1})	488 ±101	544 ±123
f_l	0.46± 0.12	0.55± 0.09
CL_R (ml·min^{-1})	264 ± 99.7	315 ± 87.4
CL_{NR}^c (ml·min^{-1})	234 ± 81.3	237 ±108
MRT (min)	101 ± 21.4	96.7 ± 29.8
MAT[c] (min)	65.7 ± 33.3	63.8 ± 32.3

[a] $t_{½}$ - elimination half-life; AUC - area under plasma concentration-time curve; V/f - apparent volume of distribution (V) divided by the fraction of dose absorbed (f); f - fraction of dose absorbed; V - apparent volume of distribution; CL - total body clearance; f_l - fraction of the dose excreted unchanged in the urine; CL_R - renal clearance; CL_{NR} - nonrenal clearance; MRT - mean residence time; MAT - mean absorption time; [b] $p<0.05$; [c] $n=7$

model for clearance (Gibaldi and Perrier 1982) and the corresponding equation given by Roberts and Denton (1980)

$$CL_R = \frac{f_u \cdot CL_{int} \cdot Q_R}{f_u \cdot CL_{int} + Q_R} \quad (3)$$

where f_u is the fraction of unbound drug, CL_{int} is the renal intrinsic clearance and Q_R is the effective renal blood flow. As benzylpenicillin excretion is primarily by tubular secretion and is largely independent of protein binding (Craig and Welling 1977) the term of f_u is approximated to unity. Equation (3) was used to examine the dependence of renal benzylpenicillin clearance on renal blood flow changes induced by posture.

Evaluation of the rate of absorption was possible for the seven subjects who had participated in the intravenous dosing study. In these subjects, the fraction remaining to be absorbed at various times was determined according to the Loo-Riegelman method (Loo and Riegelman 1968). From linear regression of these data, the rate of absorption was calculated. Extrapolation of the linear regression of the data allowed the lag time for absorption to be determined which was taken to be the time at which the fraction remaining to be absorbed was unity. The peak time (corrected for lag time) was used as another estimate of the rate of absorption of benzylpenicillin.

The noncompartmental pharmacokinetic parameter, mean residence time (MRT), based on statistical moment theory was calculated from the AUC and AUMC and is given by (Gibaldi and Perrier, 1982):

$$MRT = \frac{AUMC}{AUC} = \frac{\int_0^\infty t \cdot Cdt}{\int_0^\infty Cdt} \quad (4)$$

The mean absorption time (MAT) was determined from Eq. (5), (Riegelman and Collier 1980) for the seven subjects who had participated in the intravenous study.

$$MAT = MRT_{i.m.} - MRT_{i.v.} \quad (5)$$

The mean urinary flow rate for each subject was calculated from the urine volume collected during the first 8 h after drug administration.

Statistical comparison of the effect of bedrest and ambulation on various pharmacokinetic parameters was made by paired *t*-test.

Results

The mean plasma benzylpenicillin concentration versus time profiles are shown in Fig. 1. Although at all times, except at 10 min, the mean plasma concentrations were lower during bedrest than during ambulation, these concentrations were only signifi-

cantly different at 45 min ($p<0.05$). At all other times there was no significant difference.

The mean values for each of the variables determined for both states are shown in Table 1 from the individual data for ambulation and bedrest given in Tables 2 and 3, respectively.

The area under the plasma benzylpenicillin concentration versus time curve (AUC) for ambulation was significantly larger than the AUC for bedrest ($p<0.05$). No significant differences were found between any of the remaining pharmacokinetic variables determined ($p>0.05$).

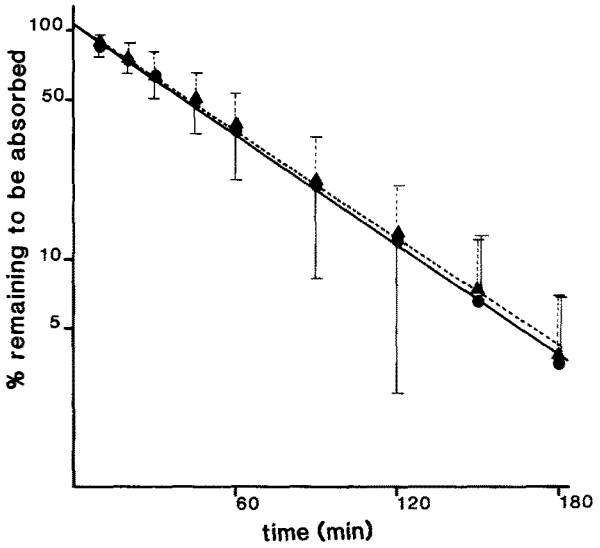

Fig. 2. Fraction of the dose remaining to be absorbed (±SD) versus time following intramuscular administration of 600 mg benzylpenicillin during ambulation and bedrest for seven subjects

Examination of the absorption profile for benzylpenicillin following intramuscular administration, using the Loo-Riegelman method, failed to show any differences between the rate of absorption during bedrest and during ambulation (Fig. 2). Table 4 gives the means for peak concentration (C_p), the peak time (t_p), the lag time for absorption (t_{lag}), the time to reach peak plasma benzylpenicillin concentration corrected for lag time (t_{corr}) and the rate constant for absorption (k_a). There were no significant differences between ambulation and bedrest for these variables.

In this study there was no significant difference between the urinary flow rate during ambulation (mean ± SD: 0.84 ± 0.11 ml/min) and the urinary flow rate during bedrest (mean ± SD: 0.88 ± 0.37 ml/min). The renal clearance of benzylpenicillin was not related to urine flow rate ($r=0.004$, $p>0.5$).

Discussion

The pharmacokinetic variables determined during this study are similar to those determined in other studies. The mean values for the terminal half-life found in the present study (52.5 min and 50.9 min during ambulation and bedrest, respectively) are similar to those found in the previous intravenous study (Rumble et al. 1986) (53.6 min during ambulation and 54.2 min during bedrest) and also to those found by Kates et al. (1980); (49.2 min and 51.2 min) and Levy (1967); (50.4 min and 55.8 min during ambulation and bedrest, respectively). The mean values for the volume of distribution during

Table 2. Experimental and pharmacokinetic data describing the disposition of benzylpenicillin in ambulant subjects following intramuscular administration of the dose

Parameter[a]	Subject							
	AU	HW	AC	EM	BM	CJ	SB	CL
Sex	F	F	F	F	M	M	M	M
Age (years)	21	23	21	21	21	22	21	22
Weight (kg)	54	60	67	73	70	72	68	75
$t_{½\beta}$ (min)	49.2	65.4	43.2	54.0	52.8	31.8	68.4	55.2
AUC (min·mg·l^{-1})	1600	920	1325	970	1434	921	1175	1053
V/f (l·kg^{-1}	0.49	1.02	0.44	0.83	0.46	0.43	0.75	0.61
f	0.93	0.93	1.06	-	1.06	0.93	0.77	0.85
V (l·kg^{-1})	0.46	0.95	0.47	-	0.49	0.40	0.58	0.52
CL (ml·min^{-1})	347.5	607	505	-	451	619	397	488
f_l	0.28	0.63	0.38	0.43	0.44	0.47	0.62	0.46
CL_R (ml·min^{-1})	106	409	179	337	189	314	318	264
CL_{NR} (ml·min^{-1})	241	198	326	-	262	305	79.3	224
MRT (min)	101	114	88.2	94.01	97.3	64.9	139	108
MAT (min)	61.5	87.1	61.5	-	67.5	0.08	108	74.3

[a] Parameters as defined in Table 1

Table 3. Experimental and pharmacokinetic data describing the disposition of benzylpenicillin in bedrested subjects following intramuscular administration of the dose

Parameter[a]	Subject							
	AU	HW	AC	EM	BM	CJ	SB	CL
Sex	F	F	F	F	M	M	M	M
Age (year)	21	23	21	21	21	22	21	22
Weight (kg)	54	60	67	73	70	72	68	75
$t_{½\beta}$ (min)	33.6	46.8	51.6	36.6	42.6	35.4	76.2	84.6
AUC (min·mg·l^{-1})	1299	838	1254	720	1060	877	1097	1110
V/f ($l \cdot kg^{-1}$)	0.41	0.80	0.53	0.61	0.50	0.49	0.88	0.88
f	0.83	1.06	0.89	–	0.93	0.87	0.97	1.09
V ($l \cdot kg^{-1}$)	0.34	0.85	0.47	–	0.47	0.43	0.85	0.96
CL ($ml \cdot min^{-1}$)	381	755	426	–	529	597	531	589
f_1	0.51	0.49	0.58	0.44	0.63	0.72	0.46	0.53
CL_R (ml/min^{-1})	236	351	276	367	252	497	254	284
CL_{NR} ($ml \cdot min^{-1}$)	145	404	150	–	277	100	277	305
MRT (min)	68.3	93.7	101	78.8	73.9	74.8	136	147
MAT (min)	35.0	40.9	76.8	–	44.7	36.6	108	104

[a] Parameters as defined in Table 1

Table 4. Mean (±SD) pharmacokinetic data describing the absorption of benzylpenicillin following intramuscular administration to eight subjects

Parameter[a]	Ambulation	Bedrest
C_p ($mg \cdot l^{-1}$)	9.59 ±2.55	8.76 ± 2.92
t_p (min)[b]	42.9 ±9.6	35.7 ±15.1
t_{lag} (min)[b]	6.40 ±4.51	7.70 ± 3.6
t_{corr} (min)[b]	36.5 ±7.7	28.0 ±13.4
k_a (min^{-1})[b]	0.021±0.010	0.023± 0.009

[a] C_p - peak plasma concentration of benzylpenicillin; t_p - time to C_p after administration; t_{lag} - lag time; t_{corr}: - (t_p-t_{lag}); k_a - rate constant for absorption.
[b] n=7

bedrest and ambulation (42.0 l and 36.4 l, respectively) were similar to those determined by Levy (1967), (47 l and 37 l, respectively) and to the values obtained from the same subjects following intravenous administration of the drug during bedrest and ambulation (47.0 l and 38.6 l, respectively) (Rumble et al. 1986). As in this study, Levy (1967) and Rumble et al. (1986) were also unable to show statistically significant changes in the values for the half-life and for volume of distribution with changes in posture. Table 5 provides a comparison of pharmacokinetic values derived by Levy (1967), Rumble et al. (1986), and the present study.

Levy (1967) in a pharmacokinetic analysis of the report by Schmidt and Roholt (1966) who administered benzylpenicillin intramuscularly, determined that the renal clearance of those subjects was significantly increased in bedrest but there was no change in total body clearance. More recently, Roberts and Denton (1980) studied the effects of posture on orally administered amoxycillin. They observed both an increased renal clearance and increased total body clearance of amoxycillin during bedrest. In the present study, the total plasma AUC of benzylpenicillin during bedrest was significantly less than during ambulation. The plasma benzylpenicillin AUC after intramuscular administration reflects both availability and clearance, Eq. (1). On more detailed pharmacokinetic analysis neither availability nor total body clearance (estimated using the i.v. data of Rumble et al. (1986)) were found to alter significantly with changes in posture. The lack of change highlights the intraindividual variability in benzylpenicillin kinetics and the marginal significance of posture on benzylpenicillin plasma concentrations after intramuscular administration. Significant changes are observed when a single parameter such as AUC is compared on two occasions but modification of this data by incorporating data from the intravenous study (and associated error) results in a loss of the statistical difference between bedrest and ambulation.

Although six of the eight subjects had a higher renal clearance of benzylpenicillin during bedrest than during ambulation, this trend was not sufficient for the difference to be significant. Levy (1967) and Roberts and Denton (1980) suggested that the changes in renal clearance observed in their studies may be due to changes in renal blood flow with changes in posture. Several haemodynamic changes occur with changes in posture, such as haemoconcentration, decreased plasma volume (Hagan et al. 1978) and reduced renal blood flow (Selkurt 1963) in the upright subject. The means for renal clearance of benzylpenicillin found in this study are of a

Table 5. Comparison of pharmacokinetic data from this study with those of Rumble et al. (1986) and Levy (1967)

Parameter[a]	Ambulation			Bedrest		
	IM	Rumble et al. (1986)	Levy	IM	Rumble et al. (1986)	Levy
$t_{½}$ (min)	52.5 ±11.7	53.6 ±32.3	50.4	50.9 ±19.3	54.2 ± 36.1	55.8
f	0.46± 0.12	0.63± 0.12	0.67	0.55± 0.09	0.58± 0.17	0.82
V (l)	36.4 ±10.6	38.6 ±30.4	37	42.0 ±18.9	47.0 ± 44.6	47
CL_R (ml·min^{-1})	264.3 ±99.7	309.4 ±93.4	340	314.6 ±87.4	324.1 ±145.3	480
CL_{NR} (ml·min^{-1})	233.6 ±81.3	178.0 ±51.3	166.5	236.9 ±10.4	218.2 ± 66.5	101.8

[a] Variables as defined in Table 1

value intermediate between glomerular filtration rate and renal plasma flow and are consistent with the suggestion by Barza and Weinstein (1976) that benzylpenicillin is removed by both active tubular secretion and glomerular filtration. According to Eq. (3), the renal clearance of benzylpenicillin is dependent on renal blood flow. If it is assumed that the renal intrinsic clearance and red blood cell - plasma partition coefficient for benzylpenicillin are unaffected by posture, and using the mean data for renal clearance (Table 5) and a bedrest renal plasma flow of 650 ml/min (Roberts and Denton 1980), a decrease in ambulatory plasma flow of approximately 28% is estimated from Eq. (3). Roberts and Denton (1980) calculated a decrease in renal plasma flow of approximately 40% for their subjects and for the data of Levy (1967). The level of exercise as well as posture can influence renal plasma flow. During light to moderate exercise renal plasma flow decreased by 15-27% compared to supine renal plasma flow (Chapman et al. 1948). As the level of exercise increases, renal plasma flow decreases even further (Radigan and Robinson 1949). The subjects in the present study undertook only light exercise, being confined mostly to the room in which the study was conducted or walking in a corridor. The larger decline in renal plasma flow in ambulant subjects estimated by Roberts and Denton (1980) may reflect a greater level of exercise undertaken in the ambulatory phase of their study than in the present study. From the results of the present study, it appears that posture per se or a change of posture accompanied by light exercise is insufficient to alter the renal clearance of benzylpenicillin. These results are consistent with our earlier findings for the intravenous administration of benzylpenicillin (Rumble et al. 1986).

Levy (1967) determined that the metabolic rate constant for penicillin elimination, k_M, was significantly increased and the fraction of the dose excreted unchanged was significantly lower in ambulation than in bedrest. In this study, neither the non-renal clearance nor metabolic rate constant (Cl_{NR}/V) of benzylpenicillin were significantly affected by posture (Table 5).

The present study confirms that significant differences in penicillin plasma concentrations after extravascular administration do occur with changes in posture. However, these differences are marginal as pharmacokinetic variables based on a comparison with intravenous data are not significant. The present results also suggest that the absorption of benzylpenicillin after intramuscular administration is independent of posture. The major source of the posturally determined differences in plasma AUC appear to be clearance. Although the study showed a trend towards reduced renal clearance in upright subjects undertaking light exercise when compared to bedrested subjects, the change failed to reach significance. The results of this study suggest that only marginal changes in benzylpenicillin pharmacokinetics occur with changes in posture and that these changes are unlikely to be of clinical significance. The much greater changes in the pharmacokinetics of the penicillins with changes in posture observed by other workers are probably related to the level of exercise undertaken by the subjects in those studies.

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