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Renal excretion of intravenously infused amoxycillin and ampicillin

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1 The aim of this study was to determine whether concentration-dependent renal clearance of ampicillin and amoxycillin occurs. The drugs were given as single 20 min i.v. infusions in doses ranging from 1.9 to 2.8 g to nine healthy volunteers using a cross-over design.

2 Plasma and urinary concentrations were determined by a selective liquid chromatographic method using frequent sampling up to 10 and 30 h respectively after termination of the infusion. The renal clearance of the drugs was independent of the plasma concentration. The mean (s.d.) renal clearances of ampicillin and amoxycillin were 167 (24) and 157 (20) ml min^{-1} 1.73 m^{-2} respectively. The net secretion was about 50% of the total renal clearance of both drugs.

3 The plasma concentration and urinary excretion rate versus time curves indicated a polyexponential decline, which could be described by both a biexponential and a triexponential equation. The former proved to be more reliable, especially in the calculation of micro rate constants. There was a tendency to more sustained plasma concentrations after amoxycillin, also illustrated by a significantly lower mean (s.d.) plasma clearance of this drug, *viz.* 185 (30) ml min^{-1} 1.73 m^{-2}, as compared to ampicillin, 210 (24) ml min^{-1} 1.73 m^{-2} ($P < 0.04$).

4 There were no major differences in the disposition rate constants and the distribution volumes of ampicillin and amoxycillin. The mean (s.d.) plasma half-life was 1.7 (0.3) h for both drugs. The urinary excretion rate indicated a slower terminal disposition rate however, with ampicillin and amoxycillin half-lives of 3.4 (2.0) and 3.9 (1.2) h respectively. The longer half-life in the terminal phase may be due to increased tubular reabsorption at low urinary concentrations. It was not possible to determine in this study whether the half-life was affected by changes in clearance or volume of distribution.

5 The urinary solubility of the drugs was dependent on pH. This could explain the massive macroscopic crystalluria seen in one subject after amoxycillin. Three hours after termination of the infusion, crystals could no longer be found in the sediment. There was no clinical or laboratory evidence of renal damage.

Keywords amoxycillin ampicillin renal excretion crystalluria urinary solubility

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Introduction

It has been suggested that ampicillin undergoes saturable tubular reabsorption (Whelton *et al.*, 1971), a mechanism known to be involved in the renal handling of some cephalosporins (Arvidsson *et al.*, 1979). One might expect the more efficient enteral absorption of amoxycillin, as compared to ampicillin (Brusch *et al.*, 1974), to correspond with a similar difference in their tubular reabsorption. The objective of the present study was to investigate the possibility of a concentration-dependent renal clearance of ampicillin and amoxycillin, with special emphasis on the occurrence of saturable tubular reabsorption.

Methods

Subjects

Nine male, non-obese volunteers aged 21 to 38 (mean 29) years, with body weights ranging from 63 to 94 (mean 75) kg participated. All were found to be healthy in routine clinical and laboratory examinations, and they had no known allergy to penicillins or cephalosporins on examination within a period of 14 days before the study. Penicilloyl-specific IgE was not detected by RAST in any subject. The subjects had not taken other drugs for at least one week before the start of the study and no other drugs were allowed during the study. The study was reviewed and approved by the local Ethics Committee and the written informed consent of the volunteers was obtained.

General data on the subjects are given in Table 1. Serum creatinine levels, determined by laboratory tests before and after the study, were used to estimate creatinine clearance (CL_{cr}) according to the formula given by Cockcroft & Gault (1976). The body surface area (BSA) was calculated according to the formula of Du Bois & Du Bois (1916).

Pharmaceutical preparations

For parenteral administration, vials of ampicillin sodium corresponding to 3 g ampicillin (Doktacillin®, Astra Läkemedel AB, batch EL 101) and amoxycillin sodium corresponding to 2 g amoxycillin (kindly supplied by Beecham Pharmaceuticals, batch CT 252/5113) were used.

Dosage

Immediately before administration ampicillin or amoxycillin was dissolved in isotonic saline. Two butterfly cannulas were inserted into the forearm veins, one on each arm. The infusion was given in one arm and the samples taken from the other. A 3 g dose was given by use of an intravenous infusion set (Mini-set) and an

Table 1 Subject characteristics

Subject	*Age (years)*	*Weight (kg)*	*Height (cm)*	*Serum-creatinine (μmol/l)*	*Estimated creatinine clearance (ml min^{-1} 1.73 m^{-2})*
1	28.5	78.5	175	77	121
				101	92
2	36.5	76.8	182	87	95
				77	107
3	34.0	68.6	176	91	89
				89	91
4	37.6	75.2	181	91	89
				88	92
5	30.7	65.0	178	84	96
				90	90
6	26.3	74.2	175	100	92
				98	94
				96	96
7	20.6	63.0	182	85	100
				87	98
8	23.7	78.0	186	104	89
				105	88
9	26.4	93.5	187	81	123
				79	126
Mean	29.4	74.7	180	90	98
s.d.	5.81	8.51	4.5	8.7	12.1

infusion pump (AGA-NAC 601) over exactly 20 min (5 ml/min). The remaining infusion fluid was analysed for its content of ampicillin or amoxycillin by h.p.l.c. in order to calculate the exact dose given.

Experimental design

The subjects received the two doses according to a randomized, two-way cross-over design with an interval of 1 week between the infusions. All subjects fasted for a minimum of 8 h from midnight to drug administration, except for 300 ml of water taken 30 min prior to drug administration to ensure diuresis. The subjects were recumbent during the infusion and until the 75 min samples were taken. They were required to continue fasting for three hours after drug ingestion, with the exception of 0.75 l of water (or juice etc) taken during this time. A meal was served 3 h after drug administration. The subjects were instructed not to engage in any strenuous or athletic activities during the days of drug sampling.

Sampling

Blood samples were taken by the 'heparin-lock' technique during the first sampling hour, after which direct puncture using heparinized Venoject® tubes were used. Samples (10 ml) were drawn just prior to dosing and at 0, 5, 10, 15, 20, 30, 45, 75 and 105 min, and 2.5, 3.5, 4.5, 5.5, 6.5, 7.5, 8.5 and 10.5 h after termination of the infusion. Plasma was quickly separated by centrifugation and filtration (Sera-Clear® filters).

The samples were frozen within 20 min of collection and were kept frozen at −70°C until assayed. Urine was collected at 0–0.5, 0.5–1, 1–1.5, 1.5–2, 2–3, 3–4, 4–5, 5–6, 6–7, 7–8, 8–9, 9–10, 10–11, and 11–12 h. Additional 1 h urine collections were taken between 22 and 30 h after the infusion. The total volume collected during each interval was recorded and an aliquot was frozen (−70°C) for assay.

Chemical assays

Ampicillin was measured as described by Westerlund *et al.* (1979). The sample workup procedure was modified in order to permit the automated quantitation of the drug. Protein-precipitated plasma and diluted urine, buffered to pH ~5 for stability reasons, were injected directly into a reversed phase liquid chromatographic system. After the separation the mercuric mercaptide penicillenic acid was formed post column in an air-segmented stream and detected by u.v. light at 310 nm. By this technique ampicillin was determined down to 100 ng/ml in plasma with a precision of 8% (CV) and down to 300 ng/ml in urine.

To assay amoxycillin, the sample work-up also involved some purifying extractions with organic phases (Carlqvist & Westerlund, 1979). The precision obtained for the determination of 100 ng/ml plasma was 3.7% (CV). The low levels of amoxycillin obtained at late urine sampling times could not be detected, however, and a more sensitive method was developed (Carlqvist & Westerlund, to be published). A small volume (20 μl) of urine was injected directly into a three-column reversed phase system. On the first short (3 cm) column, amoxycillin was retained as an ion pair with hexylsulphate in an acidic mobile phase. Amoxycillin was then back-flushed to the second column (10 cm) by an alkaline mobile phase which also contained hexylsulphate. In this environment the negatively charged amoxycillin will compete for adsorption sites on the supports with the hydrophobic anion. The compound was thus efficiently eluted from column 1 and migrated rapidly through column 2. The amoxycillin-containing fraction from the second column was captured in a large (1 ml) loop, and, finally, amoxycillin was chromatographed in the last column as an ion pair with tetrahexyl ammonium in a neutral mobile phase. The fluorescamine-derivative of amoxycillin was formed in a post-column packed bed reactor and measured fluorimetrically. By this technique amoxycillin could be assayed down to 50 ng/ml urine.

The content of the infusion solutions was measured after 200-fold dilution with water.

Control of the stability by storage at −70°C for 12 months demonstrated that both drugs were stable under the prevailing conditions.

Solubility of the aminopenicillins in urine

The experiments were performed at 37°C in a thermostated room, containing all the necessary equipment. The fresh morning urines from four volunteers were spiked with ampicillin (60 mg/ml) and amoxycillin (30-40 mg/ml). The pH of five or six 5-10-ml samples was adjusted by adding small volumes of 5 M hydrochloric acid (< 350 μl) to obtain five different pH values between 4 and 8 for the samples taken from each individual. The samples were then incubated and slowly shaken for two hours in a water bath at 37°C. They were centrifuged for 1–2 min at 2000 rev/min, pH was measured and about 1 ml was filtered (Millipore, 5 μm). The filtrate was diluted, 100 μl to 10 ml, with

deionized water and divided into two aliquots of about 3 ml, which were immediately frozen in an ethanol-carbon dioxide bath and stored at −70°C until analysis. The penicillins were measured as described above. The theoretical solubility (C_T) of the compounds in water at different pH values was calculated from solubility data and pK_a values (Tsuji *et al.*, 1978) as

$$C_T = C_o\left[\frac{10^{-pH}}{10^{-pK_1}} + 1 + \frac{10^{-pK_2}}{10^{-pH}}\right] (g/l)$$

where C_o is the solubility of the electrically neutral zwitterion, and pK_1 and pK_2 the dissociation constants. The above function was also used as a model of the solubility of the drugs in human urine. The least squares estimate $\hat{C}_o$ of C_o is obtained from the formula

$$\hat{C}_o = \frac{\sum_{i=1}^{n} C_T^i\left[\frac{10^{-pH_i}}{10^{-pK_1}} + 1 + \frac{10^{-pK_2}}{10^{-pH_i}}\right]}{\sum_{i=1}^{n}\left[\frac{10^{-pH_i}}{10^{-pK_1}} + 1 + \frac{10^{-pK_2}}{10^{-pH_i}}\right]^2} (g/l)$$

in which the summation is carried out over n (pH_i, C_T^i) observations.

Identification of crystals in urine

The crystals observed in the urine samples from one volunteer were isolated by centrifugation and removal of the supernatant. The crystals were identified by microscopy and liquid chromatography. Isolated crystals were dissolved in the mobile phase and injected into the chromatographic system, including the post-column formation of the mercuric mercaptide of penicillenic acid, described above. Since this is a very selective system for penicillins, the capacity factor of the obtained peak was used as an indication of identity.

Pharmacokinetic calculations

The pharmacokinetic parameters of the drugs were estimated from the plasma concentrations during the period after infusion employing a non-linear least squares regression analysis (NONLIN) (Metzler *et al.*, 1974). Data were examined by means of a two- and three-compartment model. In a linear multicompartment model the plasma concentration (C_p^t) after intravenous administration can be described by the following function of time (t) (Gibaldi & Perrier, 1982)

$$C_p^t = \sum_{i=1}^{n} C'_i e^{-\lambda_i t} (mg/l)$$

where C'_i are the intercepts at the y axis at t=0 (end of infusion) and λ_i the first-order disposition rate constants of the exponential decline of the curve.

A weighting factor of $1/C_p^2$ was used as plots of the weighted residuals (weight × (C_p^{obs} - C_p^{calc})) against C_p^{calc} consistently showed that this was preferable in all subjects. Initial parameter estimates used in NONLIN were calculated by means of a computer adaptation of the classical residual, peeling-off technique (CSTRIP) (Sedman & Wagner, 1976). Although the data in all subjects could be described by both biexponential and triexponential equations, the former proved to be more reliable when microconstants were calculated and was chosen for the final analysis. C'_i was adjusted for the effect of the duration of the infusion according to Loo & Riegelman (1970)

$$C_i = \frac{\tau.\lambda_1.C'_i}{1 - e^{-\tau.\lambda_1}} (mg/l)$$

where C'_i is the intercept at the time when the infusion was stopped, C_i the intercept extrapolated to the start of the infusion and τ the infusion time.

Urinary excretion data were not used for pharmacokinetic modelling as urine was not considered to be collected with sufficient frequency to enable the characterization of the distributive phase.

The total area under the plasma concentration-time curve (AUC) was estimated from

$$AUC = \sum_{i=1}^{n} \frac{C_i}{\lambda_i} (mg\ l^{-1}\ h)$$

The AUC was approximately the same regardless of whether it was based on biexponential or triexponential data. Total plasma clearance (CL_t) and plasma half-life ($t_{½}$) were calculated as

$$CL_t = \frac{Dose \cdot 1000}{AUC \cdot 60} (ml/min)$$

$$t_{½}\ (\lambda_2) = \frac{\ln 2}{\lambda_z} (h)$$

The average renal clearance (CL_r) was calculated as the slope of the regression line of the urinary excretion rate on plasma concentration at times corresponding to the mid-points of the urine collection periods from the equation

$$CL_r = \frac{\frac{dX_u}{dt}}{C_p^t} \text{ (ml/min)}$$

Deviations from the regression line are to be expected for data collected immediately after intravenous administration owing to lower concentrations in peripheral veins than in renal arteries and a delay in urine flow through the kidney. Plasma samples taken up to 0.75 h after infusions were excluded from the calculations. The fraction of drug excreted unchanged in the urine was calculated as

$$f_e = \frac{CL_r}{CL_t}$$

The renal filtration clearance (CL_{rf}) and the net renal secretion clearance (CL_{rs}) were calculated as

$$CL_{rf} = CL_{cr} \cdot f_u \text{ (ml/min)}$$

$$CL_{rs} = CL_r - CL_{rf} \text{ (ml/min)}$$

where f_u is the free fraction of drug in plasma (85% of ampicillin and 82% of amoxycillin according to Brusch *et al.* (1974)) and CL_{cr} is creatinine clearance. The apparent volume of distribution at steady state (V_{ss}) and in the β phase (V_β) was calculated as follows

$$V_{ss} = \frac{\text{Dose} \left[\sum_{i=1}^{n} \frac{C_i}{\lambda_i^2} \right]}{(AUC)^2} \text{ (l)}$$

$$V_\beta = \frac{\text{Dose}}{\lambda_z \cdot AUC} \text{ (l)}$$

There were no major differences in V_{ss} in calculations based on biexponential and triexponential data.

Statistical methods

Non-parametric signed rank methods were used to analyse differences between ampicillin and amoxycillin parameters. The Hodges-Lehmann estimator and Tukey confidence interval based on Wilcoxon's distribution-free signed rank test were used to estimate the differences (Hollander & Wolfe, 1973). A linear regression line of renal clearance on the mid-point plasma concentration was calculated for each subject. The overall slope was estimated as the mean for the individual subjects. The hypothesis of a zero slope was tested, using approximate normal theory.

Results

The mean fraction of the dose excreted unchanged in the urine was about 80% after both drugs (Table 2). Thus the kidney is the major route of elimination of the two aminopenicillins. The total renal clearance in all subjects exceeded the clearance by filtration, which was significantly lower for amoxycillin ($P < 0.04$). Thus the mean (s.d.) net tubular secretion of ampicillin and amoxycillin was respectively 49 (10)% and 48 (7)% of total renal clearance.

In five subjects on ampicillin and in four on amoxycillin, the urinary excretion rate was proportionally higher at points of time up to 0.75 h postinfusion with plasma concentrations above 50–100 mg/l. The regression lines of the urinary excretion rate on the plasma concentration at the mid-point of the urinary sampling interval had a correlation coefficient of 0.91 to 1.00. There was no evidence of concentration-dependent renal clearance in any of the sampling intervals when renal clearance was plotted against the mid-point plasma concentration (Figure 1). The renal clearance was essentially unchanged over the whole plasma concentration range for both drugs in all subjects, although the values were somewhat scattered in some subjects. The mean slope of the individual regression lines was not significantly different from zero. There was no apparent correlation between urine flow and renal clearance.

The mean plasma concentration curves normalized for dose and body surface area were similar after the amoxycillin and ampicillin infusions, but there was a slight tendency to more sustained concentrations after amoxycillin (Figure 2 and 3). This was also illustrated by a significantly higher plasma clearance of ampicillin as compared to amoxycillin ($P < 0.04$) (Table 2). The shapes of the log plasma concentration and log urinary excretion rate *vs* time curves indicate a polyexponential decline. There is evidence of a slower terminal disposition rate in respect of the urinary excretion rate versus time at late sampling times as compared to that in plasma. The mean terminal half-life calculated from the urinary excretion rate at 22–30 h postinfusion was 3.4 h after ampicillin and 3.9 h after amoxycillin. The terminal half-life in plasma from samples taken up to 10 h postinfusion was about 1.7 h (Table 3). On the basis of the plasma data, the two-compartment model was shown to be more appropriate than the three-compartment model for pharmacokinetic analysis. There were no major differences in the disposition rate constants (λ_1, λ_2), the terminal half-lives ($t_{1/2}$), or

Table 2 Pharmacokinetic parameters after single intravenous infusions of ampicillin and amoxycillin. Cross-over study in nine male volunteers.

Subject/Drug	CL_t (ml min^{-1} 1.73 m^{-2})	CL_r (ml min^{-1} 1.73 m^{-2})	f_e	CL_{rf} (ml min^{-1} 1.73 m^{-2}	CL_{rs} (ml min^{-1} 1.73 m^{-2})	V_{ss} (l/kg)	V_β (l/kg)
Ampicillin							
1	239	190	0.79	90.4	99.6	0.189	0.386
2	237	206	0.87	86.1	119.4	0.219	0.491
3	185	153	0.83	76.9	76.3	0.224	0.526
4	217	186	0.86	77.2	108.9	0.223	0.399
5	176	156	0.88	79.0	76.6	0.204	0.513
6	—	—	—	—	—	—	—
7	189	136	0.72	84.2	51.8	0.213	0.448
8	215	162	0.75	75.1	86.5	0.223	0.423
9	224	149	0.66	106.0	43.1	0.207	0.454
Mean	210	167	0.80	84.4	82.8	0.213	0.455
s.d.	24.0	23.9	0.077	10.2	26.6	0.012	0.052
Amoxycillin							
1	231	189	0.82	87.2	101.8	0.192	0.409
2	209	155	0.74	83.1	71.8	0.227	0.412
3	154	136	0.89	74.2	62.1	0.187	0.331
4	205	188	0.92	74.5	113.4	0.229	0.457
5	169	158	0.94	76.2	82.2	0.204	0.385
6	170	137	0.81	76.8	60.2	0.193	0.301
7	167	150	0.90	81.3	69.1	0.271	0.527
8	149	139	0.94	72.5	66.9	0.188	0.371
9	213	161	0.76	102.3	58.7	0.202	0.395
Mean	185	157	0.86	80.9	76.2	0.210	0.399
s.d.	29.6	19.9	0.077	9.33	19.3	0.028	0.067
Median difference, amoxycillin-ampicillin	−19.5	−5.0	0.06	−2.9	−1.6	0.001	−0.052
95% confidence limits							
upper	−9.0	8.0	0.15	−2.7	11.5	0.031	0.051
lower	−44.0	−26.0	−0.04	−3.3	−22.7	−0.021	−0.128
P-value	< 0.04	NS	NS	< 0.04	NS	NS	NS

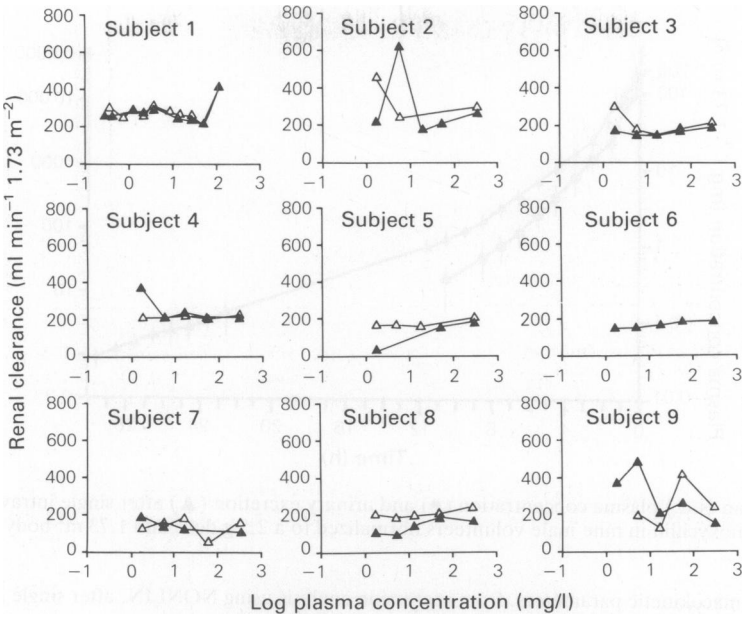

Figure 1 Renal clearance as a function of plasma concentration after single intravenous infusions of amoxycillin (▲) and ampicillin (△). Cross-over study in nine male volunteers.

the volumes of distribution between the two drugs (Table 2, 3).

In one subject (No. 6) massive macroscopic crystalluria was detected immediately after the amoxycillin infusion (Table 4). This was combined with slow diuresis. Three hours after termination of the infusion crystals could no longer be found in the sediment. The needle-like crystals were identified as amoxycillin by h.p.l.c. The subject was withdrawn from the study and not given the ampicillin dose. Laboratory values were normal. Macroscopic crystalluria was not observed in any of the other volunteers.

The solubility of ampicillin and amoxycillin under physiological conditions in human urine is dependent on pH and is higher than the theoretical solubility in water (Figure 4). The function employed in the calculations of the solubility in water was used as a model of the

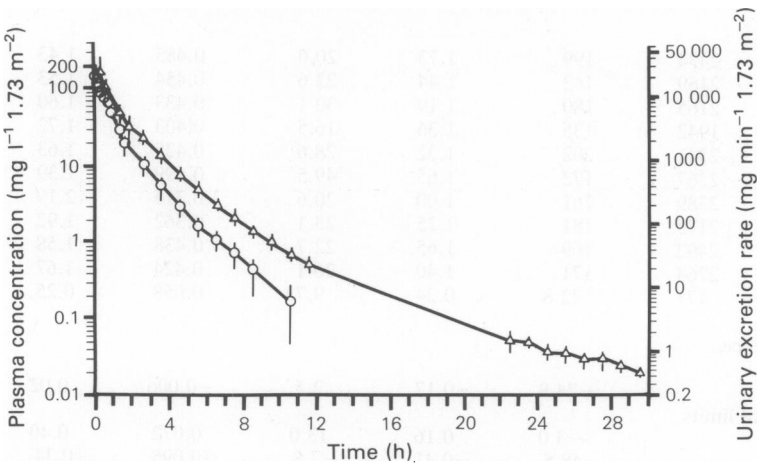

Figure 2 Mean (s.d.) plasma concentration (○) and urinary excretion (△) after single intravenous infusions of ampicillin in eight male volunteers normalized to a 2.5 g dose and 1.73 m^2 body surface area.

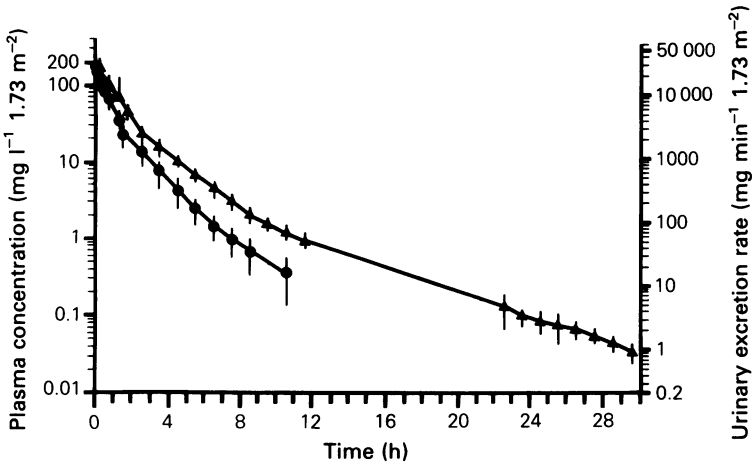

Figure 3 Mean (s.d.) plasma concentration (●) and urinary excretion (▲) after single intravenous infusions of amoxycillin in nine male volunteers normalized to a 2.5 g dose and 1.73 m^2 body surface area.

Table 3 Pharmacokinetic parameters, from regression analysis using NONLIN, after single intravenous infusions of amoxycillin and ampicillin. Cross-over study in nine male volunteers.

Subject/Drug	*Dose (mg)*	*C_1 (mg/l)*	*λ_1 (h^{-1})*	*C_2 (mg/l)*	*λ_2 (h^{-1})*	*$t_{1/2}$ (λ_2) (h)*	*$t_{1/2}$ (u)* (h)*
Ampicillin							
1	2517	211	1.91	24.6	0.532	1.30	2.48
2	2418	185	1.66	16.3	0.430	1.61	1.05
3	2590	201	1.14	14.2	0.327	2.12	3.78
4	2380	178	1.82	31.4	0.490	1.42	6.98
5	2713	227	1.05	9.9	0.332	2.09	3.12
6	—	—	—	—	—	—	—
7	2453	233	1.58	24.8	0.422	1.64	4.83
8	2472	166	1.48	23.8	0.457	1.52	—
9	2773	175	1.42	15.8	0.401	1.73	1.60
Mean	2540	197	1.51	20.1	0.424	1.68	3.41
s.d.	141	25.0	0.30	7.13	0.071	0.29	2.03
Amoxycillin							
1	2434	199	1.73	20.0	0.485	1.43	5.60
2	2169	142	1.44	23.6	0.454	1.53	4.50
3	2165	180	1.19	30.1	0.433	1.60	5.04
4	1942	135	1.36	16.5	0.403	1.72	3.50
5	2341	202	1.32	28.6	0.425	1.63	2.67
6	2267	172	1.65	49.5	0.499	1.39	2.54
7	2389	161	1.00	20.6	0.316	2.19	3.91
8	2175	181	1.25	23.1	0.362	1.92	4.73
9	2492	169	1.65	22.7	0.438	1.58	2.57
Mean	2264	171	1.40	26.1	0.424	1.67	3.90
s.d.	171	22.8	0.24	9.73	0.058	0.25	1.15
Median difference, amoxycillin-ampicillin		−24.8	−0.17	2.5	−0.006	0.02	3.12
95% confidence limits							
upper		−3.0	0.16	13.0	0.072	0.40	−0.69
lower		−48.5	−0.41	−7.8	−0.095	−0.34	−1.97
P-value		0.04	NS	NS	NS	NS	NS

*Calculated from the terminal urinary excretion rate

Table 4 Macroscopic crystalluria after a 2.3 g intravenous infusion of amoxycillin in subject No. 6

Sample interval (after end of infusion)	*Urine volume (ml)*	*Findings/comments*
0–30 min	17	Crystalluria (macroscopic)
30–60 min	17	Crystalluria (macroscopic), pH 5 Traces of protein, no cells
60–90 min	22	Crystalluria (macroscopic on standing)
90–120 min	51	
2–3 h	180	Crystalluria (in sediment), no cells
3–4 h	49	No crystals or cells in sediment
4–5 h	260	
22–23 h		Occasional white cells in sediment

solubility of the drugs in human urine. The results indicate U-shaped pH-solubility curves with no major differences between the drugs.

Subject No. 3 experienced a strong taste sensation immediately after the start of the amoxycillin infusion. No adverse reactions were reported in any of the subjects.

Discussion

The faster renal elimination immediately after drug infusion could be due to saturable tubular reabsorption at high urinary concentrations, but may also be explained by the distribution equilibrium not being reached at this time. Furthermore, the long half-life calculated from urinary samples taken 22–30 h postinfusion may indicate increased reabsorption at low urinary concentrations. As the half-life is a function of clearance and volume of distribution, and these parameters could not be estimated from the terminal phase, the reason for the longer half-life cannot be determined. In contrast to previous findings with some other β-lactam antibiotics, cephapirin and cephaloridine (Arvidsson *et al.*, 1979, 1983), the renal clearance of amoxycillin and ampicillin appears to be independent of the plasma concentration. This indicates that the plasma concentrations were well below those required for saturation of tubular secretion, a prerequisite for the study. Whether tubular reabsorption is present in man and differs between amoxycillin and ampicillin, cannot be decided from the results obtained in the present study. On the other hand, since renal clearance was independent of plasma concentration, tubular reabsorption seems unlikely. Furthermore, the lack of correlation between urine flow and renal clearance suggests that reabsorption is of minor importance with ampicillin and amoxycillin. The renal clearance of drugs that are largely reabsorbed is expected to be sensitive to changes in urine flow (Tucker, 1981). On the basis of studies in dogs showing a unity ratio of ampicillin clearance to creatinine clearance, Whelton *et al.* (1971) suggested that ampicillin undergoes tubular reabsorption in addition to secretion by the kidney. Furthermore, Kamiya *et al.* (1983) demonstrated a relatively high tubular reabsorption of cephalexin but not of ampicillin after oral 500 mg doses in volunteers.

Although the renal clearance was essentially unchanged over the whole plasma concentration range for both drugs in all subjects, the values were somewhat scattered. In the calculations performed, it is assumed that the systemic arterial and the peripheral venous blood con-

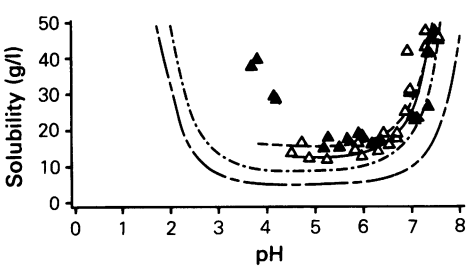

Figure 4 Solubility-pH profiles of ampicillin (△) and amoxycillin (▲) in human urine at 37°C, collected from four volunteers. The theoretical profile was calculated from data on solubility in water and pK_a values (— - — amoxycillin, —·— ampicillin). The function of the solubility in water was used as a model for the solubility in urine (—— ampicillin, – – – amoxycillin).

centrations are the same. Thus arterial-venous plasma concentration differences may have contributed to the variation in renal clearance with time as pointed out by Chiou & Lam (1982). One way to overcome this effect would be to perform the calculations at steady state. Other possible reasons for the variation are a lag time in urinary excretion and incomplete emptying of the bladder.

The apparent volume of distribution (V_{ss}), on the order of 0.2 l/kg, is similar for both drugs and represents about 21% of the body weight. This suggests that the drugs are mainly distributed to the extracellular fluid, which comprises about 17% of the body weight (Goldstein *et al.*, 1974). In the case of drugs that are rapidly cleared from the central compartment with short half-lives like the penicillins, V_β may significantly overestimate the apparent volume of distribution (Gibaldi & Perrier, 1982). This might explain the higher values of V_β as compared to V_{ss} in the present study.

The disposition rate constants and the apparent volumes of distribution did not indicate any major differences in the distribution of ampicillin and amoxycillin. This is in contrast with the findings of Zarowny *et al.* (1974), who reported a significantly larger V_{ss} after amoxycillin than after ampicillin. On the other hand, our results with ampicillin and amoxycillin agree with those reported by Bergan (1978) and Dalhoff *et al.* (1981). The same degree of tissue distribution was found for ampicillin and amoxycillin when their tissue partition indices, i.e. the ratio between the area under the curve for various body fluids and serum, were compared in a review of several studies (Sjövall, 1981).

The three-compartment model has been reported to give a better fit to the serum concentration versus time curve after intravenous amoxycillin (Dalhoff *et al.*, 1981; Dalhoff & Koeppe, 1982). In our experience, estimates of the parameters can be extremely unreliable under certain conditions. A major factor influencing the error in parameter estimation is the number of sampling points and their timing (Fell & Stevens, 1975). In our study 17 plasma samples were collected over 10.5 h, the corresponding figure in the study of Dalhoff *et al.* (1981) was 18 samples over 6 h. Although our figure must be regarded as frequent sampling, there are only 17 – 6 = 11 degrees of freedom left for the estimation of the six parameters. As a result, the subsequent calculations of micro rate constants were extremely unreliable when the three-compartment model was applied to the data. This was not improved by simultaneous modelling of plasma and urine data. On the other hand, estimates of AUC and V_{ss} were, as expected, largely independent of the model used. This supports the present tendency towards non-compartmental methods (Gibaldi & Perrier, 1982; Chiou & Lam, 1982).

In conformity with the episode in this study, subject No. 3 experienced a similar taste sensation after a rectal dose of bacampicillin, a prodrug of ampicillin (Sjövall *et al.*, 1984). This effect therefore seems to be consistent in this subject but it has not been recorded after intravenous or rectal penicillin in any other subject in our studies. The reaction may very well have a genetic background.

The solubility of ampicillin and amoxycillin in human urine at 37°C was higher than that previously described in water (Tsuji *et al.*, 1978). Our results for urine also indicate U-shaped pH-solubility curves, with minimum solubility at the pH near the isoelectric point.

The macroscopic crystalluria in one subject after amoxycillin is probably due to the urinary concentration exceeding the urinary solubility of the drug. The high concentration of the drug, the low diuresis and a urinary pH of 5 were all factors that may have favoured crystallization of amoxycillin in this subject. It was not possible to determine whether the drug precipitated at a lower temperature in the collecting flask or was already present at micturition. There was, however, no clinical or laboratory evidence of renal damage. The appearance of crystals in the urine of patients receiving large doses of intravenous ampicillin without any apparent deleterious effect has been described previously by Potter *et al.* (1971) and Jones & Schrader (1972). Similar findings have been reported after cephalothin and cephazolin (Letendre & Johnson, 1980).

Our study did not indicate any major differences in the disposition of ampicillin and amoxycillin, which contrasts with their differences in enteral absorption.

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