Br. J. clin. Pharmac. (1986), **21**, 171–181

Intra- and inter-individual variation in pharmacokinetics of intravenously infused amoxycillin and ampicillin to elderly volunteers

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1 The purpose of this study was to investigate the disposition of two aminopenicillins and their intra- and inter-individual variation in pharmacokinetic parameters in healthy, elderly volunteers. Two groups, each of 12 active, community-dwelling volunteers between 69 and 83 years of age participated. One group was given 500 mg of amoxycillin, the other group 500 mg of ampicillin as single i.v. infusions. Within the drug groups each volunteer was given the infusion at two different occasions separated by a time-period of 1 week. Amoxycillin and ampicillin were determined in plasma and urine by modern column liquid chromatographic methods.

2 The mean plasma clearance was about 200 ml min^{-1} 1.73 m^{-2} for both drugs and renal clearance accounted for approximately 80% of this. As expected, drug clearance was correlated to renal function as determined by ^{51}Cr-EDTA. The volume of distribution at steady-state (V_{ss}) was about 0.3 l kg^{-1} for both drugs. Compared to our previous results in younger subjects, plasma and renal clearances were essentially similar in this study, but slightly longer half-lives and higher V_{ss} were seen for amoxycillin and ampicillin.

3 The intra-individual variation, expressed as the error of a single determination (CV), was small, for plasma clearance 3.7% and 6.4% after amoxycillin and ampicillin. The corresponding inter-individual variation in clearance was higher, 14.4% after amoxycillin, and 11.9% after ampicillin. The results confirm a higher relative efficiency of a crossover *vs* a completely randomized parallel groups design in parenteral studies of these penicillins.

4 In our elderly subjects there was only an approximately 30% decrease in renal function. This was not enough to reduce the drug clearance and offers an explanation for the similarity between our present results in the elderly and our previous results in younger subjects. Elderly volunteers may be different from patients with disease as a confounding factor. Studies on elderly active and community-dwelling volunteers, as in this study, may therefore be more representative as to the effect of age *per se* on drug kinetics.

Keywords pharmacokinetics amoxycillin ampicillin elderly volunteers individual variation experimental design

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Introduction

Old people may differ from the young both in their response to and handling of drugs by the body. An important age-dependent decrease in the rate of elimination of many drugs is due to the decay in renal function (Rowe *et al.*, 1976). In the elderly the total body water, and the lean body mass, is proportionally smaller and they have a higher proportion of body fat (Crooks *et al.*, 1976). Thus a lipid soluble drug is expected to show a higher and a polar drug a lower apparent volume of distribution in the elderly.

The aim of this study was to investigate and compare the pharmacokinetics after intravenous amoxycillin and ampicillin to elderly volunteers with special emphasis on intra- and inter-individual variation.

Methods

Subjects

The study was conducted on 24 non-obese, active and community-dwelling volunteers, 69 years of age or older. A majority of them were members of a sports club for pensioners. Their characteristics are described in Table 1. All were determined to be healthy by history and from routine clinical and laboratory examinations within a 14-day period before the study. Haemoglobin, ASAT, ALAT, alkaline phosphatases, bilirubin and urinalysis were within normal limits. Renal function was determined by ^{51}Cr-EDTA and creatinine clearance was estimated from serum creatinine according to the formula given by Cockcroft & Gault (1976). The subjects had no known allergy to penicillins or cephalosporins and a negative RAST (penicilloyl specific IgE). They had not taken any diuretics, cardiac glycosides, antibacterials or anticholinergic drugs during the last week before the start of the study.

Pharmaceutical preparations

Vials of amoxycillin sodium corresponding to 2 g amoxycillin (kindly supplied by Beecham Pharmaceuticals, batch 2428 M 783/6178) and ampicillin sodium corresponding to 2 g ampicillin (Doktacillin®, Astra Läkemedel AB, batch IL 426) were used. Immediately before administration, amoxycillin or ampicillin was dissolved in sterile water. Two butterfly cannulae 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 500 mg dose was given using an intravenous infusion set (Imed Accuset) and an infusion pump (Imed 960, Imed Scandinavia, Stockholm) over exactly 5 min (2 ml min^{-1}). The remaining infusion fluid was checked on its content of ampicillin or amoxycillin by h.p.l.c.

Experimental design

The study was performed in two groups of volunteers, each consisting of 12 subjects. One of the two groups was given intravenous ampicillin, the other amoxycillin. The test doses were given twice to each subject with an interval of at least 1 week in order to estimate intra-individual variation. The groups were mixed on each experimental day and matched for renal function, age and sex. All subjects fasted for a minimum of 8 h (from midnight to drug administration) with the exception of 250 ml of water taken on rising, at least 1 h before dosing. The subjects continued fasting for 3 h after drug administration, except for 150 ml of water given after 1 and 2 h and permitted *ad libitum* thereafter. A standardized meal was served 3 h after drug administration. The subjects were instructed not to engage in any strenuous activities during the days of drug administration. Smoking was permitted. The study was reviewed and approved by the local Ethics Committee.

Sampling

Blood samples were collected from the antecubital vein by the 'heparinlock' technique during the first sampling hour after which direct puncture and evacuated heparinized blood collecting tubes (Venoject®, Terumo Europe, NV, 3030 Leuven, Belgium) were used. Specimens of 5 ml each were drawn just prior to dosing and at 0, 5, 10, 15, 30, 45, 60, 90, 120 min and 3, 4, 6, 8 and 10 h after end of infusion.

Plasma was quickly separated by centrifugation for 7 min at 2500 *g* followed by filtration (Sera-Clear®, Technicon AB, Stockholm, Sweden). The samples were frozen within 20 min of collection. Urine was collected prior to and over 0–1, 1–3, 3–5, 5–7, 7–9, and 9–10 h after drug administration. The total volume collected during each interval was recorded and an aliquot was frozen. All samples were stored at −70°C until assay.

Chemical assays

Assays of plasma and urine for ampicillin and amoxycillin were performed by reversed phase liquid chromatography (h.p.l.c.) according to the principles previously described (Westerlund

Table 1 Subject characteristics

Subject	*Sex*	*Age (years)*	*Weight (kg)*	*Height (cm)*	*BSA (m^2)*	*^{51}Cr-EDTA (ml min^{-1} 1.73 m^{-2})*	*Creatinine clearance* (ml min^{-1} 1.73 m^{-2})*
Amoxycillin							
2	F	77	67	162	1.72	64	56
4	F	71	57	158	1.57	89	63
6	F	72	57	155	1.55	80	66
8	F	69	60	164	1.65	69	70
10	F	69	69	171	1.81	68	69
12	M	83	63	172	1.75	55	44
14	M	74	64	163	1.69	89	66
16	M	69	72	166	1.80	101	66
18	F	72	52	153	1.48	80	67
20	F	78	62	157	1.62	77	82
22	M	70	83	176	2.00	63	75
24	M	70	73	169	1.83	82	64
Mean		73.9	64.9	164	1.71	76.4	66
s.d.		4.1	8.5	7	0.14	13.1	9.4
Ampicillin							
1	F	75	65	162	1.69	67	60
3	F	74	76	162	1.81	61	53
5	F	79	68	172	1.80	74	70
7	F	70	62	156	1.61	66	62
9	F	73	52	164	1.55	80	65
11	M	73	78	173	1.92	65	49
13	M	76	82	175	1.98	74	60
15	M	75	77	177	1.94	91	67
17	F	69	79	164	1.86	86	89
19	F	74	68	158	1.70	78	90
21	M	75	57	173	1.68	64	54
23	M	74	75	172	1.88	98	71
Mean		73.8	69.9	167	1.79	75.4	66
s.d.		2.7	9.5	7	0.14	11.7	12.9

* Estimated from serum creatinine

et al., 1979; Sjövall, *et al.*, 1985a; Carlqvist & Westerlund, 1985). By this technique ampicillin was determined at 2–3 mg l^{-1} plasma with an intra-assay precision of 0.9% (CV) and in urine at about 40 mg l^{-1} with a precision of 1.4% (CV). The detection limits were about 120 ng ml^{-1} in plasma and 900 ng ml^{-1} in urine. The intra-assay precision obtained for determination of amoxycillin at 0.35–39 mg l^{-1} plasma ranged from 5 to 1.3% (CV). The detection limits were about 25 ng ml^{-1} in urine and 10 ng ml^{-1} in plasma.

Pharmacokinetic calculations

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

$$C_p^t = \Sigma_{i=1}^{n} C_i' e^{-\lambda_i t} \text{ (mg } l^{-1}) \qquad (1)$$

where C_i' are the intercepts at the y axis at the end of infusion (t=0) 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. Initial parameter estimates used in NONLIN were calculated by means of a computer adaptation of the exponential stripping technique (CSTRIP) (Sedman & Wagner, 1976). C_i' was adjusted for the effect of the duration of the infusion according to Loo & Riegelman (1970).

$$C_i = \frac{\tau \cdot \lambda_1 \cdot C_i'}{1 - e^{-\tau \cdot \lambda_1}} \text{ (mg } l^{-1}) \qquad (2)$$

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. The microconstants were calculated as

$$k_{21} = \frac{C_1 \cdot \lambda_2 + C_2 \cdot \lambda_1}{C_1 + C_2} \quad (h^{-1}) \qquad (3)$$

$$k_{10} = \frac{\lambda_1 \cdot \lambda_2}{k_{21}} \quad (h^{-1}) \qquad (4)$$

$$k_{12} = \lambda_1 + \lambda_2 - k_{21} - k_{10} \quad (h^{-1}) \qquad (5)$$

If the time course of drug concentration in plasma (C_p^t) is treated as a probability density function, then the area under the plasma concentration time curve (AUC) is defined as the zero moment of this distribution. The mean residence time of a drug in the body (MRT) is defined as the first moment (AUMC) divided by the AUC (Yamaoka *et al.*, 1978).

$$AUC = {}_0\int^{\infty} C_p^t dt \quad (mg\ l^{-1}\ h) \qquad (6)$$

$$MRT = {}_0\int^{\infty} tC_p^t dt / {}_0\int^{\infty} C_p^t dt = \frac{AUMC}{AUC} \quad (h) \qquad (7)$$

The moments defined above were calculated by numerical integration using the linear trapezoidal rule and the logarithmic trapezoidal method in the exponential post-absorption phase (Chiou, 1978). The estimated area from the last sampling time to infinity was calculated from the plasma concentration at the last sampling time divided by the terminal disposition rate constant (λ_2), estimated by the method of least squares from the terminal linear part of the log plasma concentration *vs* time curve. MRT was adjusted for the infusion time τ (h).

$$MRT = MRT_{inf} - \frac{\tau}{2} \quad (h) \qquad (8)$$

The plasma clearance (CL_p) and plasma half-life ($t_{½}$) were calculated as

$$CL_p = \frac{Dose \cdot 1000}{AUC \cdot 60} \quad (ml\ min^{-1}) \qquad (9)$$

$$t_{½} = \frac{\ln 2}{\lambda_2} \quad (h) \qquad (10)$$

Renal clearance was calculated from the amount of unchanged drug excreted in urine during the sampling period (A_e) divided by the AUC. The fraction of drug excreted unchanged in the urine was calculated as

$$f_e = \frac{CL_R}{CL_p} \qquad (11)$$

The apparent volume of distribution in the $\beta(\lambda_2)$ phase (V_β) and at steady state (V_{ss}) was calculated as follows

$$V_\beta = \frac{Dose}{\lambda_2 \cdot AUC} \quad (l) \qquad (12)$$

$$V_{ss} = \frac{Dose \cdot AUMC}{(AUC)^2} - \frac{Dose \cdot \tau}{2 \cdot AUC} \quad (l) \qquad (13)$$

Statistical analysis

The differences in pharmacokinetic variables after repeated administration of the same dose, between amoxycillin and ampicillin, have been evaluated using analysis of variance for repeated measurements according to Winer (1962). This analysis gives information about differences between mean levels of drugs and between the two administrations as well as about the interaction between drug and administration number. This interaction is a statistical concept and expresses to which degree the difference between drugs is different for the two administrations.

The within- and between-subject variation for some key parameters was estimated using one-way analysis of variance based on two replications for each of the 12 subjects. The hypothesis of equal coefficients of variation for the two drugs was tested using a likelihood ratio test procedure (Miller & Karson, 1977).

Results were considered as statistically significant for a P-value less than 5% in a two-tailed test.

Coefficients of variation for within-subject variation (CV_W) and between-subject variation (CV_B) were calculated as

$$CV_W = \frac{\sqrt{MS_W}}{\bar{X}} \qquad (14)$$

$$CV_B = \frac{\sqrt{(MS_B - MS_W)/n_0}}{\bar{X}} \qquad (15)$$

where MS_W is the mean sum of squares within subjects, MS_B the mean sum of squares between subjects, $\bar{X}$ the overall mean for all observations and n_0 the number of replicates per subject, in our case two.

On the basis of these mean sums of squares it is possible to estimate the relative efficiency of a crossover design compared to a completely randomized parallel groups design. For this purpose the following efficiency index (E) was calculated according to Guenther (1964)

$$E = \frac{(n-1)\,MS_B + n(r-1)\,MS_W}{(n \cdot r - 1) \cdot MS_W} \qquad (16)$$

where r is the number of treatments to be compared and n is the number of subjects per treatment group in the parallel groups design and the total number of subjects in the crossover design.

Results

The individual plasma concentration curves were similar in each subject after the two infusions (Figures 1 and 2).

As expected from the similar plasma concentrations after duplicate administration, there were only small differences in the mean AUC and urinary recovery (Table 2).

The plasma clearance after repeated administration was remarkably stable for both drugs as was renal clearance (Table 3). The drugs are mainly eliminated by the kidneys ($f_e = 0.8$), and about 20% is eliminated by extra-renal routes (Table 2).

There was a correlation between plasma clearance (mean of the duplicate administrations in each subject) and renal function (estimated by ^{51}Cr-EDTA) with a coefficient of correlation of 0.69 for amoxycillin and 0.83 for ampicillin (Figure 3). The corresponding coefficients of correlation for the relationship between renal drug clearance and renal function were 0.74 and 0.83.

The apparent distribution volume was similar for both drugs but V_β was markedly higher and more variable than V_{ss} (Table 3). The plasma half-lives were also similar, as would be expected from the stable values for clearance and volume of distribution (Table 2).

There were small differences in mean residence time (MRT) after duplicate administration (Table 2) and the results were similar after both drugs. Very small differences between drugs were observed also for the other variables and the interaction between drug and administration was statistically non-significant throughout.

The intra-individual (within-subject) variation, i.e. the error of a single determination, was small in AUC and A_e for both drugs as expressed by the coefficient of variation (CV) (Table 4). The difference between amoxycillin and ampicillin was significant as regards AUC ($P < 0.05$) and renal clearance ($P < 0.01$).

The differences between the two drugs as regards the inter-individual (between-subject) variation were not statistically significant (Table 4). AUC was highly correlated to renal function with a coefficient of correlation of 0.85 and 0.94 for amoxycillin and ampicillin, indicating that 73% and 87% of the total variation in this AUC can be attributed to variation in renal function.

Although the plasma concentrations were very similar after duplicate intravenous administration of the drugs, differences were seen in some pharmacokinetic parameters estimated by non-linear regression (Table 5). The intra- and inter-individual variation, reflected by the reproducibility in these pharmacokinetic macro- and microconstants, was similar and on the whole considerably larger as compared to that for the other pharmacokinetic parameters (Table 4). The variation was smaller in λ_2 than in λ_1 and in k_{10} compared to the other microconstants (k_{12}, k_{21}). There was a smaller variation in λ_2 after amoxycillin, both regarding intra- ($P < 0.05$) and inter-individual variation ($P < 0.01$).

The large variation in the macroconstants is not reflected in the AUC estimated from these constants. The variation in this AUC was similar to that calculated by the trapezoidal method.

From the results in this study the relative efficiency of a crossover *vs* a completely randomized parallel groups design can be estimated. The efficiency index (E) was clearly greater than 1.0 for both drugs, illustrating the advantage of a crossover design. When the number of subjects is in the range of 10 to 20 and the number of treatments between two and four, the observed range of this index was 3–30. An index of three means that the number of subjects required per group in a parallel groups design is threefold compared to the total number of subjects required in a crossover design, in order to have the design equally powerful from a statistical point of view.

Subject number 20 took oxazepam plus nitrazepam on the evening before the first amoxycillin infusion and nitrazepam before the second intravenous dose. The plasma concentrations in this subject were within the range of the others (Figure 1).

No adverse reactions were recorded in any subject.

Discussion

The volunteers participating in this study were between 69 and 83 years of age, and the results should therefore be relevant to elderly subjects. Studies in 'young old' people in their 60s are not adequate for claims of suitability for the elderly as a whole (Smith *et al.*, 1983).

The renal function as determined by ^{51}Cr-EDTA and estimated creatinine clearance in the elderly volunteers was only reduced by some 30% compared to normal values in young people. Although there was a correlation between renal function and plasma clearance or renal clearance for ampicillin and amoxycillin, the plasma and renal clearances were essentially similar after amoxycillin and after ampicillin in this study compared to those previously reported in younger volunteers (Sjövall *et al.*, 1985b) (Table 6).

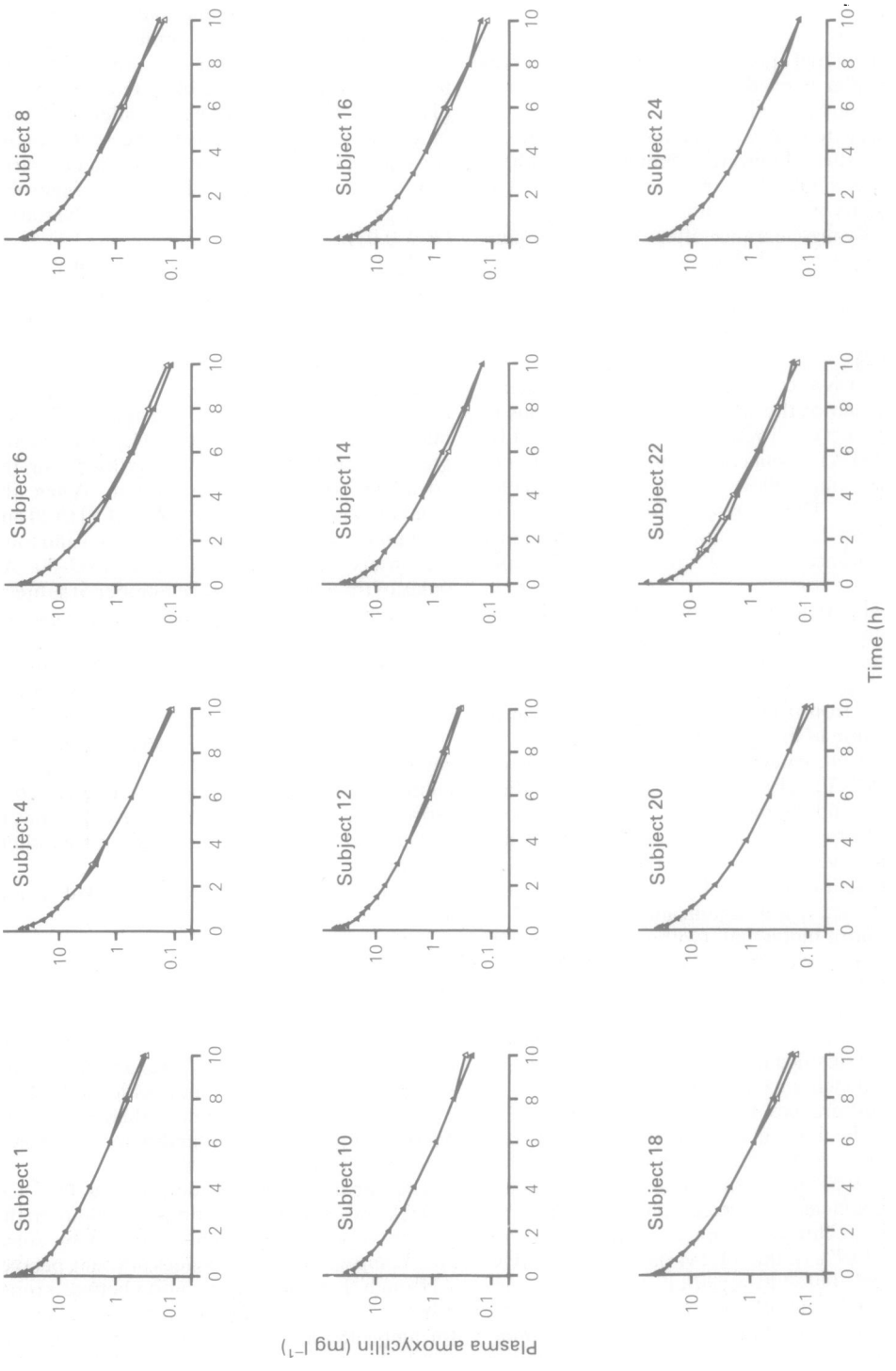

Figure 1 Plasma concentrations after duplicate administration of a single intravenous infusion of 500 mg amoxycillin to elderly volunteers.

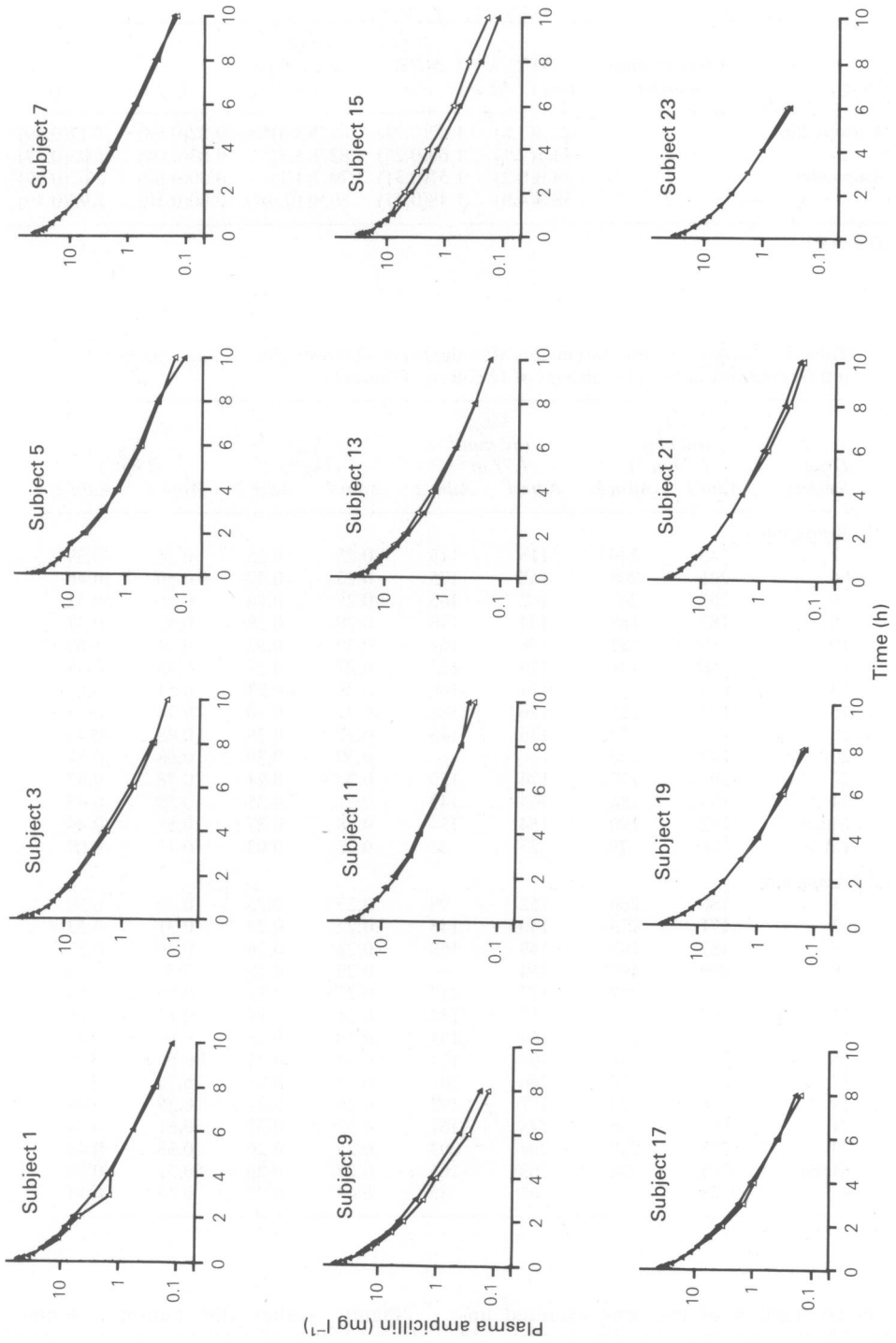

Figure 2 Plasma concentrations after duplicate administration of a single intravenous infusion of 500 mg ampicillin to elderly volunteers.

Table 2 Mean (s.d.) of pharmacokinetic parameters after duplicate administration of single 500 mg intravenous infusions to two groups, each of 12 elderly volunteers

Drug	*Administration number*	*AUC* ($mg\ l^{-1}\ h$)	*MRT* (*h*)	*Urinary recovery* (%)	f_e	$t_{1/2}$ (*h*)
Amoxycillin	1	42.8(7.5)	1.62(0.24)	81.7(3.3)[a]	0.82(0.03)	2.17(0.39)
	2	43.1(7.1)	1.60(0.23)	82.7(3.8)[a]	0.83(0.04)	1.95(0.37)
Ampicillin	1	39.0(6.2)	1.51(0.31)	79.7(4.1)	0.80(0.04)	2.02(0.79)
	2	38.9(4.8)	1.48(0.27)	80.4(10.6)[a]	0.80(0.10)	1.95(0.49)

a) $n = 11$

Table 3 Pharmacokinetic parameters after duplicate administration of single 500 mg intravenous infusions to two groups of 12 elderly volunteers

Drug/ Subject	CL_p ($ml\ min^{-1}\ 1.73\ m^{-2}$) *Adm 1*	*Adm 2*	CL_R ($ml\ min^{-1}\ 1.73\ m^{-2}$) *Adm 1*	*Adm 2*	V_{ss} ($l\ kg^{-1}$) *Adm 1*	*Adm 2*	V_β ($l\ kg^{-1}$) *Adm 1*	*Adm 2*
Amoxycillin								
2	145	146	115	115	0.25	0.25	0.36	0.39
4	201	208	165	175	0.25	0.27	0.50	0.46
6	207	207	162	165	0.25	0.28	0.56	0.51
8	183	188	144	146	0.28	0.28	0.52	0.37
10	180	181	158	164	0.30	0.33	0.44	0.65
12	146	146	119	122	0.27	0.27	0.43	0.48
14	204	203	174	168	0.28	0.27	0.51	0.60
16	217	229	176	188	0.31	0.30	0.74	0.57
18	176	174	136	143	0.27	0.26	0.48	0.44
20	242	240	—	—	0.30	0.29	0.68	0.51
22	207	177	174	155	0.32	0.24	0.78	0.37
24	195	186	164	149	0.27	0.25	0.58	0.47
Mean	192	190	154	154	0.28	0.27	0.55	0.49
s.d.	28	29	23	22	0.02	0.03	0.13	0.09
Ampicillin								
1	180	200	152	99	0.23	0.23	0.50	0.39
3	171	173	140	145	0.22	0.23	0.31	0.53
5	187	192	149	158	0.24	0.26	0.36	0.57
7	200	197	154	—	0.29	0.28	0.55	0.41
9	216	247	177	217	0.27	0.28	0.56	0.63
11	161	165	117	132	0.31	0.28	0.84	0.56
13	213	191	164	154	0.30	0.25	0.60	0.41
15	238	194	195	154	0.34	0.31	0.60	0.47
17	220	232	180	201	0.24	0.23	0.50	0.42
19	244	233	177	192	0.25	0.24	0.39	0.49
21	183	186	148	161	0.32	0.32	0.61	0.74
23	241	240	204	203	0.25	0.26	0.38	0.42
Mean	205	204	163	165	0.27	0.26	0.52	0.50
s.d.	28	27	25	35	0.04	0.03	0.14	0.11

The mean fraction of the drug excreted unchanged in the urine was the same in these old subjects as in younger ones indicating a similar degree of extra-renal elimination.

Slightly higher distribution volumes and plasma half-lives were seen in the elderly for both drugs. The results are somewhat surprising, as these drugs are considered to be distributed

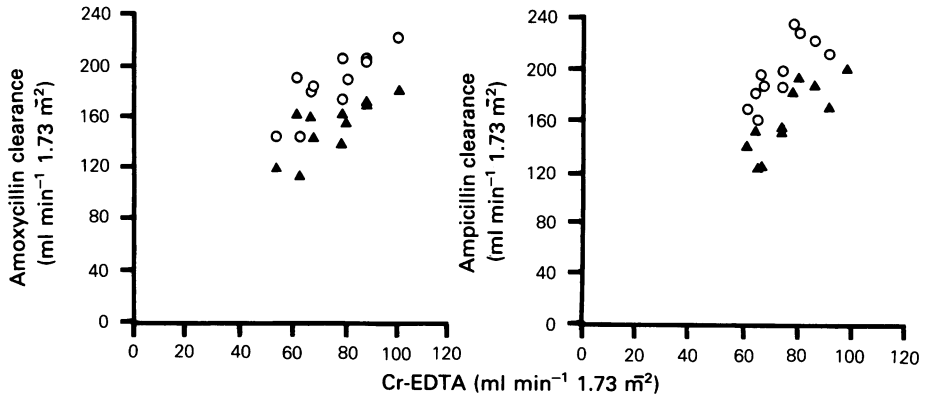

Figure 3 Renal function (Cr-EDTA) *vs* plasma clearance (○) and renal clearance (▲) of ampicillin and amoxycillin after intravenous infusion to two groups of 12 elderly volunteers. The results were calculated from the mean of duplicate administration in each subject.

Table 4 Intra- and inter-individual variation calculated as coefficients of variation, CV (%), for empirically and NONLIN estimated pharmacokinetic parameters. Duplicate administration of single 500 mg intravenous infusions to two groups of 12 elderly volunteers

	Empirically estimated				*Estimated by NONLIN*							
Drug	*AUC*	*Urinary recovery*	CL_p	CL_r	C_1	λ_1	C_2	λ_2	k_{12}	k_{21}	k_{10}	*AUC*[a]
Intra-individual variation												
Amoxycillin	3.04	2.44[b]	3.66	4.42	18.0	53.8	16.3	5.48	107.5	32.4	15.8	2.84
Ampicillin	5.70	4.57[b]	6.43	11.1	10.6	33.3	34.7	10.3	72.4	32.1	10.8	6.29
Inter-individual variation												
Amoxycillin	16.7	3.58[b]	14.4	13.5	11.7	31.4	29.4	8.67	51.8	25.6	18.0	17.5
Ampicillin	12.9	2.05[c]	11.9	14.8	17.1	26.1	27.3	19.1	43.3	29.2	19.9	12.2

[a] calculated as $\frac{C_1}{\lambda_1} + \frac{C_2}{\lambda_2}$, [b] $n = 11$, [c] $n = 10$

Table 5 Mean (s.d.) pharmacokinetic parameters from regression analysis using NONLIN on data after duplicate administration of single 500 mg intravenous infusions to two groups of 12 elderly volunteers

Drug	*Administration number*	C_1 ($mg\ l^{-1}$)	λ_1 (h^{-1})	C_2 ($mg\ l^{-1}$)	λ_2 (h^{-1})	k_{12} (h^{-1})	k_{21} (h^{-1})	k_{10} (h^{-1})	*AUC*[a] ($mg\ l^{-1}\ h$)
Amoxycillin	1	35.8	2.00	9.01	0.40	0.58	0.73	1.09	41.5
		(7.5)	(0.66)	(2.76)	(0.03)	(0.36)	(0.18)	(0.21)	(7.6)
	2	36.4	2.46	9.96	0.42	0.89	0.86	1.13	41.9
		(8.2)	(1.86)	(3.52)	(0.05)	(1.20)	(0.42)	(0.32)	(7.2)
Ampicillin	1	30.5	1.71	7.86	0.43	0.40	0.72	1.03	37.7
		(6.8)	(0.80)	(3.85)	(0.09)	(0.35)	(0.34)	(0.25)	(6.0)
	2	31.5	1.72	7.47	0.42	0.40	0.69	1.05	37.8
		(5.7)	(0.67)	(2.96)	(0.09)	(0.34)	(0.27)	(0.22)	(4.4)

[a] calculated as $\frac{C_1}{\lambda_1} + \frac{C_2}{\lambda_2}$

Table 6 Pharmacokinetic parameters after single intravenous infusions of amoxycillin and ampicillin. Crossover study in nine male volunteers, 21–38 years old with a mean (s.d.; range) creatinine clearance of 98 (12; 88–12) ml min^{-1} 1.73 m^{-2} (Sjövall *et al.*, 1985b).

Drug	*CL* (*ml* min^{-1}) (*1.73* m^{-2})	CL_R (*ml* min^{-1} *1.73* m^{-2})	$t_{½}$ (*h*)	V_{ss} (*1* kg^{-1})
Amoxycillin				
mean	185	157	1.67	0.21
s.d.	29.6	19.9	0.25	0.03
range	149–231	136–189	1.39–2.19	0.19–0.27
n	9	9	9	9
Ampicillin				
mean	210	167	1.68	0.21
s.d.	24.0	23.9	0.29	0.01
range	176–239	136–206	1.30–2.12	0.19–0.22
n	8	8	8	8

mainly to the extracellular fluid. A decrease in the volume of distribution with age is then expected, due to a decrease in the total body water with increasing age (Crooks *et al.*, 1976). On the other hand, V_{ss} of cefazolin has been reported to increase with age in rats (Tsuji *et al.*, 1985). V_β was higher than V_{ss} in this study, as well as in the study on younger subjects. In the case of drugs that are rapidly cleared from the central compartment with short half-lives, V_β has been reported to overestimate the apparent volume of distribution (Gibaldi & Perrier 1982).

The intra-individual variation was remarkably small for both drugs. The inter-individual variation was larger than the intra-individual variation but still relatively small.

The variation in the pharmacokinetic parameters estimated by non-linear regression (Table 4) was large as regards both within-subject and between-subject variation. This is probably a reflection of a major contribution from the estimation errors involved in fitting data to a biexponential compartment model (Westlake, 1971; Landaw & DiStefano, 1984). It may seem surprising that AUC estimated from these macroconstants had a small error, similar to that calculated by the trapezoidal method. But this effect is probably due to the fact that markedly different sets of macroconstants can be compatible with almost identical plasma concentration curves.

Since the variation in clearance and AUC was much greater between subjects than within subjects, resulting in an efficiency index (E) > 1, a crossover design is clearly preferable in parenteral studies of these drugs. The dominating reason for the rather wide range of E is differences in the selection of subjects included in a certain treatment group. The contribution to the variation in E from the number of subjects or the number of treatments to be compared was small in the ranges used in the calculations. The advantage of a crossover design is not of the same magnitude in studies with the sole purpose of estimating pharmacokinetic parameters in a compartmental model, probably due to the large error inherent in the estimates of the parameters.

In a small study, Triggs *et al.* (1980) found no difference in the volume of distribution for ampicillin between elderly patients with an infectious disease and young volunteers but a lower plasma clearance and a longer half-life in the elderly. Compared to young volunteers, a lower plasma clearance of ampicillin has also been reported in geriatric patients with cholelithiasis or undergoing surgery (Simon *et al.*, 1975).

The discrepancy between these results and ours may be due to differences in subject selection. Pharmacokinetic studies in the elderly are often carried out in patients in need of the tested drug. Alternatively, often elderly subjects, without any overt disease in the organs studied, are selected from hospital wards or nursing homes and may represent a chronically ill, debilitated population. When the purpose is to study the effect of age alone on drug kinetics, subjects without diseases that may interfere with this objective should be chosen. Studies on elderly, active and community-dwelling volunteers, as in this study, may therefore be more representative as to the effect of age *per se* on drug kinetics.

We are grateful to Erik Vinnars, M.D., for medical supervision of the subjects, and to Jan Carlqvist and Kerstin Lanbeck-Vallen for performing the drug assays. This study was supported by grants from the Swedish Medical Research Council (3902) and funds from the Karolinska Institute.

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(Received 20 May 1985, accepted 27 September 1985)