PHARMACOKINETICS OF FLUCLOXACILLIN AND CLOXACILLIN IN HEALTHY SUBJECTS AND PATIENTS ON CHRONIC INTERMITTENT HAEMODIALYSIS

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1 A pharmacokinetic study on flucloxacillin and cloxacillin was performed to investigate the factors contributing to the higher serum concentrations reported for the former after oral administration.

2 The results obtained in a study performed in a group of volunteers with flucloxacillin administered orally and by continuous infusion, were compared with the results of a similar investigation with cloxacillin. Patients on chronic intermittent haemodialysis received flucloxacillin orally and as a single i.v. injection. The results of this part of the study were compared with those of an earlier study on cloxacillin in haemodialysis patients. Serum and urine concentrations of flucloxacillin and cloxacillin were determined by bio-assay, and a one-compartment model was used for the calculations.

3 Higher serum concentrations reached after oral administration of flucloxacillin as compared with cloxacillin were based not only on better oral absorption (53.7% and 32.9%, respectively) but also on slower (renal and extra-renal) elimination ($T_{1/2}$: 46 and 32 min, respectively). A significant difference between the apparent volumes of distribution of flucloxacillin and cloxacillin, which could contribute to higher serum concentrations, could not be demonstrated. Considerable individual variation occurs in the rate and amount of oral absorption, especially in patients. The elimination rate of flucloxacillin in haemodialysis patients ($T_{1/2}$: 2 h 53 min) corresponds with the extra-renal elimination rate in healthy subjects. No influence of haemodialysis on the elimination rate constant of flucloxacillin was found; total plasma clearance was, however, slightly but significantly higher during dialysis.

Introduction

Cloxacillin is an isoxazoyl penicillin widely used for treatment of penicillin-resistant *Staphylococcus aureus* infections. For these bacteria the minimal inhibitory concentration of cloxacillin is virtually the same as that of other isoxazoyl penicillins, i.e. 0.25-0.5 µg/ml. A major disadvantage is, however, the rather poor and variable absorption after oral administration to healthy volunteers and patients on chronic intermittent haemodialysis (Nauta, Mattie & Goslings, 1973).

Flucloxacillin, a more recently introduced isoxazoyl penicillin, gives about two times higher serum concentrations than cloxacillin after oral administration and in this respect resembles dicloxacillin, another isoxazoyl penicillin (Sutherland, Croydon & Rolinson, 1970). Dicloxacillin has a higher serum binding than cloxacillin, which would at least partially explain higher serum concentrations, but flucloxacillin does not differ greatly from cloxacillin in this

respect (Sutherland *et al.*, 1970). Moreover, such binding would mean higher serum concentrations of unbound flucloxacillin than of dicloxacillin, which might be an advantage. Because serum concentrations of flucloxacillin are also higher than those of cloxacillin after intramuscular injection (Sutherland *et al.*, 1970), other factors besides better absorption could play a more or less important role in causing higher concentrations after oral administration.

Our study was undertaken to find out how differences in absorption, distribution, and elimination in healthy volunteers contribute to the difference between the serum concentrations of cloxacillin and flucloxacillin after oral administration. In addition, the same parameters were applied to investigate flucloxacillin in patients on chronic intermittent haemodialysis, for comparison with our earlier findings of cloxacillin in this type of patient (Nauta *et al.*, 1973).

Methods

Volunteers and patients

Seven healthy subjects and nine patients on chronic intermittent haemodialysis volunteered for the study after the nature of the experiment had been explained to them. The healthy volunteers (five men and two women ranging in age from 27 to 45 years) had a normal renal function.

The ages of the patients (six men and three women) ranged from 19 to 46 years. Two of them had undergone a bilateral nephrectomy and two a unilateral nephrectomy. Haemodialysis was performed twice weekly with an E.X.-01 coil haemodialyser (membrane: Cuprophane P.T. 150, 0.7 m²), at a dialysate flow rate of 500 ml/minute. The patients had a normal body temperature, normal liver functions, no gastro-intestinal disorders, and no signs of cardiac insufficiency or oedema. All of the experiments were done with the patients lying in bed.

Assay of flucloxacillin and cloxacillin

After collection, the samples were stored at -20°C; all assays were performed within a week. Flucloxacillin and cloxacillin concentrations in serum and urine were measured with the agar plate diffusion method according to Grove & Randall (1955), modified as a four-point bio-assay (Mattie, Goslings & Noach, 1973), with *Sarcina lutea* ATCC 9341 as test organism. The minimal concentration in serum that could be assessed accurately with this method was about 2.5 µg/ml.

Administration of flucloxacillin and cloxacillin

Healthy subjects (a) Flucloxacillin (the sodium salt in vials for parenteral administration, Floxapen®), or cloxacillin (the sodium salt in vials for parenteral administration, Orbenin®) was administered by continuous i.v. infusion (Perfusor, B. Braun Melsungen, W. Germany). Infusion was started after a priming dose of 1 g and was maintained at an infusion rate of 1.2 g/h for 3 hours. Serum samples were collected at 45 min intervals during the infusion and at 15 min intervals for 1.5 h after termination of the infusion. Urine was collected from the start until 8 h after discontinuation of the infusion. (b) Flucloxacillin (the sodium salt monohydrate in 250 mg gelatin capsules or as a suspension, Floxapen®) or cloxacillin (the sodium salt monohydrate in 250 mg gelatin capsules or suspension, Orbenin®) was administered orally, after overnight fasting, in three ways: 8 capsules of

250 mg, 80 ml of a 25 mg/ml suspension, or two capsules of 250 mg.

A light breakfast was given 1.5 h after administration of the drug. After both forms of the 2 g dosage, serum samples were collected every 30 min, for 4.5 h in the experiments with flucloxacillin and for 4 h in the experiments with cloxacillin. After these intervals, no measurable amount was present in the serum. Urine was collected during an 8-h period after administration of all three types of dosage.

Patients (a) All patients received flucloxacillin as a single intravenous injection of 1 g, between as well as during periods of haemodialysis. Serum samples were collected at hourly intervals for 6 hours. In some of the patients who had not undergone bilateral nephrectomy, urine was collected over a period of about 12 hours. (b) In seven of these patients flucloxacillin was administered orally during haemodialysis in a dose of 1 g in 4 capsules given at 17.00 h-18.00 h, 4 to 5 h after a hot lunch; these patients were given sandwiches and coffee 1.5 h after administration of the drug. Serum samples were collected at hourly intervals for 6 h in five patients, and for 8 h in two patients. In some of the patients urine was also collected.

Calculation of elimination in healthy subjects

The exponential elimination rate constants (k) of flucloxacillin and cloxacillin were calculated from the serum concentrations after termination of the continuous infusion, assuming a distribution according to a one-compartment model (Wagner, 1971). The corresponding half-life ($T_{1/2}$) was calculated as $T_{1/2} = 0.6932/k$.

From the intravenously administered dose ($D_{i.v.}$) and the total amount of flucloxacillin and cloxacillin excreted in the urine ($X_{i.v.}$), a factor

$$f_r = \frac{X_{i.v.}}{D_{i.v.}} \quad (\text{equation 1})$$

was calculated, representing renal excretion in proportion to the total dose and consequently renal elimination in proportion to total elimination.

For each individual subject an estimate was made of the renal elimination rate constant (k_r) and the extra-renal elimination rate constant (k_{er}):

$$k_r = f_r \times k \quad (\text{equation 2})$$

$$k_{er} = (1 - f_r) \times k \quad (\text{equation 3})$$

Calculation of elimination in patients

The elimination rate constant was calculated from

the exponentially declining serum concentration curve starting 2 h after a single intravenously administered dose, after an initial period of rapid distribution.

Calculation of absorption after oral administration

In the healthy volunteers the absorption after oral administration of flucloxacillin (2 g) or cloxacillin (2 g) could be calculated by two methods, i.e. from serum concentrations and from the amount of drug excreted in the urine. In the patients undergoing haemodialysis, absorption could only be calculated from serum concentrations (Nauta *et al.*, 1973).

The total absorption (A) was calculated from the excretion in the urine on the basis of the equation:

$$A = \frac{X_{\text{oral}}}{X_{\text{i.v.}}} \quad (\text{equation 4})$$

in which X_{oral} is the total amount of drug excreted in the urine after oral administration and $X_{\text{i.v.}}$ the amount excreted after intravenous administration, both during an 8-h period after administration (the amount of drug excreted after 8 h was insignificant).

The oral absorption from serum concentrations was calculated according to Wagner & Nelson (1964). With this method absorption is expressed as the absorbed dose (A_t) per ml of the apparent volume of distribution (V_d), as follows:

$$\frac{A_t}{V_d} = C_t + k \times \int_0^t C_t \times dt \quad (\text{equation 5})$$

in which:

A_t/V_d = the absorbed amount of drug per ml of V_d at time t ,

C_t = the serum concentration at time t ,

k = the elimination rate constant, calculated from the intravenous experiment,

$\int_0^t C_t \times dt$ = the area under the serum concentration curve from time 0 to time t .

To calculate the amount of drug absorbed at time t after oral administration (A_t), the values of A_t/V_d had to be multiplied by the apparent volume of distribution (V_d).

Calculation of the apparent volume of distribution

With a one-compartment model, the value of the apparent volume of distribution (V_d) could be

computed by applying equation 5 to serum concentrations during continuous infusion; division of the known infusion rate by the mean increment of the calculated values of A_t/V_d gives V_d (Nauta *et al.*, 1973).

In the haemodialysis patients, V_d was calculated by dividing the single intravenous dose by the virtual concentration at time 0, derived by extrapolating serum concentrations to time 0. From the values of V_d and k , k_r , and k_{er} , the total, renal, and extra-renal plasma clearance could be calculated respectively as:

$$V_d \times k, \quad V_d \times k_r, \quad \text{and} \quad V_d \times k_{er} \quad (\text{equation 6})$$

Statistical analysis

Data were subjected to analysis of variance or, where appropriate, covariance (Snedecor & Cochran, 1967).

Results

Elimination of flucloxacillin and cloxacillin in healthy subjects

The data on the elimination rate constants (k) of flucloxacillin and cloxacillin after continuous infusion are given in Table 1. Flucloxacillin has a significantly slower elimination than cloxacillin ($P < 0.001$), the mean value of k being 0.909 h^{-1} for flucloxacillin and 1.300 h^{-1} for cloxacillin, corresponding with a half-life ($T_{1/2}$) of 46 and 32 min, respectively. The rate of flucloxacillin elimination is therefore about 30% lower than that of cloxacillin. Both the renal and extra-renal elimination rate constants proved to be significantly lower for flucloxacillin ($P < 0.01$). There is no statistically significant difference between the fractions eliminated in the urine after intravenous administration ($P > 0.05$). The renal clearance of flucloxacillin amounted to 88.0 ml/min and that of cloxacillin to 101.9 ml/min (Table 2). This difference was significant ($P < 0.05$).

No correlation was found between the renal clearance of either flucloxacillin or cloxacillin and creatinine clearance (Table 2), but there was a strong correlation between renal clearance of flucloxacillin and that of cloxacillin. The extra-renal clearance was 34.9 and 51.3 ml/min, respectively, but this difference is not significant ($P > 0.05$).

Elimination of flucloxacillin in patients

The values obtained for the elimination rate constant of flucloxacillin after a single intravenous

Table 1 Total, renal, and extra-renal elimination rate constants (k , k_r , and k_{er}), fraction excreted in the urine (f_r), and apparent volume of distribution (V_d) of flucloxacillin and cloxacillin administered by continuous infusion to seven healthy subjects.

Subject	Body weight (kg)	Flucloxacillin					Cloxacillin				
		f_r	$\frac{k}{(h^{-1})}$	$\frac{k_r}{(h^{-1})}$	$\frac{k_{gr}}{(h^{-1})}$	$\frac{V_d}{(litres)}$	f_r	$\frac{k}{(h^{-1})}$	$\frac{k_r}{(h^{-1})}$	$\frac{k_{gr}}{(h^{-1})}$	$\frac{V_d}{(litres)}$
L	69	0.93	0.988	0.923	0.065	7.76	0.70	1.423	0.988	0.435	8.15
M	66	0.71	0.920	0.650	0.269	7.18	0.56	1.144	0.636	0.508	8.05
W	90.5	0.65	0.827	0.536	0.291	10.65	0.68	1.377	0.938	0.439	7.17
S	56	0.61	1.021	0.623	0.398	6.97	0.68	1.458	0.990	0.468	4.02
N	67	0.85	0.789	0.667	0.122	9.05	0.75	1.195	0.896	0.299	7.31
V	74	0.54	0.924	0.496	0.428	7.35	0.68	1.278	0.871	0.407	6.89
H	72	0.72	0.897	0.649	0.248	8.15	0.62	1.223	0.756	0.467	8.27
Mean		0.72	0.909	0.649	0.260	8.16	0.67	1.300	0.868	0.432	7.13
s.d.		0.14	0.082	0.137	0.133	1.30	0.06	0.121	0.130	0.067	1.47
$T_{1/2}$ (min)*			46					32			

* The mean value of the half-life ($T_{1/2}$) was calculated directly from the mean value of k .

Table 2 Creatinine clearance and total, renal, and extra-renal plasma clearance of flucloxacillin and cloxacillin administered by continuous infusion to seven healthy volunteers.

Subject	Creatinine clearance (ml/min)	Flucloxacillin clearance			Creatinine clearance (ml/min)	Cloxacillin clearance		
		Total (ml/min)	Renal (ml/min)	Extra-renal (ml/min)		Total (ml/min)	Renal (ml/min)	Extra-renal (ml/min)
L	160	128.7	119.6	9.1	154	192.9	134.5	58.4
M	125	110.1	77.8	32.3	141	153.0	85.9	68.4
W	165	147.3	95.9	51.5	191	164.9	112.3	52.6
S	126	117.4	72.0	46.5	160	97.8	66.3	31.5
N	126	119.2	101.1	18.1	99	146.2	109.7	36.6
V	100	112.7	61.3	52.7	141	147.0	99.9	47.1
H	165	122.3	88.3	34.0	104	168.2	104.8	64.8
Mean	138	122.5	88.0	34.9	141	152.8	101.9	51.3
s.d.	25	12.5	19.6	16.7	32	29.1	21.5	13.9

Table 3 Elimination rate constant (k), apparent volume of distribution (V_d), and plasma clearance of flucloxacillin in nine patients on chronic intermittent haemodialysis after administration of 1 g by a single i.v. injection.

Patient	Nephrectomy	Excretion in urine		Between periods of dialysis			During dialysis		
		(mg)	k (h^{-1})	V_d (litres)	Plasma clearance (ml/min)	k (h^{-1})	V_d (litres)	Plasma clearance (ml/min)	
B	+		0.217	8.85	32.0	0.199	11.98	39.7	
W	-		0.267	12.69	56.5	0.281	14.64	68.6	
F	-		0.219	10.37	37.9	0.252	11.23	47.2	
D	-		0.195	8.99	29.2	0.214	10.39	37.1	
R	+		0.208	11.65	40.4	0.258	11.25	48.4	
H	-	7.9	0.311	12.87	66.7	0.277	15.59	72.0	
T	-	26.7	0.262	12.63	55.6	0.221	15.34	56.5	
Br	-	11.8				0.229**	8.15**		
V	-	9.6				0.185**	12.57**		
Mean			0.240	11.15	45.5	0.243	12.92	52.8	
s.d.			0.040	1.75	14.2	0.032	2.19	13.5	
$T_{1/2}$ *			2 h 53 min			2 h 51 min			

* The mean value of the half-life ($T_{1/2}$) was calculated directly from the mean value of k .

** Not included in the mean values.

injection are given in Table 3. The mean value of k , i.e. $0.240 h^{-1}$, accords very well with the extra-renal elimination constant in healthy subjects ($0.260 h^{-1}$). No influence of haemodialysis on the elimination rate constant was detected, but the plasma clearance during haemodialysis (52.8 ml/min) was slightly but significantly greater ($P < 0.005$) than that between periods of haemodialysis (45.5 ml/min). Only a very small amount of the administered dose was excreted in the urine of these patients (Table 3).

Volume of distribution (V_d)

Comparison of the mean values of V_d for flucloxacillin and cloxacillin in healthy subjects calculated for constant infusion (Table 1) shows a higher value for flucloxacillin, but the difference is not significant ($P > 0.10$).

Absorption after oral administration in healthy subjects

The values of the absorbed dose originating from capsules, calculated on the basis of serum concentrations, are shown in Table 4. The mean value of 1074 mg for flucloxacillin is significantly higher than the 649 mg found for cloxacillin ($P < 0.001$). Both penicillins showed rapid absorption with large individual variations in the amount absorbed (Figure 1). Table 5 and Figure 2 show the absorption from the 2 g suspension. Here again, flucloxacillin was absorbed better than cloxacillin. On the other hand, absorption from the suspension was slightly lower than from capsules, but this difference is not significant at the 5% level. The smallest individual variation in absorption was observed for the flucloxacillin suspension (variation coefficient 12%).

Comparison of the amounts absorbed, as calculated from excretion in the urine (Tables 4 and 5), suggests that the difference between flucloxacillin and cloxacillin is not significant. Analysis of covariance of absorption calculated from urinary excretion and from serum concentrations was performed for the subjects for whom we had complete data on both forms of dosage. Subject V was excluded; the reason for this exclusion will be discussed below. In these five subjects the mean absorbed amount calculated from urinary excretion is higher for cloxacillin than for flucloxacillin after correction for differences in absorption calculated from serum concentrations. According to the analysis of covariance, this difference is highly significant

Figure 1 Cumulative absorption in seven healthy volunteers after oral administration of 2 g (capsules) of cloxacillin (a) and flucloxacillin (b).

Table 4 Absorption of flucloxacillin and cloxacillin in seven healthy subjects after oral administration of 2 g (capsules).

Subject	Flucloxacillin absorption (mg)		Cloxacillin absorption (mg)	
	Calculated on the basis of:		Calculated on the basis of:	
	Serum concentration	Urinary excretion	Serum concentration	Urinary excretion
L	705	735	727	1044
M	1117	1237	653	959
W	1310	1420	700	1216
S	956	1104	618	1184
N	1295	1132	933	—
V	628	1685	577	947
H	1510	1268	394	842
Mean	1074	1226	657	1032
s.d.	329	293	163	146
% of dose	53.7	61.3	32.9	51.6
s.d.	16.5	14.7	8.2	7.3

Figure 2 Cumulative absorption in seven healthy volunteers after oral administration of 2 g (suspension) of cloxacillin (a) and flucloxacillin (b).

Table 5 Absorption of flucloxacillin and cloxacillin in seven healthy subjects after oral administration of 2 g (suspension).

Subject	Flucloxacillin absorption (mg)		Cloxacillin absorption (mg)	
	Calculated on the basis of:		Calculated on the basis of:	
	Serum concentration	Urinary excretion	Serum concentration	Urinary excretion
L	906	1088	636	1063
M	868	1014	592	1021
W	734	1046	677	990
S	1021	1251	478	927
N	765	791	742	955
V	761	1412	521	905
H	898	1014	442	691
Mean	851	1088	584	936
s.d.	103	197	109	121
% of dose	42.5	54.4	29.2	46.8
s.d.	5.2	9.8	5.5	6.1

($P < 0.001$) for capsules but is not significant for the suspension ($P = 0.10$).

Because we could not determine the serum concentrations of flucloxacillin and cloxacillin with sufficient accuracy after oral administration of 0.5 g, we compared the excretion in the urine in the first 8 h after administration with that of the forms of 2 g dosage. The lower dose gave a proportionally lower urinary excretion of flucloxacillin and a slightly but significantly ($P < 0.05$) more than proportional excretion of cloxacillin (Table 6).

Absorption after oral administration in patients

For practical reasons, absorption was investigated during haemodialysis. The mean value

for the absorption of a dose of 1 g is 410 mg (Table 7). The course of the absorption is shown in Figure 3. It is evident that the rate of absorption was much slower than in the healthy volunteers and also that the absorption was very poor in three of the patients. Therefore, the absorption was followed for an additional 2 h in two of the patients, but they proved to belong to the better absorbers.

Side effects

One healthy volunteer developed phlebitis after the infusion of flucloxacillin, and some of the other volunteers developed mild diarrhoea after oral or i.v. administration of both penicillins.

Table 6 Urinary excretion of flucloxacillin and cloxacillin in seven healthy subjects after oral administration as indicated.

Subject	Urinary excretion of flucloxacillin			Urinary excretion of cloxacillin		
	2 g capsules (mg)	2 g suspension (mg)	0.5 g capsules (mg)	2 g capsules (mg)	2 g suspension (mg)	0.5 g capsules (mg)
L	687	1023	189	726	744	239
M	874	720	109	533	572	135
W	920	680	261	829	673	202
S	672	763	206	804	630	200
N	956	673	210		716	203
V	905	748	209	646	615	201
H	918	730	232	522	428	232
Mean	847	762	202	677	626	202
s.d.	117	120	47	132	105	34
% of dose	42.4	38.5	40.5	33.9	31.3	40.4

Table 7 Absorption of flucloxacillin in seven patients after oral administration of 1 g (capsules) during haemodialysis.

Patients	Amount absorbed (mg)	Time absorption followed after dose (h)	Excretion in urine (mg)
R	612	6	0
T	196	6	
D	217	6	
H	147	6	
F	628	6	5.3
Br	499	8	
V	571	8	
Mean	410		4
s.d.	214

Figure 3 Cumulative absorption after oral administration of 1 g (capsules) of flucloxacillin in seven patients on chronic intermittent haemodialysis during dialysis.

Discussion

The results of the present pharmacokinetic study on flucloxacillin and cloxacillin show that the higher serum concentrations after oral administration of flucloxacillin are due not only to better absorption but also to slower renal and extra-renal elimination, and that the distribution in the body does not play a role in these higher serum concentrations.

Four publications on flucloxacillin have appeared (Sutherland *et al.*, 1970; Bodey, Vallejos & Stewart, 1972; Simon, Malerczyk & Hodgson, 1973; Oe, Simonian & Verhoef, 1973). It is of interest to compare our results with their findings.

With regard to the absorption, our experiments confirm what the literature suggests, i.e. that flucloxacillin is absorbed about 55% better than cloxacillin after oral administration. Moreover, in all of our subjects flucloxacillin was absorbed at least as well as cloxacillin. When absorption is better one might expect less individual variation in the amount absorbed, but this was not the case.

The mean absorption of cloxacillin calculated from serum concentrations (33%) corresponds well with the value of 32% obtained in our previous study in a different group of volunteers (Nauta *et al.*, 1973). The absorption of cloxacillin calculated from the amount excreted in the urine is also similar (52 and 48%, respectively). Our value for the absorption of flucloxacillin calculated from serum concentrations is in good accordance with the 50% found by Simon *et al.* (1973).

Apparently, a discrepancy exists between the absorption calculated from urinary excretion and the absorption calculated with serum concentrations. For both methods of calculation, assumptions have to be made. One of these is that the determination of concentrations in serum and urine is specific for the unaltered drug. It is, however, quite possible that metabolites occur which are biologically active in our bio-assay. Moreover, the metabolic pattern is often different from the intravenous and oral ways of administration, because of the greater role played by the liver in elimination after oral administration. There are some indications that in our study we measured such metabolites occurring in the urine but not present in detectable concentrations in the blood. The first of these indications is that the discrepancy is not the same for cloxacillin as for flucloxacillin, and this cannot be easily explained in any other way. The other indication is that one of the subjects (V) showed a very large discrepancy between the results of the two methods of calculation for both forms of oral dosage of flucloxacillin; whereas the results for cloxacillin are consistent with those obtained in the other subjects. This would be easy to explain on the basis of the occurrence of a biologically active metabolite in a subject with a divergence in flucloxacillin metabolism. The data published so far on metabolites of both drugs (Rolinson & Batchelor, 1962; Cole, Kenig & Hewitt, 1973; Hellström, Rosén & Swahn, 1974), do not support our hypothesis, but in our view these data are not entirely conclusive.

Administration in suspension did not lead to better absorption, but since it produced less individual variation, this mode of administration is in a certain sense more reliable. It has also been found for dicloxacillin that administration in the form of a suspension does not enhance absorption (Doluisio, LaPiana, Wilkinson & Dittert, 1969).

In all of our haemodialysis patients the absorption of flucloxacillin given in capsule form was slow (Figure 2); since it seems to continue even 6 h after administration. Moreover, in three of the seven patients the total amount absorbed in 6 h was very low. This was a rather disappointing finding, because in our previous study on

cloxacillin in dialysis patients we found a very rapid absorption which was completed in 2 to 3 h (Nauta *et al.*, 1973). (In one patient the absorption of cloxacillin was also low, i.e. 16%). Besides the difference in drugs, there are other differences between the two groups of patients that offer more probable explanations for poor absorption. Cloxacillin was administered shortly after haemodialysis, after an overnight fast, and 1.5 h before a light breakfast, whereas flucloxacillin was administered (for practical reasons) between 17.00 h and 18.00 h which was 4-5 h after a hot lunch and 1.5 h before a meal with sandwiches and coffee. Moreover, most of the patients were asleep during the latter part of the experiment. It is possible that, for instance, gastric motility was strongly influenced by these differences (Prescott, 1974). It is well known from the literature that the absorption of isoxazolyl penicillins is somewhat slower and smaller shortly after a meal (Knudsen, Brown & Rolinson, 1962; Sutherland *et al.*, 1970; Bodey *et al.*, 1972; Simon *et al.*, 1973; Doluisio *et al.*, 1969; Kislak, Eickhoff & Finland, 1965; Sidell, Bulger, Brodie & Kirby, 1964). The healthy volunteers, who received the flucloxacillin and cloxacillin under the same conditions but before breakfast, showed a rapid absorption which was completed in about 2 hours.

Exact comparison of our calculations of the absorption of flucloxacillin with the data of other authors (Sutherland *et al.*, 1970; Bodey *et al.*, 1972) is not possible, because they did not relate oral to intravenous administration. The data on the excretion of flucloxacillin in the urine can, however, be compared. Sutherland *et al.* (1970) recovered 50-55% of an oral dose in the urine, and Bodey *et al.* (1972) 40%. Our data (Table 6) corresponds best with those of Bodey *et al.* (1972). For flucloxacillin the percentage excreted in the urine appears to be mainly independent of the dose. The same has been found for dicloxacillin (Doluisio *et al.*, 1969).

There is a distinct difference in the elimination rate: flucloxacillin was eliminated more slowly than cloxacillin. Therefore, this factor too must contribute to the higher serum concentrations. Our calculated mean half-life of 46 min for flucloxacillin is in close agreement with the value of 48 min found by Simon *et al.* (1973). This will not lead to much higher peak concentrations but will contribute to higher concentrations thereafter. In our opinion, this factor plays at least as important a role as better absorption in the realization of higher serum concentrations. The elimination rate found for cloxacillin in healthy subjects corresponds well with the findings in the earlier study (Nauta *et al.*, 1973).

Our value for the total plasma clearance of cloxacillin (152.8 ml/min) differs considerably from the value calculated by Modr & Dvoracek (1969), possibly because they overestimated the apparent volume of distribution, having calculated this value in a one-compartment model from data obtained in an experiment with a single i.v. injection (Nauta *et al.*, 1973). They computed a renal clearance of 287.7 ml/min and an extra-renal clearance of 131.5 ml/minute. Rosenblatt, Kind, Brodie & Kirby (1968) found a total plasma clearance of 162.2 ml/min per 1.72 m^2 for cloxacillin administered by continuous infusion. This value is not much higher than our own value. The lack of correlation in healthy subjects between the renal clearance values of flucloxacillin and cloxacillin on the one hand and that of creatinine on the other is not very surprising because, compared with tubular excretion, glomerular filtration apparently plays only a minor role in renal elimination.

It is striking that the total elimination rate of flucloxacillin in haemodialysis patients corresponds with the extra-renal elimination rate in healthy subjects. We found the same phenomenon for cloxacillin (Nauta *et al.*, 1973). The value of the half-life (1 h 50 min) corresponds well with 1 h and 15 min found by Oe *et al.* (1973). Haemodialysis did not influence the elimination rate. The elimination rate of the other isoxazolyl penicillins is not affected to a measurable degree by haemodialysis either (McCloskey & Hayes, 1967; Williams, Lawson, Brook, Ory & Morgan, 1967; Bulger, Lindholm, Murray & Kirby, 1964; Oe *et al.*, 1973; Nauta *et al.*, 1973). However, the somewhat higher plasma clearance during haemodialysis indicates a clearance by the artificial kidney. With an *in vitro* model of the artificial kidney, Verhoef, Oe & Simonian (1973) also found some clearance of flucloxacillin (at a rate of 6.9 ml/min).

With respect to the apparent volume of distribution of flucloxacillin, the mean value is somewhat greater than that of cloxacillin, but the difference is not statistically significant. In any case, this difference does not contribute to the higher serum concentrations; quite the contrary. It does, however, seem to contribute to the slower elimination, since the plasma clearance of both compounds is essentially the same.

In haemodialysis patients we found a relative volume of distribution for flucloxacillin amounting to 17.8% of the body weight; in our previous study in another group of patients we computed a value of 25.5% for cloxacillin (Nauta *et al.*, 1973). It is striking that a smaller volume of distribution is calculated for flucloxacillin between

than during periods of haemodialysis. This can be explained by the overhydration occurring in most haemodialysis patients.

In conclusion, higher serum concentrations of flucloxacillin than of cloxacillin are due to both a 30% slower elimination and a 55% better absorption after oral administration. Both factors offer a distinct advantage. The main disadvantage of cloxacillin, i.e. its large individual variation in absorption, also applies for flucloxacillin. Therefore, we do not feel that flucloxacillin is

essentially a more reliable drug than cloxacillin.

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