Comparative pharmacodynamics and clinical pharmacokinetics of phenoxymethylpenicillin and pheneticillin

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- 1 In this study the antimicrobial effects of phenoxymethylpenicillin (PM) and pheneticillin (PE) *in vitro* and in an experimental animal infection model were compared as well as the pharmacokinetic properties of both drugs in patients.
- 2 For the inhibitory effect of PM on short-term (3 h) growth of *S. aureus in vitro*, this drug was 2.13 times more potent than PE.
- 3 The protein binding of both drugs was similar (78–80%).
- 4 The potency ratio of PM to PE against *S. aureus* in an experimental mouse-thigh infection was only 1.25 to 1. This is explained by the difference in the AUC after subcutaneous administration of PM (0.47 mg l⁻¹ h) and PE (0.92 mg l⁻¹ h).
- 5 The plasma clearance after intravenous administration of PM was 476.4 ml/min and that of PE was 295.1 ml/min; the plasma clearance of both drugs was strongly correlated with the creatinine clearance.
- 6 The volume of distribution in the steady state of PM was 35.4 l and that of PE 22.5 l.
- 7 In 10 patients, the absorption after oral administration of PM as the acid was 48% and that of the potassium salt of PE was 86% of the dose.
- 8 From the present results it can be concluded that a difference in effectiveness of different formulations of PM and PE would depend entirely on differences in absorption.

Keywords phenoxymethylpenicillin pheneticillin short-term growth curve experimental infection pharmacokinetics

Introduction

Phenoxymethylpenicillin (penicillin V; PM) and phenoxymethylpenicillin (pheneticillin; PE) are two oral penicillins used for the same indications. Preference for either drug seems to be based on quantitative differences in pharmacokinetic or pharmacodynamic properties. However, direct comparison of all these properties combined has never been reported. As long as these drugs are used only for the treatment of uncomplicated respiratory tract infections, this may not be too important. But for the long-term treatment of complicated infections, such as follow-up treatment of osteomyelitis or endocarditis, a proper

quantitative assessment of the relative efficacy of these drugs becomes necessary. The present study represents an attempt to do this by comparing the pharmacokinetic properties with the antimicrobial effect *in vitro* and in an experimental infection.

The effect *in vitro* was assessed on the basis of short-term growth curves. The effect *in vivo* was assessed in an experimental infection in mice, irradiated to exclude the interference of granulocytes. In patients being treated with an oral penicillin, the absorption, distribution, and clearance of the drugs were studied.

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Methods

Antibiotics

Standard solutions of phenoxymethylpenicillin (PM) (Gist-brocades, Delft) and pheneticillin (PE), (Beecham Pharmaceuticals International Division, England) were used in all *in vitro* and *in vivo* experiments.

PM as free acid was provided by Gist-brocades, Delft, The Netherlands and PE, as potassium salt by Beecham-Pharma, Amstelveen, The Netherlands. Solutions for intravenous administration were prepared in the hospital pharmacy immediately before administration. PM was dissolved in saline under addition of 0.1 N NaOH to a pH of 7.5. PE dissolved rapidly in saline. Both solutions contained 250 mg of the drug in 50 ml. They were filtered under aseptic conditions through a 0.2 µm pore filter.

For oral administration, capsules containing 250 mg PM as the free acid were used (Acipen®; Gist-brocades, Delft) and coated tablets of 250 mg PE as the potassium salt (Broxil®; Beecham Pharmaceuticals International Division, England).

Micro-organisms

All *in vitro* and *in vivo* experiments were performed with a *Staphylococcus aureus* strain, type 421.

Protein binding assay

Plasma protein binding was determined in a Dianorm® dialysis apparatus (Diachema AG, Zürich, Switzerland). This apparatus has two chambers separated by a membrane and is available in two types. The chambers of the small type have a volume of 0.22 ml and a membrane surface area of 2 cm²; the large chambers hold 2.4 ml and the membrane surface measures 4.52 cm².

For murine plasma the small type was used, with 0.20 ml plasma in one chamber and 0.20 ml saline with various concentrations of antibiotic in the other. After equilibration under rotation at 37°C for 4 h, the concentrations in both chambers were measured by an agar diffusion method, modified to a four-point bio-assay by Mattie *et al.* (1973), against standards in murine plasma or, where appropriate, in saline, with *Bacillus stearothermophilus* var. *calidolactis* as test organism.

For human plasma the larger type was used, with 0.7 ml plasma in one chamber and 0.7 ml saline containing the antibiotic in the other. The procedure was similar to that described for

murine plasma. The binding to bovine serum albumin (BSA) was determined as described for human plasma but with 4% BSA in saline instead of plasma.

Minimal inhibitory concentrations (MIC)

Twofold serial dilutions of PM and PE were prepared in nutrient broth in concentrations ranging from 0.004 to 0.063 mg/l, to which 50 µl of an 18 h culture of *Staphylococcus aureus* diluted to 10⁶ CFU/ml was added. After incubation for 18 h at 37°C, the lowest concentration giving no visible growth was indicated as the MIC.

Growth curve of *S. aureus*

Growth-curve experiments were performed as described elsewhere in detail (Mattie & van der Voet, 1981). A thousand fold-diluted 18 h culture of *S. aureus* was incubated for 1 h in 50 ml brain heart infusion (BHI) broth in 100 ml Erlenmeyer flasks at 37°C. Antibiotics were added to the culture, which contained 10⁶ *S. aureus* per ml. Concentrations of PM ranged from 0.01 to 0.16 mg/l and concentrations of PE from 0.04 to 0.32 mg/l. Samples were taken at 15 min intervals for up to 2 h after addition of the drugs and CFU were counted in appropriate dilutions on Difco sensitivity agar (DST) along with CFU of a control (without drug). The same procedure was performed in broth with 4% BSA.

Mathematical analysis of growth curves

The effect of the antibacterial drugs at various time-points during exposure was expressed as a log ratio, which is the difference between the logarithms of the number of CFU in the absence and presence of the drug. Because the exponential growth-rate of *S. aureus* in the presence of antimicrobial drugs is not constant but time-dependent, the plot of the values of the log ratio at various time-points shows a curved line. In most cases these values can be fitted to a curved line according to the following equation:

$$\text{log ratio} = i \times (t + e^{-t} - 1) \quad (1)$$

At zero time this equation takes the value zero, but when time increases, e^{-t} approaches zero and equation (1) approaches a straight line with slope i . The value i therefore characterizes the effect of the drug over the whole period of exposure of the micro-organism to a given concentration of the drug (Mattie & Vaishnav, 1983). The effect of the addition of 4% BSA to the culture medium on the potency of both drugs was calculated in the same way.

Experimental infection

Use was made of specific pathogen free (SPF) male Swiss mice, weighing 20–25 g, provided by the Central Institute for the Breeding of Laboratory Animals, TNO, Zeist, The Netherlands. The animals were made granulocytopenic by total body irradiation with 6 Gray (dose rate 4 Gy/min), in a 5 MV linear accelerator (Philips SL 75/5). Experiments were performed on day 5 following irradiation, when the number of granulocytes is minimal (van der Voet *et al.*, 1984).

The mice were inoculated in a thigh muscle with 0.1 ml of a 1:40 dilution of an 18 h culture of *S. aureus* containing 2×10^6 CFU. Two hours after the inoculation, PM or PE was administered subcutaneously; three dose levels were used for each antibiotic, randomized to a 6×6 Latin square. Four hours after inoculation the animals were killed by cervical dislocation and the thigh muscle was dissected from the femur and homogenized in a Potter Elvehjem tube with a teflon pestle at 0°C. The homogenate was plated on DST agar, and CFU counting took place after 18 h of incubation at 37°C. This procedure has been described elsewhere in detail (Kunst & Mattie 1978).

Determination of antibiotic levels in mouse blood

Antibiotics were administered subcutaneously in a dosage of 2 µg/g. Tail blood was collected at 15, 30, 45, 60, 90, and 120 min. Erythrocytes were lysed with distilled water to a dilution of 1:80. Concentrations were determined by an agar diffusion method with *B. stearothermophilus* var. *calidolactis* and a dilution in mouse blood as standard. The area under the blood concentration curve was calculated according to the trapezoid method. Blood concentrations at 30, 45, 60, and 90 min were used to calculate the elimination rate constant and the half-life in blood.

Patients

Ten hospitalized patients, for whom an oral penicillin was prescribed for treatment of a bacterial infection, entered the study. Most of them been treated initially with intravenous benzylpenicillin and were about to continue with an oral preparation. They received verbal and written information about the aims and the nature of the investigation before giving their free consent, according to the Declaration of Helsinki.

Design of the clinical pharmacokinetic experiments

On 4 consecutive days the patients received either an oral or an intravenous dose of either PM or PE, the sequence being determined according to a Latin square. Treatment with other (non-antibiotic) drugs was continued. The patients had not received antibiotics for at least 8 h before administration, and had fasted overnight before receiving the oral dose. During and after administration of the antibiotics the patients were in the supine position.

Intravenous administration of phenoxymethylpenicillin and pheneticillin

PM or PE (250 mg in 50 ml saline) were administered intravenously by continuous infusion over 10 min with a perfusor (B. Braun Melsungen, W. Germany). Plasma samples were collected before the infusion was started and at 0, 10, 20, 30, 60, 120, 180, and 240 min after the end of the infusion.

Oral administration

PM and PE (500 mg) were administered orally after overnight fasting. A light breakfast was given 1 h after administration of the drug. Plasma samples were collected before, and 0.5, 1, 1.5, 2, 3, 4, and 6 h after administration of the drug.

Assay of phenoxymethylpenicillin (PM) and pheneticillin (PE)

Plasma samples were stored at 5°C until assay within 24 h. PM and PE levels were measured by the agar plate diffusion method described above. The lowest concentration in plasma that could be assessed accurately with this method was 0.3 mg/l.

Calculation of pharmacokinetic parameters

The pharmacokinetic parameters (Rowland & Tucker, 1982) of the penicillins were calculated according to a two-compartment open model (Wagner, 1971). The drug concentration-time data starting at the end of infusion were fitted using the non-linear least-squares computer program NONLIN (Metzler *et al.* 1974), according to the following equation:

$$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} \quad (2)$$

With the parameters C_1 , C_2 , λ_1 , λ_2 the elimination-rate constant (k_{10}) was calculated as follows:

$$k_{10} = \frac{\lambda_1 \times C_1 \times (1 - e^{-\lambda_2 t'}) + \lambda_2 \times C_2 \times (1 - e^{-\lambda_1 t'})}{C_1 \times (1 - e^{-\lambda_2 t'}) + C_2 \times (1 - e^{-\lambda_1 t'})} \quad (3)$$

in which t' is the duration of the infusion. The rate constants of distribution from the central to the peripheral compartment (k_{12}) and *vice versa* (k_{21}) were calculated as follows:

$$k_{21} = \frac{\lambda_1 \times \lambda_2}{k_{10}}, \text{ and} \quad (4)$$

$$k_{12} = \lambda_1 + \lambda_2 - k_{10} - k_{21}. \quad (5)$$

The volume of distribution of the central compartment was calculated as follows:

$$V = \frac{R_o}{C_1 \times k_{10}} \times \frac{k_{10} - \lambda_2}{\lambda_1 - \lambda_2} \times (1 - e^{-\lambda_1 t'}), \quad (6)$$

in which R_o is the infusion rate.

Finally, the plasma clearance (CL) and the volume of distribution were calculated by the area method as:

$$CL = k_{10} \times V \quad (7)$$

$$V_{\text{area}} = \frac{CL}{\lambda_2} \quad (8)$$

With the above parameters the amount absorbed (A_{abs}) at each sample time-point after oral administration could be calculated from the plasma concentrations according to Loo & Riegelman (1968). The calculated values of A_{abs} were subtracted from the apparent maximum value of A_{abs} ($A_{\text{abs, max}}$) and plotted logarithmically against time. The absorption-rate constant (k_{01}) could then be calculated according to the following equation:

$$\ln(A_{\text{abs, max}} - A_{\text{abs}}) = \ln A_{\text{abs, max}} - k_{01} t \quad (9)$$

by the least squares method. The AUC after oral administration (AUC_{po}) was calculated by the trapezoid method and extrapolated to $t = \infty$ by adding C_{tn}/β in which t_n was the last time point at which a plasma concentration could be measured. The fraction of the absorbed dose (F) was calculated (Dost, 1970) as:

$$F = \frac{CL \times AUC_{\text{po}}}{D_{\text{po}}} \quad (10)$$

Estimation of creatinine clearance

For comparison of the plasma clearance of the two drugs in relation to the creatinine clearance, the latter was estimated as described by Siersbaek-Nielsen *et al.* (1971). Serum creatinine concentrations were determined with a Technicon-SMAC® automated analyser (Technicon Instruments Corp. Tarrytown, New York, USA

(Chaon *et al.*, 1961). For serum concentrations of creatinine in $\mu\text{mol/l}$ the creatinine clearance in ml/min can be calculated as follows:

for male patients:

$$CL_{\text{cr}} = \frac{88.5 \times [\text{body weight}] \times (1 - 3.39 \times 10^{-4} \times C_{\text{cr}}) \times (29.3 - 0.203 \times [\text{age}])}{C_{\text{cr}}} \quad (11a)$$

for female patients:

$$CL_{\text{cr}} = \frac{88.5 \times [\text{body weight}] \times (1 - 3.39 \times 10^{-4} \times C_{\text{cr}}) \times (25.3 - 0.175 \times [\text{age}])}{C_{\text{cr}}} \quad (11b)$$

where the body weight is in kg, the age of the patient in years, and C_{cr} represents the serum creatinine concentration in $\mu\text{mol/l}$.

Results

Activity of phenoxymethylpenicillin and pheneticillin against *S. aureus* in vitro

The MIC against *S. aureus* of PE in broth was 0.031 mg/l and the MIC of PM was 0.016 mg/l. In broth the number of CFU increased from 1.91×10^6 to 1.36×10^8 in 3 h, which corresponds with a generation time of 29 min. Therefore, a value of the inhibition coefficient, (representing the slope of the log ratio curve) amounting to more than 0.62 implies killing. Values of i are shown in Figure 1. The four slopes of the two drugs in broth as well as in broth with 4% BSA, are parallel. According to the standard bio-assay procedure, PM was 2.13 times more potent than PE, and BSA reduced the potency of both drugs to the same degree, i.e., by 74%. This corresponds well with the binding of both drugs to BSA, which ranged between 65% and 70% at various concentrations.

Experimental infections

The outgrowth of *S. aureus* in thigh muscle in the absence of antibiotics was about five-fold in 4 h, rising from 7.5×10^6 to 3.5×10^7 CFU/ml. The CFU counts after administration of PM and PE are given in Table 1. The potency ratio of PM to PE in the mouse thigh model was 1.25 (variation coefficient 21%). This indicates that PM was slightly more potent than PE.

In order to calculate the potency ratio for concentrations *in vivo* the AUC of the free drug was used as a parameter of the total exposure of the bacteria to the antibiotic. Plasma concentrations after subcutaneous administration of 2 $\mu\text{g/g}$ were measured in two mice for each antibiotic.

Figure 1 Effect of phenoxymethylpenicillin (open symbols) and pheneticillin (closed symbols) on the growth of *S. aureus* *in vitro*. (For calculation of the inhibition coefficient (*i*), see under **Methods**). Circles represent growth inhibition in broth and squares that in 4% bovine serum albumin.

Table 1 Experimental infection in irradiated granulocytopenic mice. CFU counts of *Staphylococcus aureus* in the thigh muscle 4 h after subcutaneous administration of various doses of phenoxymethylpenicillin and pheneticillin

Antibiotic	Dose ($\mu\text{g/g}$)	CFU (counts/ml)
Controls*		3.53×10^7
Phenoxymethylpenicillin**	0.063	2.52×10^7
	0.13	1.87×10^7
	0.25	1.34×10^7
Pheneticillin**	0.063	2.94×10^7
	0.13	1.99×10^7
	0.25	1.46×10^7

**n* = 11 mice

***n* = 6 mice per dose level

The mean AUC was $0.92 \text{ mg l}^{-1} \text{ h}$ for PE and $0.47 \text{ mg l}^{-1} \text{ h}$ for PM, the plasma half-life of PE was 85 min and that of PM was 61 min. The protein binding of PE to murine plasma amounted to 54% and that of PM to 58%. From these data and the potency ratio of 1.25 for dosages a potency ratio of 2.68 in favour of PM can be calculated for AUCs. This is slightly higher than the potency ratio of 2.13 found *in vitro*.

Clinical pharmacokinetic study

Patients The diagnosis and the physical condition of the patients are given in Table 2.

Pharmacokinetic parameters The calculated pharmacokinetic parameters after intravenous administration of PM and PE are given in Tables 3 and 4. The values of the AUC_{iv} are shown in Figure 2. The mean AUC_{iv} of PE was $19.9 \text{ mg l}^{-1} \text{ h}$, nearly twice that of PM ($12.1 \text{ mg l}^{-1} \text{ h}$). At a concentration range from 10 to 15 mg/l , PE binding to human plasma amounted to 78% and that of PM to 80%. The mean plasma clearance of PM (476 ml/min) was also about twice that of PE (295 ml/min). The individual values of the plasma clearance are shown in relation to the creatinine clearance in Figure 3. The plasma clearance of the drugs differed significantly ($P < 0.001$). Because of the difficulty involved in the collection of urine, encountered in investigations done in hospital patients (urinary incontinence, inability to void prior to the start of the study), precluded the measurement of the renal excretion of both drugs. However, we found a significant correlation between plasma clearance and creatinine clearance ($P < 0.001$). The mean volume of distribution of PE in the

Table 2 Relevant clinical data on the patients in the study

Number	Patients			Diagnosis	Micro-organism	Clinical condition	Remarks
	Sex	Age (years)	Body weight (kg)				
1	F	61	61	Sternum osteomyelitis	<i>S. aureus</i>	good	bed rest
2	M	50	78	Pneumonia	<i>S. pneumoniae</i>	poor	recently on artificial ventilation; underlying condition rheumatoid arthritis and Felty's syndrome
3	M	56	71	Prostatitis	<i>S. haemolyticus</i>	good	recent renal transplantation
4	M	67	66	Bronchopneumonia	<i>S. pneumoniae</i>	good	
5	M	35	53	Erysipelas		good	recent renal transplantation; 'pure red cell aplasia'
6	M	72	77	Aspiration pneumonia		poor	bed rest poorly controlled diabetes mellitus; diarrhoea recent uroseptic shock
7	M	69	65	Pneumonia	<i>S. pneumoniae</i>	good	
8	F	52	70	Septic gonarthritits	<i>S. aureus</i>	good	
9	M	53	70	Infected osteosynthesis material hip	<i>S. epidermidis</i> <i>peptostreptococcus</i>	good	bed rest
10	M	64	80	Pneumonia	<i>S. pneumoniae</i>	poor	bed rest serious mental depression

Figure 2 Area under the plasma concentration curve after intravenous administration of phenoxymethylpenicillin (PM, open symbols) and pheneticillin (PE, closed symbols). The lines connect the values of the AUC_{iv} of the two drugs in individual patients, whose numbers correspond with the patient numbers in Table 2.

steady state (22.5 l) was smaller than that of PM (35.4 l). The mean plasma half-life of both drugs was very similar: 63 min for PE and 56 min for PM.

The individual values for the total amount of drug absorbed (F) after oral administration of 500 mg are shown in Tables 3 and 4. The mean F value was 401.2 mg for PE and 240.5 mg for PM. The absorption curves for both drugs in individual patients, calculated according to Loo & Riegelman (1968), are shown in Figure 4. Inspection of the values of $\ln(A_{abs, max} - A_{abs})$ plotted against time did not show any systematic deviation from a first order process. The calculated absorption half-life of PE was 36 min and that of PM 43 min.

Discussion

The relative efficacy of PM and PE against *S. aureus* was assessed *in vitro* and in an experimental infection in mice. The pharmacokinetics of these drugs in patients were established to insure proper assessment of the relative therapeutic efficacy, taking into account the differences in intrinsic antibacterial activity. According to the MIC, PM was about twice as active as PE against the strain of *S. aureus* used in our experiments. For most micro-organisms against which these two antibiotics are used, the MIC is lower for PM than for PE. Garrod (1960) found lower MICs for PM than for PE against streptococci and *Neisseria gonorrhoea*, although not for *S. aureus*. Other authors have reported findings similar to ours (Barber & Waterworth, 1962; Bond *et al.*, 1963; Simon *et al.*, 1976). However, in a twofold dilution series a twofold difference represents a large error. Our assessment of the effect on short-term growth makes a more accurate assessment possible. The results confirmed the crude estimate based on MICs. The same method also showed that protein binding indeed decreased the antibacterial activity compared with that of the free drug. The protein binding should therefore be taken into account in the assessment of the therapeutic value *in vivo*. However, we found no difference in the binding of the two drugs in either murine or human plasma. With respect to human plasma, other authors have reported similar findings (Bond *et al.*, 1963; Kunin, 1966; Biagi *et al.*, 1970; Bergan, 1978) but Scholtan & Schmidt (1962) found protein binding amounting to 58% and 75% for PM and PE, respectively, at concentrations similar to those we used. The reason for this discrepancy is not clear.

In the mouse thigh model both the intrinsic antibacterial effect and pharmacokinetic factors are considered. Our results show that the antibacterial effect *in vivo* of the two drugs under study is indeed determined by the intrinsic activity, as established *in vitro*, together with such pharmacokinetic parameters as the AUC and binding to mouse plasma proteins. The choice of the AUC as a parameter was arbitrary, since the shape of the plasma concentration curve may also play a role in the antibacterial effect of a drug. However, because the shape of the curve proved to be similar for both drugs, the AUC is apparently a suitable and comparable measure of the total exposure of the micro-organisms to a single dose. According to the AUC for free drug, the relative potency *in vivo* (2.68) is at least very close to that *in vitro* (2.13). Therefore, it may be concluded from the results obtained *in vitro* and *in vivo* that PM is about twice as active as PE.

Table 3 Pharmacokinetic parameters for phenoxymethylpenicillin

	<i>I</i> *	Patient number										Mean	s.d.
		2	3	4	5	6	7	8	9	10			
<i>C</i> ₁	—	8.17	11.70	12.80	16.10	10.80	22.10	9.35	15.00	5.40	12.38	4.92	
<i>C</i> ₂	8.89	1.13	2.44	15.20	9.29	3.78	3.65	3.10	2.48	7.34	5.73	4.38	
λ_1	(h ⁻¹)	—	2.64	3.45	1.75	3.84	8.89	7.87	11.60	9.15	6.34	3.47	
λ_2	(h ⁻¹)	1.071	0.774	0.854	0.586	0.588	1.010	1.450	0.397	0.914	0.836	0.28	
<i>k</i> ₁₂	(h ⁻¹)	—	0.344	0.684	0.306	1.388	2.870	2.290	6.927	3.734	2.440	2.12	
<i>k</i> ₂₁	(h ⁻¹)	—	1.97	1.23	3.68	0.99	1.69	2.56	1.18	4.45	2.00	1.28	
<i>k</i> ₁₀	(h ⁻¹)	—	2.10	2.39	1.53	1.76	5.34	4.47	3.89	1.88	2.71	1.49	
<i>V</i>	(l)	25.8	22.1	13.9	8.8	13.4	5.4	12.3	6.9	13.6	12.9	6.7	
<i>V</i> _{area}	(l)	25.8	60.0	38.9	13.7	40.1	26.2	37.9	67.2	28.0	35.4	17.5	
<i>AUC</i> _{i.v.}	(mg l ⁻¹ h)	10.3	5.4	7.6	27.3	10.6	9.2	4.8	9.7	10.0	12.1	7.9	
<i>AUC</i> _{po}	(mg l ⁻¹ h)	9.4	7.1	8.0	23.5	7.5	6.7	13.5	5.9	3.9	9.3	5.6	
<i>F</i>	(mg)	227.4	342.7	78.0	215.1	176.7	181.4	701.8	151.5	97.7	240.5	178.4	
<i>k</i> ₀₁	(h ⁻¹)	0.831	1.029	0.816	1.669	0.910	0.776	1.080	1.044	0.357	0.961	0.331	
<i>CL</i>	(ml min ⁻¹)	459.7	773.5	553.7	153.2	393.1	480.6	916.4	444.8	426.1	476.4	236.0	
<i>CL</i> _{cr}	(ml min ⁻¹)	62	145	21	33	69	68	89	132	122	83.2	40.9	

*Calculated according to a one-compartment model; $CL = \frac{R_0}{C} \times (1 - e^{-\lambda_2 t})$; $V = \frac{CL}{\lambda_2}$.

Table 4 Pharmacokinetic parameters for pheneticillin

	<i>I</i>	2*	3	4	5	6	7	8	9	10	Mean	s.d.
<i>C</i> ₁	15.15	—	14.5	11.4	22.1	12.0	23.7	11.7	16.7	9.3	15.2	4.9
<i>C</i> ₂	3.13	9.56	7.08	20.2	12.3	8.90	3.98	5.01	4.47	10.1	8.47	5.1
λ_1	(h ⁻¹)	1.33	—	3.75	8.25	2.00	3.42	8.66	5.49	17.1	6.05	4.8
λ_2	(h ⁻¹)	0.434	1.313	0.831	0.508	0.413	0.641	1.310	0.685	0.876	0.760	0.328
<i>k</i> ₁₂	(h ⁻¹)	0.184	—	1.041	3.418	0.603	0.831	3.11	2.115	9.796	2.540	2.94
<i>k</i> ₂₁	(h ⁻¹)	0.58	—	1.65	4.38	0.93	0.97	2.79	1.44	5.4	2.23	1.66
<i>k</i> ₁₀	(h ⁻¹)	1.0	—	1.89	0.96	0.88	2.26	4.07	2.62	2.78	1.98	1.07
<i>V</i>	(l)	12.4	23.5	9.3	6.0	6.5	7.1	9.0	8.3	6.4	9.8	5.2
<i>V</i> _{area}	(l)	28.6	23.5	21.0	11.2	13.8	25.0	28.0	31.6	20.3	22.5	6.4
<i>AUC</i> _{i.v.}	(mg l ⁻¹ h)	20.2	8.1	14.3	44.1	43.9	15.7	7.1	11.7	14.5	19.9	13.4
<i>AUC</i> _{po}	(mg l ⁻¹ h)	26.6	6.9	26.8	31.8	60.4	32.0	16.5	12.4	24.2	29.3	17.2
<i>F</i>	(mg)	329.5	211.6	469.1	180.2	343.8	510.0	580.0	265.8	417.0	401.2	167.5
<i>k</i> ₀₁	(h ⁻¹)	0.993	2.449	0.680	1.203	0.963	1.528	1.083	1.453	0.528	1.138	0.579
<i>CL</i>	(ml min ⁻¹)	206.7	514.0	291.4	95.0	211.9	267.4	611.9	361.1	296.5	295.1	166.1

*Calculated according to a one compartment model.

Figure 3 Relation between plasma clearance of phenoxymethylpenicillin (open symbols) and pheneticillin (closed symbols) and the creatinine clearance in patients. The lines connect the values of the plasma clearance of the two drugs in individual patients, whose numbers correspond with those in Table 2.

Figure 4 Calculated absorption of phenoxymethylpenicillin and pheneticillin after an oral dose of 500 mg. The dotted line represents the administered dose. The patient numbers correspond with those in Table 2. (a) pheneticillin, (b) phenoxymethylpenicillin.

In the clinical pharmacokinetic part of our study the clearance and volume of distribution of PM and PE could be derived from plasma concentrations after intravenous administration in patients. The plasma clearance of PM was roughly twice that of PE. The volume of distribution of PM was also about twice that of PE, resulting in a similar $t_{1/2}$. Since the protein binding of both drugs was equal, the above holds for the free drug as well. This means that any difference in therapeutic efficacy between the two drugs must depend entirely on differences in absorption.

Earlier studies performed to compare PM and PE as K salts indicated that PE was absorbed better than PM, but this conclusion was based on a comparison of AUCs after oral administration only, the differences in disposition not being taken into account (McCarthy & Finland, 1960; Bond *et al.*, 1963; Simon *et al.*, 1976). Calculation with these authors' data showed that the differences in AUC_{pos} are small, and when the twofold difference in clearance between PM and PE is taken into account the absorption of the potassium salt of PM is apparently better than that of PE. Bioavailability studies on the acid and the potassium salt of PM in volunteers showed that the potassium salt was absorbed better than the acid (Berlin & Brante, 1959; Kraushaar & Giovannini, 1959; Peck & Griffith, 1958; Spitz & Doujak, 1959). However, in these studies the differences were small. AUCs for both drugs as estimated from the data obtained in both sets of studies are shown in Table 5. In our study the acid salt of PM was compared with the potassium salt of PE, because these two drugs have been widely used for many years in The Netherlands. The formulation of PM we used was absorbed less well than PE.

It is well known that disease and age influence the absorption and disposition of drugs (Sabath, 1970; Palatsi & Kaipainen, 1971; Bolme &

Eriksson, 1975; Kunst & Mattie, 1975; George, 1976; Klotz, 1976; Nimmo, 1976; Kates *et al.*, 1980; Welling & Tse, 1982; Yashuara *et al.*, 1982), and these effects probably explain the wide range of the values we obtained in patients as well as the differences between our findings and those of other authors. The relatively high AUC_{po} we found for both drugs might be partly explained by the differences in the degree of renal dysfunction among our patients, since we found a strong correlation between the plasma clearance and the creatinine clearance of both drugs. Pharmacokinetic parameters may even differ between days in the same subject (Dagrosa *et al.*, 1981). Because in our study oral and intravenous administration was not performed on the same day, this between-day divergence probably also explains calculated values of more than 100% absorption.

In summary, it may be said that provided absorption of different formulations of PM and PE is the same, the two drugs will be equally effective. However, the present results show once again that due to the large interindividual variation in the absorption of oral penicillins, the oral route of administration of antibiotics should not be relied on in serious infections.

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Table 5 AUC (mg l⁻¹ h) for phenoxymethylpenicillin (PM), acid and potassium salt, and pheneticillin (PE), potassium salt, after oral administration, calculated from published data

Author	Oral dose	PM acid	PM potassium salt	PE
Berlin & Brante (1959)	150	2.21	3.23	—
Kraushaar & Giovannini (1959)	240	2.84	3.02	—
Peck & Griffith (1958)	250	4.21	6.20	—
Spitz & Doujak (1959)	250	3.50	3.78	—
McCarthy & Finland (1960)	500	—	1.85	2.24
Bond <i>et al.</i> (1963)	250	—	4.04	5.55
Simon <i>et al.</i> (1976)	600	—	6.81	5.07
Present study	500	9.29	—	29.32

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