*J. vet. Pharmacol. Therap.* **15**, 221–230, 1992.

# Bioavailability of oral penicillins in the horse: a comparison of pivampicillin and amoxicillin

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Ensink, J.M., Klein, W.R., Mevius, D.J., Klarenbeek, A., Vulto, A.G. Bioavailability of oral penicillins in the horse: a comparison of pivampicillin and amoxicillin. *J. vet. Pharmacol. Therap.* **15**, 221–230.

The pharmacokinetics of ampicillin and amoxicillin following intravenous administration at a dose rate of 15 and 10 mg/kg respectively were studied in four healthy adult horses. Pharmacokinetics of pivampicillin and amoxicillin were studied after oral administration to four healthy adult horses. Pivampicillin, a prodrug of ampicillin, was administered orally to starved and fed horses at a dose rate of 19.9 mg/kg, which is equivalent on a molecular basis to 15 mg/kg ampicillin. Amoxicillin was administered orally to starved horses only, at a dose rate of 20 mg/kg. Ampicillin and amoxicillin concentrations in plasma, synovial fluid and urine were determined. Mean biological half-life of intravenously administered ampicillin and amoxicillin was 1.72 and 1.43 h respectively, whilst the distribution volume ($V_{ss}$) appeared to be 0.180 and 0.192 l/kg. Orally administered pivampicillin and amoxicillin were rapidly absorbed. A maximum concentration in plasma of 3.80 μg/ml was reached 2 h after administration of pivampicillin to starved horses; in fed horses a maximum concentration of 5.12 μg/ml was reached 1 h after administration. After oral administration of amoxicillin a maximum concentration of 2.03 μg/ml was reached after 1 h. The (absolute) bioavailability of pivampicillin administered orally was 30.9% in starved horses and 35.9% in fed horses. The bioavailability of amoxicillin administered orally was 5.3% in starved horses.

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## INTRODUCTION

In dogs and cats, as in humans, most antibiotics are administered orally. In horses, however, oral administration of antibiotics is not common. There are two main reasons for this fact. The first is the low bioavailability of most orally administered antibiotics in the horse (Brumbaugh, 1987) and the second is the fear of inducing dysbacteriosis (White & Prior, 1982; Cook, 1973).

Pharmacokinetic studies have been performed in adult horses after oral administration of penicillin V (Ducharme *et al.*, 1983; Schwark *et al.*, 1983), amoxicillin (Wilson *et al.*, 1988), trimethoprim and sulfadiazine (Sigel *et al.*, 1981; Morgan & White, 1983) and metronidazole (Sweeney *et al.*, 1986). Studies on the pharmacokinetics in foals of oral amoxicillin (Love *et al.*, 1981; Baggot *et al.*, 1988) and ampicillin trihydrate (Brown *et al.*, 1984) have been reported.

Bioavailability of penicillin V in the horse is low, therefore the recommended dose is five times higher than the intramuscular dose of penicillin G. Amoxicillin showed a bioavaila-

bility of 10.4% after oral administration in adult horses (Wilson *et al.*, 1988) and 36.2% in foals (Baggot *et al.*, 1988). Metronidazole was absorbed very well, having a bioavailability of 85% (Sweeney *et al.*, 1986). No exact figures concerning the bioavailability of ampicillin trihydrate in foals are given, and the same is true for the combination of trimethoprim and sulfadiazine. In general, the bioavailability of these antibiotics is lower in the horse than in dogs and humans (Jordan *et al.*, 1970; Loo *et al.*, 1974; Verbist, 1974; Watson *et al.*, 1986; Watson *et al.*, 1987).

There are no studies on the bioavailability of pivampicillin in the horse. Pivampicillin is the pivaloyl-oxymethyl-ester of ampicillin which is hydrolysed to ampicillin as it is absorbed from the gastrointestinal tract. The use of pivampicillin has been studied in calves (Ziv *et al.*, 1977) and also extensively in humans (Jordan *et al.*, 1970; Loo *et al.*, 1974; Verbist, 1974). In both species, bioavailability of pivampicillin was higher than bioavailability of ampicillin and amoxicillin.

The present study reports the kinetics of intravenously administered ampicillin and amoxicillin in adult horses, and the disposition kinetics and bioavailability of pivampicillin and amoxicillin after oral administration to adult horses.

## MATERIAL AND METHODS

### *Horses*

Four healthy adult horses, one gelding and three mares, were used in this study. The horses ranged in age from 7 to 14 years (mean 9.5 years). Their weight ranged from 580 to 660 kg. They were judged to be in good condition on the basis of physical examination, total blood cell count, plasma protein, urea and gamma GT determination. They were housed in stalls. The horses were fed hay and concentrates and had free access to water. In Experiments 1 and 4, food intake was not limited. In Experiment 2, food was withheld from 16 h before to 4 h after the first administration of pivampicillin. The following days the animals were starved for 6 h before and 4 h after each administration. Thus, the horses were allowed 2 h twice daily to eat 2 kg of concentrates and hay *ad libitum*. In Experiment 3 the horses were fed hay *ad libitum* and were given 2 kg of concentrates 0.5 to 1 h before administration of pivampicillin. On each occasion the concentrates were eaten before the administration. In Experiment 5, food was withheld from 16 h before to 4 h after oral administration of amoxicillin.

### *Administration and sampling procedure*

In all experiments blood samples of 10 ml were collected in heparinized tubes. They were centrifuged immediately and plasma was drawn off and stored in a plain tube. Two millilitres of synovial fluid were collected by arthrocentesis and stored in a heparinized tube. Urine samples were collected by catheterization of the bladder at the sampling times and 7 ml were stored in a plain tube. The volume of urine was not measured. All samples were frozen at −20°C within 1 h of collection, and they were kept frozen until assayed.

### *Experiment 1: intravenous administration of ampicillin*

The equivalent of 15 mg/kg ampicillin was administered as a 30% aqueous solution of sodium ampicillin (Ampicillinum®, Kombivet, Etten-Leur, The Netherlands) into the right jugular vein. Blood samples were collected in heparinized vacuum tubes from the left jugular vein before and at 5, 15 and 30 min, and 1, 1.5, 2, 4, 8 and 12 h after administration. Synovial samples were collected from the radiocarpal, intercarpal and tibiotarsal joints before and at 1, 2, 4, 8, 12 and 24 h after administration. From two mares (horses A and C) urine samples were collected before and at 1, 4, 8, 12 and 24 h after administration.

### *Experiments 2 and 3: oral administration of pivampicillin*

Experiments 2 and 3 differed only in the feeding of the horses. Administration of pivampicillin and sampling procedures in

both experiments were as listed below. The dose of pivampicillin was 19.9 mg/kg, which is equivalent on a molecular basis to 15 mg/kg ampicillin, the latter being the active form of this antibiotic after hydrolysis of the ester. Pivampicillin (Pondocillin granulate®, Leo Pharmaceuticals, Copenhagen, Denmark) was given on Day 1 at time 0 h and on Days 2 and 3 at times 0 and 12 h. The pivampicillin was suspended in 0.5 l of water and administered by nasogastric tube. The nasogastric tube was then flushed with 0.5 l of water. On Day 3 the pivampicillin was given to horses C and D into the mouth after mixing it with approximately 35 ml of syrup.

Blood samples were collected from the jugular vein using a 14-gauge Teflon catheter. On Day 1 sampling times were 0, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 16, 20 and 24 h. On Days 2 and 3, in addition to the sampling times of Day 1, blood samples were collected at 12.25, 12.5, 13 and 14 h. Synovial fluid was collected on Day 1 at 0, 1, 2, 4, 8, 12 and 24 h; on Days 2 and 3 additional samples were collected at 14 and 18 h. Synovial fluid samples were taken from radiocarpal, intercarpal and tibiotarsal joints. One joint was sampled consecutively until blood was found in the sample. Then the next sample was taken from another joint. A maximum time interval was allowed before resampling the first joint. In most cases three consecutive samples could be taken from each joint. Urine samples were collected from horses A and C only. Sampling times were 0, 1, 2, 4, 8, 12 and 24 h on Day 1; on Days 2 and 3 samples were also collected at 14 and 18 h.

*Experiment 4: intravenous administration of amoxicillin*

The equivalent of 10 mg/kg amoxicillin was administered as a 20% aqueous solution of sodium amoxicillin (horses A and B: Clamoxyl®, Beecham, Amstelveen, The Netherlands; horses C and D: Flemoxin®, Gist Brocades, Delft, The Netherlands) into the right jugular vein. Blood samples were collected from a 14-gauge Teflon catheter in the left jugular vein before and at 5, 15, 30 and 45 min, and 1, 1.5, 2, 4, 8, 12 and 16 hours after administration. Synovial samples were taken before and 1, 3, 6, 12 and 24 h after administration. From horses A and C urine samples were collected before and at 3, 6, 12 and 24 h after administration.

*Experiment 5: oral administration of amoxicillin*

Amoxicillin (Paracilline®, Mycofarm, de Bilt, The Netherlands) was administered orally at a dose rate of 20 mg/kg. The powder was dissolved in 0.5 l of water and administered by nasogastric tube. The nasogastric tube was then flushed with 0.5 l of water. Blood samples were taken from the jugular vein using a 14-gauge Teflon catheter. Sampling times were before and 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 16 and 24 h after administration. Synovial samples were taken before and 1, 3, 6, 12 and 24 h after administration. From horses A and C urine samples were collected before and 3, 6, 12 and 24 h after administration.

*Ampicillin and amoxicillin assay*

Ampicillin or amoxicillin concentrations were assayed microbiologically by the agar diffusion method (Nouws, 1978) using Sarcina lutea ATCC 9341 as test organism and standard preparations of ampicillin and amoxicillin as reference compounds. The detection limit of the assay was 0.02 μg ampicillin per ml and 0.01 μg amoxicillin per ml.

*Data analysis*

Non-linear least-square regression analysis was performed using the NONLIN computer program (Metzler *et al.*, 1974). Plasma concentrations after intravenous administration were fitted in a two-compartment open model. In this model the plasma concentration ($C$) is described by the biexponential equation

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

The method for calculating the mathematical coefficients A and B and the distribution and elimination constants $\alpha$ and $\beta$ are described by Gibaldi & Perrier (1982). From these parameters the first-order rate constants for drug transfer between the central and

peripheral compartment ($k_{12}$ and $k_{21}$) and the first-order rate constant for elimination of the drug from the central compartment ($k_{10}$) were calculated. The distribution half-life ($t_{1/2\alpha}$) and the elimination half-life ($t_{1/2\beta}$) were calculated from the equations

$$t_{1/2\alpha} = 0.693/\alpha$$
$$t_{1/2\beta} = 0.693/\beta$$

The area under the plasma concentration–time curve from the time of injection to $t = \infty$ ($AUC_{i.v.}$) was calculated from the equation

$$AUC_{i.v.} = A/\alpha + B/\beta$$

The volume of the central compartment ($V_c$) was calculated as the ratio of the dose of drug (D) to its plasma concentration at $t = 0$ ($C_0$):

$$V_c = D/C_0$$

The volume of distribution at pseudo-equilibrium ($V_{area}$) and the volume of distribution at steady state ($V_{ss}$) were calculated from the equations

$$V_{area} = D/(A/\alpha + B/\beta)\beta \text{ and}$$

$$V_{ss} = \frac{D(A/\alpha^2 + B/\beta^2)}{AUC_{i.v.}^2}$$

The total body clearance ($Cl$) was calculated as the ratio of dose and $AUC_{i.v.}$:

$$Cl = D/AUC_{i.v.}$$

After oral administration of pivampicillin we failed to observe a distribution phase. This phenomenon is seen following oral administration of drugs displaying two-compartment characteristics after intravenous administration when $t_{1/2\alpha}$ is smaller than $t_{1/2abs}$ (Gibaldi & Perrier, 1982). Therefore, plasma concentrations after oral administration were fitted in a one-compartment model with first-order absorption and first-order elimination. The absorption half-life ($t_{1/2abs}$) and elimination half-life ($t_{1/2\beta}$) were calculated using the absorption rate constant $k_a$ and the elimination rate constant $\beta$ in the following equations:

$$t_{1/2abs} = 0.693/k_a$$
$$t_{1/2\beta} = 0.693/\beta$$

The area under the plasma concentration–time curve after oral administration ($AUC_{oral}$) was calculated as

$$AUC_{oral} = B/\beta - Aabs/k_a$$

The bioavailability after oral administration ($F$) is calculated as

$$F = \frac{AUC_{oral}}{AUC_{i.v.}} \times \frac{D_{i.v.}}{D_{oral}}$$

Pharmacokinetic parameters were estimated for each horse and these values were used to calculate the mean and standard deviation for each pharmacokinetic parameter.

## RESULTS

### *Experiment 1: intravenous administration of ampicillin*

After intravenous administration of ampicillin, distribution and elimination half-lives were 0.308 ± 0.026 h and 1.72 ± 0.157 h respectively. Results are given as mean ± standard deviation. Mean plasma and synovial fluid concentrations are shown in Fig. 1A.

### *Experiments 2 and 3: oral administration of pivampicillin*

After oral administration of 19.9 mg/kg pivampicillin to starved horses, a maximum plasma concentration of 3.80 ± 0.638 μg/ml was reached 2 h after administration, whereas in fed horses a maximum of 5.12 ± 1.18 μg/ml was reached 1 h after administration. Absorption and elimination half-lives were 0.827 ± 0.293 (mean ± SD) and 1.33 ± 0.320 h in starved horses and 0.529 ± 0.117 and 1.36 ± 0.436 h in fed horses. Bioavailability of pivampicillin appeared to be 30.9% ± 3.8% in starved horses and 35.9% ± 8.3% in fed horses. Ampicillin concentrations in

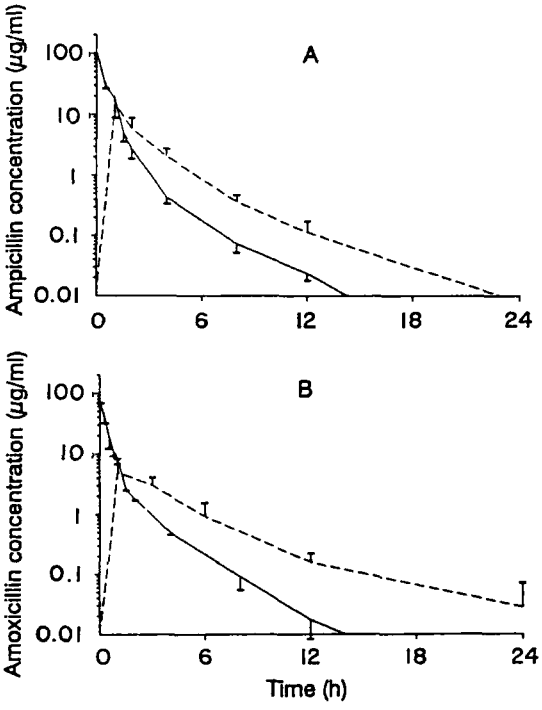


FIG. 1(A) Mean (± SD) ampicillin concentrations (μg/ml) in plasma (——) and synovial fluid (----) after intravenous administration of 15 mg/kg ampicillin (as sodium ampicillin). $n = 4$. (B) Mean (± SD) amoxicillin concentrations (μg/ml) in plasma (——) and synovial fluid (----) after intravenous administration of 10 mg/kg amoxicillin (as sodium amoxicillin). $n = 4$.

plasma and synovial fluid after oral administration of pivampicillin to starved and fed horses are shown in Figs 2A and 2B respectively. In starved horses there appeared to be no difference between plasma concentrations after administration of pivampicillin in syrup and after administration as an aqueous suspension by nasogastric tube. No statistical comparison was made between these subgroups because of the small group numbers. The data of all four starved horses are presented in Fig. 2A. In fed horses, however, absorption from the syrup medication was markedly irregular. Therefore, the concentrations shown in Fig. 2B at Day 3 represent only horses A and B. The results of oral administration of pivampicillin mixed with syrup to horses C and D in Experiment 3 are shown in Fig. 3.

*Experiment 4: intravenous administration of amoxicillin*

After intravenous administration of amoxicillin, the distribution and elimination half-lives were 0.218 ± 0.026 h (mean ± SD) and 1.43 ± 0.272 h respectively. There appeared to be no difference between the two brands of amoxicillin (no statistical comparison was made because of small subgroup numbers). Mean plasma and synovial fluid concentrations are shown in Fig. 1B.

*Experiment 5: oral administration of amoxicillin*

After oral administration of amoxicillin, maximum plasma concentration of 2.03 ± 0.665 μg/ml was reached at 1 h. Absorption and elimination half-lives were 0.382 ± 0.156 and 0.745 ± 0.218 h (mean ± SD) respectively. Bioavailability of amoxicillin in starved horses was 5.3% ± 1.1%. Plasma and synovial fluid concentrations are shown in Fig. 4.

*Urine samples*

Figure 5 shows the urine concentrations as measured during the experiments. From the starved horses urine samples were also taken 36 and 108 h after the last administration of pivampicillin. After 36 h the mean concentration was 0.71 μg/ml; after 108 h it was below the level of detection (0.02 μg/ml).

*Pharmacokinetic parameters*

The values of several important pharmacokinetic parameters following intravenous administration are shown in Table I, and those after oral administration are shown in Table II.

## DISCUSSION

In equine medicine the oral administration of antibiotics has several advantages. There is no risk of local reactions at the injection site as is often the case in intramuscular injections. Furthermore, in those horses not treated in a

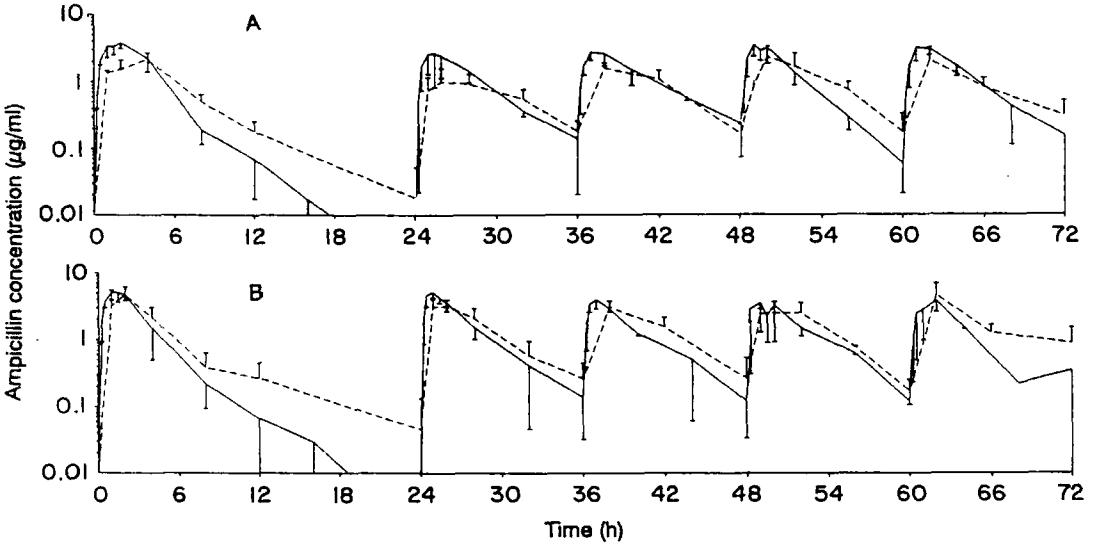


FIG. 2. Mean (± SD) ampicillin concentrations (µg/ml) in plasma (——) and synovial fluid (----) after oral administration of 19.9 mg/kg pivampicillin, equivalent on a molecular basis to 15 mg/kg ampicillin. Pivampicillin was administered once daily on Day 1 and twice daily on Days 2 and 3. (A) Starved horses. Administration was by nasogastric tube, except on Day 3 when pivampicillin was administered into the mouth mixed with syrup to 2 of the 4 horses. $n = 4$. (B) Fed horses. Administration was by nasogastric tube. Day 1 and 2, $n = 4$, Day 3, $n = 2$.

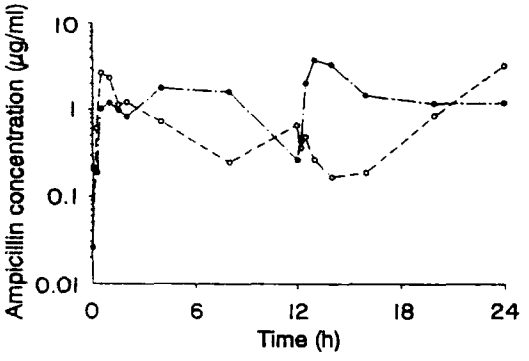


FIG. 3. Mean (± SD) ampicillin concentrations (µg/ml) in plasma after administration into the mouth of 19.9 mg/kg pivampicillin, equivalent on a molecular basis to 15 mg/kg ampicillin, mixed with syrup to fed horses. $n = 2$. Horse C (--O--), horse D (—●—).

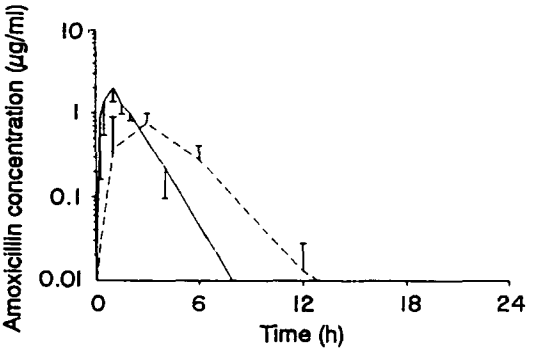


FIG. 4. Mean (± SD) amoxicillin concentrations (µg/ml) in plasma (——) and synovial fluid (----) after oral administration of 20 mg/kg amoxicillin to starved horses. Amoxicillin was administered by nasogastric tube. $n = 4$.

veterinary hospital, an oral dosage form can easily be administered by the owner. Disadvantages are the low bioavailability of most orally administered antibiotics in the horse and the possibility of inducing dysbacteriosis.

The fear of inducing dysbacteriosis also applies to oral penicillins. Pseudomembranous colitis after oral administration of antibiotics, including ampicillin, is a well-known phenomenon in humans (Yost & Gotz, 1985) and guinea pigs (De Somer *et al.*, 1955). In horses, treatment with broad-spectrum antibiotics may cause a serious syndrome commonly known as colitis X (Cook, 1973). White

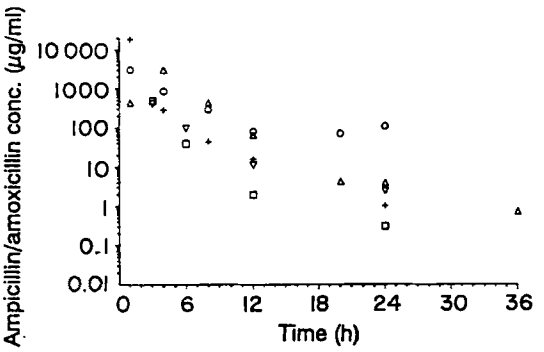


FIG. 5. Mean ampicillin concentrations (µg/ml) in urine after intravenous administration of 15 mg/kg ampicillin (as sodium ampicillin) (+), after oral administration of 19.9 mg/kg pivampicillin, equivalent on a molecular basis to 15 mg/kg ampicillin, to starved horses (△) and after oral administration of 19.9 mg/kg pivampicillin, equivalent on a molecular basis to 15 mg/kg ampicillin, to fed horses (○). Mean amoxicillin concentrations in urine after intravenous administration of 10 mg/kg amoxicillin (as sodium amoxicillin) (▽) and after oral administration of 20 mg/kg amoxicillin to starved horses (□). $n$ = 2 in all experiments.

& Prior (1982) have shown that diarrhoea caused by antibiotic therapy is accompanied by changes in the faecal flora. The hazard of inducing dysbacteriosis is smallest when the concentration of active antibiotic reaching the caecum and colon is low. This can be achieved in various ways. A drug which is almost completely absorbed in the jejunum and does not recirculate via an enterohepatic pathway will reach the caecum and colon only in small quantities. Alternatively, an antibiotic may be administered as an inactive prodrug, such as pivampicillin. Pivampicillin cannot affect the flora in caecum and colon, as long as it is not converted into ampicillin, because pivampicillin is not antimicrobially active.

In this study the elimination half-lives of intravenously administered ampicillin and amoxicillin, 1.72 and 1.43 h respectively, correspond well to the estimates in other studies: 1.55 h for ampicillin in horses (Duerr, 1976), 1.25 h for ampicillin and amoxicillin in dogs (Huber, 1988), 1.20 h for ampicillin in cows (Baggot *et al.*, 1988) and 1.0–1.5 h for ampicillin and amoxicillin in humans (Kwan & Rogers, 1983). In this study the $V_{area}$ appeared to be 0.705 l/kg for ampicillin and 0.556 l/kg for amoxicillin. This is higher than the values reported in horses (0.29 l/kg) and dogs (0.20 l/kg) and in calves (0.35 l/kg) (Ziv *et al.*, 1977; Huber, 1988). The $V_{ss}$, relating the amount of drug in the body to the drug concentration in plasma at steady state, is likely to be a more useful estimate of the apparent distribution space (Gibaldi & Perrier, 1982). In this study the $V_{ss}$ appeared to

TABLE I. Pharmacokinetic parameters (mean ± SD) after intravenous administration of 15 mg/kg ampicillin (Experiment 1) and 10 mg/kg amoxicillin (Experiment 4). $n$ = 4 in both experiments

| Parameter | Units | Experiment 1 | Experiment 4 |
|---|---|---|---|
| Dose | mg/kg | 15.0 ± 0 | 10.0 ± 0 |
| Body weight | kg | 620.0 ± 34.6 | 625.0 ± 41.2 |
| $k_{10}$ | $h^{-1}$ | 2.09 ± 1.74 | 2.58 ± 0.232 |
| $k_{12}$ | $h^{-1}$ | 0.140 ± 0.015 | 0.512 ± 0.139 |
| $k_{21}$ | $h^{-1}$ | 0.439 ± 0.038 | 0.620 ± 0.137 |
| $V_c$ | l/kg | 0.136 ± 0.012 | 0.106 ± 0.009 |
| $V_{area}$ | l/kg | 0.705 ± 0.098 | 0.556 ± 0.049 |
| $V_{ss}$ | l/kg | 0.180 ± 0.019 | 0.192 ± 0.010 |
| *Cl* | l/h/kg | 0.285 ± 0.037 | 0.273 ± 0.028 |
| α | $h^{-1}$ | 2.26 ± 0.185 | 3.22 ± 0.409 |
| $t½_{\alpha}$ | h | 0.308 ± 0.026 | 0.218 ± 0.026 |
| β | $h^{-1}$ | 0.406 ± 0.035 | 0.496 ± 0.092 |
| $t½_{\beta}$ | h | 1.72 ± 0.156 | 1.43 ± 0.272 |
| *AUC* | mg.h/l | 53.4 ± 7.13 | 37.0 ± 3.82 |

TABLE II. Pharmacokinetic parameters (mean ± SD) after oral administration of 19.9 mg/kg pivampicillin to starved horses (Experiment 2) and fed horses (Experiment 3) and after oral administration of 20 mg/kg amoxicillin to starved horses (Experiment 5). $n = 4$ in all experiments

| Parameter | Units | Experiment 2 | Experiment 3 | Experiment 5 |
|---|---|---|---|---|
| Dose | mg/kg | 15.0 ± 0 | 15.0 ± 0 | 20.0 ± 0 |
| Body weight | kg | 620.0 ± 34.6 | 620.0 ± 34.6 | 625.0 ± 41.2 |
| $k_a$ | $h^{-1}$ | 0.944 ± 0.409 | 1.37 ± 0.345 | 2.04 ± 0.744 |
| $t^{1}/_{2abs}$ | h | 0.827 ± 0.293 | 0.529 ± 0.117 | 0.382 ± 0.156 |
| $\beta$ | $h^{-1}$ | 0.542 ± 0.125 | 0.549 ± 0.171 | 1.01 ± 0.260 |
| $t^{1}/_{2\beta}$ | h | 1.33 ± 0.320 | 1.36 ± 0.436 | 0.745 ± 0.218 |
| *AUC* | mg·h/l | 16.4 ± 2.33 | 19.0 ± 4.66 | 3.98 ± 1.09 |
| *F* | — | 0.309 ± 0.038 | 0.359 ± 0.083 | 0.053 ± 0.011 |

be 0.180 l/kg for ampicillin and 0.192 l/kg for amoxicillin.

After oral administration of pivampicillin at a dose rate of 19.9 mg/kg, the following peak plasma concentrations were reached: 3.80 μg/ml in starved horses and 5.12 μg/ml in fed horses. A peak plasma concentration of 2.03 μg/ml was reached following oral administration of amoxicillin at a dose rate of 20 mg/kg. In this study synovial fluid concentrations exceeded plasma concentrations starting 2 h after intravenous or oral administration of both pivampicillin and amoxicillin. The same phenomenon was observed by Beech *et al.* (1979) after intramuscular administration of sodium ampicillin at a dose rate of 11 mg/kg. Synovial fluid concentrations roughly equalled plasma concentrations when the dose rate was decreased to 4.4 mg/kg. After intravenous administration of 11 mg/kg ampicillin, synovial fluid concentrations exceeded serum concentrations from 1 h onwards (Bowman *et al.*, 1986). After intramuscular administration of ampicillin trihydrate in horses, synovial fluid concentrations were lower than serum concentrations (Brown *et al.*, 1982). In man, synovial fluid concentrations equal concurrent plasma concentrations (Howell *et al.*, 1972).

Following intravenous administration of both ampicillin and amoxicillin, urine concentrations are high. Oral administration of pivampicillin also causes high concentrations of ampicillin in urine. Oral administration of amoxicillin produces the lowest concentrations in urine because of low bioavailability. No ampicillin could be detected in urine at 108 h after the last oral administration of pivampicillin. Because the volume of urine was not measured, this study yields only qualitative information about urine concentrations.

Bacteria having a minimum inhibitory concentration (*MIC*) under 1 μg/ml are generally thought to be susceptible to ampicillin (Adamson *et al.*, 1985). In this study it was demonstrated that oral administration of pivampicillin (dose rate 19.9 mg/kg, equivalent on a molecular basis to 15 mg/kg ampicillin) caused plasma concentrations higher than 2 μg/ml, which is twice this *MIC*. The concentration remained above 2 μg/ml for 3 to 3.5 h and above 1 μg/ml for 4.5 to 5 h. Highly susceptible bacteria such as *Streptococcus zoöepidemicus*, an important pathogen in the horse, have an *MIC* of 0.25 μg/ml (Adamson *et al.*, 1985). Plasma ampicillin concentrations above 0.5 μg/ml (i.e. two times *MIC*) last for approximately 6 h. Furthermore, ampicillin causes a post-antibiotic effect, which is the persistent suppression of bacterial growth after short exposure to antimicrobial agents. Bundtzen *et al.* (1981) demonstrated a post-antibiotic effect of ampicillin lasting 1 to 4 h with gram-positive bacteria. Therefore, infections caused by highly susceptible bacteria would be expected to respond positively to the dosage regimen used in this study. After oral administration of 20 mg/kg amoxicillin, the plasma concentrations failed to reach 2 μg/ml, but

remained above 1 μg/ml for approximately 1.5 h and above 0.5 μg/ml for 2.5 h.

In this study, the bioavailability of pivampicillin appears to be the highest of all oral penicillins in adult horses, being 30.9% in starved horses and 35.9% in fed horses. After oral administration of pivampicillin at a dose rate of 19.9 mg/kg (equal to 15 mg/kg ampicillin), bioavailability was higher than that of penicillin V 110 000 IU/kg (approximately 66 mg/kg) administered orally (Ducharme *et al.*, 1983; Schwark *et al.*, 1983). It is also demonstrated that bioavailability of pivampicillin was higher than the bioavailability of amoxicillin, the latter being as low as 5.3%. Wilson *et al.* (1988) reported a bioavailability of 10.4% after oral administration of 20 mg/kg amoxicillin. Therefore amoxicillin can be regarded as less suitable for oral administration in adult horses.

The bioavailability of orally administered penicillins in adult horses is lower than in foals and other species. In week-old foals, a bioavailability of 36% was reported following a dose of 20 mg/kg amoxicillin (Baggot *et al.*, 1988). In man a urinary excretion of 54–82% of the dose of pivampicillin was reached within 8 h (Jordan *et al.*, 1970). In the same study it was shown that oral administration of ampicillin trihydrate caused an 8-h urinary excretion of 41–46%. Loo *et al.* (1974) reported a bioavailability of pivampicillin of 82–89% in man. Bioavailability of oral penicillins in the dog is generally higher than in horses (Watson *et al.*, 1986, 1987). Ziv *et al.* (1977) demonstrated in calves that the bioavailability of pivampicillin was 29% when given with milk whereas this figure was 35% when given without milk. These figures are in good agreement with those obtained in this study. In the same study, bioavailability of amoxicillin was calculated as 29% and 32% with and without milk respectively.

This study shows that the bioavailability of pivampicillin is not adversely affected when horses are fed prior to administration. This corresponds well with the results obtained in humans. Jordan *et al.* (1970) reported that the bioavailability of pivampicillin was higher when this drug was given with food than during fasting, whereas the bioavailability of ampicillin trihydrate was higher in fasting subjects. However, in calves the bioavailability of pivampicillin was higher when given without milk than when given with milk (Ziv *et al.*, 1977). Bogan *et al.* (1984) have shown that the bioavailability of trimethoprim and phenylbutazone is markedly lower after administration to recently fed horses. It appears a practical advantage that pivampicillin causes satisfactory plasma concentrations regardless of the horse's feeding regimen.

It is concluded that pivampicillin has a potential place in the oral medication of adult horses. In order to facilitate oral administration in horses it is common practice that the drug to be administered is mixed with syrup. Unfortunately, simple mixing of pivampicillin with syrup resulted in an irregular pattern of absorption in fed horses. The bioavailability, however, seemed no less than in fasting horses. Therefore, an oral paste may still be useful provided the pharmaceutical formulation can be optimized, lacking the irregular resorption of the simple mix with syrup used in this study. It has been demonstrated that in most species pivampicillin shows an excellent bioavailability. Among oral penicillins in horses it appears to be the most promising candidate for studying the site, extent and mechanism of absorption in order to improve the biopharmaceutical characteristics of these valuable antibiotics. Further studies aimed at this goal are in progress.

## ACKNOWLEDGMENTS

Thanks are due to Mr J. C. P. van Mameren of Leo Pharmaceuticals for supplying the Pondocillin® and to Mr A. J. de Wit and his staff for care of the horses and assistance with the experiments.

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