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EFFECT OF URINARY ACIDIFIERS AND ALKALISERS ON URINARY EXCRETION OF AMPICILLIN SODIUM IN CAMEL

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ABSTRACT

Manipulation of cameline urine pH and its effect on urine disposition of ampicillin in camels was studied. Urine alkalinity (pH 8.5) achieved by oral administration of 900 mg of sodium bicarbonate/kg/day (5 animals). Urine acidity (pH 4.5) was achieved by oral administration of 800 mg of ammonium chloride/kg/day (5 animals). Normal urine (pH 7.4) was achieved by oral administration of normal saline (5 animals, controls). Ampicillin was administered intravenously to camels at a single dose of 4 mg/kg body weight. Ampicillin kinetics was estimated by microbiological method using *Bacillus subtilis* as a test organism. The mean percentage dose of ampicillin excreted unchanged in urine over 8 hours was 19.3 ± 0.3, 19.7 ± 0.3, 18.9 ± 0.2% in normal, alkaline and acidic urine, respectively. The maximum peak of excretion was 0.29, 0.31 and 0.30 mg/ml in normal, alkaline and acidic urine, respectively. The time taken to reach that peak of excretion was 5, 5.3 and 5.1 hours in normal, alkaline and acidic urine, respectively. The half-life of drug was 0.277, 0.271 and 0.274 hour in normal, alkaline and acidic urine, respectively. These results indicate that changes in urinary pH over the range studied did not affect ampicillin kinetics in urine of camel.

Key words: Acidic, alkaline, ampicillin, camel, excretion

Knowledge of mechanisms for elimination of antibiotics is essential, especially when excessive plasma or tissue concentrations of the drug cause serious toxicity. Most antibiotics and their metabolites are eliminated primarily by the kidneys (Sande *et al*, 1991). The increased concentration of antibiotic occurring after the first dose may result from the absorption from the kidney or bladder as it has been shown that antibiotics are extensively reabsorbed from the urinary tract in ruminant species (Nouws *et al*, 1982). Furthermore, the nephron in the camel is twice as long as that of the cow or goat (Abdalla and Abdalla, 1979). It has been demonstrated that benzylpenicillin elimination occurs more slowly in the dromedary than in sheep (Oukessou *et al*, 1990), suggesting that the use of the same dosage regimen for both ruminant species may lead to significant differences in plasma concentration, therapeutic efficacy and may be toxicity. Such variations indicate that the dose regimen of ampicillin and other drugs should be based on kinetic studies of these drugs. Urine pH has been reported to directly affect the rate of renal excretion of many drugs. For instance, studies carried out in horses indicated that physiological or artificial alterations of urine pH had direct effects on renal excretion of phenylbutazone (Moss and Haywood, 1973), amphetamine (Baggot *et al*, 1972) and procaine (Evans and Lambert, 1974). The objective of the study was to determine the effects of urine pH changes on urinary disposition of ampicillin in camels.

Materials and Methods

Fifteen adult camels of 2-4 years old and weighing 200-250 kg were used in this study. They were housed in individual pens with water and hay provided *ad libitum*. Blood was collected in heparinised tubes by venipuncture at specified times, blood plasma was separated and stored until analysis. The overall daily urine production in all camels were regularly collected during experiments. The urine was collected either in plastic bags or using a Foley catheter implanted in the urinary bladder. The plastic bags were designed to fit the camel penis or vulva. Bags were glued on surrounding skin and changed or drained at least 5 times a day. In all cases, the volume collected was measured, pH estimated and 5 ml were taken and stored for subsequent analysis. Animals were divided randomly into 3 groups. Group 1 (n=5) animals were given saline, group 2 (n=2) animals were given alkaliser and group 3 (n=5) animals were given

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acidifier. Ampicillin at a single dose of 4 mg/kg body weight was administered intravenously to animals before and after alkalisation and acidification of urine.

Alkalisation of urine: Urine pH was monitored for 2 days before administration of alkaliser. Sodium bicarbonate (BDH Analar, England) was diluted in 1 litre of water, then was administered by stomach tube during 6 consecutive days at dose rates of 100, 200, 400, 600, 900 and 900 mg/kg body weight, until the urine becomes consistently alkaline (pH > 7.9).

Acidification of urine: Acidification of urine was carried out by administration of ammonium chloride (BDH Analar, England) via stomach tube. Ammonium chloride was diluted in 1 litre of water, and then administered during 5 consecutive days at a dose of 200, 400, 600, 800 and 800 mg/kg body weight, until the urine becomes consistently acidic (pH < 4.3).

Urine pH measurements: The pH of urine was determined by a portable pH meter (Whatman, England) which was calibrated before each measurement using standard pH buffers.

Antibiotics measurements: Ampicillin concentration in urine was determined using the agar diffusion microbiological assay using *Bacillus subtilis* as a test organism (Nouws *et al*, 1982).

Kinetic analysis: The extent and rate of bioavailability of drugs shall be used to compare the different products. The percentage dose excreted (PDE) unchanged in urine (over hours) and the maximum peak of excretion (MPE) with the time taken to reach that peak (TTP). Elimination constant (Ke) and half-life ($t_{1/2}$) were calculated from log urinary excretion rate versus time curves (Ritschel, 1976).

Statistical analysis

A Mann-Whitney U-test for non-parametric data was used to compare pharmacokinetic variables after urine acidification or alkalisation. A value of ($p < 0.05$) was considered statistically significant (Kirkwood, 1988).

Results

Oral administration of saline maintanied pH of urine at 7.4. Administration of 100-900 mg/kg body weight sodium bicarbonate resulted in an increase in urine pH from 7.6 on the 2nd day to more than 8.4 ($P < 0.01$) on the 6th day. Administration of 200-800 mg/kg body weight ammonium chloride to camels resulted in a decrease in urine pH from 7.1 on the 1st day to less than 4.5 ($P < 0.01$) on the 5th day. (Table 1.)

Urine concentration of ampicillin in the 3 groups was similar (Fig 1). Urine pharmacokinetic variables of ampicillin sodium after saline, alkalisation or acidification are given in table 2. Significant differences were not observed.

Table 1. Urine pH in camels during administration of saline, sodium bicarbonate and ammonium chloride (n = 5 each).

Time (h)	pH values		
	Group 1 (control)	Group 2 (alkalised)	Group 3 (acidified)
0	7.4 ± 0.1	7.4 ± 0.1	7.4 ± 0.1
1	7.3 ± 0.1	7.4 ± 0.1	7.1 ± 0.1
2	7.4 ± 0.1	7.6 ± 0.1	6.6 ± 0.2
3	7.3 ± 0.1	7.8 ± 0.1	5.5 ± 0.2
4	7.4 ± 0.1	7.9 ± 0.2	4.9 ± 0.1
5	7.4 ± 0.1	8.4 ± 0.1	4.7 ± 0.1
6	7.3 ± 0.1	8.5 ± 0.1	4.5 ± 0.2
7	7.3 ± 0.1	8.4 ± 0.2	4.5 ± 0.2

Table 2. Pharmacokinetic parameters describing the excretion of ampicillin in urine of camels after a single intravenous bolus of 4 mg/kg body weight before and after alkalisation and acidification of urine (n=5, each).

Parameters	Treated animals		
	Group 1 (control)	Group 2 (alkalised)	Group 3 (acidified)
PDE (%)	19.3 ± 0.3	19.7 ± 0.3	18.9 ± 0.2
MPE (mg/ml)	0.29 ± 0.01	0.34 ± 0.01	0.30 ± 0.01
TMP (hour)	5 ± 0.1	5.3 ± 0.1	5.1 ± 0.1
Ke ($hour^{-1}$)	2.5 ± 0.02	2.48 ± 0.02	2.51 ± 0.02
$t_{1/2}$ (hour)	0.277 ± 0.001	0.271 ± 0.002	0.274 ± 0.002

PDE= percentage dose excreted, MPE= maximum peak of excretion, TMP= time to maximum peak, Ke= elimination constant, $t_{1/2}$= half-life.

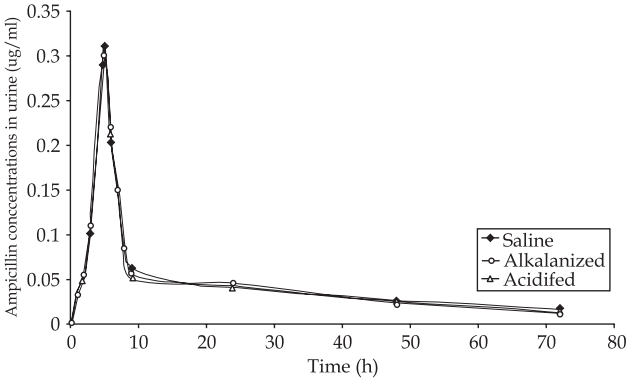

Fig 1. Mean semi-log concentrations of ampicillin in urine versus time following intravenous administration of a single dose of 4 mg/kg body weights to healthy camels before and after alkalisation and acidification of urine. (n=5, each).

The mean percentage dose excreted unchanged in urine over 8 hours following intravenous administration of ampicillin to saline treated camels was 19.3%. This value corresponds to 19.7 and 18.9% in alkalised and acidified urine, respectively. Similar values for the maximum peak of excretion (MPE), time taken to reach that peak (TTP), elimination constant (Ke) and half-life ($t_{1/2}$) in saline treated camels were similar to values in alkalised and acidified urine.

Discussion

Oral administrations of sodium bicarbonate and ammonium chloride have successfully resulted in alkalisation and acidification of camel urine, respectively. Sodium bicarbonate is a saline diuretic (Brander *et al,* 1985). The diuretic effect is principally an osmotic one for sodium salts with an increased excretion of bicarbonate which gives a strong alkaline reaction to urine. Likewise ammonium chloride is also a saline diuretic (Gilman *et al,* 2005). The ammonium ion enters the ornithine cycle, yields a hydrion and converted into urea. The urea acts as an osmotic diuretic and the excess chloride retains sodium in the filtrate.

Urine pH has been reported to directly affect the rate of renal excretion of many drugs. The doses of drugs used to produce alkalisation and acidification of urine was twice as high as the doses used in the horse (Liv *et al,* 1992). This may be due to the high buffering capacity of the camel kidney. Under hydration, normal conditions the glomerular filtration rate and renal plasma flow expressed in relation to body weight are 2 to 4 times higher in sheep (Kaufman and Bergman, 1978) than in dromedary (Etzion and Yagil, 1985). Furthermore, the nephron in the camel is twice as long as in cows or goat (Abdalla and Abdalla, 1979).

Ampicillin has been shown to undergo little metabolism and excreted almost unchanged (Gilman *et al,* 1991). Approximately 20% of the administered dose was excreted by the kidney in the first 8 hours. The presence of high concentration of the drug in urine may be of value in treating urinary tract infection in this species.

Significant differences were not observed in urinary pharmacokinetic variables of ampicillin sodium after alkalisation or acidification. One possible explanation is that ampicillin sodium is a weak organic acid with pKa of 2.8 and therefore will exist in an ionised and unionised form and that penicillins are water-soluble in ionised and unionised form. Therefore, they will be excreted rapidly in a wide range of pH and urine pH may not have a major role in the rate of excretion (Baggot *et al,* 1972).

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