

Correlations between milk production and kinetic variables in milk of cephalothin administered to lactating goats

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ABSTRACT: The aim of the present study was to correlate the milk production and the kinetic variables in milk of cephalothin administered to goats. Twenty healthy creole goats in milk production were used. Cephalothin was administered by intravenous route (20 mg/kg b.w.). Milk samples were collected at 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0 and 12.0 hours postadministration of the antibiotic. Cephalothin concentrations were measured in milk samples by high performance liquid chromatography. The values (mean \pm standard error) of milk production collected during 24 hours previous to the administration of the antibiotic were 761.5 ± 111.1 ml. The results of the kinetic variables (mean \pm standard error) of cephalothin in milk were: $AUC = 5.4 \pm 1.6$ $\mu\text{g/ml/h}$; $C_{\text{max}} = 1.1 \pm 0.3$ $\mu\text{g/ml}$ and $t_{\text{max}} = 1.7 \pm 0.1$ h. The correlation coefficients AUC-milk production, C_{max} -milk production and t_{max} -milk production were: 0.602 ($P < 0.01$), 0.596 ($P < 0.01$) and 0.398 ($P < 0.1$), respectively. In conclusion, the areas under the curve and the maximum concentrations and the time to reach them in milk are in fact related to the volume of milk produced by the goats.

Keywords: cephalothin; kinetic variables; correlation coefficients; lactating goats

Cephalothin is a first-generation cephalosporin that is poorly absorbed in the digestive tract and thus has to be administered parenterally to obtain a systemic effect. This antibiotic is distributed mainly in the extracellular fluid and excreted by the kidneys, being hard to find in the cephaloraquideal liquid (Booth and McDonald, 1987; Caprile, 1988). The distribution of cephalothin in the mammary gland is related to the diffusion of the nonionized, lipid soluble form of this drug through the epithelial cells of the gland. The proportion of drug in the nonionized form depends on the dissociation constant (pKa) of the drug and on the pH of the medium in which it is dissolved (Rasmussen, 1971).

In general only a few drugs are approved for use in lactating goats. That is why Veterinaries are allowed to prescribe antibiotics in an off-label manner. On the other hand, they must make sure that residues do not enter food chain.

Cephalothin is an antibiotic used in dairy goats. Therefore it is important to take into account the possible exposure to this drug among people consuming goat milk. This inconvenience can be avoided by allowing appropriate withdrawal periods for the milk of dairy goats.

Cephalothin is used also for the treatment of mastitis. In order for this treatment to be effective, some things should be taken into account the physicochemical characteristics of the drug, the formulation, the dose, the volume of distribution, permeability through the blood-milk barrier, the rate of drug elimination and the sensitivity of the udder pathogen, among others. It is not yet fully understand the influence of the volume of milk production on the kinetic variables in milk of cephalothin administered to lactating goats.

The aim of this study was to determine the correlations between the kinetic variables in milk of

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cephalothin administered by intravenous route and the milk production volume in goats.

MATERIAL AND METHODS

Twenty healthy creole goats of different levels of milk production were used.

Cephalothin was administered by intravenous route to goats (10 mg/kg b.w.). Milk samples were collected at 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0 and 12.0 hours postadministration of the antibiotic. The goats were manually milked twice a day.

Cephalothin concentrations were measured in the milk samples by high-performance liquid chromatography. Briefly, the samples were allowed to thaw and then mixed in 250- μ l aliquots with 100 μ l of 0.02 mol/l $\text{H}_3\text{PO}_4/\text{KH}_2\text{PO}_4$ buffer (pH 2.6), 20 μ l of 30% (v/v) perchloric acid and 250 μ l of methanol. The specimens were then centrifuged at 1 000 g for 5 min and the supernatants recovered. Finally, 20 μ l of each supernatant was injected into a Lichrosphere cc125/4, RP 18, 100-5 column (Merck, USA) with a 13% (v/v) acetonitrile solution in 0.02 mol/l $\text{H}_3\text{PO}_4/\text{KH}_2\text{PO}_4$ buffer as the mobile phase of a high-performance liquid chromatography system (Thermo Separation, USA), equipped with an UV absorbance detector at 254 nm wavelength to analyse cephalothin concentrations. This method has intra- and inter-run coefficients of variations lower than 6% and a minimum limit of detection of 0.01 $\mu\text{g/ml}$.

The milk concentration-time data of cephalothin were assessed by non-compartmental analysis (Ritschel, 1986). The maximum milk concentration (C_{max}) and the time to achieve C_{max} (t_{max}) were directly observed from the data obtained for individual animals. Least-square regression analysis was employed on the terminal elimination phase to estimate the elimination rate constant (k_{el}). The area under the curve from time zero to infinity ($\text{AUC}_{0-\infty}$) was estimated by trapezoidal integration as:

$$\text{AUC}_{0-\infty} = \text{AUC}_{0-t} + C_t/k_{\text{el}}$$

where: AUC_{0-t} = the AUC from time zero to time t

C_t = the concentration of cephalothin in the last milk sample collected at time t

Linear regression analysis was used to compare the kinetic variables AUC, C_{max} and t_{max} with the milk production. The interaction between these variables and milk production was examined by analysis of variance. All statistical analysis was performed using Statgraphics Plus.

RESULTS AND DISCUSSION

The values (mean \pm standard error) of milk production (MP) collected during 24 hours previous to the administration of the antibiotic were 761.5 ± 111.1 ml.

The time-concentrations (mean \pm standard error) of cephalothin in milk are shown in Figure 1.

The results (mean \pm standard error) of the kinetic variables were: $\text{AUC} = 5.4 \pm 1.6$ $\mu\text{g/ml/h}$; $C_{\text{max}} = 1.1 \pm 0.3$ $\mu\text{g/ml}$ and $t_{\text{max}} = 1.7 \pm 0.1$ h.

The correlation coefficients equal 0.602 and 0.596 indicating a moderately strong relationship between the AUC and C_{max} and MP, respectively (see Figure 2).

The P values are lower than 0.01, there is a statistically significant relationship between AUC-MP and C_{max} -MP at the 99% confidence level.

However, the correlation coefficient equals 0.398 indicating a relatively weak relationship between the variables t_{max} and MP. The P value is lower than 0.10 and there is a statistically significant correlation between t_{max} and MP volume at the 90% confidence level.

In human milk the concentration of cephalosporins is generally low. Following administration of cephalothin by intravenous route Bergan (1987) and Kafetzis et al. (1981) found C_{max} in milk at 1 and 2 hours, respectively. In our work C_{max} is achieved between the first and the second hour postadministration of the drug.

In general terms, it is accepted that C_{max} is proportional to the amount of antibiotic that diffuses into milk and that t_{max} depends on the rate of such process, whereas the AUC is proportional to the amount of drug that reaches the mammary gland and is not related to the rate at which it enters the compartment. Lactation is associated with a high blood flow to

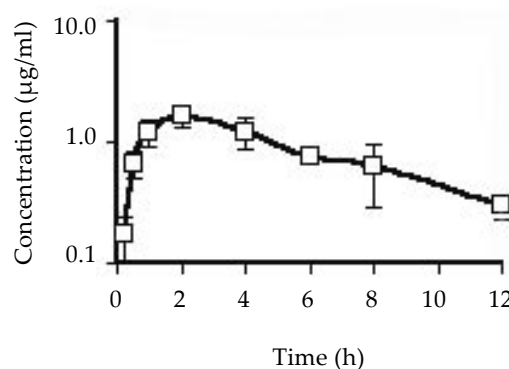


Figure 1. Semilogarithmic plot of time-concentration in milk of cephalothin administered to lactating goats

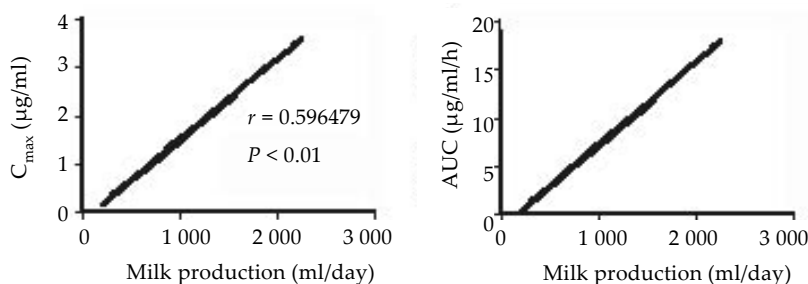


Figure 2. Linear regression analysis between areas under the curve (AUC), maximum milk concentration (C_{max}) of cephalothin and milk production volume in goats

the mammary glands (Pickles, 1953), capable of influencing the pharmacokinetic variables of the drug in milk. The mammary glands that produce more milk have greater blood perfusion and a greater passage of the drug compared to the glands with less blood flow. The time to reach the C_{max} was weakly correlated with the milk production and it could be observed that the highest maximum concentrations were seen later compared to the lower C_{max} with an early appearance. This could be due to a higher milk production that would give the gland a higher functional volume, influencing together with other tissues the subsequent redistribution and consequently the time-concentrations of the drug in milk.

It is well known that one of the main aims of pre-clinical pharmacokinetics is to generate information describing the absorption, distribution, metabolism and excretion processes in animals, that can be extrapolated to human pharmacokinetic processes. The results obtained through the present work could be extrapolated to humans, however we should be cautious on doing so and also take into account that the rate of distribution of a drug to the mammary gland is determined by the blood flow perfusing the tissue and the ease with which the drug molecules cross the capillary barrier and penetrate in milk. We should also consider the influence of the drug protein binding in plasma and tissue. It is well known that the extent of binding of drugs to plasma proteins differs considerably among species (Callan and Sunderman, 1973; Kragh-Hansen, 1981; Caprile, 1988).

In conclusion, the areas under the curve, the maximum concentrations of cephalothin in milk and the time to reach them, were related to the milk volume produced by the animals. It could be observed that the volume determines the passage of the antibiotic to the milk, producing in relatively longer times

not only greater maximum concentrations but also greater areas under the curve.

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