

THE PHARMACOKINETICS OF THIAMPHENICOL IN LACTATING COWS

N. MESTORINO, M.F. LANDONI, M. ALT AND J.O. ERRECALDE
Cátedra de Farmacología, Farmacotecnia y Terapéutica, Facultad de Ciencias Veterinarias, Universidad Nacional de La Plata, Calle 60 y 118, cc 296 (1900) La Plata, Argentina

ABSTRACT

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The pharmacokinetics of thiamphenicol were studied after intravenous and intramuscular administration of 25 mg/kg body weight in lactating cows. Distribution ($t_{1/2\alpha}$) and elimination ($t_{1/2\beta}$) half-lives of 6.10 ± 1.39 min and 1.60 ± 0.30 h, respectively, were obtained after intravenous administration. The body clearance was 3.9 ± 0.077 ml/kg per min and the apparent volume of distribution was 1220.79 ± 256.67 ml/kg. The rate at which thiamphenicol appeared in the milk, as indicated by the penetration half-life ($t_{1/2p}$) (serum to quarters), was found to be 36.89 ± 11.14 min. The equivalent elimination half-life ($t_{1/2e}$) (quarters to serum) from the milk was 3.62 ± 1.06 h and the peak thiamphenicol concentration in the milk was 23.09 ± 3.42 μ g/ml at 2.5 ± 0.32 h.

After intramuscular injection, the elimination half-life was 2.2 ± 0.40 h, the absorption half-life was 4.02 ± 1.72 min and the peak concentration in the serum was 30.90 ± 5.24 μ g/ml at 23 ± 8.4 min. The bioavailability after intramuscular administration approached 100%. The penetration half-life was 50.59 ± 6.87 min, the elimination half-life was 5.91 ± 4.97 h and the mean peak concentration in the milk was 17.37 ± 2.20 μ g/ml at 3.4 ± 0.22 h.

Keywords: cows, intramuscular, intravenous, lactation, milk, pharmacokinetics, serum, thiamphenicol

Abbreviations: AUC, area under the concentration–time curve; CAP, chloramphenicol; C_{max} , peak concentration; IM, intramuscular; IV, intravenous; TAP, thiamphenicol; $t_{1/2\alpha}$, distribution half-life; $t_{1/2\beta}$, elimination half-life; V_c , volume of central compartment; V_d , volume of distribution

INTRODUCTION

The toxicity of chloramphenicol has been the cause of its use being banned or strictly regulated worldwide. This has accentuated the need for an effective broad-spectrum antibiotic to be used in food-animal medicine. Thiamphenicol is a structural analogue of CAP with marked toxicological differences (see comparative structures in Figure 1). TAP has a greater *in vitro* activity against pathogenic bacteria than either of its structural analogues. It is active against some bacteria that are resistant to CAP (Neu and Fu, 1980).

CAP has been reported to cause reversible, dose-related bone marrow suppression in humans by a mechanism involving inhibition of mitochondrial protein synthesis (Yunis, 1981). It also causes irreversible non-dose-related aplastic anaemia in humans by a mechanism that is not well understood (Yunis, 1981).

TAP is a bacteriostatic/bactericidal antibiotic with the same mode of action as CAP. Reversible, dose-dependent bone marrow suppression caused by inhibition of

mitochondrial protein synthesis is also a side-effect of TAP (Yunis *et al.*, 1973; Keiser, 1974) but an irreversible aplastic anaemia has not been reported following the use of this drug (Yunis *et al.*, 1973; Ferrari and Pajola, 1981). The fact that the *p*-methylsulphonyl group in TAP has replaced the *p*-nitro group on the aromatic ring of CAP (see Figure 1) gives support to the hypothesis that the *p*-nitro group of CAP is responsible for the aplastic anaemia.

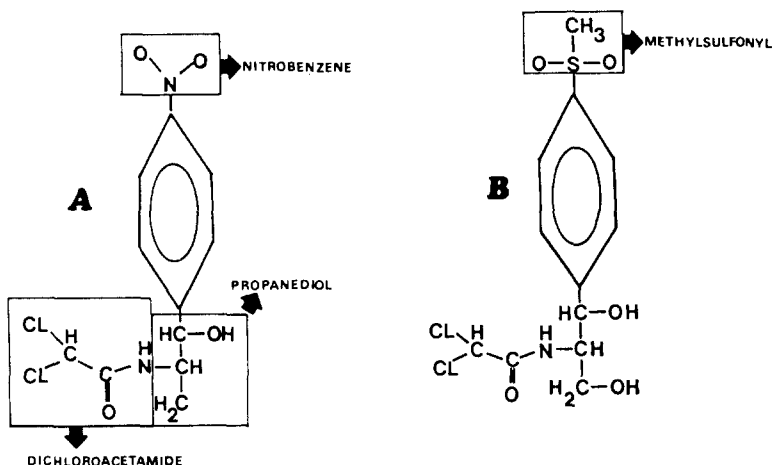


Figure 1. Structural formulae of chloramphenicol (A) and thiamphenicol (B)

Although TAP has a similar antibacterial spectrum to that of CAP (Van Beers *et al.*, 1975), there are marked pharmacological differences between the two drugs. Thus, TAP is more stable in solution (Azzolini *et al.*, 1970), is not appreciably protein bound in the body and does not undergo significant biotransformation (Azzolini *et al.*, 1970). The drug diffuses into intracellular spaces, the central nervous system and the aqueous humour (Huber, 1965).

In view of the limited kinetic data available on this antibiotic in ruminants, we decided to investigate the disposition kinetics of TAP after a rapid single intravenous injection in cows and to compare these data with those obtained after intramuscular administration of an equal dose in the same animals.

MATERIALS AND METHODS

Six healthy lactating Holstein cows (weighing 468 ± 54.05 kg) each received single doses of 25 mg/kg thiamphenicol glycinate chlorhydrate (26.66% solution in phosphate buffer, pH 6) by both the intravenous and the intramuscular routes following a 3×3 cross-over design. Three weeks elapsed between injections. The drug was administered IV in the right jugular vein. For IM administration, half the volume was injected into each ischiotibial muscle zone.

Blood samples were drawn through a polyethylene catheter placed in the left jugular vein. Samples were taken immediately before the injection (control) and at the

following times after injection: 5, 10, 15 and 30 min and 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h. After clotting, the serum was separated by centrifugation and stored at -20°C until assayed. Milk samples were collected from the left front quarter through a teat catheter immediately before the injection (control) and at 5, 10, 15, 30 and 40 min and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10 and 12 h after injection. The milk samples were kept at -20°C until assayed. TAP concentrations were determined microbiologically by a modified cylinder-plate diffusion method (Grove and Randall, 1955). The test organism was *Sarcina lutea* ATCC 9341 and the culture medium was antibiotic medium number 1 (Difco Laboratories, Detroit, MI, USA). The sensitivity of the assay was $5\text{ }\mu\text{g/ml}$ of serum or milk. The average of four replicates of each sample was compared with a standard curve produced from bovine serum containing known amounts of thiamphenicol. The same procedure was adopted for assay of the milk samples.

The pharmacokinetic models that best fitted the TAP plasma profiles after both IV and IM administration were derived by means of the MAICE (Minimum Akaike Information Criterion) Test (Akaike, 1976; Yamaoka *et al.*, 1978).

The means and standard deviations were calculated for the thiamphenicol concentrations in serum and milk at the various times. The pharmacokinetic parameters were estimated for each cow by weighted least-squares non-linear regression employing a package of programs known as ADAPT (D'Argenio and Schumitzky, 1979), which uses the Simplex algorithm (Nelder and Mead, 1965). The bioavailability of thiamphenicol administered by the IM route (defined by F , the absorbed fraction) was obtained as the ratio between the areas under the curves of concentration versus time after IV and IM administrations. The areas under the blood or milk curves for concentration versus time were calculated by the trapezoidal rule (Baggot, 1978).

The withdrawal time (T) for milk following intramuscular administration was calculated by employing the formula reported by Nouws and Ziv (1978) modified as follows:

$$T = \frac{t_{1/2} [\ln R \cdot C_{\max} - \ln C_{\lim}]}{\ln 2}$$

where $t_{1/2}$ is the biological or disposition half-life, C_{\max} is the peak plasma TAP concentration, and R is the milk:plasma ratio of the TAP concentration. C_{\lim} represents the maximum permitted residue level of 20 ng/ml , as recommended by Boisseau (1985).

RESULTS

The TAP concentration-time profiles for serum and milk after IV and IM administration of 25 mg/kg are shown in Figures 2 and 3, respectively. The mean pharmacokinetic parameters corresponding to the IV and IM routes in serum and milk are given in Tables I and II, respectively.

In the case of IV administration, the disappearance of TAP from the blood was clearly a two-rate phenomenon and this was confirmed by the MAICE Test.

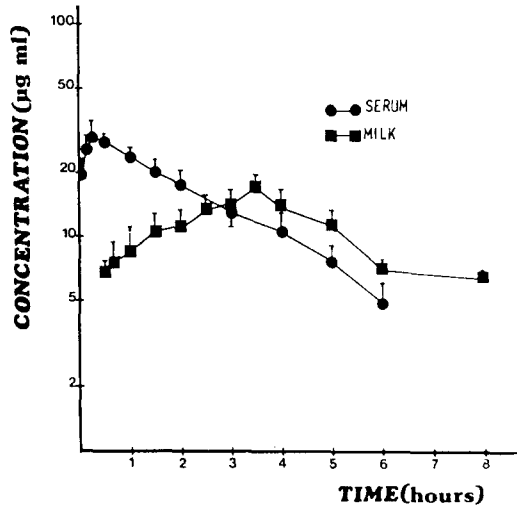


Figure 2. Semilogarithmic plots of averaged serum and milk thiamphenicol concentrations for six lactating cows following intravenous administration of 25 mg thiamphenicol/kg body mass

A one-compartment pharmacokinetic model with first-order absorption was selected by means of the MAICE Test to describe the serum disposition of TAP after IM administration to lactating cows.

The other parameters indicate a liposoluble drug with a high volume of distribution and penetration into milk.

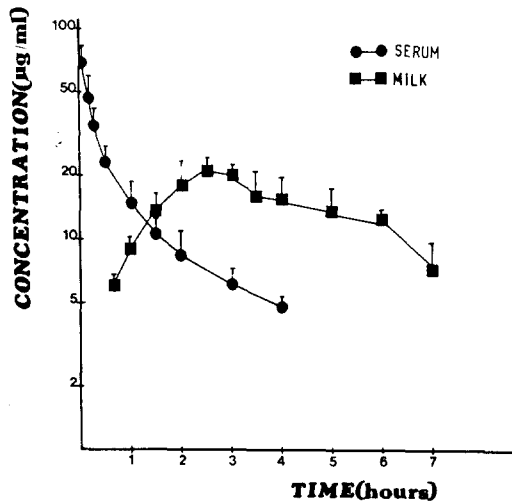


Figure 3. Semilogarithmic plots of averaged serum and milk thiamphenicol concentrations for six lactating cows following intramuscular administration of 25 mg thiamphenicol/kg body mass

TABLE I

Mean pharmacokinetic parameters in serum determined for six lactating cows after intravenous and intramuscular administration of 25 mg thiamphenicol/kg body mass

| Parameter ^a | Administration route | |
|---------------------------------|----------------------|--------------------|
| | IV ^b | IM ^b |
| A ($\mu\text{g/ml}$) | 86.15 ± 55.05 | — |
| α (h^{-1}) | 7.06 ± 1.32 | — |
| $t_{1/2\alpha}$ (min) | 6.10 ± 1.39 | — |
| B ($\mu\text{g/ml}$) | 23.26 ± 5.39 | — |
| β (h^{-1}) | 0.45 ± 0.09 | 0.32 ± 0.07 |
| $t_{1/2\beta}$ (h) | 1.6 ± 0.30 | 2.2 ± 0.40 |
| K_{ab} (h^{-1}) | — | 12.52 ± 6.75 |
| $t_{1/2ab}$ (min) | — | 4.02 ± 1.72 |
| C_0 ($\mu\text{g/ml}$) | 109.40 ± 53.37 | — |
| V_c (ml/kg) | 268.00 ± 0.13 | — |
| K_{12} (h^{-1}) | 3.66 ± 0.94 | — |
| K_{21} (h^{-1}) | 2.06 ± 0.86 | — |
| K_{el} (h^{-1}) | 1.81 ± 0.93 | — |
| AUC ($\mu\text{g.h/ml}$) | 47.89 ± 7.60 | 65.71 ± 14.16 |
| Cl_B (ml/kg per min) | 3.90 ± 0.077 | — |
| V_d (area) (ml/kg) | 1220.79 ± 256.67 | — |
| C_{\max} ($\mu\text{g/ml}$) | — | 30.90 ± 5.24 |
| T_{\max} (min) | — | 23.00 ± 8.40 |
| Lag-obs (min) | — | 5.00 |
| F (%) | — | 100.33 ± 22.82 |

^a A and B are y-axis intercepts of regression lines best fitting distribution and elimination data points respectively; α and β are distributive and eliminative rate constants, and $t_{1/2\alpha}$ and $t_{1/2\beta}$ their respective half-lives; AUC is the area under the serum concentration-time curve; V_c is the apparent volume of the central compartment, and V_d (area) is the apparent volume of distribution calculated by the area method; Cl_B is the body clearance; K_{12} , K_{21} and K_{el} are microconstants associated with the two-compartment pharmacokinetic model; K_{ab} is the absorption rate constant and $t_{1/2ab}$ its half-life; Lag-obs is the interval between drug administration and its detection in serum; C_{\max} is the maximum observed serum concentration and T_{\max} is the time at which the maximum concentration occurred; F is bioavailability

^bValues are mean \pm SD

TABLE II

Mean pharmacokinetic parameters in milk determined for six lactating cows after intravenous and intramuscular administration of 25 mg thiamphenicol/kg body mass

| Parameter ^a | Administration route | |
|--|----------------------|-------------------|
| | IV ^b | IM ^b |
| B ($\mu\text{g/ml}$) | 33.44 ± 12.39 | 25.14 ± 8.40 |
| K_e (h^{-1}) | 0.21 ± 0.067 | 0.16 ± 0.07 |
| $t_{1/2E}$ (h) | 3.62 ± 1.06 | 5.91 ± 4.97 |
| K_p (h^{-1}) | 1.23 ± 0.41 | 0.83 ± 0.11 |
| $t_{1/2P}$ (min) | 36.89 ± 11.14 | 50.59 ± 6.87 |
| C_{\max}^M ($\mu\text{g/ml}$) | 23.09 ± 3.42 | 17.37 ± 2.20 |
| T_{\max}^M (h) | 2.5 ± 0.32 | 3.4 ± 0.22 |
| $C_{\max}^{\text{Sim}}:C_{\max}^{\text{Mim}}$ | — | 1.88 ± 0.58 |
| AUC^M ($\mu\text{g}\cdot\text{h/ml}$) | 85.22 ± 24.55 | 73.96 ± 10.65 |
| $\text{AUC}^M:\text{AUC}^S$ | 1.81 ± 0.56 | 0.92 ± 0.20 |
| Withdrawal (h) | — | 52.54 ± 17.11 |

^a K_e is the elimination-from-milk rate constant and $t_{1/2E}$ its half-life; K_p is the penetration-in-milk rate constant and $t_{1/2P}$ its half-life; C_{\max}^M is the C_{\max} in milk; $C_{\max}^{\text{Sim}}:C_{\max}^{\text{Mim}}$ is the ratio between the C_{\max} in serum and C_{\max} in milk after IM administration; AUC is area under the curve; $\text{AUC}^M:\text{AUC}^S$ is the ratio between AUC concentration vs time in serum and milk after IV and IM administration; Withdrawal is the withdrawal time needed to obtain milk with TAP levels of less than 20 ng/ml

^bValues are mean \pm SD

DISCUSSION

For IV administration, the distribution half-life of TAP of 6.10 ± 1.39 min from the central compartment was slightly shorter than those reported for CAP in cows of 9.6 min (Burrows *et al.*, 1978) and 11.5 min (Anderson *et al.*, 1983), or those for florfenicol of 7.94 min in male veal calves (Adams *et al.*, 1987) and 12.6 min in lactating cows (Signorini *et al.*, 1986). However, a lower value of 1.84 min was reported for CAP in swine (Mercer *et al.*, 1978). These differences may have arisen because of the early blood samples taken in the present work.

The mean volume of the central compartment was 268 ± 0.13 ml/kg, a value that is comparable with that of 361 ml/kg reported for CAP in calves (Burrows *et al.*, 1978) but smaller than that of 920 ml/kg reported in cows (Van Der Lee *et al.*, 1982). The mean apparent volume of distribution of 1220.79 ± 256.67 ml/kg obtained by the area method was relatively large. This value correlates with the high lipid solubility of TAP, suggesting excellent penetration and distribution of the drug in the body fluids, including the intracellular water. Similar values were reported by Signorini and

colleagues (1986) (1440 ml/kg) in the same kind of animals, by Burrows and colleagues (1978) for CAP in young calves (1264 ml/kg) and by Anderson and colleagues (1983) in adult cows (1110 ml/kg). In old lactating cows, however, a value of 2900 ml/kg, more than double that reported here was found by Van Der Lee and colleagues (1978). Although those authors did not discuss this point, it is possible that this reported increase in V_d in older animals may be attributed to the fact that such animals have less total body water than younger animals: as a consequence there could be a diminution of V_c and an increase in V_d .

The elimination half-life of 1.6 ± 0.30 h indicates that cows eliminate TAP rapidly. Our value is smaller than the mean value of 2.57 h reported by Signorini and colleagues (1986), who did not specify the vehicle used, that of 3.45–4.11 h reported for florfenicol in male veal calves, with no specification as to age or weight, by Adams and colleagues (1987), that of 3.5 h reported in cattle by Pilloud (1973), and those of 11.7 h and 4.9 h reported for CAP in day-old and 10- to 12-week-old calves by Reiche and colleagues (1980). The longer half-life reported in neonatal calves could be due to their underdeveloped hepatic drug-metabolizing enzyme systems. For the 3.5 h reported by Pilloud, we have no explanation other than that 3 of the 5 experimental animals were in late pregnancy. For a liposoluble drug like CAP, extensive distribution in the pregnant uterus and fetus might contribute to retarding the elimination process.

The total body clearance for TAP (3.9 ± 0.077 ml/kg per min) agrees with the value of 3.9 ml/kg per min reported by Signorini and colleagues (1986) in cows. However, a slightly lower value was reported for CAP in 7-day-old calves (1.9 ml/kg per min) (Reiche *et al.*, 1980).

Following IV administration of 25 mg/kg of TAP, the drug concentration in serum at 5 min was 68.54 ± 24.58 μ g/ml and a concentration exceeding 4 μ g/ml persisted for about 4 h.

Therapeutic levels of TAP (≥ 5 μ g/ml) were maintained in the milk for between 40 min and 8 h after IV administration. These data compare well with the value of between 2 and 8 h reported for CAP in cows (Sisodia *et al.*, 1973). The elimination half-life from the milk of 3.62 ± 1.06 h indicates that accumulation of TAP takes place in the mammary gland. This could be explained by the marked affinity of TAP for lipids. This fact must be carefully considered when calculating milk withdrawal times.

The ratio of AUC in milk to AUC in serum of 1.81 ± 0.56 suggests extensive penetration of TAP into the mammary gland. This agrees with the mammary accumulation data (Table II).

Thiamphenicol administered IM was absorbed rapidly and completely. The mean half-life of absorption of 4.02 ± 1.72 min was much shorter than that of 30 min reported for CAP in cows (Nouws and Ziv, 1979; Archimbault *et al.*, 1980). The interval between administration of the drug and its detection in serum was only 5 min and the peak serum concentration was achieved after about 23 min. The early and intensive sampling scheme used in our work may have contributed to a better definition of the absorptive phase and a smaller estimate for the half-life of absorption.

The mean intramuscular bioavailability of about 100% was similar to values reported for various formulations of CAP in cattle (Archimbault *et al.*, 1980; Reiche *et al.*, 1980) and that reported for TAP by Signorini and colleagues (1986). This finding

is in agreement with the high lipophilicity of the drug. The elimination half-life of 2.2 ± 0.40 h was similar to that of 2.29 reported by Signorini and colleagues (1986) but much shorter than the mean values of 13.9 h reported for CAP in cows (Guillot and Mouro, 1987) and 10.3 ± 3.1 h reported in cattle (Nouws *et al.*, 1986). These differences may be due to the characteristics of the formulation, since in the present study the vehicle used was phosphate buffer, whereas the other workers used unspecified organic vehicles that may have modified the absorption profile and, as a consequence, the elimination half-life.

Therapeutic levels of TAP (≥ 5 $\mu\text{g/ml}$) were maintained in milk for between 30 min and 8 h after IM administration. The increased milk $t_{1/2E}$ of 5.91 ± 4.97 h as compared with the $t_{1/2\beta}$ for serum may be explained in the same way as for IV administration, namely by mammary gland accumulation. The high lipid contents of milk and of the mammary gland could clearly induce some trapping of TAP, with rapid penetration and slow elimination. The ratios of the elimination half-life ($t_{1/2E}$) in milk to that ($t_{1/2\beta}$) in serum were 2.26 and 2.69 for intravenous and intramuscular injections, respectively.

Rapid penetration from blood into milk after IM administration is characterized by the drug having a short appearance time in the milk (Ziv, 1978), with a ratio of C_{max} in serum to C_{max} in milk of 2 or less, a very short lag time between C_{max} serum and C_{max} milk, and a ratio of AUC in milk to AUC in serum of 1 or more. TAP fulfils all these requirements and is clearly a drug that penetrates easily into milk.

The average withdrawal time to obtain a concentration of 20 ng/ml was 52.54 ± 17.11 h.

In summary, it has been shown that TAP, a broad-spectrum antibiotic, has advantageous pharmacokinetic properties for treating cows. From the serum concentrations (Figures 2 and 3) and pharmacokinetic information it can be concluded that, depending on the minimum inhibitory concentration for the microorganisms involved, three treatments per day would be effective in treating susceptible infections and might be recommended where no other effective antibiotic with a narrower spectrum was available.

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