PHARMACOKINETICS OF THIAMPHENICOL IN VEAL CALVES

A. GAMEZ, Y. PEREZ, G. MARTI, C. CRISTOFOL and M. ARBOIX

Divisió de Farmacologia, Facultat de Veterinària, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain

Thiamphenicol is a semi-synthetic structural analogue of chloramphenicol. The antibacterial spectrum of thiamphenicol is similar to that of chloramphenicol (Sutter & Finegold, 1976) with comparable minimum inhibitory concentration (MIC) values against bacteria such as *Streptococcus faecalis, Pasteurella* spp. and *Brucella* and lower MIC values against bacteria such as *Neisseria meningitidis* and *Streptococcus viridans* (Laplassotte & Brunaud, 1961; Van Beers *et al.*, 1975).

Studies on thiamphenicol kinetics in a number of species (rat, dog, human and calf) show that it is well absorbed by the intramuscular (i.m.) and oral (p.o.) routes. The drug shows little tendency (5–10%) to bind to plasma proteins (Kawabe *et al.*, 1966). Data on the distribution in human tissues and body fluids indicate a high penetration of the drug into lung tissue, kidney, bile, etc. (Cambieri *et al.*, 1970; Ferrari, 1984). It undergoes some slight metabolism in liver and it is mainly excreted in unmetabolized form by the renal route (Nakagawa *et al.*, 1975). Thiamphenicol is considerably less toxic than chloramphenicol. Side-effects reported in the literature are gastrointestinal (diarrhoea, nausea, pyrosis, vomiting) and cutaneous eruptions and haematological dyscrasias have also been reported, but the incidence is low and related to dosage and duration of treatment (Najean *et al.*, 1981).

There is little information in the literature on thiamphenicol kinetics in animals intended for meat production. However, in view of the possible therapeutic use of thiamphenicol for the treatment of bovine respiratory complex (BRC), a study of its kinetic profile in the calf after intravenous and intramuscular administration is of interest. BRC is caused by several microorganisms, one of the most frequent pathogens being *Pasteurella* spp.

Five healthy Friesian calves 8 weeks of age of mean weight (±SD) 75±6.4 kg were used. Each calf received a single i.v. dose (30 mg/kg) of a 30% solution of thiamphenicol glycinate in physiological saline. Three weeks later, the same animals received a second dose (30 mg/kg) of 30% solution of thiamphenicol in dimethylacetamide and propylene glycol by the i.m. route. Blood samples were collected at pre-established intervals after administration and assayed using a high-perform-

Correspondence to Dr Margarita Arboix, Divisió de Farmacologia, Facultat de Veterinària, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain.

ance liquid chromatography (HPLC) method as described for florfenicol by Varma *et al.* (1986). The column used was a Nucleosil C18 5 μ (250×4.6 mm i.d.) with a 30% acetonitrile in water as a mobile phase. The internal standard was chloramphenicol.

The plasma concentration–time curve was fitted and analysed by an iterative non-linear regression programme PCNONLIN (Metzler & Weiner, 1986). When the drug was administered i.v., the following equation was used to describe a biexponential curve:

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

where C_p is the plasma concentration at t time, A and B are the intercepts of the fast and slow phases, α and β are the apparent first-order fast and slow disposition rate constants and where $\alpha+\beta=K_{12}+K_{21}+K_{10}$, where K_{12} and K_{21} are the transfer rate constants from the central to the peripheral compartment, and from the peripheral to the central compartment respectively. K_{10} is the elimination rate constant.

A one-compartment open model with first-order absorption and elimination was fitted to the thiamphenicol plasma concentrations from each calf after i.m. administration and the model was described by the following equation:

$$C_p = \frac{D \cdot F}{V_d} \cdot \frac{K_{01}(e^{-K_{10}t} - e^{-K_{01}t})}{(K_{01} - K_{10})}.$$

Where D is the dose of the drug when it was administered i.v., F is the bioavailability of thiamphenicol, V_d is the apparent volume of distribution of the drug in the body. K_{01} and K_{10} are absorption and overall elimination rate constants respectively. The areas under the curve (AUC) were calculated by the method of trapezoids with addition of the extrapolated area from the last time point to infinity. Bioavailability was calculated from the areas under the curves for each of the two administrations (i.v. and i.m.) for each calf using the following equation: $F = (AUC_{i.m.}/AUC_{i.v.})\times 100$.

A Student's t-test was used to compare the differences between the pharmacokinetic parameters obtained after i.v. and i.m. administration of thiamphenicol. Results were considered significant at $P<0.01$.

The graphs corresponding to the curves of plasma thiamphenicol concentrations versus time after i.v. and i.m. administration of thiamphenicol are shown in Fig. 1. It can be seen that plasma concentrations remained over 5 μg/ml for more than 8 hours. The data obtained from i.v. administration fitted well to a biexponential equation (R=0.99). Fitting of the data corresponding to the i.m. administration shows a fast absorption phase with a maximum plasma concentration (C_{max}) of 18.6 μg/ml, 88.1 minutes after drug administration.

The pharmacokinetic parameters obtained by the analysis of the plasma concentration curve for i.v. and i.m. administration are shown in Table I. The values of the first-order distribution rate constants K_{12} and K_{21} do not differ significantly between one another in each of the five animals studied. A fast first-order absorption rate constant (K_{01}) and a low half-life of the drug related to the absorption

rate constant ($t_{\frac{1}{2}K_{01}}$) are shown after i.m. administration. The mean AUC_0^{∞} calculated for each of the plasma concentration curves resulting from i.m. administration was similar to that resulting from i.v. administration. The mean bioavailability (±SD) was 94.6±2.7%.

There are few data concerning thiamphenicol kinetics in the calf in literature and these do not analyse the kinetic model, but it may be deduced from these studies that plasma levels versus time would also fit a biexponential curve

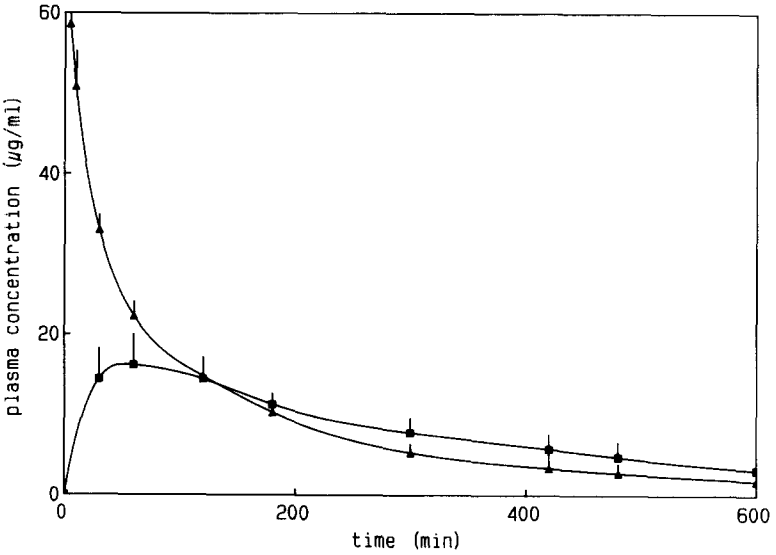

Fig. 1 Mean curve of plasma concentration of thiamphenicol versus time after i.v. (▲) and i.m. (■) administration of 30 mg/kg to 5 calves.

Table 1
Pharmacokinetic parameter kinetics of thiamphenicol in calves following i.v. and i.m. administration of 30 mg/kg; mean of five calves

i.v.	α (min^{-1})	β (min^{-1})	K_{10} (min^{-1})	K_{12} (min^{-1})	K_{21} (min^{-1})	$t_{\frac{1}{2}\beta}$ (*min*)	AUC_0^{∞} (*µg·min/ml*)	$V_{d\beta}$ (*l/kg*)	*Cl* (*ml/min*)
$\bar{x}$	0.063	0.005	0.011	0.029	0.028	142.3	6810.9	0.93	326.8
±SD	0.002	0.001	0.002	0.009	0.008	34.0	1395.3	0.06	63.0

i.m.	C_{max} (*µg/ml*)	t_{max} (*min*)	K_{01} (min^{-1})	K_{10} (min^{-1})	$t_{\frac{1}{2}K_{01}}$ (*min*)	$t_{\frac{1}{2}K_{01}}$ (*min*)	AUC_0^{∞} (*µg·min/ml*)	*MRT* (*min*)	*F* (%)
$\bar{x}$	18.6	88.1	0.039	0.0037	26.4	195.4	6438.8	280.5	94.6
±SD	4.6	29.2	0.028	0.0007	14.9	41.3	1302.7	59.0	2.7

t_{max}, time corresponding to C_{max}; $t_{\frac{1}{2}K_{01}}$, half-life of the drug related to the elimination rate constant; MRT, mean residence time.

(Signorioni & Bonanomi, 1985; Signorioni & Ferrari, 1986). The curve obtained after i.m. administration emphasizes the fast absorption rate of thiamphenicol with the maximal plasma level being achieved between 1 and 2 hours. Plasma concentrations are considerably below those obtained by i.v. administration. These data differ somewhat from those reported by other authors who found C_{max} of 17 μg/ml 15 min post-administration (Signorioni & Bonanomi, 1985; Signorioni & Ferrari, 1986). This variation could be due to the different formulations of thiamphenicol administered (Signorioni *et al.* used a glycinate of thiamphenicol with acetylcysteine and in the present study a solution of thiamphenicol with dimethylacetamide and propylene glycol was administered). Studies of i.m. administration of thiamphenicol glycinate in humans have revealed that C_{max} is reached in about 1 hour (Tacquet *et al.*, 1974; Ferrari, 1984).

The calculated pharmacokinetic parameters (Table I) show that tissue distribution of thiamphenicol is rapid. The ratio between constants α/β is high, which clearly points to the two-compartmental model already suggested by the statistical adjustment of the plasma concentration curves. In addition, the ratio of K_{12}/K_{21} distribution constants is close to 1, thus suggesting that the drug does not bind to tissues.

The mean value of $V_{d\beta}$ suggests that the drug is widely distributed in well perfused tissues. These values are similar to those reported by Signorioni & Ferrari (1986). The data are also in agreement with the high liposolubility of thiamphenicol observed in man (Cambieri *et al.*, 1970; Ferrari, 1984). In these studies, good diffusion of thiamphenicol was found in lung and kidney; lung tissue concentration was similar to that found in plasma, in contrast to the low concentration present in muscle and fat tissue. Cambieri *et al.* (1970) and Ferrari (1984) analysed the relationship between tissue levels of thiamphenicol and the minimum effective concentrations inhibiting bacterial growth and concluded that tissue concentrations were therapeutically useful against the majority of thiamphenicol-sensitive microorganisms.

The values obtained for the elimination half-life ($t_{1/\beta}$) and for the total clearance (Cl) show that calves eliminate thiamphenicol fairly quickly. Our results are comparable to those reported for humans by Tacquet *et al.* (1974).

Analysis of the parameters corresponding to the curves of thiamphenicol plasma levels after i.m. administration leads to the observation that the absorption constant is fast and shows a high bioavailability value. All these findings suggest that thiamphenicol when administered intramuscularly in a solution of dimethylacetamide and propylene glycol is quickly and completely absorbed although the plasma concentrations achieved are only half those obtained when administered by the i.v. route. Nevertheless, plasma levels after i.m. administration remain similar for a considerably longer period of time than after i.v. administration. This pharmaceutical formulation could be therapeutically useful against *Pasteurella* (the most commonly involved bacteria in BRC). In addition, the therapeutic margin of thiamphenicol would allow a considerable increase in drug dosage with a consequent rise in plasma and tissue concentrations and with the possibility of spacing out the administration intervals which would be of great value in clinical practice when dealing with livestock farming.

ACKNOWLEDGEMENTS

This work was carried out with the support of the CIRIT (Comissió Interdepartamental de Recerca i Innovació Tecnològica) and Laboratories JAER (Barcelona).

REFERENCES

CAMBIERI, F., GAMBINI, A. & LODOLA, E. (1970). Diffusion of thiamphenicol in the bronchial secretions and in the lung tissue. *Chemotherapy* **15,** 336–41.

FERRARI, V. (1984). Salient features of thiamphenicol: review of clinical pharmacokinetics and toxicity. *Sex. Transm. Dis.* **11** (Suppl), 336–40.

KAWABE, K., YAMAMOTO, S., KANAZAWA, T., TAKIMOTO, G., MYAMOTO, A. & IKEDA, T. (1966). Basic studies on thiamphenicol, a new chemotherapeutic. *Chemotherapy* **14,** 421–6.

LAPLASSOTTE, J. & BRUNAUD, M. (1961). Recherches expérimentales sur le thiophénicol: activité antibacterianne, concentrations humorales, elimination. Compáraison avec le chloramphénicol. *Thérapie* **16,** 101–5.

METZLER, C. M. & WEINER, D. L. (1986). *P.C. NONLIN User's Guide.* Lexington, Kentucky: Statistical Consultants Inc.

NAJEAN, Y., TOGNONI, G. & YUNIS, A. A. (1981). *Safety Problems related to Chloramphenicol and Thiamphenicol Therapy.* New York: Raven Press.

NKAGAWA, T., MASADA, M. & UNO, T. (1975). Gas chromatographic determination and gas chromatographic mass spectrometric analysis of chloramphenicol, thiamphenicol and their metabolites. *J. Chromatogr.* **111,** 335–40.

SIGNORIONI, G. C. & BONANOMI, L. (1985). Farmacocinetica ematica del tianfenicolo nel bovino. *Atti Soc. Ital. Buiatria* **17,** 311–15.

SIGNORIONI, G. C. & FERRARI, A. (1986). Livelli plasmatici ed escrezione mammaria del tianfenicolo nel bovino. *Ob. Docum. Vet.* **11,** 61–3.

SUTTER, V. I. & FINEGOLD, S. M. (1976). Susceptibility of anaerobic bacteria to 23 antimicrobial agents. *Antimicrob. Agents Chemother.* **10,** 736–41.

TACQUET, S., CUVELIER, D., DEVURDEL, D. & LEGROS, J. (1974). Pharmacokinetic aspects of thiamphenicol in subjects with normal renal function and in patients with chronic renal insufficiency, with or without haemodialysis. *Postgrad. med. J.* **50** (Suppl. 5), 36–41.

VAN BEERS, D., SCHOUTENS, E., VAN DER LINDEN, M. P. & YOURASSOWSKY, E. (1975). Comparative *in vitro* activity of chloramphenicol and thiamphenicol on common aerobic and anaerobic gram-negative bacilli (salmonella and shigella excluded). *Chemotherapy* **21,** 73–7.

VARMA, K. J., ADAMS, T. E., POWERS, J. D., POWERS, T. E. & LAMENDOLA, J. F. (1986). Pharmacokinetics of florfenicol in veal calves. *J. vet. Pharmacol. Ther.* **9,** 412–25.

(Accepted for publication 26 May 1992)