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Pharmacokinetics of Sulphadiazine-Trimethoprim in Lactating Dairy Cows

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Kaartinen L, Löhönen K, Wiese B, Franklin A, Pyörälä S: Pharmacokinetics of sulphadiazine-trimethoprim in lactating dairy cows. Acta vet. scand. 1999, 40, 271-278. – Five Finnish Ayrshire cows in mid or end-lactation were treated with 40 mg sulphadiazine/kg and 8 mg trimethoprim/kg using intravenous (i.v.), intramuscular (i.m.) and subcutaneous (s.c.) routes. Elimination of sulphadiazine was not affected by the route of administration (median $t_{1/2}$ 4.4-5.0 h) while elimination of trimethoprim was strongly limited by slow absorption from the injection site after s.c. and i.m. administration (median for apparent $t_{1/2}$ 21-25 h) compared to that after i.v. administration (median $t_{1/2}$ 1.2 h; $p<0.05$). The median bioavailability of trimethoprim was also decreased, being 37% and 55% after s.c. and i.m. administration, respectively. When i.v. administration was used, trimethoprim concentration exceeded 0.1 mg/l in milk between 0.15-8 h while sulphadiazine concentrations above 2 mg/l were maintained from 0.5-2 h to 8 h. After s.c. and i.m. administration sulphadiazine in milk behaved similar to that after i.v. administration, while trimethoprim time-concentration curves were flat and trimethoprim concentrations were around 0.1 mg/l for an extended period of time (8-12 h). Median C_{max} values in milk were only 0.07 mg/l and 0.10 mg/l for s.c. and i.m. administrations, respectively. After s.c. administration, 4 out of 5 cows showed signs of pain. After i.m. administration, 2 of the cows showed clear signs of pain and one had some local tenderness at the site of injection.

bovine; antimicrobial substances; potentiated sulphonamides; trimethoprim; intramuscular; subcutaneous; intravenous; milk.

Introduction

Sulphonamides in combination with trimethoprim are commonly used for broad spectrum antimicrobial therapy in veterinary medicine. The main indications in cattle are infections of the alimentary and urinary tract, mastitis and metritis. Sulphonamides are weak acids while trimethoprim is a weak base. The proportion of ionized forms of the compounds which are not able to pass through the cell membranes varies in accordance with the pH of the fluid in the particular body compartment. Consequently sulphonamides and trimethoprim concentrate in different body tissues.

Pharmacokinetic properties of the trimethoprim-sulphadiazine combination have been investigated on calves (*Guard et al.* 1986, *Shoaf et al.* 1986, *Shoaf et al.* 1987) and young cattle (*Clarke et al.* 1989). Pharmacokinetic behaviour of trimethoprim has also been studied in lactating cows using intravenous administration (*Davitiyananda & Rasmussen* 1974a,

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Davitiyananda & Rasmussen 1974b, *Nielsen et al.* 1978). However, there are only limited data on transfer of trimethoprim into milk in lactating cattle. Some information exists on pharmacokinetics of sulphadiazine in adult cattle after intravenous administration (*Nielsen & Rasmussen* 1977, *Atef et al.* 1981, *Nouws et al.* 1988) but again data on transfer into milk is limited. Furthermore, the effect of intramuscular or subcutaneous route on pharmacokinetics of these compounds has not been studied in lactating cows. Information on pharmacokinetic behaviour of trimethoprim and sulphonamide is essential when defining the optimal dosage and route of administration.

We carried out this study in order to find out the effect of different routes of administration on pharmacokinetics of sulphadiazine and trimethoprim and the transfer of the compounds into milk in lactating dairy cattle.

Materials and methods

Experimental design

Five Finnish Ayshire cows (age 2-4 years, weight 450-520 kg) in mid- or end-lactation with a milk yield of 6.4-15.3 kg/day were used as experimental animals. Each of them was given the treatment using intravenous (i.v.), intramuscular (i.m.) and subcutaneous (s.c.) routes using a cross-over design. The wash-out period between the administrations was one week.

Tribrissen vet inj. (Mallinckrodt Veterinary Ltd) containing trimethoprim 80 mg/ml and sulphadiazine 400 mg/ml was administered at a dose of 8 and 40 mg/kg active substances, respectively. Intravenous injection was given as single bolus into the jugular vein. Intramuscular and subcutaneous injections were divided into 2 and administered on both sides of the neck. Animals were clinically monitored for any signs of pain at the injection sites. Blood and milk samples were collected before the administration and 2, 4, 8, 16, 32 min and 1, 2, 4, 8, 12, 24 and 32 hours after the administration. Bucket milk samples were also taken at each morning and evening milking during the experiment in order to determine the total amount of compounds transferred into milk. Serum and milk samples were stored frozen (–20 °C) until analyzed.

Analysis of trimethoprim and sulphadiazine

Trimethoprim and sulphadiazine were analysed at the National Veterinary Institute, Uppsala, Sweden. As no suitable reference methods were available 2 in-house methods were used. Trimethoprim was analysed using coupled-column high performance liquid chromatography (HPLC) and sulphadiazine using conventional isocratic HPLC method.

Standard curves: Standard curves were plotted using the intervals of 0.005-5 mg trimethoprim/ml milk or serum and 0.01-100.0 mg sulphadiazine/ml milk or serum; the lowest concentrations represents the determination limits (r^2>0.999). The peak area was used to calculate the concentrations of trimethoprim and sulphadiazine. Coefficients of variation were ± 11.0% for 0.020 mg trimethoprim/ml serum (n = 6) and ± 3.6% for 10 mg sulphadiazine/ml serum (n = 6).

Apparatus and chemicals: The liquid chromatograph consisted of 2 (for sulphadiazine, one) 880 pumps with internally controlled time programs and a 875 UV detector (Jasco, Tokyo, Japan). The autoinjector was a CMA 200 (Carnegie Medicin AB, Stockholm, Sweden). The chromatograms were processed by a CR4A Chromatopac (Shimadzu, Tokyo, Japan). The guard columns (3×10 mm) and the analytical columns (4.6×150 mm) were packed with CT-CIL C18, 5 mm (ChromTech, Hägersten, Sweden). All chemicals were of analytical grade (E. Merck).

Sample preparation: Protein precipitation was made by mixing the sample (200 microliters for trimethoprim, 50 microliters for sulphadiazine) with 2 parts of acetonitrile. After centrifugation the supernatant was poured into a new tube and the volume was reduced at 60 °C under a stream of air for 5 minutes. The sample volume was then increased with water to 200 microlitres and all injected onto the chromatographic column. The recoveries of the drugs were in all cases >90%.

Analysis of trimethoprim: Two isocratic HPLC systems were coupled together via a 6 port valve. After separation on the first column the trimethoprim fraction (1.8 ml eluting after about 10 min) was transferred on line by the 6 valve onto the second column where trimethoprim was finally separated. The mobile phase I was 0.1 M imidazole in water; pH was adjusted to 4.0 by phosphoric acid:acetonitril (94:6 v/v). Column temperature was +40 °C. Mobile phase II was 0.075 M imidazole in water; pH adjusted to 6.4 by phosphoric acid:acetonitrile 81:19 (v/v). The second analytical column was operated at ambient temperature and no guard column was used. Flow rate was 1.0 ml/min in both columns. Trimethoprim was detected by UV at 235 nm.

Analysis of sulphadiazine: The mobile phase used was 0.02 M phosphate buffer (pH 3.2):acetonitrile (95:5 v/v). The column temperature and flow rate were as above. Sulphadiazine was detected by UV light at 266 nm.

Data analysis

The drug concentration-time data in serum was analyzed with software based on statistical moment theory (*Yamaoka et al.* 1978). The terminal elimination slope β was calculated by linear least-squares regression analysis, using the last 4 to 6 concentrations versus time points. The elimination half-life ($t_{1/2}$) was calculated as $t½ = \ln 2/\beta$. The mean residence time (MRT) was determined according to the equation MRT = AUMC/AUC, where AUC is the area under the concentration-time curve from zero time to infinity and AUMC is the area under the curve of a plot of the product of the time and the serum drug concentration versus time from time zero to infinity. Both AUC and AUMC were calculated by use of the trapezoidal method and were extrapolated to infinity. The volume of distribution at steady state ($V_{d(ss)}$) was estimated from the equation $V_{d(ss)}$ = Dose $\times$MRT/AUC. The clearance (Cl) was calculated from the equation Cl = Dose/AUC and bioavailability (F) = $(AUC_{non\text{-}iv} \times Dose_{iv})/(AUC_{iv} \times Dose_{non\text{-}iv})$. Mean absorption time (MAT) was calculated according to the equation $MAT = MRT_{non\text{-}iv} - MRT_{iv}$.

Statistical analysis was carried out using Statgraphics (Manugistics Inc., Maryland, USA). The non-parametric Mann-Whitney test was chosen due to the skewed distribution of the data.

Results

Pharmacokinetic parameters of sulphadiazine and trimethoprim are shown in Table 1. Elimination of sulphadiazine was not affected by the route of administration while elimination of trimethoprim was strongly limited by slow absorption from the injection site after s.c. and i.m. administration (Fig. 1). After i.m. administration, the range in T_{max} for sulphadiazine was smaller (1-2 h) than after s.c. administration (2-8 h). Also Cmax values for sulphadiazine after i.m. administration were significantly higher than those after s.c. administration ($p<0.05$). Due to flip-flop phenomenon the apparent median $t_{1/2}$ life of trimethoprim was 21-25 h for extravascular routes compared with $t_{1/2}$ of 1.2 h after i.v. administration ($p<0.05$). Four of 5 cows had low trimethoprim concentrations in plasma

Table 1. Pharmacokinetic parameters of sulphadiazine and trimethoprim after intravenous, subcutaneous and intramuscular administration to 5 dairy cows. Sulphadiazine dose 40 mg/kg and trimethoprim dose 8 mg/kg.

Pharmacokinetic parameters	Sulphadiazine		Trimethoprim	
	Median	Range	Median	Range
Intravenous				
AUC (mg × h/l)	468	404 – 492	4.6	2.5 – 6.9
MRT (h)	5.2	4.1 – 5.7	1.0	0.9 – 1.1
$t_{1/2}$ (h)	4.3	4.1 – 4.9	1.2	0.9 – 1.4
$V_{d(ss)}$ (l/kg)	0.42	0.35 – 0.54	1.5	1.2 – 3.5
Cl (l/kg × h)	0.09	0.08 – 0.10	1.7	1.2 – 3.2
Intramuscular				
AUC (mg × h/l)	432	370 – 576	2.5	2.1 – 4.5
MRT (h)	6.9	6.4 – 8.5	31	19 – 43
$t_{1/2}$ (h)	5.0	4.2 – 5.9	21	13 – 31
MAT (h)	2.7	0.6 – 3.5	30	18 – 42
C_{max} (mg/l)	49.6	41 – 55	0.1	0.09 – 0.12
T_{max} (h)	2.0	1 – 2	0.5	0.3 – 8.0
F (%)	92	90 – 120	55	30 – 110
Subcutaneous				
AUC (mg × h/l)	455	376 – 521	1.9	1.0 – 2.8
MRT (h)	8.0	6.7 – 10.9	38	22 – 64
$t_{1/2}$ (h)	4.4	4.2 – 5.7	25	16 – 45
MAT (h)	3.4	2.2 – 6.7	37	21 – 63
C_{max} (mg/l)	36.8	34 – 43	0.07	0.05 – 0.12
T_{max} (h)	2.0	2 – 8	4	0.1 – 8.0
F (%)	100	90 – 101	37	30 – 60

AUC = the area under concentration-time curve, MRT = mean residence time, $t_{1/2}$ = elimination half-life, $V_{d(ss)}$ = volume of distribution in steady-state, Cl = clearance, MAT = mean absorption time, C_{max} = maximum concentration, T_{max} = time of maximum concentration, F = bioavailability.

between 12 and 36 h after i.v. administration but it was not possible to calculate any $t_{1/2}$ for this third phase. The bioavailability of trimethoprim was decreased, median being 37% and 55% after s.c. and i.m. administration, respectively. The difference in bioavailability was not statistically significant.

After s.c. administration, 3 out of 5 cows showed general discomfort and pain at the injection sites and one showed minor signs of pain at the injection site. After i.m. administration, 2 of the cows showed clear signs of pain and one had some local tenderness at the site of injection.

When i.v. administration was used, sulphadiazine concentrations above 2 mg/l in milk were maintained from 0.5-2 h to 8 h while trimethoprim concentration exceeded 0.1 mg/l in milk between 0.15-8 h. After s.c. and i.m. administration sulphadiazine in milk behaved similar to that after i.v. administration. On the other hand, time-concentration curves of trimethoprim in milk were flat after extravascular administration (Fig. 1). After i.m. administration, trimethoprim concentration above 0.1 mg/l in milk was maintained from 0.5-2 h to 8-12 h but concentration of 0.2 mg/l was never exceeded. When s.c. administration was used, trimetho-

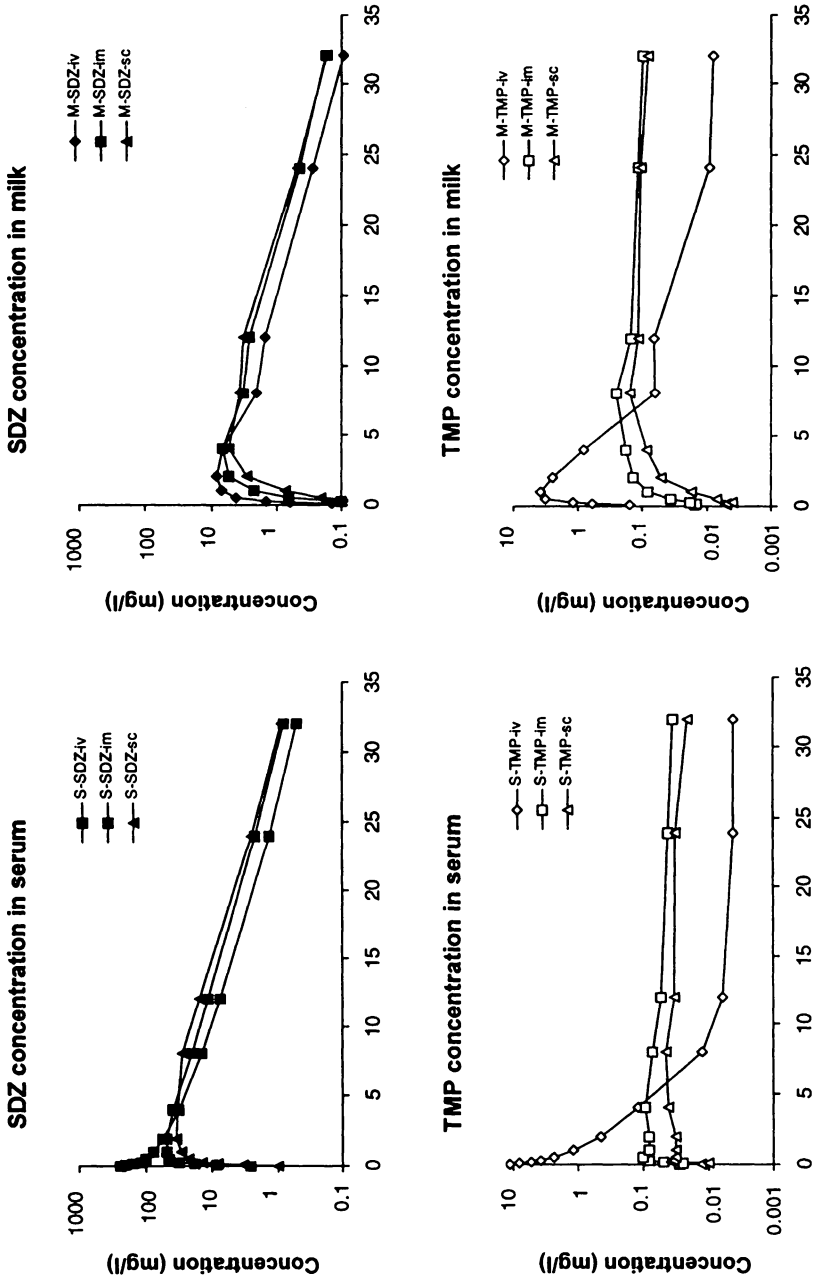

Figure 1. Mean concentration-time curves of sulphadiazine in serum (top left) and in milk (top right) and those of trimethoprim in serum (bottom left) and in milk (bottom right). The drugs were given intravenously, intramuscularly and subcutaneously to 5 cows at doses of 40 mg/kg for sulphadiazine and 8 mg/kg for trimethoprim.

prim concentration in milk of only temporarily exceeded 0.1 mg/l and this limit was not exceeded in milk of all cows. During the first 24 h after the administration 0.04%-1.14% of the total sulphadiazine dose was found in milk. The respective figure for trimethoprim was 0.01%-0.09%. The route of administration had no effect on the amount transferred into milk during this period.

Discussion

In Finland, the recommended dosage for the combination of trimethoprim and sulphadiazine is 15-22 mg of active substances per kilogram of body weight once daily. The route of administration can be i.v. or i.m. (Pharmaca Fennica Veterinaria 1996-1997). This is also the dosage for the drug generally used in veterinary medicine for large animals (*Bishop* 1996). We selected to use a higher dose (8 mg and 40 mg of active substances per kg) to achieve higher concentrations in milk. A dose of 48-50 mg/kg every 12 h intravenously has been recommended for treatment of acute mastitis (*Prescott & Baggot* 1993) due to relatively poor udder penetration of sulphonamides and suggested low bioavailability of trimethoprim after intramuscular administration. It is also commonly known that the elimination of trimethoprim in adult cattle is rapid, $t_{1/2}$ being 1-2 h after i.v. administration (*Nielsen et al.* 1978). We were interested to find out if therapeutic concentrations could be maintained in milk for reasonable periods of time and which proportions of trimethoprim and sulphadiazine were transferred into milk.

The elimination kinetics of sulphadiazine was not affected by the route of administration. In our study, the median elimination $t_{1/2}$ was 4.3-5.0 h for i.v, i.m. and s.c. administration. *Nouws et al.* (1988) have reported the $t_{1/2}$ of 4.1 h after i.v. administration for lactating cattle. In adult Friesian cows, $t_{1/2}$ of 5.4 h and volume of distribution of 0.47 l/kg for sulphadiazine have been obtained by *Atef et al.* (1981). These values are in the same range as our results.

The elimination of trimethoprim was dependent on the route of administration: the absorption was highly delayed after s.c. as well as after i.m. administration as indicated by long MAT (Table 1). Median elimination $t_{1/2}$ of 1.2 h after i.v. administration was close to the $t_{1/2}$ of 1-2 h reported by *Nielsen et al.* (1978) and 0.8-1.1 h reported by *Davitiyananda & Rasmussen* (1974). After i.m. and s.c. administration, the median apparent elimination $t_{1/2}$ was extended to 21-25 h in our study and concentrations in serum were low following these routes of administration. *Guard et al.* (1986) have reported that little or no trimethoprim was detected in serum after oral or subcutaneous administration of sulphadiazine-trimethoprim to ruminating calves at a dose of 12.5 mg/kg sulphadiazine and 2.5 mg/kg trimethoprim. *Shoaf et al.* (1987) were not able to detect trimethoprim after administration of 5 and 25 mg/kg trimethoprim and sulphadiazine, respectively, via subcutaneous route to calves. Based on the studies on urinary excretion, they concluded that these low concentrations in serum were due to delayed absorption from the site of injection. It has been shown that sulphadiazine-trimethoprim combination causes moderate tissue irritation when injected i.m., which can also slow the absorption of the drug from the injection site (*Pyörälä et al.* 1994).

Sulphadiazine concentrations in milk were below those found in serum while trimethoprim concentrations in milk exceeded those in serum (Fig. 1). This result is in agreement with the results of *Davitiyananda & Rasmussen* (1974) who reported that trimethoprim concentrations in milk were equal or higher than in plasma after single i.v. injection. Higher trimethoprim concentrations in milk may be explained by

lower pH of milk compartment compared to that of serum, as well as by lipid-solubility of trimethoprim and low binding to plasma proteins of the drug (approximately 60%, *Prescott & Baggot* 1993), allowing it to distribute well and penetrate cellular barriers. The higher proportion of sulphadiazine found in milk during the first 24 h-period compared with that of trimethoprim was unexpected as acidic drugs generally are transferred to milk much less than basic drugs (*Prescott & Baggot* 1993). Poor distribution of trimethoprim into milk could be explained by rapid elimination from the body. In case of extravascular administration, the absorption of trimethoprim was delayed and this limited the fraction of trimethoprim available for transfer into milk.

Mastitis is not a main indication for trimethoprim-sulphonamide combination in cattle; however the combination is used to treat acute mastitis. Susceptible *Escherichia coli* strains usually have a MIC value of less than 2 mg/l for the trimethoprim and sulphonamide combination in the ratio of 1:20 (*Pyörälä & Myllys* 1995). The optimal ratio of trimethoprim and sulphonamide for synergism is equal to the ratio of the MICs of these drugs acting independently. In most cases this ratio is one part of trimethoprim and 20 parts of sulphonamide (*Mandel & Sande* 1990). The concentrations exceeding at the same time 0.1 mg/l for trimethoprim and 2 mg/l for sulphadiazine were detected in milk only from 0.5 to 4 h, from 2 to 12 h and from 8 to 12 h after i.v., i.m. and s.c. administration, respectively. The MIC values for susceptible gram-positive bacteria are higher than those for coliform bacteria. Such concentrations were only temporarily obtained in milk. Despite the high dose of the combination used in this study, maintaining therapeutic concentrations against mastitis pathogens in milk for a sufficient time period seems difficult. Thus, efficacy of the combination in treatment of acute mastitis is questionable based on pharmacokinetic data.

From a pharmacokinetic point of view it seems likely that the dosage recommendations of the combination for adult cattle are generally too low. There is no consensus on the *in vitro* breakpoint value to be used in veterinary medicine for susceptible bacteria; however a value of <8 μg/ml for sulphonamide-trimethoprim has been suggested as a break-point (*Franklin et al.* 1979, *Casals & Pringler* 1984) and a MIC value of 0.5 /9.5 μg/ml (trimethoprim/sulphonamide) has been considered as a good susceptibility (*Franklin et al.* 1979, *Prescott & Baggot* 1993). These are far too high concentrations to be achieved in any tissues of adult cattle for reasonable periods with the current dosage regimens. If high dosages are used, the drug should be given i.v. due to the large injection volumes and tissue irritation caused by the drug. However, the longer persistence of residues must then also be considered.

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Sammanfattning

Sulfadiazin-trimetoprims farmakokinetik hos lakterande mjölkkor.

Fem finska Ayrshirekor i mitt- eller slutfasen av mjölkproduktionsperioden behandlades intravenöst, intramuskulärt och subkutant med 40 mg sulfadiazin och 8 mg trimetoprim per kg kroppsvikt. Administreringssättet påverkade inte elimineringen av sulfadiazin (median $t_{1/2}$ 4.3-5.0 h). Halveringstiden för trimetoprim var på grund av dålig absorption från injektionsstället efter subkutan och intramuskulär behandling mycket längre (median för skenbar $t_{1/2}$ 21-25 h) än efter intravenös administration ($t_{1/2}$ 1.2 h; $p<0.05$). Medianen för trimetoprimets biotillgänglighet var också lägre (37% och 55% efter subkutan respektive intramuskulär behandling). Trimetoprimkoncentrationen var högre än 0.1 mg/l i mjölk 0.15 h-8 h efter intravenös behandling, medan sulfadiazinkoncentrationen överskred 2 mg/l efter 0.5-2 h till 8 h. Sulfadiazins farmakokinetik var likartad oberoende av administrationssätt. Tid-koncentrationskurvan för trimetoprim i mjölk var flack efter intravenös behandling och cirka 0.1 mg/l uppmättes under en längre tidsperiod (8-12 h). Efter subkutan och intramuskulär behandling uppgick maximalkoncentrationernas medianvärden endast till 0.07 respektive 0.1 mg/l. Efter subkutan behandling visade 4 av 5 kor tecken på smärta. Efter intramuskulär behandling visade 2 av 5 behandlade kor tydliga smärtsymptom och hos en ko påvisades lindrig omhet på injektionsstället.

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