J. vet. Pharmacol. Therap. **16**, 110–113, 1993. **SHORT COMMUNICATION**

Pharmacokinetics of sulphadiazine and trimethoprim in carp (*Cyprinus carpio L.*) acclimated at two different temperatures

J. F. M. NOUWS,*† V. J. T. VAN GINNEKEN,‡ J. L. GRONDEL§ & M. DEGEN*

*RVV-District 6, PO Box 40010, Nijmegen, The Netherlands; †Present address: Farma Research BV, Snelliusstraat 6, 6533 NV Nijmegen, The Netherlands; ‡Gorlaeus Laboratories, State University of Leiden, Leiden, The Netherlands and §Agricultural University, Zodiac, Wageningen, The Netherlands

Pharmacokinetics of antimicrobial agents vary widely between fish species. Moreover temperature, salinity, pH of the water and food composition may have a large influence on the absorption, metabolism and excretion of drugs. These factors may markedly affect the efficacy of drug therapy and residue persistence in fish (Grondel *et al.*, 1989; Nouws *et al.*, 1992; Rasmussen, 1988; Salte *et al.*, 1983; Schmid 1980). Recently the effect of temperature on pharmacokinetics has been described for oxytetracycline and sulphadimidine in trout and carp (Ginneken *et al.*, 1991; Nouws *et al.*, 1992).

This paper deals with the effect of temperature on the pharmacokinetics and metabolism of sulphadiazine and trimethoprim in the carp.

Twelve carps (*Cyprinus carpio L.*) bred at Zodiac, Agricultural University, Wageningen were divided into two equal groups over flow-through systems in temperature acclimation chambers. One group was acclimated at 10°C and the other at 24°C for 6 weeks. The mean body weight of the carp was 380 ± 25 g; they were fed daily with pelleted dry food (Trouw & Co., The Netherlands) by an automatic feeder. Sulphadiazine (SDZ) and trimethoprim (TMP) were administered intravenously (caudal vene) as Diatrim® (AUV, The Nether-

TABLE I. Effect of temperature on selected mean pharmacokinetic parameters (mean ± SD) for sulphadiazine and trimethoprim (Diatrim®) in the carp

Antibiotic	Sulphadiazine		Trimethoprim	
Dose, mg/kg	100	100	20	20
Number	6	6	6	6
Temperature	10°C	24°C	10°C	24°C
V_{Darea}, l/kg	0.53 ± 0.07	0.60 ± 0.06	3.1 ± 0.41	4.0 ± 1.2
Cl_B, l/h/kg	0.0079 ± 0.0011	0.0122 ± 0.0012*	0.047 ± 0.018	0.141 ± 0.045*
B_{t_0}, µg/ml	190 ± 27	173 ± 15	6.5 ± 1.6	4.5 ± 1.0
$t_{1/2\beta}$, h	47.1 ± 8.7	33.0 ± 4.8*	40.7 ± 5.6	20.0 ± 4.7*
% N_4-SDZ†	5.1 ± 1.0	3.8 ± 0.8	×	×
% N_4-SDZ‡	8.4 ± 2.6	10.8 ± 5.5	×	×
t_{max}, h (N_4-SDZ)	54 ± 15	21 ± 14*	×	×
C_{max}, µg/ml (N_4-SDZ)	9.1 ± 3.8	3.1 ± 1.1*	×	×

*A temperature related significant difference ($P < 0.05$); †Based on AUC of N_4-SDZ vs. that of SDZ; ‡Based on plasma concentrations of N_4-SDZ vs. SDZ beyond 72 h p.i., × not relevant.

lands) in a dosage of 100 mg SDZ + 20 mg TMP/kg to both groups of carps. Heparinised blood samples (volume 100 µl) were taken at 0–1–2–3–7–10–14–24–48–72–96–144 and 192 h from the caudal vene, centrifuged and deep frozen pending HPLC analysis (Nouws *et al.*, 1987; 1991). Pharmacokinetic and statistical analyses were performed using standard procedures (Baggot, 1977; Mendenhall, 1971).

In Table I the effect of temperature on selected pharmacokinetic parameters for sulphadiazine and trimethoprim in the carp is shown. For both drugs a significantly larger body clearance (Cl_B), and a significantly shorter elimination half-life were found at 24°C than at 10°C. No obvious alteration in metabolism of SDZ was observed. The percentage of N_4-acetylsulphadiazine in plasma gradually increased with post injection time (Fig. 1), and based on the *AUC* values, it was similar at both temperatures; an equilibrium between the parent drug and its N_4-acetyl metabolite was not achieved in the 192 h sampling period. No hydroxy metabolites of SDZ or their glucuronide conjugates could be detected in plasma of carp.

At 10–12°C the elimination half-life of TMP in the carp is at least three times longer than that in the trout (Nouws *et al.*, 1992). Metabo-

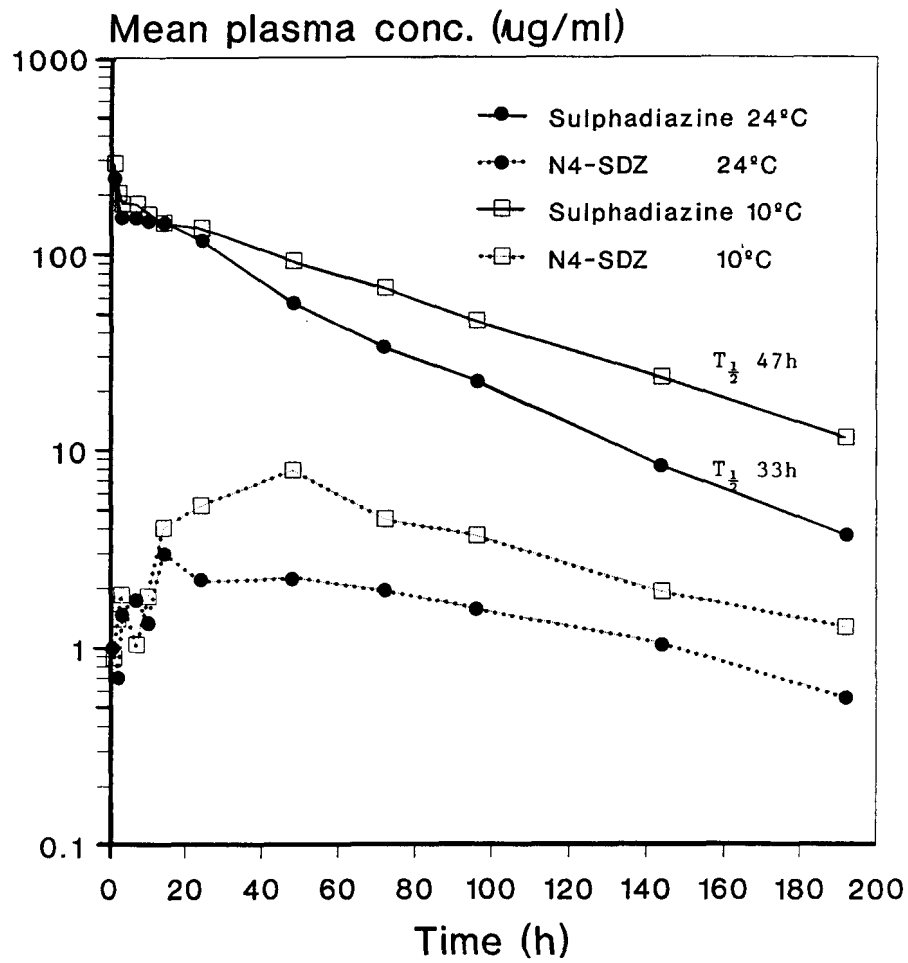

FIG. 1. Mean plasma concentration-time curves of sulphadiazine (SDZ) and its N_4-acetyl metabolite (N_4-SDZ) at two different temperature levels (10°C and 24°C) in six carps (*Cyprinus carpio L.*, n = 6) following intravenous administration of 100 mg SDZ + 20 mg TMP/kg ($t_{1/2}$ = elimination half-life).

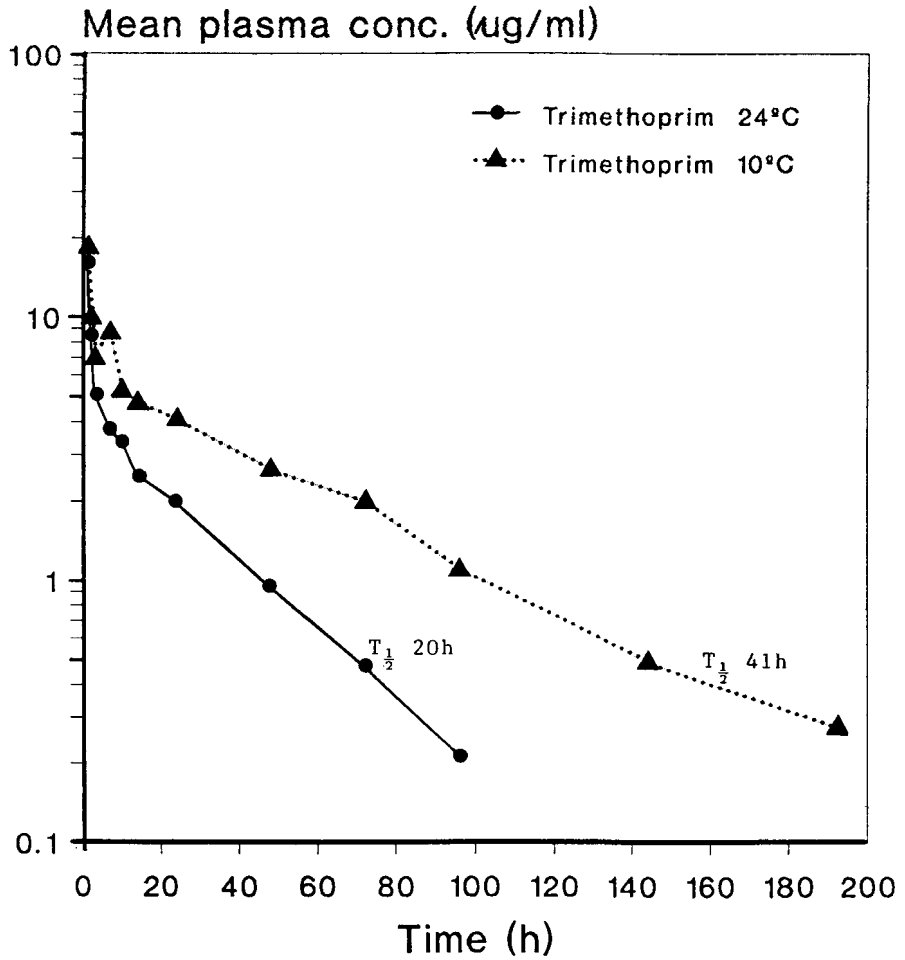

FIG. 2. Mean plasma concentration-time curves of trimethoprim (TMP) at two different temperature levels (10°C and 24°C) in six carps (*Cyprinus carpio L.*, $n = 6$) following intravenous administration of 20 mg TMP + 100 mg SDZ/kg ($t_{1/2}$ = elimination half-life).

lites of trimethoprim (e.g. 4-hydroxy-trimethoprim or 3-hydroxytrimethoprim) or their glucuronide conjugates could not be detected in plasma. Figure 2 demonstrates an entero-hepatic effect for TMP at 10°C at about 14 h p.i.; this phenomenon was observed only in three carps. Studies with radio-active labelled antibiotics showed that antimicrobials like chloramphenicol, sulphadiazine and trimethoprim in fish are excreted mainly by the biliary route and to a lesser extent in urine or through the skin or gills (Bersjø *et al.*, 1979; Cravedi *et al.*, 1985). Thus for fish an entero-hepatic circulation of drugs may be a predominant feature for lipophylic drugs like TMP.

The effect of temperature on the pharmacokinetic behaviour of drugs was recently demonstrated for sulphadimidine (SDM) and oxytetracycline (OTC) (Ginneken *et al.*, 1991; Nouws *et al.*, 1992). For SDM a significant increase in acetylation and a decrease in hydroxylation was observed in the carp at 20°C vs. 10°C. In the trout no significant change in acetylation could be demonstrated (Ginneken *et al.*, 1991). In trout and carp SDM exhibited a shorter elimination half-life at 20°C than at 10°C. For OTC not only an

alteration in elimination half-life was observed, but also a species dependent, temperature related change in tissue distribution of OTC (Nouws *et al.*, 1992). In this study, no significant change in distribution volume was observed for either SDZ or TMP; however tissue distribution studies are needed to clarify the physiological meaning of this.

REFERENCES

Baggot, J.D. (1977) Principles of drug disposition in domestic animals. W. B. Saunders Co., Philadelphia.

Bersjø, T., Nafsted, I. & Ingebrigtsen, K. (1979) The distribution of ^{35}S-sulfadiazine and ^{14}C-trimethoprim in rainbow trout, Salmo Gairdneri. *Acta Veterinaria Scandinavica*, **20**, 25–37.

Cravedi, J.-P., Heuillet, G., Peleran, J.-C. & Wal, J.-M. (1985) Disposition and metabolism of chloramphenicol in trout. *Xenobiotica*, **15**, 115–121.

van Ginneken, V.J.Th., Nouws, J.F.M., Grondel, J.L. *et al.* (1991) Pharmacokinetics of sulphadimidine in carp (Cyprinus carpio L.) and rainbow trout (Salmo Gairdneri Richardson) acclimated at two different temperature levels. *The Veterinary Quarterly*, **13**, 88–96.

Grondel, J.L., Nouws, J.F.M., Schutte, A.R. *et al.* (1989) Comparative pharmacokinetics of oxytetracycline in rainbow trout (Salmo Gairdneri) and African catfish (Claria gariepinus). *Journal of Veterinary Pharmacology and Therapeutics*, **12**, 157–162.

Mendenhall, W. (1971) Introduction to Probability and Statistics. Wadsworth Publ. Co., Belmont, USA.

Nouws, J.F.M., Firth, E.C., Vree, T.B. *et al.* (1987) Pharmacokinetics and renal clearance of sulfamethazine, sulfamerazine, and sulfadiazine and their N_4-acetyl and hydroxy metabolites in horses. *American Journal of Veterinary Research*, **48**, 392–402.

Nouws, J.F.M., Vree, T.B., Degen, M. *et al.* (1991) Pharmacokinetics of a sulphamethoxazole/trimethoprim formulation in pigs after intravenous administration. *The Veterinary Quarterly*, **13**, 148–154.

Nouws, J.F.M., Grondel, J.L., Boon, J.H. *et al.* (1992) Pharmacokinetics of antimicrobials in some fresh water fish species. In *Chemotherapy in Aquaculture: from Theory to Reality*. Eds Michel, C. & Alderman, D.J. pp. 437–447. Office International des Epizooties, Paris.

Rasmussen, F. (1988) Therapeutics used in fish production. Pharmacokinetics, residues, withdrawal times. FAO-Report of the working party on withdrawal periods for drugs. European Inland Fisheries Advisory Commission, XV/88/inf. 13.

Salte, R. & Liestol, K. (1983) Drug withdrawal from farmed fish. *Acta Veterinaria Scandinavica*, **24**, 418–430.

Schmid, A. (1980) Arzneimittelrückstände bei Fischen. *Tierärztliche Praxis*, **8**, 237–244.