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

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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; Kasniusseri, 1988; Sake 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 acclimatized 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-

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<tr>
<th>Antibiotic</th>
<th>Sulphadiazine</th>
<th>Trimethoprim</th>
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<tr>
<td>Dose, mg/kg</td>
<td>100</td>
<td>20</td>
</tr>
<tr>
<td>Number</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Temperature</td>
<td>10°C</td>
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<td></td>
<td>24°C</td>
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V_D, l/kg          | 0.53 ± 0.07   | 0.60 ± 0.06  |
G_L, l/h/kg        | 0.0079 ± 0.0011 | 0.0122 ± 0.0012* |
B_I, µg/ml         | 190 ± 27      | 173 ± 15     |
\( t_{\text{max}} \), h | 47.1 ± 8.7   | 33.0 ± 4.8*  |
\% N_I-SDZ†        | 5.1 ± 1.0     | 3.8 ± 0.8    |
\% N_I-SDZ‡        | 8.4 ± 2.6     | 10.8 ± 5.5   |
\( t_{\text{max}} \), h (N_I-SDZ) | 54 ± 15 | 21 ± 14* |
G_{max}, µg/ml (N_I-SDZ) | 9.1 ± 3.8 | 3.1 ± 1.1* |

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

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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 vena, 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 ($C_{lb}$), 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 N₄-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 N₄-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-
Mean plasma conc. (µg/ml)

- Trimethoprim 24°C
- Trimethoprim 10°C

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 (t½ = elimination half-life).

... 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


