Short Paper

Effect of aspirin on the disposition of tetracycline in sheep

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Summary

Aspirin has been shown to increase the rate of urinary excretion of tetracycline in humans. To understand the mechanisms involved in this drug interaction, the effect of aspirin on the kinetics of tetracycline was investigated in sheep. Tetracycline was administered intravenously in six mixed-breed sheep at various stages: first, tetracycline alone; second, immediately after intravenous injection of salicylic acid and third, three hours following oral administration of tetracycline. Blood samples were collected during 6 hours after administration of tetracycline followed by the separation of sera. Tetracycline content of each sample was assayed using fluorescence spectroscopy. The concentration of tetracycline in the first blood sample was higher when tetracycline was administered alone compared with those given after oral aspirin or with salicylic acid. Serum tetracycline concentration was more rapidly approached to the minimum when it was administered in conjunction with salicylic acid. In addition, the area under the curve for serum tetracycline concentration versus time (AUC) was smaller compared to when tetracycline was administered alone. In contrast, when aspirin was given orally prior to the intravenous administration of tetracycline, the rate of decline in serum tetracycline concentration was less and AUC was higher compared to when it was injected alone. As the underlying mechanism(s) will have pharmacokinetics impact, which may be important in clinical pharmacology point of view, further in vivo and in vitro studies should be carried out to elucidate the exact nature of the interaction between these drugs.

Key words: Aspirin, Tetracycline, Drug interaction, Sheep

Introduction

Tetracyclines are antibiotics with broad spectrum bacteriostatic activity. Tetracycline antibiotics are used for the treatment of several microbial diseases in human and animal patients (Adams, 2001; Hardman and Limbird, 2001). Their efficacy, easy administration and low cost, allow them to be used, either as a food additive or in parenteral formulations for the treatment of infectious diseases (Adams, 2001). Several drug interactions, at the pharmacokinetics level, have been reported when these antibiotics are used with other chemicals or food components. For example, bivalent metals such as calcium bind with tetracycline molecules induces a lower solubility that causes a precipitation and reducing its absorption rate (Stockley, 1994). Metoclopramide, on the other hand, is reported to enhance the oral absorption of tetracycline (Nimmo, 1973). Non-steroidal anti-inflammatory drugs, such as aspirin, may simultaneously be applied for their analgesic, antipyretic and anti-inflammatory effects. Aspirin has been shown to increase the rate of urinary excretion of tetracycline in human beings following oral administration (Alipoor, 2001). This finding should be considered when bivalent metals are concurrently used with antibiotics such as tetracycline. In order to understand the mechanism(s) involved in this drug interaction, the effect of aspirin on the disposition of tetracycline was investigated in sheep.
Materials and Methods

Animals
Six mixed breed apparently healthy adult sheep weighing 37 to 54 kg were used in this study. The animals had access to water and food ad libitum.

Drugs
Tetracycline hydrochloride (250 mg capsules; Daroopakhsh, Tehran, Iran) and aspirin (325 mg tablets; Kimidaroo, Tehran, Iran) were used in this study. The tetracycline antibiotic was pooled from capsules and a 10% solution was prepared by dissolving it in sterilized distilled water. The purity of the drug product was examined by comparing it with the standard chemical (Merk Co., Lot no. K21003089). All other chemicals including salicylic acid were obtained from usual suppliers. Salicylic acid was dissolved in sterilized distilled water to make a 3% solution.

Experimental design
Aqueous solution of tetracycline hydrochloride (20 mg kg⁻¹) was administered intravenously via right jugular vein at various stages: first, tetracycline alone; second, immediately after intravenous injection of salicylic acid (5 mg kg⁻¹) and third, three hours following administration of aspirin (100 mg kg⁻¹). Aspirin tablets were given orally as such after dissolution in water. Blood samples were collected from left jugular vein at various time intervals (5, 15 and 30 minutes and 1, 1.5, 2, 3, 4 and 6 hours) after administration of the antibiotic at various stages. After the separation of sera, tetracycline content of each sample was assayed using fluorescence spectroscopy (Elsayed et al., 1985; Rajaian and Jalaei, 2003).

Pharmacokinetic analysis
Blood concentration-time data were analyzed by non-linear least squares regression analysis (Wilson et al., 1986). A two-compartmental analysis was found to be appropriate to estimate major pharmacokinetic parameters. Area under the concentration-time curve (AUC) from zero time to infinity was obtained by the trapezoidal rule; apparent first-order rate constants (α and β) and distribution and elimination half-lives (t₁/₂α and t₁/₂β) were obtained from the slopes of the log concentration-time data. Drug apparent volume of distribution (Vd) and clearance (Cl) were calculated from: Vd = Dose/(AUC x Kd) and Cl = Dose/AUC, respectively.

Statistical analysis
Data are presented as mean ± s.e.m. and a Student’s t-test was used to examine the significance of differences between means.
Table 1: Concentrations (μg ml⁻¹) of tetracycline hydrochloride in serum samples obtained at various time intervals after intravenous injection of the drug (20 mg kg⁻¹) in sheep at different stages

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Stage Ia</th>
<th>Stage IIb</th>
<th>Stage IIIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.08</td>
<td>187.4±16.5d</td>
<td>70.8±19.9f</td>
<td>177.4±4.3</td>
</tr>
<tr>
<td>0.25</td>
<td>89.7±12.1</td>
<td>44.8±17.5e</td>
<td>127.6±9.7e</td>
</tr>
<tr>
<td>0.5</td>
<td>50.9±7.0</td>
<td>33.9±15.7</td>
<td>80.8±13.4f</td>
</tr>
<tr>
<td>1.0</td>
<td>41.9±7.4</td>
<td>25.9±15.8</td>
<td>72.8±17.4f</td>
</tr>
<tr>
<td>1.5</td>
<td>32.9±7.0</td>
<td>19.9±14.3</td>
<td>67.8±16.6f</td>
</tr>
<tr>
<td>2.0</td>
<td>28.9±6.1</td>
<td>18.9±15.6</td>
<td>65.8±15.7f</td>
</tr>
<tr>
<td>3.0</td>
<td>26.9±7.0</td>
<td>17.9±14.6</td>
<td>55.8±14.1f</td>
</tr>
<tr>
<td>4.0</td>
<td>26.9±7.0</td>
<td>11.0±11.0</td>
<td>35.9±14.6f</td>
</tr>
<tr>
<td>6.0</td>
<td>25.1±7.1</td>
<td>7.0±7.0</td>
<td>23.9±8.6f</td>
</tr>
</tbody>
</table>

a Tetracycline (50 mg kg⁻¹) administered intravenously
b Tetracycline (50 mg kg⁻¹) administered intravenously with salicylic acid (5 mg kg⁻¹)
c Tetracycline (50 mg kg⁻¹) administered intravenously following oral aspirin (100 mg kg⁻¹)
d Mean ± s.e.m. (n=6)
Significantly (P<0.05) different from the value in stage I (non-paired Student’s t-test).

Table 2: Pharmacokinetic parameters obtained for tetracycline hydrochloride after intravenous injection of the drug (20 mg kg⁻¹) in sheep at various stages

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Stage Ia</th>
<th>Stage IIb</th>
<th>Stage IIIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₁ (μg ml⁻¹)</td>
<td>187.4</td>
<td>70.8</td>
<td>177.4</td>
</tr>
<tr>
<td>Vd (L kg⁻¹)</td>
<td>0.24</td>
<td>0.33</td>
<td>0.14</td>
</tr>
<tr>
<td>AUC (μg h ml⁻¹)</td>
<td>220.6</td>
<td>110.2</td>
<td>340.5</td>
</tr>
<tr>
<td>α (h⁻¹)</td>
<td>0.38</td>
<td>0.55</td>
<td>0.41</td>
</tr>
<tr>
<td>β (h⁻¹)</td>
<td>0.06</td>
<td>0.12</td>
<td>0.13</td>
</tr>
<tr>
<td>t₁/₂α (h)</td>
<td>1.8</td>
<td>1.3</td>
<td>1.7</td>
</tr>
<tr>
<td>t₁/₂β (h)</td>
<td>11.0</td>
<td>5.7</td>
<td>5.2</td>
</tr>
<tr>
<td>CL (L kg⁻¹ h⁻¹)</td>
<td>0.09</td>
<td>0.18</td>
<td>0.062</td>
</tr>
</tbody>
</table>

a Tetracycline (20 mg kg⁻¹) administered intravenously
b Tetracycline (20 mg kg⁻¹) administered intravenously with salicylic acid (5 mg kg⁻¹)
\c Tetracycline (20 mg kg⁻¹) administered intravenously following oral aspirin (100 mg kg⁻¹)

C₁, concentration of tetracycline in the first serum sample; Vd, apparent volume of distribution; AUC, area under the serum concentration versus time from time zero to the last blood sampling; CL, clearance; α, distribution phase rate constant; β, elimination phase rate constant; t₁/₂α, distribution phase half-life; t₁/₂β, elimination phase half-life.
Fig. 1: Plots of serum drug concentration versus time after intravenous injection of 20 mg kg\(^{-1}\) tetracycline hydrochloride in sheep

- **Tetracycline alone**
- **Tetracycline with salicylic acid (5 mg kg\(^{-1}\))**
- **Tetracycline following oral aspirin (100 mg kg\(^{-1}\))**

**Results**

Table 1 shows serum concentrations (mean ± s.e.m.) of tetracycline in sheep at various stages. The average concentration of tetracycline in the first blood sample was significantly (P<0.05) lower when tetracycline was administered with salicylic acid compared with those given alone or after oral aspirin (71 versus 187 and 177 μg ml\(^{-1}\), respectively). Figure 1 shows that the concentration of tetracycline in serum approaches more rapidly to the minimum when it was administered in conjunction with salicylic acid. The AUC for serum tetracycline concentration versus time from time zero to the last blood sampling was non-significantly (P>0.05) smaller (110 μg ml\(^{-1}\) h) when tetracycline was administered with salicylic acid compared with the situation that tetracycline was given alone (220 μg ml\(^{-1}\) h). Furthermore, when aspirin was applied orally, prior to intravenous administration of tetracycline, the decline in serum tetracycline concentration was slower and AUC was significantly higher (P<0.05) compared to when the antibiotic was injected with salicylic acid (340 versus 110 μg ml\(^{-1}\) h). These differences may be more emphasized when one considers the values obtained for half-lives (t\(_{1/2a}\)) and clearances (Cl). As it is depicted in Table 2, t\(_{1/2a}\) is slightly greater, but Cl is lower when tetracycline was administered alone (1.8 h and 0.09 L kg\(^{-1}\) h\(^{-1}\), respectively) compared with those given with salicylic acid (1.3 h and 0.18 L kg\(^{-1}\) h\(^{-1}\), respectively). Moreover, elimination rate constant (β) was found to be smaller when tetracycline was administered alone.
compared to the values obtained when the drug was given with salicylic acid or after aspirin (0.06 versus 0.12 and 0.13 h⁻¹, respectively, Table 2).

Discussion

A lower serum tetracycline concentration and a shorter half-life found in the present study may be explained by an increase in the unbound form of tetracycline molecules possibly due to the competition between tetracycline and salicylic acid or aspirin for plasma protein binding sites (Mc Arthur, 1969). As a result, tetracycline can be more easily distributed to various organs, for example gastrointestinal tract. This is reflected in the results (Table 2) obtained for apparent volumes of distribution and t₁/₂B. A greater V_d and a shorter t₁/₂B (about one half) are illustrated when tetracycline was applied with salicylic acid (0.33 L kg⁻¹ and 5.7 h, respectively) compared with those values found when tetracycline was administered alone (0.24 L kg⁻¹ and 11.0 h). However, a higher distribution was not parallel to an increase in reabsorption of the antibiotic back into the blood stream. It can be suggested that large volume of the bowel contents in sheep may be involved in this respect. This will prevent the availability of tetracycline molecules for absorption because of the adherence to food particles.

In summary, it was shown that salicylate compounds exert pharmacokinetic interaction with tetracycline in sheep. As the underlying mechanism(s) will have pharmacokinetics impact, which may be important in clinical pharmacology point of view, further in vivo and in vitro studies should be carried out to elucidate the exact nature of this drug interaction.

Acknowledgment

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References


