PHARMACOKINETICS OF SULFAMETHAZINE IN BUFFALOES
F.H. Khan, M. Nawaz, S. Anwar-Ul-Hassan

To cite this version:
F.H. Khan, M. Nawaz, S. Anwar-Ul-Hassan. PHARMACOKINETICS OF SULFAMETHAZINE IN BUFFALOES. Annales de Recherches Vétérinaires, INRA Editions, 1980, 11 (1), pp.9-12. hal-00901243

HAL Id: hal-00901243
https://hal.archives-ouvertes.fr/hal-00901243
Submitted on 1 Jan 1980

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
PHARMACOKINETICS OF SULFAMETHAZINE IN BUFFALOES

F.H. KHAN, M. NAWAZ1 and S. ANWAR-UL-HASSAN

Department of Physiology and Pharmacology, Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan

Material and Methods

The experimental animals were 8 healthy lactating buffaloes maintained under the same conditions at the University Experimental Station. The buffaloes ranged in weight from 434 to 586 kg, with a mean value of 497 kg. The animals were restrained in a stall and a sterilized plastic cannula was inserted into the jugular vein. After withdrawing a control blood sample, each buffalo was given a single dose (100 mg/kg) of sodium sulfadimidine (sulfamethazine) injection (Diadin 33.33 % injection, Pfizer Lab. Ltd.) by the intravenous route. Through the venous cannula, blood was collected in glass tubes containing heparin. The blood samples were collected at 5, 10,
15, 20, 30 min, after that at every 30 min until 5 hours, and finally at 6, 12, 18 and 24 h after drug administration. Plasma was separated from whole blood by centrifugation and kept in the refrigerator at 4 °C until the next day for analysis. The samples were analyzed spectrophotometrically in duplicate by the method of Bratton and Marshall (1939) for «free amine», which also included conjugated drug.

The plasma sulfonamide concentration-time data were analyzed separately for each buffalo. Pharmacokinetic analysis was performed according to the methods described by Riegelman et al. (1969). The mean value and standard deviations (S.D.) were calculated for each pharmacokinetic parameter. The average steady-state amount of drug in the body (Wagner and Northam, 1965), minimum steady-state concentration and the optimal dosage and dosing intervals were calculated (Baggot, 1977).

Results

The values of the kinetic parameters showing the distribution and elimination of sulfamethazine in normal buffaloes are given in Table 1. Following intravenous injection, the time required for 50 % of the drug to be eliminated from the body i.e., half-life was calculated at 5.54 ± 0.41 h (mean ± S.D.).

A semilogarithmic plot of the decline in plasma sulfamethazine concentration against time is shown in Figure 1. The curve is divided into distribution and elimination components. The distribution phase is based on the calculated points, which were obtained by subtracting the extrapolated portion of the elimination phase from the experimental data points by the procedure known as the method of residuals or feathering technique (Baggot, 1977). The coefficient A (230 µg/ml) and B (240 µg/ml) and the rate constants α (4.18 h⁻¹) and β (0.0528 h⁻¹) were calculated.

The apparent volume of distribution relates drug concentration in plasma to the total amount of drug in the body. The relatively small value of the apparent volume of distribution calculated by the area method Vd(area) i.e., 0.44 ± 0.17 l.kg⁻¹, reflects either restricted distribution or low tissue level. Volume

<table>
<thead>
<tr>
<th>Kinetics parameters†</th>
<th>Mean ± S.D.</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>264 ± 75</td>
<td>µg.ml⁻¹</td>
</tr>
<tr>
<td>B</td>
<td>223 ± 47</td>
<td>µg.ml⁻¹</td>
</tr>
<tr>
<td>Half-life time (t1/2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-distribution</td>
<td>5.38 ± 4.40</td>
<td>min</td>
</tr>
<tr>
<td>β-elimination</td>
<td>5.54 ± 0.41</td>
<td>h</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vd(area)</td>
<td>0.44 ± 0.17</td>
<td>l.kg⁻¹</td>
</tr>
<tr>
<td>Volume of central compartment</td>
<td>0.21 ± 0.07</td>
<td>l.kg⁻¹</td>
</tr>
<tr>
<td>Clearance</td>
<td>56 ± 7</td>
<td>ml.kg⁻¹.h⁻¹</td>
</tr>
<tr>
<td>Transfer constants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$K_{12}$</td>
<td>1.92 ± 0.66</td>
<td>h⁻¹</td>
</tr>
<tr>
<td>$K_{21}$</td>
<td>1.98 ± 0.66</td>
<td>h⁻¹</td>
</tr>
<tr>
<td>$K_{12}/K_{21}$</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>Elimination constant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$K_{e}$</td>
<td>0.268 ± 0.03</td>
<td>h⁻¹</td>
</tr>
</tbody>
</table>

†: kinetic parameters have been described by Baggot (1977).
of central compartment \((V_c)\) was \(0.21 \pm 0.07 \text{ l.kg}^{-1}\).

Body clearance represents the sum of metabolic and excretory processes and on an average \(56 \pm 7 \text{ ml.kg}^{-1} \text{ h}^{-1}\).

The ratios between the transfer rate constants \((K_{21}/K_{12})\) are close to unity (average 0.97) and the concentration of the drug in the plasma at 24 h was \(19 \pm 6 \mu g/ml\).

**Discussion**

According to Silvestri *et al.* (1967) the half-life of sulfamethazine ranges from 7 to 9 h in cattle. The half-life value in sheep and goats are 3.88 h and 4 h, respectively (Nawaz and Khan, 1979) and in lambs the half-life of the drug is 7.2 h (Bourne *et al.*, 1977). The half-life of sulfamethazine is shorter in buffaloes than in cattle and lambs but is slightly longer than in sheep and goats. The volume of distribution \((V_d)\), 44 % of the body weight is little higher than that in heifers (40 %, Silvestri *et al.*, 1967).

Since sulfonamides are bacteriostatic agents, the plasma concentration during the course of therapy should not fall below minimum inhibitory concentration (MIC). A value of MIC 25 \(\mu g/ml\) of plasma is considered adequate. When a fixed dose of drug is administered repeatedly at constant time intervals, a steady-state will be established eventually and the plasma concentration-time curves will be the same during the successive dosage intervals (Wagner *et al.*, 1965). Based on this concept, the average steady-state amount of drug in the body \((A_{t,\infty})\) can be predicted:

\[
A_{t,\infty} = \frac{\text{Dose (i.v.)}}{\beta \times t} \frac{\beta \times t}{\beta \times t}
\]

Where \(\beta\) is the overall elimination rate constant of the drug and \(t\) is the dosage interval.

If one administers the usual maintenance dose (100 mg/kg) at 24 h intervals and uses 0.1251 h\(^{-1}\) as the value of \(\beta\) (corresponds to \(t/2 = 5.54\) h), the minimum steady-state concentration \(C_p,\infty (\text{min})\) at the end of dosing interval is calculated by the formula:

\[
C_p,\infty (\text{min}) = \frac{D}{V_d \left(e^{\beta t} - 1\right)}
\]

Thus, \(C_p,\infty (\text{min})\) will be 12 \(\mu g/ml\) and corresponds to the fraction remaining at the end of dosage interval and is lower than the usually accepted MIC. On the basis of MIC 25 \(\mu g/ml\), usually considered adequate and repeating the dose at 24 h, the optimal dosage level is calculated:

\[
D = C_p,\infty (\text{min}) \times V_d \left(e^{\beta t} - 1\right)
\]

With these calculations the optimal dose should be 210 mg/kg body weight. Experience in buffaloes showed that sulfamethazine at a dosage level exceeding 150 mg/kg, injected intravenously, produced toxic symptoms such as salivation, lacrimation and tremors. Therefore, lower dosage levels should be used in buffaloes. If the dosing interval is fixed at 12 h, to attain \(C_p,\infty (\text{min})\) or MIC 25 \(\mu g/ml\) at the end of dosing interval, the appropriate dosage level should be 38.4 mg/kg body weight. However, influence of bacterial disease and febrile states on the predicted plasma level and dose needs to be investigated.

Accepted for publication July 2nd 1979.
Summary

Pharmacokinetic parameters which describe distribution and elimination of sulfamethazine were determined in buffaloes. Following intravenous administration of a single dose (100 mg/kg), disposition of the drug was described in terms of biexponential expression: 
\[ C_p = A e^{at} + B e^{bt} \]. Based on total (free and bound) sulfonamide levels in the plasma, pseudo-distribution equilibrium was rapidly attained and the half-life value of 5.54 ± 0.41 h (mean ± S.D., n = 8) was recorded. Body clearance was 56 ± 7 ml.kg⁻¹.h⁻¹. Based on this study we suggest an intravenous dosage regimen consisting of 38.4 mg sulfamethazine/kg body-weight repeated at 12 h intervals. With this dosage level the predicted plasma concentrations will oscillate between 125 and 25 μg/ml during the steady-state. The influence of febrile states and bacterial diseases on predicted levels remains to be verified experimentally.

References


