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PHARMACOKINETICS OF SULFAMETHAZINE IN BUFFALOES

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Résumé

PHARMACOCINETIQUE DE LA SULFAMETHAZINE CHEZ LE BUFFLE. — On a déterminé les paramètres pharmacocinétiques qui décrivent la distribution et l'élimination de la sulfaméthazine chez le buffle. Après injection intraveineuse d'une dose unique (100 mg/kg), la disponibilité du produit s'exprime par une courbe biexponentielle : \( C_p = Ae^{-\alpha t} + Be^{-\beta t} \). Sur la base du taux total de sulfamide plasmatique (libre + lié), l'équilibre de pseudo-distribution était atteint rapidement, et la valeur de la demi-vie était de 5,54 ± 0,41 (moyenne ± S.D., n = 8). La cléarence corporelle était de 56 ± 7 ml·kg\(^{-1}\)·h\(^{-1}\). Sur la base de cette étude, nous suggérons un système d'administration intraveineuse consistant en 38,4 mg de sulfaméthazine/kg de poids vif répété à intervalles de 12 h. De cette façon, les concentrations plasmatiques prévisibles oscillèrent entre 125 et 25 μg/ml pendant l'état d'équilibre. L'influence des états fébriles et des maladies microbiennes sur ces niveaux prévisibles restent à examiner.

Kinetics which describes the distribution and elimination of sulfamethazine provides a basis for the determination of an optimal dosage regimen for the sulfonamide. The pharmacokinetics of sulfadimidine (sulfamethazine) in sheep and goats have clearly shown that there is a need for such studies in the animals and environments in which the drug is used clinically (Nawaz and Khan, 1979).

This investigation describes the pharmacokinetics and dosage of sulfamethazine in buffaloes.

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 487 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 A</td>
<td>264 ± 75</td>
<td>µg.ml⁻¹</td>
</tr>
<tr>
<td>Coefficients 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 Vd(area)</td>
<td>0.44 ± 0.17</td>
<td>l.kg⁻¹</td>
</tr>
<tr>
<td>Volume of central compartment Vc</td>
<td>0.21 ± 0.07</td>
<td>l.kg⁻¹</td>
</tr>
<tr>
<td>Clearance Cl</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>K₁₂</td>
<td>1.92 ± 0.66</td>
<td>h⁻¹</td>
</tr>
<tr>
<td>K₂₁</td>
<td>1.98 ± 0.66</td>
<td>h⁻¹</td>
</tr>
<tr>
<td>K₁₂/K₂₁</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>Elimination constant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kₑₛ</td>
<td>0.268 ± 0.03</td>
<td>h⁻¹</td>
</tr>
</tbody>
</table>

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

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

The ratios between the transfer rate constants \((K_{12}/K_{21})\) 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 \((V_d,\text{avg})\), 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 \((A_{ss})\) can be predicted:

\[
A_{ss} = \frac{\text{Dose (i.v.)}}{\beta \times \tau}
\]

Where \(\beta\) is the overall elimination rate constant of the drug and \(\tau\) 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 \(C_{p_{\text{MIN}}}\) at the end of dosing interval is calculated by the formula:

\[
C_{p_{\text{MIN}}} = \frac{D}{V_d \left( e^{\beta \tau} - 1 \right)}
\]

Thus, \(C_{p_{\text{MIN}}}\) 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:

\[
D = C_{p_{\text{MIN}}} \times V_d \left( e^{\beta \tau} - 1 \right)
\]

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 \(C_{p_{\text{MIN}}}\) 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.

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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: 
\[ C_p = A e^{-t} + B e^{-t/\alpha}. \]
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


