Short Communication

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EFFECT OF WATER DEPRIVATION ON THE DISPOSITION KINETICS OF SULPHADIMIDINE

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The effect of water deprivation on drug disposition kinetics has been reported by different workers [1-3]. Water deprivation results in significant physiological, [4] hormonal, [5] and enzymatic [6] changes in the biological system. Most frequently the biological system may become dehydrated due to polyurea, diarrhoea, and accidental fluid loss as in severe muscular exercise. Physiological changes alongwith possible changes in the drug disposition kinetics provided a new basis to formulate a dosage regimen. The present study was undertaken to evaluate the changes due to water deprivation on the disposition kinetics of sulphadimidine in sheep. Sulphadimidine was selected firstly because of its widespread use in veterinary medicines and secondly because it is a model compound for phenotyping.

Disposition kinetics of sulphadimidine was determined in five dehydrated (48 hr. dehydration) sheep of the Lohi/Kajli breed. Prior to the treatment studies the animals were used as their own control in kinetic studies. A single dose of 100 mg/kg body weight of sulphadimidine sodium (Diadin 33.33%, Pfizer Lab., Karachi) was given intravenously to sheep in both states. Blood samples were collected at different intervals and then analysed for total (free + metabolized) sulphadimidine. Total sulphadimidine in plasma was determined by the Bratton Marshall method [9]. Table 1 reports the average plasma levels in normal and dehydrated conditions. Average drug profiles in plasma are shown in Fig. 1.

There was a significant change in extrapolated zero time drug concentration (C_1) of the distribution phase. The values found for control and treated states were found to be 172.1 and 377.6 μg/ml respectively which indicate a reduction in the blood volume in dehydrated condition. It is also evident from the initial volumes of distribution, V_c, which were found to be 0.292 and 0.179 L/kg body weight. It indicates an almost 39% reduction in blood volume which is quite significant.

Table 1. Mean plasma levels of total sulphadimidine in dehydrated sheep (n = 5) after intravenous administration of a single dose of 100 mg/kg body weight.

Time (hours)	Mean plasma level (μg/ml)	
	Normal	Dehydrated
0.083	306.10 ± 35.1	390.90 ± 92.72
0.166	280.88 ± 23.92	208.24 ± 19.29
0.25	237.50 ± 13.88	211.00 ± 22.09
0.50	204.80 ± 15.82	172.14 ± 13.87
1.00	179.90 ± 9.35	150.67 ± 14.97
1.50	211.80 ± 11.15	163.68 ± 13.60
2.00	199.60 ± 7.62	177.55 ± 5.75
2.50	184.30 ± 9.76	168.10 ± 15.01
3.00	186.16 ± 10.14	135.20 ± 19.86
6.00	130.10 ± 11.37	— —
12.0	91.10 ± 5.25	79.55 ± 15.15
18.0	62.33 ± 1.67	70.61 ± 21.06
24.0	53.64 ± 2.61	91.58 ± 22.61

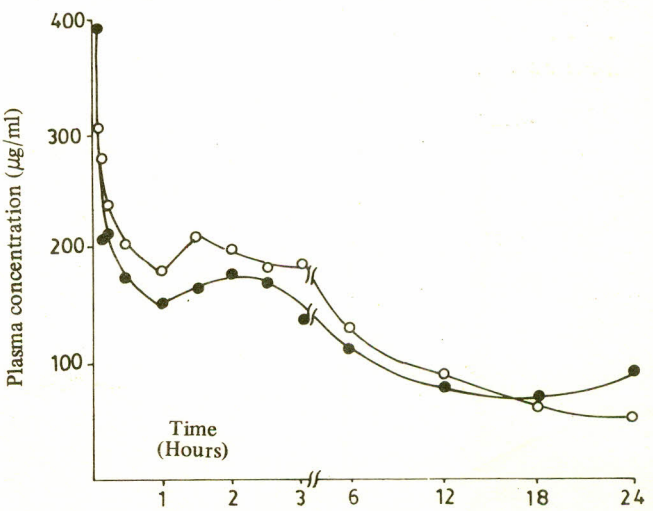

Fig. 1. Time course of sulphadimidine in plasma of normal (o) and dehydrated (●) sheep after 100 mg/kg I.V. dose.

Faster drug perfusion in tissues in dehydration was observed. The transfer rate constant (k_{12}) was found more than five fold higher in dehydration. Similarly, a significant difference was observed in distribution half-life, $t_{\lambda 1}$ 0.5 and the time of steady state concentration, t_{ss}. Some pharmacokinetic parameters are summarized in Table 2.

Table 2. Effect of water deprivation on disposition kinetics of sulphadimidine in sheep.

Parameters	Normal	Dehydration
C_1; μg/ml	172.100	377.600
k_{12}; hr^{-1}	−1.455	−7.413
V_c; K/kg	0.292	0.179
t_{λ_1}; 0.5; hr	0.228	0.062
t_{ss}; hr	1.230	0.370

These observations necessitate further investigations in this direction, particularly to evaluate the kinetics of metabolites in dehydration and to modify the dosage regimen.

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