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Pharmacokinetics of sulfisoxazole in rabbits with experimental renal failure after single and multiple dosing

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Summary

In rabbits injected intravenously with 0.75 mg/kg uranyl nitrate to precipitate acute renal failure, the renal elimination of sulfisoxazole was essentially non-existent 3 days after the injection. In addition a significant (40%) reduction in the metabolic elimination (unbound clearance) was observed in the renal failure animals. Whether the decrease in metabolic clearance is due to a decrease in renal or non-renal metabolism is not clear from the available data. The protein binding dramatically decreased in renal failure animals, with the lowest binding occurring during the multiple dosing therapy. The half-life is greater (2–3 times) and the apparent volume of distribution (unbound) is significantly decreased due to decreased binding in plasma and tissues.

Introduction

Reidenberg et al. (1969) suggested that the metabolism of sulfisoxazole is decreased in subjects having reduced renal function. This suggestion was, however, based upon an observed reduction in the metabolic elimination rate constant. Because the metabolic elimination rate constant is dependent upon both the metabolic clearance and the apparent volume of distribution, the conclusion that there is a reduced metabolic elimination (clearance) of sulfisoxazole in renal failure patients

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must be made with caution. That the metabolic clearance may be affected is supported on two accounts.

(1) When the concentration of the main metabolite of sulfisoxazole, acetylsulfisoxazole, is elevated by infusion, the metabolic clearance of sulfisoxazole (with respect to unbound concentration) is reduced both in rats (Øie, 1979) and rabbits (Jung and Øie, 1981). Because acetylsulfisoxazole is mainly eliminated via the renal route, an accumulation of acetylsulfisoxazole is expected in renal failure subjects. Product inhibition of N-acetylation has also been observed for other compounds (Weber, 1973). However, when the acetylsulfisoxazole concentration was allowed to increase in normal (Øie et al., 1982) patients by multiple administration of sulfisoxazole, no alteration in the metabolic ability to eliminate sulfisoxazole was seen. The levels of acetylsulfisoxazole obtained in these subjects were lower than those found to show product inhibition in animals and also lower than those expected in severe renal failure patients.

(2) Bekersky and Colburn (1980) recently reported that sulfisoxazole is acetylated in the isolated kidney. Subjects with renal dysfunction may, therefore, show a decreased metabolic clearance due to a decreased renal metabolism of sulfisoxazole.

However, because it is known that the protein binding of sulfisoxazole is decreased in renal failure (Levy et al., 1976), the apparent volume of distribution is expected to be larger and consequently the metabolic elimination rate constant smaller, i.e. the changes in the metabolic rate constant may not be due to any changes in the metabolism, provided that the binding changes do not alter the clearance to the same degree as the volume.

In order to determine the changes taking place in the elimination and distribution during renal failure, a single and multiple sulfisoxazole dosing study was carried out in normal and renal failure rabbits.

Materials and Methods

Animals

Twenty-two New Zealand white male rabbits weighing 2.0–3.6 kg were studied. Before each study the marginal ear vein of each ear was cannulated with an Intracath catheter (22-gauge; Deseret, Sandy, UT). One catheter was used for blood collection and the other used for drug injection. The urethra was cannulated with a French Foley catheter No. 8 (D.R. Bard, Ind. Murray Hill, NJ). No food was given for the 24 h prior to and during the experiments. Water was given ad libitum.

Renal failure

Twelve animals were injected with 0.75 mg/kg uranyl nitrate via the marginal ear vein to create acute renal failure (Day 1). The animals were all studied 72 h after the uranyl nitrate injection when the serum creatinine level was approximately 9 mg/dl (Fig. 1) (Day 4).

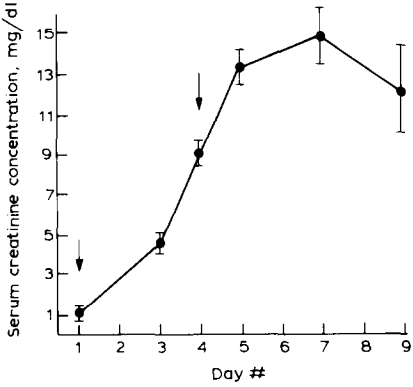

Fig. 1. Creatinine serum concentrations as a function of time after a 0.75 mg/kg uranyl nitrate injection. Each point represents the average of 12 animals except on day 9 which represents 9 animals only. Arrows indicate injection of uranyl nitrate (Day 1) and initiation of sulfisoxazole study (Day 4). Vertical bars indicate standard error of the mean.

Experimental design

Single dose study

Five control and 5 renal failure rabbits were studied. In order to maintain a constant urinary pH throughout the study, a sterile, isotonic sodium bicarbonate solution (1.39%) was infused at a constant rate of 0.3 ml/min for 7 h. One hour after the start of the bicarbonate infusion an injection of 10 mg/kg sulfisoxazole (10 mg/ml) was administered. Blood samples of 3 ml were obtained just prior to and at 0.25, 0.5, 1.0, 2, 3, 4, 6, 8, 10 and 24 h after the dose. The blood was obtained from an ear vein in the opposite ear of sulfisoxazole injection and bicarbonate infusion. The blood samples were allowed to clot (1 h), the samples were then centrifuged, and the serum stored frozen ($-20°C$) until assayed. The urine was collected before the start of the study and at 2, 4, 6, 8, 10 and 24 h after the sulfisoxazole administration. The urine was allowed to drain into a covered beaker between urine samples and at the collection time 2×10 ml isotonic saline was used to rinse the bladder to assure complete recovery of the drug excreted during the collection interval. The urine pH was measured in the combined sample. The addition of 20 ml isotonic saline to urine did not affect the measured urine pH unless < 1 ml urine was formed during the collection period. Six hours from the start of the experiment, after the majority of sulfisoxazole was eliminated, the bicarbonate infusion was terminated.

Multiple dose study

Five control and 7 renal failure animals were studied. Ten milligrams per kilogram sulfisoxazole was given every 6 h via the marginal ear vein. After the fifth dose when steady-state conditions were reached, blood and urine samples were taken, and infusion of isotonic sodium bicarbonate was carried out as described for the single dose studies.

Protein binding

The unbound concentration was determined by ultrafiltration.

One milliliter serum was placed in a Millipore 10-mm dialysis cell (xx 4201310) equipped with a magnetic stirrer. Plasma water was filtered through a 25000-MW cutoff filter (Millipore PSED), using 3.5 bar pressure of nitrogen containing 1.4% CO_2 ($\sim$ 50 mbar). The ultrafiltration was carried out at 37°C. Two aliquots of 100 μl plasma water each were collected and assayed for sulfisoxazole. The concentration of sulfisoxazole in the second 100-μl aliquot never exceeded the first by more than 10%, and this aliquot was used to calculate the unbound concentration of sulfisoxazole.

Analysis

Sulfisoxazole. Sulfisoxazole and its major metabolite, N_4-acetylsulfisoxazole, were determined by a specific high-performance liquid chromatographic method, described earlier (Jung and Øie, 1980). 'Total' sulfisoxazole was determined by the Bratton-Marshall method (Bratton and Marshall (1939) as described by Rieder (1972)).

Creatinine. Creatinine serum levels were assayed using the Sigma test kit as described in Sigma Procedure Book no. 555.

Pharmacokinetic treatment. The unbound plasma concentrations of sulfisoxazole were fitted to one- and two-compartment pharmacokinetic models, using the MULTIFUN (Holford, 1979) procedure, available through the PROPHET computer system (Castleman et al., 1974). A two-compartment model was used whenever a distribution phase could be discerned and a one-compartment model was employed at all other times. Correction for the initial sulfisoxazole level in the multiple dose studies was made in the fitting by assuming that the distribution was completed within 6 h.

The various pharmacokinetic parameters were calculated from the fitted model parameters.

The average renal clearance was determined from the total amount excreted unchanged in the urine and the area under the plasma concentration–time curve. The metabolic clearance was determined as the difference between the total clearance and the renal clearance.

Results

The injection of 0.75 mg/kg uranyl nitrate resulted in a significant reduction in renal function which is reflected in a rapid increase in serum creatinine concentration with time over the first 4 days (Fig. 1). The serum creatinine concentration leveled off after about 6 days; it showed a decrease in 5 animals between days 6 and 8 and remained essentially unchanged in 4 animals. The remaining three animals having received an injection of uranyl nitrate were sacrificed between days 6 and 8 as they were deemed to be in physical distress, with a 10–20% weight loss and signs of diarrhea. No animals showed visible signs of distress until after the completion of the sulfisoxazole studies. The serum levels of creatinine showed similar changes as found by Sudo et al. (1977).

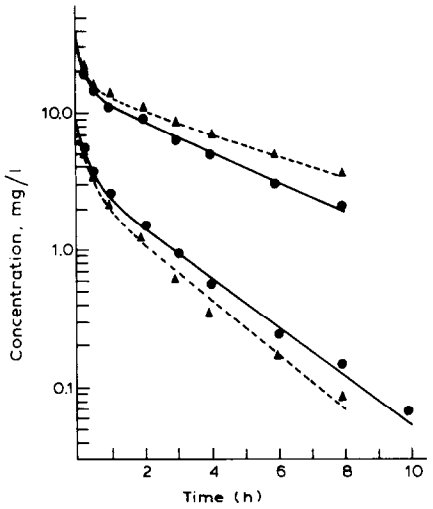

Fig. 2. Log-averaged serum concentrations of unbound sulfisoxazole after single (●) and multiple i.v. sulfisoxazole dosing (▲) of 10 mg/kg and 10 mg/kg every 6 h in normal rabbits (lower two curves) and rabbits injected 0.75 mg/kg uranyl nitrate (upper two curves).

Infusion of bicarbonate had small effects on plasma bicarbonate levels. In the renal failure animals the serum bicarbonate concentration increased 3.4 ± 0.9 (mean $\pm$ S.D.) mM and 2.9 ± 0.6 mM in the control animals. In separate preliminary studies we observed a 0.10 pH serum increase during the bicarbonate studies. In vitro binding studies revealed no changes in the plasma protein binding of sulfisoxazole to serum based upon these changes in pH and bicarbonate concentrations.

The majority of animals in all 4 groups studied showed a concentration–time

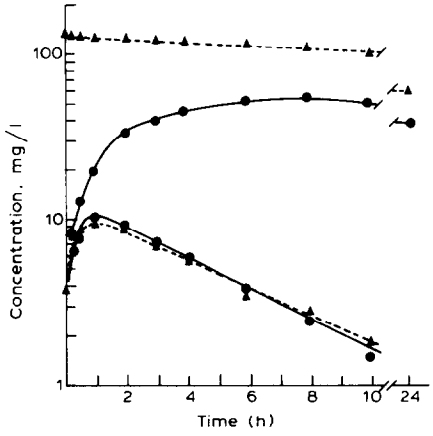

Fig. 3. Log-averaged serum concentrations of total (bound + unbound) acetyl-sulfisoxazole after single (●) and multiple i.v. sulfisoxazole dosing (▲) of 10 mg/kg and 10 mg/kg every 6 h in normal rabbits (lower two curves) and rabbits injected 0.75 mg/kg uranyl nitrate (upper two curves).

TABLE 1

PHARMACOKINETIC PARAMETERS [a] OF *UNBOUND* SULFISOXAZOLE IN CONTROL AND RENAL FAILURE RABBITS AFTER SINGLE AND MULTIPLE DOSES OF 10 mg/kg SULFISOXAZOLE

Rabbit groups	Cl_R (ml/h/kg)	Cl_M (ml/h/kg)	Cl_T (ml/h/kg)	V_{ss} (ml/kg)	$t_{1/2\lambda_1}$ (h)	$t_{1/2\lambda_2}$ (h)	f_u	No. of animals
Renal failure								
Single dose	3 ± 3	171 ± 21	174 ± 23	704 ± 123	0.46 ± 0.39	3.12 ± 0.56	0.302 ± 0.043	5
Multiple dose	0	154 ± 62	154 ± 62	990 ± 212	0.76 ± 0.48	5.93 ± 2.15	0.590 ± 0.049	7
Control								
Single dose	730 ± 174	306 ± 68	1036 ± 207	2110 ± 700	0.41 ± 0.15 [b]	1.78 ± 0.29	0.076 ± 0.012	5
Multiple dose	1147 ± 370	246 ± 38	1393 ± 358	2630 ± 870	0.46 ± 0.17	1.90 ± 0.31	0.076 ± 0.031	5

[a] Cl_R = renal clearance, Cl_M = metabolic clearance, Cl_T = total clearance, V_{ss} = apparent volume of distribution at steady-state, $\tau_{1/2\lambda_1}$ and $\tau_{1/2\lambda_2}$ = fast and slow half-lives, f_u = unbound fraction in plasma.

[b] n = 3; 2 animals had no discernible distribution phase.

relationship of unbound sulfisoxazole that followed two-compartment characteristics. Two of the control animals receiving a single dose of sulfisoxazole showed a serum–water concentration–time profile that was not discernible from one-compartment characteristics. The logarithmically averaged unbound concentration–time profile of sulfisoxazole and the logarithmically averaged acetylsulfisoxazole concentrations in the various groups are given in Figs. 2 and 3. The averaged values of the individual pharmacokinetic parameters in the 4 groups are given in Tables 1 and 2.

A number of differences between the control and renal failure animals were seen. Renal clearance of sulfisoxazole and acetylsulfisoxazole was essentially nonexistent in the renal failure animals. In addition, the metabolic unbound clearance of sulfisoxazole was significantly lower in the renal failure animals when compared to control animals (Tables 1 and 3). The apparent steady-state volume of distribution of unbound drug was smaller in the renal failure animals than in the control animals (Tables 1 and 3). It is interesting to note that multiple dosing increased the apparent steady-state volume of distribution (Tables 1 and 3). The terminal half-life was significantly larger in the renal failure animals than in the control animals (Tables 1 and 3). The terminal half-life is also increased upon multiple dosing (Tables 1 and 3). The unbound fraction of sulfisoxazole, as well as of acetylsulfisoxazole was significantly larger in the renal failure animals than in the control animals (Tables 1, 2 and 3). The unbound fraction was also larger in the multiple dose studies than in the single dose studies (Tables 1, 2 and 3). However, the major reason for this latter observation appears because the renal failure animals had a much larger unbound fraction during the multiple dose than in the single dose studies. When the control animals were evaluated separately, no difference could be observed in the animals given single and multiple doses either for sulfisoxazole or acetyl sulfisoxazole

TABLE 2

PHARMACOKINETIC PARAMETERS [a] OF *UNBOUND* N-ACETYLSULFISOXAZOLE AFTER SINGLE AND MULTIPLE DOSES OF 10 mg/kg SULFISOXAZOLE

Rabbit groups	Cl_R (ml/h/kg)	AUC [b] (mg·h/l)	$t_{1/2}$ (h)	f_u	f_e	No. of animals
Renal failure						
Single dose	5 ± 5	155 ± 19	25 ± 7 [c]	0.093 ± 0.023	0.025 ± 0.023	5
Multiple dose	1 ± 1	147 ± 44	21 ± 7 [c]	0.193 ± 0.030	0.006 ± 0.006	7
Control						
Single dose	905 ± 179	2.28 ± 0.50	3.5 ± 4.2	0.036 ± 0.010	0.19 ± 0.05	5
Multiple dose	1431 ± 597	1.36 ± 0.75	3.7 ± 0.8	0.037 ± 0.007	0.13 ± 0.03	5

[a] Cl_R = renal clearance, AUC = area under the curve, $t_{1/2}$ = terminal half-life, f_u = unbound fraction in plasma, f_e = fraction of dose excreted unchanged in the urine as N-acetylsulfisoxazole.

[b] Area under the curve from 0 to ∞ given for single doses and area during a dosing interval for multiple dosing.

[c] Due to continuous formation of acetylsulfisoxazole during the study period, values must be evaluated with caution.

TABLE 3

ANOVA STATISTICS FOR THE VARIOUS PHARMACOKINETIC PARAMETERS FOR *UNBOUND DRUG*

	Disease		Dosing		Disease-Dosing Interaction	
	F value	Probability [a]	value	Probability [a]	F value	Probability [a]
Total clearance	37.32	< 0.001	0.14	N.S.	1.84	N.S.
Renal clearance	53.33	< 0.001	0.77	N.S.	4.06	N.S.
Metabolic clearance	26.33	< 0.001	4.17	N.S.	0.63	N.S.
Apparent volume of distribution	34.72	< 0.001	5.44	< 0.05	8.51	< 0.01
Terminal half-life	28.20	< 0.001	10.74	< 0.005	3.26	N.S.
Unbound fraction of sulfisoxazole	585.20	< 0.001	131.27	< 0.001	35.24	< 0.001
Unbound fraction of acetyl-sulfisoxazole	134.47	< 0.001	36.18	< 0.001	14.86	< 0.005

[a] N.S. indicates $P > 0.05$.

($t = 0.00$ and $t = 0.534$, respectively). This latter observation also explains the observation of interaction between dosage regimen and disease in the a nova test (Table 3). The elimination of acetylsulfisoxazole was significantly reduced in the renal failure animals which is reflected in a substantially larger area under the curve of acetylsulfisoxazole in renal failure animals and an almost nonexistent renal elimination of acetylsulfisoxazole.

Discussion

The decrease in the renal clearances in the renal failure animals is a natural consequence of the induced renal failure. The increase in the serum creatinine concentration over the first few days after the uranyl nitrate injection (approximately 4.5 mg/dl/day between days 2 and 4) indicates an essential shut-down of renal creatinine elimination and severe acute renal failure.

The mechanism for the decreased metabolic clearance (unbound) of sulfisoxazole is not clear. Several possibilities exist, reduction in hepatic metabolism due to the induction of renal failure, reduction in metabolism due to accumulation of sulfisoxazole metabolites (product inhibition) and/or a reduction in renal metabolism of the drug.

Over the last few years several reports have been published demonstrating a decreased presystemic metabolism of drugs in renal failure (Gibson et al., 1980; Bianchetti et al., 1976; Balant et al., 1983), indicating that hepatic metabolism may be affected in renal failure. Recently Terao and Shen (1984) also reported a similar observation for propranolol in rats with uranyl nitrate induced renal failure. Although most other literature reports make no suggestions of changes in metabolic clearance in renal failure, the results cited above suggest that oxidation of certain

compounds may be affected by renal failure. Whether conjugation or acetylation processes are similarly affected, is unknown as no indication is as yet present in the literature.

In separate studies, we have previously found that acetylsulfisoxazole can inhibit its own formation from sulfisoxazole when infused at a constant rate to generate high plasma concentrations (Øie, 1979; Jung and Øie 1981). However, in the renal failure animals given a single dose of sulfisoxazole, the average acetylsulfisoxazole during the elimination of sulfisoxazole was 33 mg/l (first 10 h), while in the multiple dose groups the average acetylsulfisoxazole concentration was 126 mg/l. The levels in the single dose animals were much lower than those used to demonstrate product inhibition of sulfisoxazole acetylation in rabbits, 93 mg/l (Jung and Øie, 1981), and lower than values that were found to have no effect on sulfisoxazole acetylation in man, 47 mg/l (Øie et al., 1982). The concentrations of acetylsulfisoxazole in the multiple dose animals, on the other hand, were higher than those used to demonstrate product inhibition in animals (Øie, 1979; Jung and Øie, 1981). Because the unbound clearance was similar in the multiple and single dose studies in the renal failure animals and the acetylsulfisoxazole was substantially different it therefore appears that product inhibition is not the primary mechanism for the reduced renal clearance in these animals.

Bekersky and Colburn (1980) using the isolated perfused kidney demonstrated that sulfisoxazole is acetylated in the kidney. The reduced metabolism observed could therefore be a result of a reduced kidney metabolism due to the reduced kidney function. The quantitative role of the kidney as a metabolizing organ is largely unknown and further information is needed to assess its role in the results observed here.

The reduction in the apparent steady-state volume of distribution of unbound drug in renal failure animals is, according to the theory by Øie and Tozer (1979), most likely due to changes in the tissue and plasma protein binding. For a drug such as sulfisoxazole the unbound apparent volume of distribution at steady state can be described by

$$V_{u,ss} = \frac{V_p}{f_u} + (V_{EC} - V_p) + \frac{V_R}{f_{u_R}} \tag{1}$$

where V_p is the apparent plasma volume; f_u is unbound fraction in plasma; V_{EC} is the extracellular water space; V_R is tissue volume to which the drug distributes, and f_{u_R} is the unbound fraction of drug in tissues. From normal values of the apparent volume of distribution of plasma protein (albumin) and the extravascular space, the following approximate equation is obtained:

$$V_{u,ss}(\text{ml/kg}) = \frac{100}{f_u} + 120 + \frac{V_R}{f_{u_R}} \tag{2}$$

The change in f_u alone would suggest that the apparent volume of distribution in renal failure animals given a single dose would be 1380 ml/kg and in multiple dose

animals, 1220 ml/kg. In order to explain the lower-than-expected apparent steady-state volumes of distribution for unbound drug, the tissue binding must have decreased. The mechanism for the higher apparent steady-state volume of distribution of unbound drug in the renal failure animals receiving multiple dose drug therapy in comparison with the animals receiving only a single dose of sulfisoxazole is not apparent. It would suggest an increase in tissue binding—not very likely upon multiple dosing.

The binding changes seen in plasma from renal failure animals is probably due to several factors such as accumulation of endogenous displacers in renal failure (Kinniburgh and Boyd, 1981) and/or displacement of sulfisoxazole by accumulation of acetylsulfisoxazole (Øie, 1979). The latter is probably the main reason for the observed difference in binding between renal failure animals having received single and multiple doses of sulfisoxazole.

The values for metabolic elimination of sulfisoxazole found in this study for normal rabbits are at odds with data reported previously from this laboratory (Jung and Øie, 1981). The unbound metabolic clearance of sulfisoxazole is twice as high in this study as was found previously. In addition, only 66% of the extrarenally eliminated sulfisoxazole could be found as acetylsulfisoxazole in the urine in this study, while essentially all extrarenally eliminated sulfisoxazole was found as acetylsulfisoxazole in the previous report. Using the method by Rieder (1972) the total sulfisoxazole recovered in urine after acid hydrolysis was 105% and direct sulfisoxazole was identical to that found by HPLC (69 versus 70%). This indicates that an unknown metabolite that can be hydrolyzed to yield a primary amine is present in the urine of these animals. The dose used, the strain, age and weight of the rabbits, and the analytical methodology used in this study are essentially the same as those used in our previous report. The reason for this difference in metabolism is, therefore, unknown; the only discernible difference is that the animals used in this study were from a different supplier as the former supplier is no longer in business. We were thus unable to determine whether a genetic difference existed between the animals from the two different suppliers.

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