KINETICS OF SULPHAFURAZOLE IN UNDERNUTRITION

R. ARUNKUMAR SHASTRI

Food & Drug Toxicology Research Centre,
National Institute of Nutrition,
Indian Council of Medical Research,
Hyderabad-500007, India

- 1 An oral dose of 75 mg/kg body weight was used to study the kinetics of sulphafurazole in wellnourished and undernourished adult subjects.
- 2 There were no differences in the half-life, volume of distribution and total body clearance of the drug in the two groups of subjects.
- 3 The plasma protein binding of sulphafurazole was significantly reduced in the undernourished subjects.
- 4 It is concluded that alterations in the dosage schedule may not be necessary in the treatment of undernourished adults with sulphafurazole.

Introduction

In recent years there have been a number of reports on the influence of malnutrition on drug metabolism in man (Shastri & Krishnaswamy, 1976; Krishnaswamy & Naidu, 1977; Mehta, Kalsi, Jayaraman & Mathur, 1975; Shastri & Krishnaswamy, 1979; Homeida, Karrar & Roberts 1979). These studies have emphasised the importance of considering nutritional status in the planning of therapeutic regimen.

Low priced drugs such as sulphonamides continue to enjoy an important place in the chemotherapy of bacterial infections particularly among poor income groups who are also malnourished. Earlier studies (Shastri & Krishnaswamy, 1979) reported from this Institute indicated that the half-life of sulphadiazine was shortened in undernourished adult subjects. Sulphadiazine is not highly bound to plasma protein, unlike some other sulphur compounds, which are highly protein bound. A study was undertaken to determine whether the kinetics of sulphafurazole, a highly protein bound drug, were altered in undernourished adults. Sulphafurazole (SFZ) is a sulphonamide with a half-life of about 7 h. After a single oral dose, about 95% of the drug is excreted in the urine in 24 h, of which about 30% is in the acetylated form (Svec, Rhoads & Rohr, 1950). It is reported that 85% of the drug circulating in plasma is bound to proteins. It is a weakly acidic drug with a pKa value of 4.9 (Heel & Avery, 1980).

Methods

Six wellnourished adult male volunteers aged between 25 and 35 years, drawn from the staff of the

National Institute of Nutrition, Hyderabad and eight undernourished male adults of similar age composition were investigated in a metabolic ward. None of the subjects investigated had any evidence of infection. The nature of the study was explained and oral consent was obtained from the subjects before the study was undertaken. The subjects were categorised as wellnourished or undernourished based on their anthropometry. Subjects whose anthropometric index $\text{weight/height}^2 \times 100$ (weight in kg; height in cm) was below 0.18 were considered undernourished (Jayarao, Mukherjee & Rao, 1972). All subjects received a single dose of 75 mg/kg body weight of SFZ by mouth after an overnight fast and blood samples obtained at the end of 4, 6, 8 and 24 h after drug administration. Samples of 24 h urine were collected. To ensure complete absorption of the drug, subjects were not allowed any food for 3 h after drug administration.

SFZ in blood and urine was determined by a standard method (Richterich, 1969). $T_{1/2}$ of the drug in plasma was calculated by the method of least squares and the elimination rate (K_e) by the formula $0.693/T_{1/2}$. Relative volume distribution (V_d) was calculated by dividing the dose given by the 0 h concentration (C_{p0}) of drug obtained by extrapolation of the regression line to time zero. The total body clearance rate of the drug (Cl) was calculated by the standard formula $Cl = V_d \times K_e$ and expressed per hour per kg body weight. Plasma albumin concentrations were determined by the biuret method (Gornall, Bardawill & David 1949). Statistical analyses were done using the Student's *t*-test and $P < 0.05$ was considered significant.

The *in vitro* plasma protein binding of SFZ was determined by incubating plasma obtained from six wellnourished subjects of whom three had participated in the kinetics study and five undernourished subjects with 20 mg % of SFZ at 37°C for 60 min and then subjecting the plasma to ultrafiltration through a cellophane membrane at a pressure of 400 psi. SFZ concentration was then determined in the ultrafiltrate and the binding of the drug calculated.

Results

The anthropometric index, serum albumin concentrations, half-life and urinary excretion of SFZ of the subjects investigated are given in Table 1. There was a significant difference between the two groups in both the anthropometric index ($P < 0.001$) and serum albumin concentrations ($P < 0.01$). However there was no difference in the plasma $T_{1/2}$ of sulphafurazole between the two groups of subjects. There were no differences either in the total amount of drug excreted or in the excretion of the acetyl form of the

drug between the two groups. The pH of the urine was also similar in the two groups (Table 1).

The V_d , Cl and plasma concentrations of SFZ are presented in Table 2. It was seen that these pharmacokinetic parameters were essentially similar in both wellnourished and undernourished subjects. The plasma protein binding of the drug in undernourished subjects was $64.00 \pm 6.471\%$, a value significantly lower than $87.67 \pm 2.109\%$ seen in wellnourished subjects ($P < 0.001$; Table 2).

Discussion

Several reports from this Institute and elsewhere have shown a difference in the kinetics of drugs in the undernourished subjects as compared to the wellnourished (Shastri & Krishnaswamy 1976; Mehta *et al.*, 1975; Shastri & Krishnaswamy 1979; Krishnaswamy & Naidu 1977). Data presented here are different. It is interesting to note that whereas single dose kinetic studies with sulphadiazine (Shastri & Krishnaswamy, 1979) showed a difference in the

Table 1 Anthropometric index, serum albumin, half-life and urinary excretion in 24 h of sulphafurazole (75 mg/kg) (mean $\pm$ s.d.).

Groups	$\frac{Wt. \times 100}{H^2}$	Serum albumin (g%)	$T_{1/2}$ (h)	Total drug excreted (% of dose given)	Acetyl drug excreted (% of dose given)	Acetyl drug (% of drug excreted)	pH of urine
Well-nourished	0.20 ± 0.020 (6)	3.84 ± 0.218 (6)	7.69 ± 1.987 (6)	79.32 ± 21.313 (6)	20.33 ± 5.972 (6)	25.94 ± 4.412 (6)	6.19 ± 0.318 (6)
Under-nourished	$0.14 \pm^{**} 0.014$ (8)	$2.64 \pm^* 0.707$ (8)	6.91 ± 0.857 (8)	74.95 ± 9.306 (6)	20.81 ± 8.074 (6)	25.42 ± 6.268 (6)	6.11 ± 0.245 (6)

Figures in parentheses indicate number of observations.

* $P < 0.01$; ** $P < 0.001$.

Table 2 Relative volume distribution (V_d), total body clearance (Cl), plasma protein binding and plasma concentrations (mg%) of sulphafurazole (mean $\pm$ s.d.)

Groups	V_d (l kg ⁻¹)	Cl (ml h ⁻¹ kg ⁻¹)	Plasma protein binding (%)	Plasma concentrations (h)			
				4	6	8	24
Wellnourished	0.35 ± 0.092 (6)	32.74 ± 9.695 (6)	87.67 ± 2.109 (6)	18.7 ± 6.00 (6)	15.5 ± 2.35 (6)	12.2 ± 2.11 (6)	3.1 ± 1.36 (4)
Undernourished	0.38 ± 0.126 (8)	37.27 ± 11.877 (8)	$64.00 \pm^{*} 6.471$ (5)	14.9 ± 7.01 (7)	12.9 ± 3.73 (7)	9.6 ± 2.63 (8)	2.03 ± 0.563 (6)

Figures in parentheses indicate number of observations.

* $P < 0.001$

acetylation and clearance rate of the drug in undernourished adults as compared to the wellnourished, studies with SFZ, a compound chemically related to sulphadiazine did not reveal any differences. This may be because in general, the elimination of sulphonamides from the body, depends on several factors such as protein binding of the drug, the pKa of the drug, the pH of the urine and also in the case of some sulphonamides, on the acetylation phenotype of an individual.

The route of elimination of SFZ is mainly the kidney (Weinstein, 1975). In spite of a plasma protein binding of 85%, the drug has a short half-life because of a high renal clearance (Cohen & Pocelinko, 1973). It is reported (Cohen & Pocelinko, 1973) that as the pH of urine moves towards alkalinity the clearance of SFZ equals or even exceeds the endogenous creatinine clearance. Hepatic acetylation may therefore not be important in the clearance of SFZ from the body. It has, in fact been reported that only 30% of the drug administered is normally excreted in the acetyl form in urine. Newbould & Kilpatrick (1960) have demonstrated that although protein binding determines the rate of glomerular filtration, different sulphonamides are reabsorbed by the renal tubules at different rates, thus masking the effects of protein binding on glomerular filtration.

Data presented here show that despite a significant reduction in the bound fraction of the drug in undernourished subjects, there seems to be no alteration in the kinetics of SFZ. There could be two reasons for the lack of difference in the urinary excretion of SFZ. One is the low pKa value of the drug (4.9), since it is known that the degree of ionisation of a drug in urine, in addition to lipid solubility determines tubular reabsorption (Struller, 1968). At a urinary pH of 6.19 and 6.11 in the wellnourished and undernourished subjects respectively, a large percentage of the drug would exist in an ionized form and thereby go unabsorbed by the renal tubule leading to a high proportion of the administered drug being excreted by the kidney. It is also reported that SFZ is actively secreted by the renal tubule (Cohen & Pocelinko 1973), a process known to be independent of plasma protein binding. This may be the second reason for the similar urinary excretion of the drug in the two groups of subjects.

Newbould & Kilpatrick (1960) reported that the plasma protein binding of sulphonamides determines the rate of acetylation of these drugs. Evidently, SFZ

does not seem to follow this general law, for in spite of a lowered protein binding of the drug found in the undernourished subjects, the rate of acetylation was not altered as seen by values of the acetyl SFZ in urine. That the capacity to acetylate SFZ by the liver in the undernourished is impaired seems unlikely for, as reported earlier (Shastri & Krishnaswamy, 1979) the acetylation of sulphadiazine occurred in the undernourished at a rate faster than normal. On the other hand, the results observed here seem to suggest that the renal excretory mechanism seems to overwhelm the capacity of the liver to eliminate the drug by acetylation, even though a greater proportion of the drug seems to exist in an unbound form in the undernourished subjects.

For calculation of V_d , it is assumed that the absorption of the drug is complete. C_{po} is therefore taken as the amount of the drug present in the plasma at zero time. Values reported for V_d in the wellnourished and undernourished groups were similar, despite a difference in plasma protein binding of SFZ and comparable to values reported by Marshall (1948) who observed that the V_d for SFZ is about 25–30% of the bodyweight. It is reported that the distribution of SFZ is confined to extra cellular water. Absence of differences in the V_d between the two groups may be due to the fact that at physiologic pH the drug is almost completely ionised in both groups and may be unable to readily leave the extracellular fluid.

Data presented here seems to suggest that although there is a significant reduction in the plasma protein binding of SFZ in undernourished subjects pharmacokinetics of the drug was not altered probably because of rapid renal elimination which is independent of plasma protein binding of the drug. Because of its short half-life and a rapid renal clearance SFZ is more useful as an urinary antimicrobial agent than a systemic antibacterial drug. Even though the concentration of unbound drug in the plasma is three times higher in the undernourished as compared to the wellnourished, since the renal excretion of the drug is similar in the two groups, it may be concluded from the present study that alteration in dosage schedule of SFZ may not be necessary in the treatment of undernourished adults with this sulphonamide.

The author would like to thank Dr S. G. Srikantia, Director and Dr Kamala Krishnaswamy, Assistant Director, National Institute of Nutrition, Hyderabad for their keen interest in the study. The technical help of Mr R. Nageswar Rao is also acknowledged.

References

- COHEN, M. & POCELINKO, R. (1973). Renal transport mechanisms for the excretion of sulfisoxazole. *J. Pharmac. exp. Ther.*, **185**, 703–712.
- GORNALL, A.G., BARDAWILL, C.J. & DAVID, M.M. (1949). Determination of serum proteins by means of the biuret reaction. *J. biol. Chem.*, **177**, 751–766.

- HEEL, R.C. & AVERY, G.S. (1980). In *Drug Treatment*, Ed. Avery, G.S., pp. 1211–1224. Sydney, New York: ADIS Press.
- HOMEIDA, M., KARRAR, Z.A. & ROBERTS, C.J.C. (1979). Drug metabolism in malnourished children; a study with antipyrine. *Archs. Dis. Childh.*, **54**, 299–302.
- JAYARAO, K.S., MUKHERJEE, N.R. & RAO, K.V. (1972). A survey of diabetes mellitus in a rural population in India. *Diabetes*, **21**, 1192–1196.
- KRISHNASWAMY, K. & NAIDU, A.N. (1977). Microsomal enzymes in malnutrition as determined by plasma half-life of antipyrine. *Br. med. J.*, **1**, 538–540.
- MARSHALL, E.K. (1948). Distribution of 3,4-dimethyl-5-sulfanilamidoisoxazole in the body. *Proc. Soc. exp. Biol. Med.*, **68**, 472–473.
- MEHTA, S., KALSI, H.K., JAYARAMAN, S. & MATHUR, V.S. (1975). Chloramphenicol metabolism in children with protein-calorie malnutrition. *Am. J. clin. Nutr.*, **28**, 977–981.
- NEWBOULD, B.B. & KILPATRICK, R. (1960). Long-acting sulphonamides and protein binding. *Lancet*, **i**, 887–891.
- RICHTERICH, R. (1969). In *Clinical chemistry—theory and practice*, pp. 287–288. Basel: S. Karger.
- SHASTRI, R.A. & KRISHNASWAMY, K. (1976). Undernutrition and tetracycline half-life. *Clinica Chim. Acta*, **66**, 157–164.
- SHASTRI, R.A. & KRISHNASWAMY, K. (1979). Metabolism of sulphadiazine in malnutrition. *Br. J. clin. Pharmac.* **7**, 69–73.
- STRULLER, T. (1968). Progress in sulfonamide research. *Fortschr. Arzneimittel Forsch.*, **12**, 389–457.
- SVEC, F.A., RHOADS, P.S. & ROHR, J.H. (1950). New sulfonamide (Gantrisin): Studies on solubility, absorption and excretion. *Arch. intern. Med.*, **85**, 83–90.
- WEINSTEIN, L. (1975). In *The Pharmacological Basis of Therapeutics*, Eds. Goodman, L.S. & Gilman, A., p. 1108, New York, Toronto, London: Macmillan.

(Received March 3, 1980)