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Pharmacokinetic Variations of Sulfafurazole in 'Fast' and 'Slow' Acetylators

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Abstract

A number of therapeutically important drugs are reported to show the phenomena of fast and slow acetylation. The bimodal Acetylation of sulfafurazole has not yet been reported, although there is a distinct possibility. Individual sulfonamides differ in the extent they are absorbed in the extent they reach body tissues, and in the rate they are eliminated from the body. The present report describes the phenomena of two acetylator phenotypes for sulfafurazole.

Keywords: Sulfafurazole (sulfisoxazole), bimodal acetylator phenotypes

Introduction

The metabolism of most drugs in human volunteers seems to be under multifactorial or polygenetic control. Metabolism data for some drugs show a bimodal distribution. They are assumed to represent two distinct phenotypes. Polymorphic acetylation is a good example of two distinct phenotypes. On the basis of bimodal acetylation of some drugs, population is categorized as slow acetylator type and fast acetylator type for a particular drug. Sulfadiazine, sulfamethazine and sulfapyridine are subject to polymorphic acetylation (Carr *et al.*, 1978, Das, 1976, Evans, 1968, Gulaid, *et al.*, 1978, Hamilton, *et al.,* 1986., Lima 1978, Lunde, *et al.*, 1977, white 1968).

The present study is undertaken to describe the possibility of polymorphic acetylation of sulfafurazole (sulfisoxazole). Though, the number of the human volunteers taken for study was very low, usually unsatisfactory for such studies, it may be useful for further studies to explore genuine phenotypic bimodal acetylation of sulfafurazole.

Materials

Sulfafurazole (Roche Products Ltd., Bombay, India), potato starch (Sisco Res. Lab., Bombay, India), Cab-o-Sil (Cabot corporation, Tuscola, U.S.A), magnesium stearate (Chemilon Laboratories Chemicals, Bombay, India), polyvinyl pyrrolidone (Loba Chemic Industrial co., Bombay, India), lactose (BDH, Bombay, India), mannitol (Sarabhai Chemicals, Baroda, India), citric acid (IDPL, Hyderabad, India), Hydrochloric acid (BDH, India), commercial sulfafurazole tablets (Western Chemicals, Indore), sucrose (BDH, India), ethyl alcohol

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(Bengal Chemicals & Pharmaceuticals Works, Ltd., Calcultta, India), polyethylene glycol 4000 (Loba Chemie Industrial Co. Bombay, India), ammonium sulfamate (Sarabhai Chemicals, Baroda, India}, Bratton– Marshall Reagent (Loba Chemic Industrial Co., Bombay, India), ammonium hydroxide (BDH, India), and other reagents were procured from commercial sources. They were used as received.

Methods

Except lime flavour and the lubricants, weighed amounts of the ingredients (Table1) were moistened gradually with 5% Polyvinyl pyrrolidone in ethyl alcohol, the granules were then passed through 20 mesh sieve. The granules so obtained were dried in air. The dried granules were again passed through 20 mesh sieve and the portion retained above 40 mesh sieve was separated. 1.0% talc and o.5% Cab-o-Sil on dry weight basis were added to the granules and mixed well.

Table 1. Formulations of tablets

Ingredients in mg per tablet	C_1*	C_2	S
Sulfafurazole	250	250	500
Mannitol	250	250	-
Lactose	-	250	-
Polyethylene glycol 4000	-	5 mg in a small volume of ethanol	5 mg in a small volume of ethanol
Talc	7.5	5.0	-
Starch	-	-	50 mg
Magnesium stearate	-	-	5.0
Sucrose	250	-	500
Polyvinyl pyrrolidone	12.5 mg in ethanol	-	-
Citric acid	7.5	-	-
Cab-o-Sil	3.75	-	-
Water	-	-	Q.S
Starch paste	-	-	-

Tablet C_1 (Chewable)

Immediately prior to compression, the granules were mixed with the lime flavour dissolved in a small volume of ethanol. Tablets were compressed using ½ inch flat diepunch set. The hardness was kept around 7.0 kg/cm^2.

Tablet C_2 (Chewable)

Weighed amounts of the ingredients (Table 1) except the flavour and lubricant were moistened gradually with 5% polyethylene glycol 4000 in ethyl alcohol which was then passed through 20 mesh sieve. The dried granules were again passed through 20 mesh sieve and the portion retained above 40 mesh sieve was separated. 0.5% poly-ethylene glycol 4000 dissolved in alcohol were added to the granules and mixed well. Then 0.5% talc on dry weight basis was added to the granules and mixed well. Prior to compression, the granules were mixed with the lime flavour dissolved in a small volume of ethanol. Tablets were compressed using ½ inch flat die-punch set at the hardness around 5 kg/cm^2. The hardness was deliberately kept lower than that of tablet. C_1.

Tablet S (Swallow)

The ingredients were mixed in geometric proportion and moistened gradually with distilled water (Table1). The dough of suitable consistency was passed through 20 mesh sieve and dried in an oven at 50°C for 1½ hours.

The dried granules were again passed through 20 sieve and the portion retained above sieve number 40 were separated. 1% poly-ethylene glycol dissolved in small volume of ethyl alcohol was sprayed evenly over the granules. Then granules were dried. Immediately prior to compression 1.0% magnesium stearate and 0.5% talc was added.

Granules were then compressed into tablets in a Manesty E_2 type single punch tablet machine using ½ inch flat die punch set. The hardness was kept around 7.0 kg/cm^2.

In vivo study

Four healthy human volunteers (PC, DM, BC and MT) of age group 23-27 years and weight ranging 55 -60 kg were instructed to adhere to a standard protocol and abstain from taking any medication during the course of study. Four tablet formulations (One commercial (M) and three fabricated (S, C_1 and C_2))of sulfafurazole were tested, out of which, two (M and S) were swallow tablets and two chewable (C_1 and C_2). The components of S, C_1 and C_2 are given in Table 1. The swallow tablets (M and S) exceeded the dissolution minima as described in U.S.P XIX (not less than 70% of drug dissolved in 30 minutes in O. IN hydrochloric acid).

Dosing of the volunteers was done in a single 1 g design with adequate cross over. A light breakfast was consumed by the subjects in the morning two hours before the drug administration. They were instructed to avoid caffeinated drinks till the expiry of about 9 hours post administration and to control carefully their fluid intake. The swallow tablets (M and S) were ingested with 200 ml of tap water and chewable tablets (C_1 and C_2) were masticated well and washed with 200 ml of tap water. Urine samples were collected at 0, 1, 2, 3, 5, 7, 9 and 24 hours after dosing. Urine samples voided beyond 9 hours and upto 24 hours were pooled.

Volume of urine samples were measured and a 10ml aliquot was frozen till assayed. The pH of all urine samples were recorded to keep a check. The samples of urine were estimated for 'Total' and 'Free' sulfafurazole by the method of Bratton and Marshall (1939). Total sulfafurazole (unchanged and metabolite) in urine was determined by hydrolysis of urine samples with hydrochloric acid at 98°C for 60 minutes and then following the same procedure for free sulfafurazole (Bratton and Marshall 1939). N^4 – acetyl sulfafurazole metabolite was estimated by deducting 'Free' sulfafurazoel from 'Total' amount of sulfafurazole.

Results and Discussion

The commercial (M) and fabricated tablets (C_1, C_2 and S) were subjected to all pharmacopoeial and non- pharmacopoeial tests and found complied in all respects. The swallow tablets M and S released 94.13% and 90.08% of drug in 30 minutes in 0.lN HCl medium. Dissolution study was done for sulfafurazole tablet as prescribed in U.S.P. XIX.

It has been reported that sulfafurazole presence modifies the renal clearance of its conjugate (Bekersky, and Colburn 1980). From Table 2, Table 3 and Table 4, subject DM shows a clear bimodal excretion rate for both 'total' and 'free' drug. The $t_{1/2}$ values (obtained from log-sigma minus curve) of this subject is more close to the range of values reported (Table 4). It shows that initial higher plasma and tubular concentrations of sulfafurarzole competes for active tubular reabsorption sites. A small amount of deacetylation of the N^4 – acetyl derivative is also responsible to some extent for the bimodal excretion pattern. Subject PC usually shows a very long $t_{1/2}$ (Table 4), being of slow acetylator type and for tablet S, the $t_{1/2}$ is so long that it could not be calculated from the sigma-minus plot (Fig. 1).

Table 2. Cumulative Recovery of Sulfafurazole (TOTAL) form Urine Analysis Following Oral Administration of Commercial and Fabricated Tablets

Hours	M				S				C_1				C_2			
	DM	PC	BC	MT	DM	PC	BC	MT	DM	PC	BC	MT	DM	PC	BC	MT
1	3.20	2.90	26.4	31.5	5.4	0.0	58.8	0.0	24.2	16.4	50.0	9.9	116.6	22.5	37.3	32.0
2	23.2	17.0	124.8	12.07	62.4	1.5	206.8	53.2	119.4	38.2	59.1	90.9	135.8	69.3	89.6	59.0
3	78.2	125.0	216.2	260.7	132.8	50.1	276.0	115.0	158.2	55.4	250.1	125.9	191.8	88.9	240.0	86.0
5	330.2	293.2	403.7	380.7	421.6	86.2	415.2	269.0	250.8	125.2	333.3	199.9	239.4	177.9	318.0	198.5
7	488.2	353.2	526.9	415.7	497.1	141.2	512.2	308.0	378.1	146.2	342.8	299.7	382.7	229.2	363.0	311.5
9	682.6	424.6	592.0	513.7	602.6	180.1	652.2	329.0	479.1	212.8	391.4	340.7	477.0	261.6	523.0	376.5

Table 3. Cumulative Recovery of Sulfafurazole (FREE) form Urine Analysis Following Oral Administration of Commercial and Fabricated Tablets

Hours	M				S				C_1				C_2			
	DM	PC	BC	MT	DM	PC	BC	MT	DM	PC	BC	MT	DM	PC	BC	MT
1	2.3	0.0	25.6	25.2	3.8	0.0	40.3	0.0	16.8	9.4	43.2	8.3	85.6	20.1	32.1	26.0
2	14.4	9.6	96.9	89.9	46.8	1.3	153.7	24.5	80.3	29.2	48.0	62.8	97.9	56.5	72.6	48.9
3	39.4	97.1	176.6	199.9	107.1	22.8	187.9	60.9	104.6	37.2	213.6	83.6	143.5	69.3	164.3	63.0
5	193.7	184.1	270.3	275.7	300.9	58.0	288.7	139.3	159.7	82.4	264.8	144.1	181.0	127.8	206.3	136.4
7	281.1	217.0	341.2	294.9	361.4	88.5	360.7	160.5	234.0	94.3	269.8	217.6	272.2	153.6	231.2	199.5
9	362.7	234.4	382.7	354.4	421.4	104.3	446.7	194.5	290.2	139.1	294.8	237.4	343.3	174.0	332.9	244.3

In comparison to this, the elimination rate constants, K, (Table 4) are not much different. Sulfafurazole is a drug with a low renal extraction ratio. In this case, the clearance of the drug will depend largely on the enzymatic system metabolizing drug since the half life ($t_{½}$) will reflect changes in the elimination organ functions. In the present study, it was found that although the absorption rates of sulfafurazole from fabricated dosage forms (C_1, C_2 and S) differed significantly from the commercial product (M), the average half lives ($t_{½}$) and elimination rate constants were similar (Table 4).

Drug, like the present one, that is highly sequestered by non-fatty or lean tissues does not necessarily have weight related volumes of distribution, because renal and hepatic clearances are not necessarily weight related. Urine excretion rate-time curves were plotted for both 'total' and 'free' sulfafurazole, time in hours versus drug excreted in mg, A_U^{∞} - AU (mg log scale) estimated from Table 2 and Table 3. The curve for 'total' sulfafurazole was found parallel to 'free' sulfafurazole for all four human volunteers (sample example fig.1). It indicates that N^4 – acetylsulfafurazole is eliminated faster than parent compound, independent of the acetylator status of the volunteer. The renal clearance of sulfafurazole is low, due to its high protein binding and tubular reabsorption. It is independent of the rate of acetylation and acetylator status.

However, the acetylator status of a volunteer may not be construed as a sign of generic inequivalence of sulfafurazole. In a study of the bioavailability of 1 'brand' and 2 'generic' tablets of sulfafurazole, the rate, but not extent of urinary excretion were found different (Martin *et al.*, 1968).

Table 4. Pharmacokinetic parameters of tablets.

Product	Subject	Cumulative Percent of Sulfafurazole (total) in 24 hours	Cumulative Percent of Sulfafurazole (free) in 24 hours	Half life ($t_{1/2}$) of sulfafurazole (total)	Elimination Rate Constant of Sulfafurazole (total) K
M	PC	62.36	33.74	5.77	0.12
	BC	68.46	43.96	2.47	0.28
	DM	96.94	64.27	4.33	0.16
	MT	88.07	53.74	2.77	0.25
C_1	PC	62.48	33.79	8.66	0.078
	BC	57.68	44.26	4.95	0.14
	DM	80.21	48.02	4.95	0.14
	MT	60.32	39.44	4.77	0.15
C_2	PC	37.61	24.46	4.33	0.16
	BC	56.78	36.68	4.33	0.16
	DM	63.29	43.85	3.01	0.23
	MT	47.15	32.13	2.77	0.25
S	PC	53.01	30.28	-	-
	BC	82.72	55.59	4.88	0.14
	DM	81.42	51.77	3.4	0.20
	MT	60.04	33.96	6.02	0.114

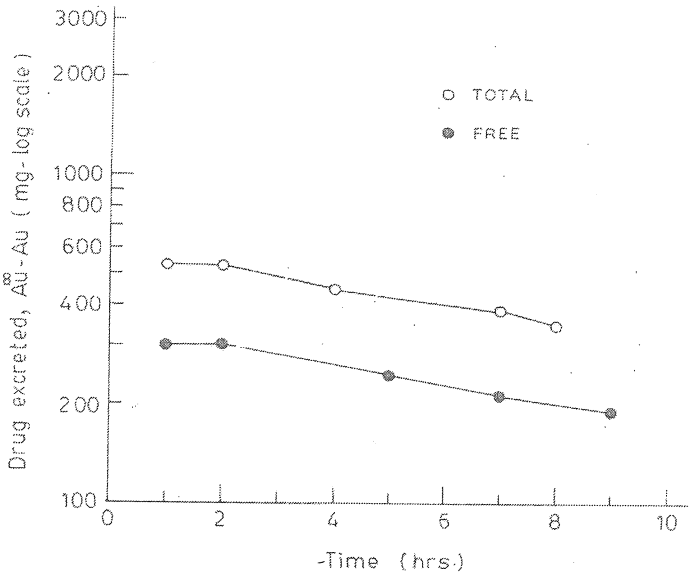

Figure 1. log sigma – minus plot for the urinary excretion of free and total sulfafurazole of fabricated tablet (s) Subject : pc

References

Bekersky, I., and Colburn, W. A. (1980). Acetylation of Sulfisoxazole by Isolated Perfused Rat Kidney. *J. Pharm. Sci.* 69 : 1359.

Bratton, A.C., and E.K. Marshall, Jr. (1939). A New Coupling Component for Sulfanilamide Determination. *J. Bio. Chem.* 120 : 537 – 550.

Carr, K., et al. (1978). Simultaneous Analysis of Dapsone and Monoacetyldapsone Employing High Performance Liquid Chromatography: A Rapid Method for Determination of Acetylator Phenotype. *Br. J. Clin. Pharmacol.*6 : 421.

Das, K.M. et al. (1973). Adverse Reactions During Salicylazosulfapyridine Therapy and the Relation with Drug Metabolism and Acetylator Phenotype. *N. Engl. J. Med.* 289 : 491.

Dass, K.M., and Dublin, R. (1976).Clinical Pharmacokinetics of Sulphasalazine. *Clin. Pharmacokinet.*1: 406.

Evans, D.A.P. (1968). Genetic Variations in the Acetylation of Isoniazid and Other Drugs. Am. NY Acad: Sci. 151 : 723.

Evans, W.E. et al. (1989). Dextromethorphan and Caffeine as Probes for Simultaneous Determination of Debrisoquin – oxidation and N – Acetylation Phenotypes in Children. *Clin. Pharmacol Ther.* 45 : 568.

Gulaid, A., et al. (1978). Lack of correlation between Acetylator Status and the Production of the Acetyl Metabolite of Acebutolol in Man. *Br. J.Clin. Pharmacol.*5 : 261.

Hamilton, R.A., et al. (1986). Effect of Acetylator Phenotype on Amrinone pharmacokinetics. *Clin. Pharmacol. Ther.*40 : 615.

Lima, J.J and Jusko, W.J. (1978). Determination of Procainamide Acetylator Status. *Clin. Pharmacol. Ther.* 23 : 25.

Lunde, P.K.M., Foslid, K., and Hunstreet, V. (1977). Disease and Acetylation Polymorph. *Clin. Pharmacokinet.* 2 : 182.

Martin, C.M., Rubin, M., O' Malley, W.E., Garagusi, V.F. and Mc Canby, C.E. (1968). Comparative Physiological Availability of Brand and Generic Drugs in Man, Chloramphenicol, Sulfisoxazole and Diphenylhydantoin. *Pharmacologist.*10 : 167.

Shepherd, A.M.M., et al. (1981). Plasma concentration and Acetylator Phenotype Determine Response to Oral Hydralazine. *Hypertension.* 3 : 580.

White, T.A, and Evans, D.A.P. (1968). The Acetylation of Sulfamethazine and Sulfamethoxypyridiazine by Human Subjects. *Clin. Pharmacol. Ther.* 9 :80.

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