A COMPARATIVE STUDY OF THE AVAILABILITY OF SULPHAFURAZOLE FROM COMMERCIAL BRANDS OF SULPHAFURAZOLE TABLETS

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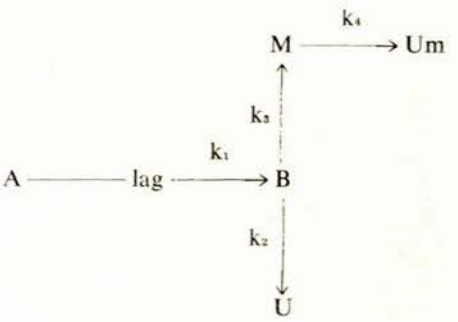
It has been shown by several authors that the physical properties of a drug, such as particle size, solubility, dissolution rate, etc., may have an effect on the biological availability of the drug.[1-4] In the course of a study aimed at the determination of the effect of variables in the formulation of sulphafurazole tablets on the biological availability of this drug, pharmacokinetic parameters for sulphafurazole were determined as part of the preliminary investigations, using 4 brands of local, commercially available sulphafurazole tablets.

The tablets were administered after an alkali load in order to eliminate diurnal fluctuations in urinary pH.

PHARMACOKINETIC MODEL

The following pharmacokinetic model is presented to describe the kinetics of sulphafurazole absorption, metabolism and excretion in man after administration of tablets.



The following differential equations are proposed to describe the model:

$$\frac{dA}{dt} = -k_1A \qquad 1.$$

$$\frac{dB}{dt} = k_1A - (k_2B + k_3B) = k_1A - KB \qquad 2.$$

$$\frac{dU}{dt} = k_2B \qquad 3.$$

$$\frac{dM}{dt} = k_3 - k_4M \qquad 4.$$

$$\frac{dUm}{dt} = k_4M \qquad 5.$$

TABLE I. ANALYTICAL DATA, AND RATE AND OTHER CONSTANTS INVOLVED IN THE ABSORPTION, METABOLISM AND EXCRETION OF SULPHAFURAZOLE IN MAN

Constants and other data	*Subject*	*Product*			
		A	*B*	*C*	*D*
Lag (hr)	A	1·2580	1·2379	0·8046	0·5038
	B	0·2550	0·6561	1·0679	0·0000
	L	0·4218	0·3905	0·6386	0·5390
k_1 (hr^{-1})	A	1·8480	1·3517	5·9450	2·4917
	B	1·5137	5·6020	0·8867	2·2849
	L	2·2344	1·3711	2·6055	1·6250
k_2 (hr^{-1})	A	0·0987	0·1134	0·1175	0·1075
	B	0·1003	0·1173	0·1088	0·1028
	L	0·0999	0·1252	0·0974	0·1083
k_3 (hr^{-1})	A	0·0363	0·0388	0·0346	0·0341
	B	0·0375	0·0481	0·0359	0·0419
	L	0·0288	0·0312	0·0324	0·0301
K (hr^{-1})	A	0·1350	0·1522	0·1521	0·1416
	B	0·1378	0·1654	0·1447	0·1447
	L	0·1287	0·1564	0·1298	0·1384
k_4 (hr^{-1})	A	0·1565	0·0953	0·1019	0·1605
	B	0·1696	0·1710	0·1416	0·1292
	L	0·1453	0·1925	0·1311	0·1038
Elimination half-life for free sulphafurazole (hr)	A	5·1306	4·5509	4·5541	4·8919
	B	5·0264	4·1882	4·7896	4·7866
	L	5·3815	4·4290	5·3360	5·0043
Excretion half-life for acetylsulphafurazole (hr)	A	4·4264	7·2733	6·8022	4·3181
	B	4·0858	4·0513	4·8923	5·3611
	L	4·7704	3·6007	5·2846	6·6718
Theoretical amount of free sulphafurazole excreted in 48 hours (mg.)	A	59·43	63·82	54·27	67·88
	B	60·56	62·04	58·14	57·66
	L	64·92	65·75	58·15	60·87
Theoretical amount of acetylsulphafurazole excreted in 48 hours (mg.)	A	21·70	21·21	15·63	21·42
	B	22·58	25·42	19·01	23·28
	L	18·57	16·34	19·09	16·55
Theoretical amount of total sulphafurazole excreted in 48 hours (mg.)	A	81·13	85·03	69·91	89·30
	B	83·15	87·46	77·15	80·94
	L	83·49	82·09	77·24	77·42
Period of urine collection (hours)	A	26	48	30·5	48
	B	26	48	35	47
	L	24	28	35	36
Content of sulphafurazole (% of label claim)		105·00	101·70	102·60	103·80
Disintegration time (min.) B.P.-method		1·56	9·18	3·63	1·02
Hardness of tablets (kg.) (Monsanto hardness tester)		10·02	4·29	6·50	6·11

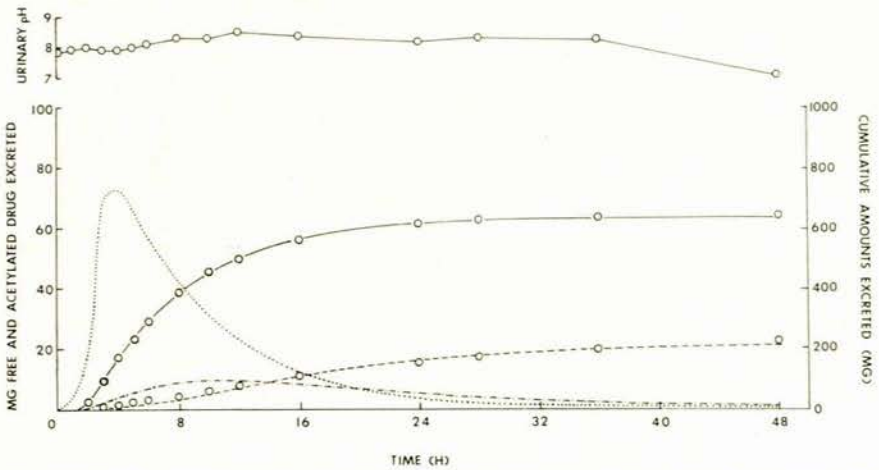


Fig. 1. Urinary excretion of sulphafurazole (subject A, product B) under controlled alkaline urine conditions after oral administration of 1,000 mg. of drug. o = experimental values; . . . . . = free drug (hourly); ———— = free drug (cumulative); —.—.— = acetylated drug (hourly); - - - - = acetylated drug (cumulative).

where t = time in hours after ingestion of the dose;
lag = the time interval between ingestion of the dose and commencement of absorption;
A = concentration of sulphafurazole in gastro-intestinal tract;
B = concentration of sulphafurazole in the body;
M = concentration of metabolites of sulphafurazole in body;
U = concentration of free sulphafurazole in urine;
U_m = concentration of metabolites in urine;
k_1 = rate constant for the absorption of sulphafurazole from the tract into the body;
k_2 = rate constant for the excretion of free sulphafurazole from the body into the urine;
k_3 = rate constant for the formation of metabolites of sulphafurazole;
k_4 = rate constant for the excretion of metabolites from the body into the urine;
K = rate constant for the elimination of sulphafurazole by all processes, i.e. $K = k_2 + k_3$.

Two tablets (1,000 mg. sulphafurazole) were administered, on fasting stomachs, to 3 male subjects in apparent good health. No ingestion of food was allowed until at least 2 hours after the tablets had been taken. Alkaline urine conditions were maintained by ingesting approximately 4 G of sodium bicarbonate 1·5 hours before the tablets were taken, followed by the same dose every 3 hours. Urine samples were collected hourly for at least the first 5 hours after ingestion of the tablets. Thereafter samples were collected at increasing intervals up to the times stated in Table I. Treating a sample collected before dosage of the drug as a blank, the urine samples were assayed for free and total sulphafurazole by the Bratton and Marshall method.[5]

RESULTS AND DISCUSSION

Analytical data as well as the computed rate and other constants involved in the absorption, metabolism and excretion of sulphafurazole are listed in Table I. The theoretical curves, defined by the above equations, for subject A (product B) are shown in Fig. 1. The experimental values are in close agreement with those computed from the differential equations, and the proposed model may be accepted as suitable to describe the kinetics of the absorption, metabolism and excretion of sulphafurazole.

The tablets used in the study are of unknown composition, but differences in the formation, manufacturing procedures, and raw materials used must be assumed as most likely because the tablets are being manufactured by 4 different local pharmaceutical companies. This assumption is confirmed by differences found in the content of sulphafurazole, appearance, hardness, average weight, and disintegration time of the different products. The pharmacokinetic parameters, on the other hand, show hardly any differences. In all cases absorption of the drug starts within a reasonably short period of time, and the peak urinary concentration is reached in 2 - 4 hours. The elimination half-life of free drug, on which the dosage interval is based, is of the same order for all 4 products, ranging from approximately 4 to 5 hours. In the light of these similarities, the products should be regarded as equally effective.

SUMMARY

Urinary excretion data were used in a comparative study of the biological availability of sulphafurazole from 4 commercial brands of sulphafurazole tablets. The tablets were administered after an alkali load. Urine samples were assayed for free and total sulphonamide content and from the experimental values the rate and other constants involved in the absorption, metabolism and excretion of sulphafurazole were computed by means of differential equations proposed to describe a pharmacokinetic model. Experimental values were in close agreement with computed values. The similarity in the pharmacokinetic parameters of the 4 products shows that there is very little difference, if any, in the availability of sulphafurazole from the different brands of tablets, and all 4 products can be regarded as equally effective.

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