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Determination of pharmacokinetic parameters for rapid and slow acetylators of sulphadimidine

M. C. B. VAN OUDTSHOORN AND F. J. POTGIETER

Department of Pharmaceutics, Potchefstroom University, Potchefstroom, South Africa

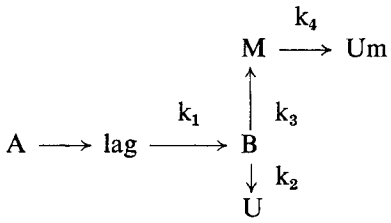
The pharmacokinetic parameters for twenty test subjects were determined after oral administration of sulphadimidine a urinary excretion method was used. The rate constant for the formation of acetylsulphadimidine shows that the acetylation polymorphism can be attributed to the rate of metabolism. The evidence of bimodality was also confirmed when expressing the data in terms of biological half-life rather than percentage acetylation. With seven test subjects more than 90% of the sulphadimidine ingested was metabolized.

It is a recognized fact that hereditary variations may exist among individuals in their rate of metabolism of some drugs and that parameters taken to represent rate of metabolism form bimodal distributions (Kalow, 1962; Evans & White, 1964). According to White & Evans (1968) there is a Mendelian polymorphism in man for the acetylation of sulphadimidine. As with isoniazid, the ability to inactivate sulphadimidine is bimodally distributed in the population; those who acetylate 62–90% of the drug being clearly different from those who acetylate only 40–53%. Active acetylators of sulphadimidine correspond with rapid inactivators of isoniazid (Evans & White, 1964). *In vitro* studies have demonstrated that this genetic system controls liver acetyl transferase.

We have previously pointed to the need to ensure a minimum rate of flow in therapy with sulphadimidine for which minimum rates of flow were calculated for rapid and slow acetylators (Potgieter & Van Oudtshoorn, 1969; Van Oudtshoorn & Potgieter, 1971). Recently, Rao, Mitchison & others (1970) indicated that a sulphadimidine acetylation experiment could be used to distinguish between rapid and slow inactivators of isoniazid, and that this experiment had advantages over the method of determining serum concentrations of that drug. We have determined the pharmacokinetic parameters for rapid and slow acetylators of sulphadimidine in order to quantify its rate of metabolism.

Pharmacokinetic model

The pharmacokinetic model overleaf is proposed to describe the kinetics of absorption, metabolism and excretion of sulphadimidine in man after oral administration of a solid dosage form. The differential equations used are the same as those of Goossens & Van Oudtshoorn (1969). The apparent half-life $t_{\frac{1}{2}}$ (h) was calculated from the equation $t_{\frac{1}{2}} = 0{\cdot}693/K$.



Where:

A = amount of sulphadimidine present in the gastro intestinal tract
B = amount of sulphadimidine in the body
M = amount of metabolites of sulphadimidine in the body
U = amount of sulphadimidine in the urine
Um = amount of metabolites of sulphadimidine in the urine
k_1 = the rate constant for the absorption of sulphadimidine from the gastrointestinal tract into the body (h^{-1})
k_2 = the rate constant for the excretion of sulphadimidine from the body into the urine (h^{-1})
k_3 = rate constant for the formation of metabolites of sulphadimidine (h^{-1})
k_4 = the rate constant for the excretion of metabolites of sulphadimidine from the body into the urine (h^{-1})
K = rate constant for the elimination of sulphadimidine by all processes, i.e., $K = k_2 + k_3$.

MATERIAL AND METHODS

Twenty Caucasian male test subjects, ages 22–35, in apparent good health and with no history of sulphonamide sensitivity, ingested 1·0 g sulphadimidine in the form of two compressed tablets, a representative sample of which assayed at 99·45%. The drug was taken on a fasting stomach in the morning and no food was taken until about 2 h after ingestion of the dose. Urine specimens were taken at hourly intervals up to 6 h and thereafter at 9, 12, 15, 24, 27, 30, 36 and 48 h. The urine specimens were assayed by the method of Bratton & Marshall (1939) for free and acetylated drug. A blank was taken for each subject immediately before ingestion of the dose. A digital computer program was used to calculate the various pharmacokinetic parameters.

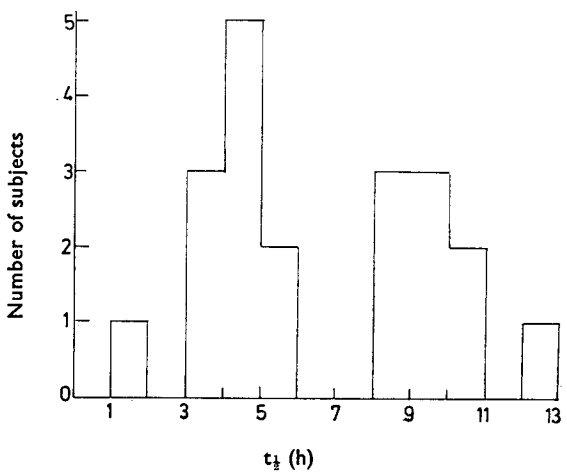


FIG. 1. The distribution of the biological half-life of sulphadimidine in 20 male test subjects.

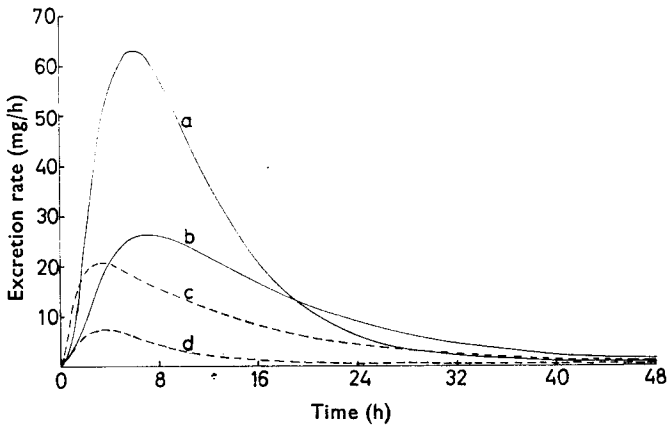


FIG. 2. The urinary excretion rate of free and acetylated sulphadimidine for a slow (subject XIV) and a rapid (subject VII) acetylator as theoretically calculated from the cumulative amounts excreted. – – – – free sulphadimidine. ——— acetylated sulphadimidine. Curves a and d for rapid acetylator. Curves b and c for slow acetylator.

Table 1. *Pharmacokinetic parameters of sulphadimidine for rapid and slow acetylators as calculated according to the proposed model.*

	Parameters						Acetylation (%) after	Acetylation (%) after
Subjects	lag	k_1 (h^{-1})	k_2 (h^{-1})	k_3 (h^{-1})	k_4 (h^{-1})	K (h^{-1})	$t_{\frac{1}{2}}$ (h)	9 h	48 h
I	0·1074	4·3710	0·0248	0·3872	0·1613	0·4120	1·7	91	93
II	0·0019	1·8984	0·0193	0·1904	0·3886	0·2097	3·3	88	91
III	0·5195	5·4648	0·0168	0·1745	0·4753	0·1913	3·6	85	91
IV	0·4589	4·8398	0·0211	0·1557	0·8621	0·1768	3·9	86	89
V	0·6777	5·8320	0·0138	0·1560	0·6308	0·1698	4·1	90	93
VI	0·0019	0·6914	0·0191	0·1457	0·4722	0·1648	4·2	85	89
VII	0·0097	0·6757	0·0138	0·1432	0·4394	0·1570	4·4	89	92
VIII	0·3496	0·2070	0·0340	0·1202	0·1222	0·1542	4·5	56	78
IX	1·3867	0·7226	0·0130	0·1294	0·4964	0·1424	4·9	87	91
X	0·0019	0·9335	0·0362	0·1040	0·3082	0·1402	5·1	69	76
XI	0·4003	2·1914	0·0077	0·1187	1·5925	0·1284	5·5	93	94
XII	0·0019	0·8320	0·0292	0·0536	0·2394	0·0828	8·4	52	65
XIII	0·0019	0·6445	0·0294	0·0514	0·2941	0·0808	8·6	52	64
XIV	0·0019	1·0039	0·0302	0·0482	0·3761	0·0784	8·8	55	62
XV	0·0136	0·6210	0·0241	0·0508	0·4722	0·0749	9·2	61	69
XVI	0·0019	1·0273	0·0204	0·0521	0·3035	0·0725	9·5	63	72
XVII	0·0019	0·8789	0·0245	0·0453	0·3855	0·0698	9·9	57	66
XVIII	0·2500	0·7500	0·0238	0·0445	0·7499	0·0683	10·1	56	66
XIX	0·0019	0·6757	0·0262	0·0405	0·4027	0·0667	10·4	52	61
XX	0·0019	2·2695	0·0172	0·0378	0·5941	0·0550	12·6	61	69

RESULTS

The pharmacokinetic parameters obtained are in Table 1. The frequency distribution histogram is given in Fig. 1 where the half-life is plotted against the number of test subjects. The urinary excretion rate of sulphadimidine and acetylsulphadimidine for a slow acetylator and a rapid acetylator (Fig. 2) is given. The rate was calculated from the slope of the cumulative amount excreted over a 48 h period.

DISCUSSION

The existence of human acetylation polymorphism for isoniazid and sulphadimidine has been previously confirmed. The purpose of this investigation was to determine the pharmacokinetic parameters for the two phenotypes.

According to Nelson (1963), it is probably better to express results in terms of half-life, rather than rate constant, when data on rate of metabolism is examined for evidence of bimodality, because the dimension of rate constant is reciprocal time which will cause a distortion of a frequency distribution plot. This fact we confirmed during this study and for that reason the half-life was used in Fig. 1. The results so obtained correspond well with the bimodal distribution obtained when the frequency is plotted against the percentage of subjects acetylating the drug. All the test subjects except subject VIII, could be so grouped.

From the results in Table 1 it can be seen that there is no correlation of the rate constant for absorption (k_1), excretion of free sulphadimidine (k_2) and of acetylsulphadimidine (k_4) and the half-life or the percentage acetylation. There is however, a correlation of the half-life and the rate constant for the formation of acetylsulphadimidine (k_3). Because the rate constant for the elimination of sulphadimidine (K) is obtained from $k_2 + k_3$, the same relation is found between half-life and K.

The rate constant for the formation of acetylsulphadimidine (k_3) is almost three times higher for rapid acetylators than for slow acetylators. The use of this terminology is therefore justified in distinguishing between the phenotypes.

It is furthermore of interest to note that the average half-life for the 20 test-subjects is 6·4 h which corresponds well with the 7 h given by Struller (1968) who did not discuss acetylation polymorphism. We found the average biological half-life was 4·0 h for rapid and 8·8 h for slow acetylators. The usefulness of urinary excretion methods for the determination of pharmacokinetic parameters is thus again illustrated.

The reproducibility of the results was confirmed with five test subjects who repeated the experiment eight times over long intervals. With test-subject XIV (slow acetylator), the percentage acetylation after 48 h varied from 60 to 70% (average 65%), whereas with subject III the variation was between 83 and 93% (average 89%). Subject XI acetylated as much as 94% of the sulphadimidine ingested.

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