STUDIES ON THE CRYSTALLURIA POTENTIAL OF SULPHONAMIDES: ACETYLATION OF SULPHADIMIDINE UNDER CONTROLLED ALKALINE URINE CONDITIONS

F. J. POTGIETER AND M. C. B. VAN OUDTSHOORN, *Department of Pharmaceutics, Potchefstroom University, Potchefstroom, Tvl*

The kinetics of absorption, metabolism and excretion of sulphonamides have been studied by examination of blood and, in certain cases, urine.[1-4] Studies on the acetylation of sulphafurazole[2] and sulphamethylthiadiazole[3] in human test subjects indicate that excretion of the acetylated drug is the terminal step in a two-step consecutive first-order process of which the first step is acetylation. This was also shown to be the case for sulphadimidine.[5]

Although the metabolism of sulphonamides is discussed in standard textbooks, no attention is given to the fact that the acetylation of sulphadimidine by man exhibits genetic polymorphism.[6] It was shown that there are two recognizable phenotypes, namely, rapid and slow acetylators, and that slow acetylation is a Mendelian-recessive character. In a recent publicaton we have described the kinetic parameters for absorption and excretion of rapid and slow acetylators of sulphadimidine.[5]

The work reported now was conducted as part of a programme on the evaluation of various pharmaceutical dosage forms of sulphadimidine. The possibility of the occurrence of crystalluria in the therapy with sulphonamides should always be considered, since its consequences may be quite serious if precipitation of the drug occurs in the kidney.

METHODS

A test panel of 4 healthy young male adults was used in the study; 1·0 G sulphadimidine in the form of two compressed tablets was ingested in the morning on stomachs that had been fasted overnight. No food was taken until 2 hours after ingestion of the dose. Sufficient water was taken to maintain an adequate urine flow. After drug ingestion quantitative urine collections were obtained at intervals as shown in Table I. Free and total sulphonamide concentrations in urine were estimated by the Bratton-Marshall[7] procedure. Alkaline urine conditions were maintained with an alkali load of 2·0 G of sodium bicarbonate every 3 hours.

RESULTS AND DISCUSSION

The minimum urine flow-rate needed to prevent the occurrence of crystalluria may be calculated by the following expression.[8]

Minimum flow-rate = Excretion rate/Solubility.

In this expression excretion rate refers to the acetylsulphadimidine expected to precipitate and is taken to be in units of mg./hr. If solubility is taken in units of mg./ml., then minimum flow-rate will be in units of ml./hr.[9] The solubility of acetylsulphadimidine at pH 7 and 37°C was taken as 1·45 mg./ml.[10]

The minimum flow-rates calculated using the above expression for the 4 test subjects are given in Table I.

Using the method described by White and Evans,[11] subject C was phenotyped as a rapid acetylator of sulphadimidine with an acetylation of more than 80%. From the results in Table I it can be seen that the excretion rate of acetylated drug for subject C is considerably higher than for the other 3 test subjects; a much higher urine flow-rate is also necessary.

At a dose level of 3·0 G, which is recommended as the initial dose for sulphadimidine, a much higher urine flow-rate is necessary and a much higher excretion rate of acetylated drug can be expected. Special attention should be given to the urine flow-rate of a rapid acetylator of sulphadimidine even under controlled alkaline urine conditions.

SUMMARY

Using a single oral dose of 1·0 G of sulphadimidine as 2 compressed tablets, different concentrations of acetylsulphadimidine were recovered in the urine after 48 hours. One test subject was phenotyped as a rapid acetylator of sulphadimidine with an acetylation of more than 80%. The minimum urine flow-rate needed to prevent the occurrence of crystalluria due to precipitation of ^{4}N acetylated drug is calculated for 4 test subjects.

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TABLE I. MINIMUM URINE FLOW-RATE NECESSARY TO PREVENT CRYSTALLURIA FOLLOWING 1·0-G ORAL DOSE OF SULPHADIMIDINE AT pH 7

Time	*Excretion rate of acetylated drug (mg./hr)*				*Flow-rate (ml./hr)*			
	Subject A	*Subject B*	*Subject C*	*Subject D*	*Subject A*	*Subject B*	*Subject C*	*Subject D*
0–1	4·1	0	7·6	0	2·8	0	5·2	0
1–2	6·6	6·2	45·9	2·0	4·5	4·3	31·7	1·4
2–3	15·1	14·0	79·8	11·2	10·4	9·7	55·0	7·7
3–4	12·2	15·9	77·7	14·7	8·4	11·0	53·6	10·1
4–5	14·8	21·2	83·5	24·7	10·2	14·6	57·6	17·0
5–6	22·6	16·5	78·2	22·8	15·6	11·3	53·9	15·7
6–9	17·7	24·4	61·7	31·9	12·2	16·8	42·6	22·0
9–12	23·6	29·3	46·4	0·9	16·3	20·2	32·0	0·6
12–24	13·0	11·1	8·5	13·3	9·0	7·7	5·9	9·2
24–36	9·1	7·1	2·3	4·1	6·3	4·9	1·6	2·8
36–48	2·8	1·2	0·5	0·1	1·9	0·8	0·3	0·1
% acetylation	64·8%	61·8%	86·90%	66·3%				