Acetylation of Sulfamethylthiadiazole

By SHUN-ICHI NAITO† and EINO NELSON

PREVIOUS studies with several sulfonamides, after absorption of a dose and attainment of an apparent equilibrium between drug in blood and drug in other fluids of distribution, show the disposition of the drugs can be described by competing first-order processes (1–4). One of these processes is acetylation of the sulfonamide and the other is excretion of free drug. With those sulfonamides that are excreted in part as N-glucuronides, the rate constant for excretion of free drug includes the rate constant for formation of the N-glucuronide (4–5).

This communication is specifically concerned with the magnitude of the rate constant for acetylation of sulfamethylthiadiazole found in studies conducted in Japan in comparison to the magnitude of this constant found in studies conducted in the U. S. The data from the latter studies has been previously published (2).

EXPERIMENTAL

Normal adult humans ingested 0.5-Gm. tablets of sulfamethylthiadiazole in the morning on overnight fasted stomachs. No food was taken until 2 hours after ingestion of the doses. Preingestion blank urines were obtained and after ingestion of the tablets urine collections were made at appropriate times and assayed for free and total drug by the method of Bratton and Marshall (6). This is the same assay as used in the work done in the U. S. (2). The sulfamethylthiadiazole tablets were 9 mm. in diameter and made with standard concave punches. The tablets were made of finely powdered drug and had the following formula

Sulfamethylthiadiazole	25 parts
Dried potato starch	5 parts
Polyvinyl pyrrolidone 5% in 50% isopropanol	10 parts
Calcium stearate	0.5 per cent

The tablets disintegrated on the average in about 1 minute when tested by the U.S.P. method.

Excretion data were subjected to mathematical analysis by methods previously described (1) to determine the values for the following constants: K, hr.$^{-1}$, the overall rate of removal of drug from the body; k_1, hr.$^{-1}$, the rate constant for acetylation; and k_3, hr.$^{-1}$, the rate constant for excretion of unchanged drug; and f, the fraction of a dose ultimately excreted in the urine as unchanged drug.

TABLE I.—VALUES OF RATE AND OTHER CONSTANTS (TESTS IN JAPAN)

Constant	Subjects H	W	S	T	Mean
K, hr.$^{-1}$	0.589	0.567	0.589	0.658	0.601
k_1, hr.$^{-1}$	0.226	0.225	0.249	0.236	0.234
k_3, hr.$^{-1}$	0.363	0.342	0.340	0.422	0.367
f	0.617	0.604	0.577	0.642	0.610

TABLE II.—MEAN VALUES OF RATE AND OTHER CONSTANTS (TESTS IN THE U. S.)

Constant	Value	Ratio (Japan/U. S.)
K, hr.$^{-1}$	0.514	1.17
k_1, hr.$^{-1}$	0.046	5.11
k_3, hr.$^{-1}$	0.468	0.78
f	0.911	0.670

RESULTS AND DISCUSSION

Table I lists the values of the various constants determined in the experiments.

For the sake of comparison, the mean values of constants found in previously published work with sulfamethylthiadiazole (2) are listed in Table II.

An examination of Table II will show that a more than five-fold difference existed between the values of the rate constant for acetylation obtained in the two sets of experiments. The t test showed a highly significant difference ($P < 0.01$) between the two sets of values of the rate constants. However, there was significantly greater variance in the set obtained in the studies conducted in the U. S. as compared to the variance in the set obtained in Japan.

It is difficult to assign a reason for the difference in k_1 found in the two sets of tests. In the tests conducted in the U. S. (2), two of the test subjects were of Japanese ancestry but their rate constants for acetylation were of the same order as for subjects of Caucasian ancestry. The average age of the test subjects in the U. S. tests was 30 years and in the Japan tests, 20 years. It does not seem likely that the difference could be attributable to this small difference in average age. Both sets of tests were conducted in the spring of the year. Differences in diet seem the most likely explanation, but it is difficult to accept this since first-order kinetics were followed.

Received September 6, 1962, from the Kyoto College of Pharmacy, Kyoto, Japan, and the Pharmacokinetic Laboratory, School of Pharmacy, University of Buffalo, Buffalo 14, N. Y.

Accepted for publication October 1, 1962.

† Present Address: Kyoto College of Pharmacy, Kyoto, Japan.

Note Added in Proof.—It recently came to the attention of one of us (E.N.) that 90% of Nisei Japanese and presumably native Japanese are rapid phenotypes with respect to the rate with which they inactivate isoniazid [Harris, H. W., Knight, R. A., and Selin, M., *J., Amer. Rev. Tubercul.*, **78**, 944(1958)]. Inactivation of this drug is mainly by acetylation. Further, humans may be grouped in rapid and slow categories with respect to the rate with which they acetylate sulfadimidine and rapid acetylators of sulfadimidine are rapid inactivators of isoniazid [unpublished work of D. A. Price Evans, Department of Medicine, University of Liverpool; cited by Clark, C. A., *J. Pharm. Pharmacol.*, **14**, (Suppl.), 20T(1962)]. The possibility exists that the results we report might represent the same phenomenon. Absence of difference in acetylation rate in the earlier U.S. tests may have been due to chance.

REFERENCES

(1) Nelson, E., and O'Reilly, I., *J. Pharmacol. Exptl. Therap.*, **129**, 368(1960).
(2) Nelson, E., and O'Reilly, I., THIS JOURNAL, **50**, 417 (1961).
(3) Nelson, E., *ibid.*, **50**, 912(1961).
(4) Nelson, E., *J. Pharm. Med. Chem.*, **5**, 211(1962).
(5) Nelson, E., *J. Theoret. Biol.*, **2**, 193(1962).
(6) Bratton, A. C., and Marshall, E. K., Jr., *J. Biol. Chem.*, **128**, 537(1939).