Correlation of *In Vivo* Metabolism Rate and Physical Properties of Sulfonamides

Sir:

It has been shown (1–3) that the post-equilibration phases of the disposition of several sulfonamides can be described mathematically in terms of two competitive first-order processes: one is excretion of apparent unchanged drug, and the other is metabolism. By measuring the appearance of apparent unchanged drug and metabolite in the urine, apparent first-order rate constants can be assigned to these two processes (1–3). In a series of antibacterial sulfonamides, for which the major metabolic fate is acetylation, attempts were made to correlate the rate constant for the metabolic process (k_m) with the lipid/water partition ratio, assuming the rate limiting step to be diffusion to the site of acetylation (3). However, such correlation apparently did not exist.

In addition to the sulfonamides already referred to (3), rate constants for *in vivo* acetylation (k_m) have been calculated for six additional sulfonamides using data available in the literature (5). The partition ratios of these sulfonamides in the system chloroform/pH 7.4 phosphate buffer range from 0.03 to 3.13 (6). To minimize possible variations in experimental technique, single literature sources were used for ionization constants (5) and extent of plasma protein binding (6). Assuming plasma to be at pH 7.4, the proportion of the sulfonamide which is both free from protein binding and nonionized may be calculated (Table I).

Considering the current theories of drug diffusion across cell membranes (4), it appears that for a molecule to cross such a membrane it must be (*a*) free of plasma protein binding, (*b*) nonionized, and (*c*) sufficiently lipophilic. If the lipophilicity of the nonionized molecule is of sufficient magnitude, however, it is conceivable that this property is no longer rate limiting in the diffusion process; this rate is limited instead by the proportion of the molecule in plasma which is both free of protein binding and in the nonionized form.

The data presented in Table I were subjected to statistical analysis (7) to obtain the rank order correlation coefficients for the relationship between k_m and "per cent free," "per cent nonionized," and "per cent free and nonionized," respectively. A significant correlation existed between k_m and per cent free (correlation coefficient 0.73; $p < 0.01$) and between k_m and per cent nonionized (correlation coefficient 0.63; $p < 0.05$). Most strikingly, a highly significant correlation was found between k_m and "per cent free and nonionized" (correlation coefficient 0.85; $p <$ 0.001). Therefore, it appears that in the series of sulfonamides studied, rate of metabolism *in vivo* can be correlated with ionization constant and extent of plasma protein binding.

TABLE I.—PHYSICAL PROPERTIES AND RATE CONSTANTS FOR METABOLISM OF SULFONAMIDES

Compd.	pKa	% Plasma Binding[a]	% Free	% Nonionized at pH 7.4	% Free and Nonionized at pH 7.4	k_m, Hr.$^{-1}$
Sulfanilamide	10.5	13	87	99.92	86.93	0.043
Sulfacetamide	5.3	19	81	0.79	0.64	0.016
Sulfaphenylpyrazole	5.8	99	1	2.45	0.03	0.0012
Sulfamethoxypyridazine	7.0	92	8	28.47	2.28	0.0078
2-Sulfapyrimidine	6.4	47	53	9.09	4.82	0.013
2-Sulfa-5-methoxypyrimidine	6.5	90	10	11.19	1.12	0.0053
2-Sulfadimethylpyrimidine	7.4	81	9	50.0	9.50	0.06
4-Sulfadimethoxypyrimidine	5.9	99	1	3.07	0.03	0.0017
Sulfaethylthiadiazole	5.1	97	3	0.50	0.02	0.0020
Sulfathiazole	7.0	78	22	28.47	6.26	0.0302
Sulfisomidine	7.4	90	10	50.00	5.00	0.0097

[a] The source of binding data (6) gave extent of binding at three plasma concentrations; the average of the values quoted for the two lower concentrations was used.

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