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Acute Toxicity, Absorption and Excretion of Sulfathiazole and Certain of its Derivatives.*

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It has been repeatedly shown that the use of the peroral route of administration is not valid in assaying the acute toxicity of certain poorly soluble derivatives of sulfanilamide. Sulfathiazole[1, 2] is such a derivative and hence, in determining the acute toxicity of this drug and of its methyl and phenyl derivatives in mice, we have used the sodium salts of these compounds and have administered them by the

TABLE I.

Acute Toxicity of Sodium Salts of Sulfanilamide, Sulfapyridine, Sulfathiazole, Sulfathiazole Methyl and Sulfathiazole Phenyl When Injected by Parenteral Route in Mice.

Compound	Dose g/kilo mouse subcutaneous	No. of mice	No. dead	% dead
Sodium Sulfanilamide	3.0	25	11	44
" Sulfapyridine	0.5	15	1	7
	1.0	14	7	50
	1.5	14	13	93
" Sulfathiazole	0.5	25	3	12
	1.0	25	3	12
	1.5	25	6	24
	1.75	25	6	24
	2.0	40	17	42
	2.25	25	20	80
	2.5	10	10	100
" Sulfathiazole Methyl	0.5	25	1	4
	0.75	25	17	68
	1.0	25	20	80
	1.5	10	9	90
" Sulfathiazole Phenyl	0.5	25	5	20
	0.75	25	7	28
	1.0	25	18	72
	1.5	10	9	90
	2.0	10	10	100

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1 Fosbinder, R. J., and Walter, L. A., *J. Am. Chem. Soc.*, 1939, **61**, 2032.

2 Van Dyke, H. B., Greep, R. O., Rake, G., and McKee, C. M., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 410.

TABLE II.
Blood Concentrations of Sulfathiazole Following Single Peroral Doses of the Drug.

Species	Dose, g/kilo	Blood concentrations mg%, hr following administration of sulfathiazole													
		1		2		4		8		12		24		48	
		F	T	F	T	F	T	F	T	F	T	F	T	F	T
Mouse	0.5	10.2	11.09	9.8	11.0	3.4	4.2	1.8	2.2			S.Tr	Tr		
”	1.0	17.5	17.8	8.0	8.6	9.6	10.2	4.0	5.6			S.Tr	Tr		
Man	0.05	6.3	7.3			6.3	7.3	3.2	5.3	2.2	4.0	S.Tr	1.6		
”	0.05	3.3	4.3			8.2	8.6	3.6	5.0	2.5	3.1	S Tr	1.5		
”	0.05	4.8	5.9	5.9	7.2	4.6	5.7	2.3	4.2	Tr	1.3	S.Tr	S.Tr		
Child	0.05	3.5	4.6			3.0	4.5	1.3	2.2			S.Tr	Tr		
”	0.05	2.7	3.3			3.1	3.8	1.5	2.1			S.Tr	Tr		
”	0.05			4.7	4.8	3.3	3.6	0.9	2.1			S.Tr	Tr		
”	0.05	5.6	6.3			3.4	4.1	1.3	2.1			S.Tr	Tr		

F = Free Sulfathiazole
T = Total Sulfathiazole
Tr = Trace
S.Tr = Slight trace

parenteral route. Solutions of the sodium salts of sulfanilamide, sulfapyridine and of sulfathiazole and its derivatives in distilled water are very alkaline (pH 10-11) and, when they are absorbed into the blood and tissues, the sodium ion is split off, leaving the parent compound. Hence, by employing the sodium derivatives, it is possible to determine with accuracy the true toxicity of the poorly soluble parent drug.

In Table I are recorded data dealing with the acute toxicities of these compounds in mice. It is noteworthy that sulfathiazole, in comparison with sulfapyridine, has a relatively low degree of toxicity. Using the data presented in Table I we have calculated the LD_{50} for the sodium salts of sulfapyridine, sulfathiazole, sulfathiazole methyl and sulfathiazole phenyl. The LD_{50} for sodium sulfapyridine is 1.0 g per kilo with a standard error of $\pm.08$, for sodium sulfathiazole 1.95 g per kilo with a standard error of $\pm.08$, for sodium sulfathiazole methyl 0.86 g per kilo with a standard error of $\pm.06$, and for sodium sulfathiazole phenyl 0.9 g per kilo with a standard error of $\pm.08$. These results show, therefore, that the introduction of the methyl and phenyl groups increases the acute toxicity of sulfathiazole for mice by more than 50%.

It has been shown before that unless data regarding the absorption and excretion of new sulfanilamide derivatives are available, the interpretation of experimental therapeutic results and the clinical use of such new compounds is difficult. In Table II are given data regarding the concentrations of sulfathiazole noted in the blood when the drug is administered by the oral route to mice and human beings. It is of interest that the curves of the concentrations of sulfathiazole in the blood of mice following a single peroral dose of the drug, more closely resemble those previously observed for comparable doses of sulfanilamide than those noted from single doses of sulfapyridine. The drug is absorbed more readily and its concentration in the blood decreases more rapidly than does that previously noted for sulfapyridine. While it is impossible to judge accurately the degree of acetylation of the drug in the tissues of human beings from single dose experiments, our experience in the use of sulfathiazole in about 50 patients leads us to believe that its percentage of conjugation in the tissues is somewhat less than that noted for sulfapyridine. These observations are in harmony with those made by Van Dyke, *et al.*,[2] upon monkeys.

These latter observers[2] have reported that the degree of acetylation of sulfathiazole in the urine of rats and monkeys is definitely less than that of sulfapyridine. Our studies upon the excretion of this

TABLE III.
Urinary Excretion of Sulfathiazole Following Administration of Single and Repeated Doses of the Drug.

Subject	Dose of drug	Urine Volume, Excretion in mg %—Days									Total drug excreted g	% of dose excreted
		1			2			3				
		U.V.cc	F	T	U.V.cc	F	T	U.V.cc	F	T		
J.T.	Single 0.05 g/kilo Total = 3.7	760	155	191	435	30	62.5				1.7	46
L.	Single 0.05 g/kilo Total = 3.7	1550	107	235	980	S.Tr	Tr				3.64	98
P.	Single 0.05 g/kilo Total = 2.8	1500	71.5	83.7	750	8.5	13.25				2.25	80
W.L.	Single 0.05 g/kilo Total = 1.7	1640	69	100	1700	S.Tr	Tr				1.64	96
B.W.	Single 0.05 g/kilo Total = 1.8	1300	65.5	116	2360	Tr	9.1				1.72	95
W	6.0 per day	980	338	443	910	296	346				8.45	70

U.V. = Urine volume
F = Free sulfathiazole
T = Total sulfathiazole
Tr = Trace
S.Tr = Slight trace

compound in human subjects confirm these observations. In Table III are presented data bearing upon the excretion of sulfathiazole in the urine of human beings. At once, one is struck by the fact that in comparison with sulfapyridine, definitely less of the excreted sulfathiazole is present in the conjugated form. It is also interesting that the excretion of this compound, following a single oral dose, is generally complete within 24 hours, and that following such a dose, from 80% to 90% of the drug was recovered in the urine, thus denoting that the absorption of sulfathiazole under conditions of the test, was much more complete than one would expect had the subject been given sulfapyridine.

Conclusions. It has been shown that the acute toxicity of sulfathiazole (as measured by the parenteral injection of sodium salts) for mice is one-third greater than that of sulfanilamide, and about half that of sulfapyridine, sulfathiazole methyl and sulfathiazole phenyl. Sulfathiazole is absorbed more readily and is excreted more rapidly than is sulfapyridine. Because of its rate of excretion it is probable that doses of sulfathiazole spaced at intervals of 4 hours will maintain adequate concentrations of the drug in the blood of patients.

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Agent of Lymphogranuloma Venereum in the Yolk-Sac of the Developing Chick Embryo.

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In the course of chemotherapeutic studies, experiments were performed with a strain of the agent of lymphogranuloma venereum* in which passage-mouse brain was used as a source of virus. About one-third of all mice given intracerebrally 0.03 ml of 1:100 dilution died. The L_D50[1] was obtained with a dilution of 1:14. Because of

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[1] Reed, L. H., and Muench, H., *Am. J. Hyg.*, 1938, **27**, 493.