11816

Absorption and Excretion of Sulfadiazine.*

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Sulfadiazine,† the pyrimidine analogue of sulfapyridine, was synthesized by Roblin, Williams, Winnek, and English.[1] Its toxicity, absorption, and chemotherapeutic activity in experimental animals have been investigated by Feinstone, Williams, Wolff, Huntington, and Crossley,[2] who found that the drug caused less tissue damage and yielded higher blood concentrations than either sulfapyridine or sulfathiazole, and had a high therapeutic activity in pneumococcal, streptococcal, staphylococcal and Group B Friedlander's bacillus infections.

We have studied the effects of oral administration of single and of multiple doses of sulfadiazine in patients. Frequent estimations of the blood levels were made and the urinary excretion of the drug was determined by the method of Bratton and Marshall.[3]

Four patients were given a single 2 g dose of sulfadiazine. The average blood level for free and total drug is illustrated in Fig. 1. As can be seen, sulfadiazine is rapidly absorbed into the blood stream, and the average level attained exceeds that absorbed with the same dose of either sulfapyridine or sulfathiazole. The proportion of acetylated drug is small, and excretion by the kidney is relatively slow. At the end of 24 hours there is an appreciable amount of the drug in the blood, and at the end of 48 hours at least traces are still present. By the end of 12 hours, an average of .359 g of free and .202 g of conjugated sulfadiazine had been excreted in the urine;

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1 Roblin, R. O., Jr., Williams, J. H., Winnek, P. S., and English, J. P., *J. Am. Chem. Soc.*, 1940, **62**, 2002.

2 Feinstone, W. H., Williams, R. D., Wolff, R. T., Huntington, E., and Crossley, M. L., in press.

3 Bratton, A. C., and Marshall, E. K., Jr., *J. Biol. Chem.*, 1939, **128**, 537.

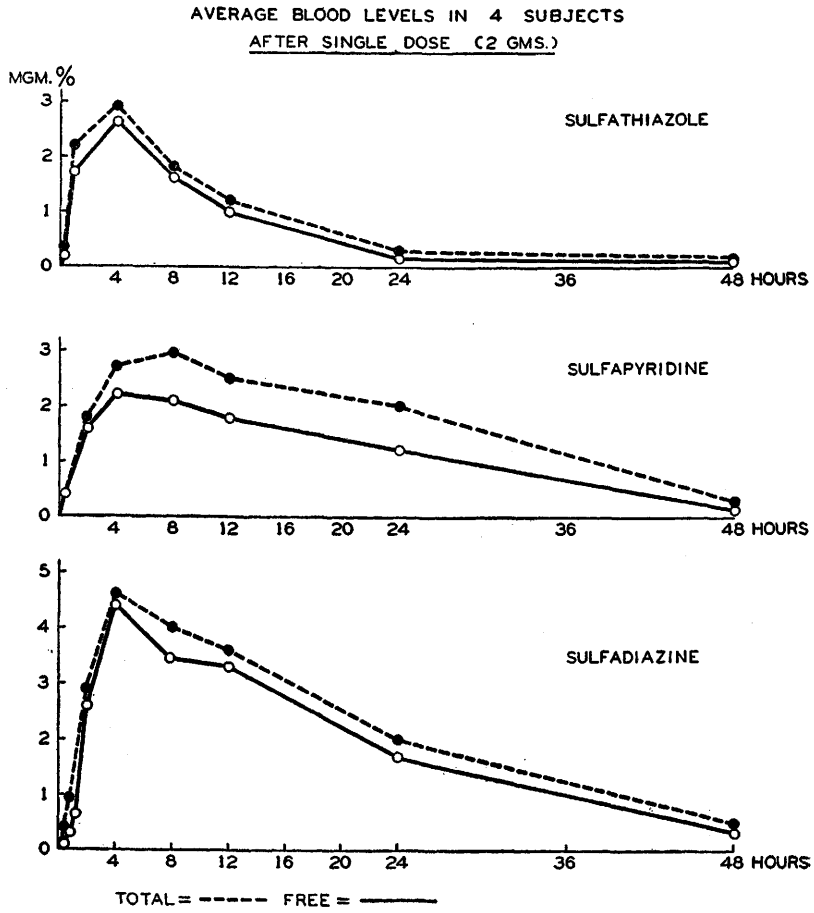

FIG. 1.

Average blood levels after single 2 g doses of sulfathiazole, sulfapyridine and sulfadiazine. Four different subjects were used to obtain each curve.

during the next 12 hours, an average of .215 g of free and .183 g of conjugated drug was excreted. In one case, .198 g of free and .240 g of conjugated sulfadiazine was excreted during the following 24 hours.

Eight patients were given 2 g of sulfadiazine as an initial dose followed by 1 g every 4 hours, in most cases until a total of 16 g had been given. The observations in these cases are tabulated in Table I. The average level of sulfadiazine in the blood is higher than that achieved with sulfapyridine or sulfathiazole in the same dosage. The proportion of acetylated drug is low. The blood level falls relatively slowly after the drug is discontinued, and from 40 to

TABLE I.

Blood Levels and Urinary Excretion Following Repeated Doses of Sulfadiazine (2 g, then 1 g Every 4 Hours).

Patient			Blood		Urine						Blood levels after stopping drug		
					Sulfadiazine								
Init. Age Ding.	Wt in kg	Hr after admin.	Free	Total	Free	Total	Excreted, g Free	Excreted, g Total	Benzidine Test	Albumin	Hr after last dose	Free	Total
			Mg per 100 cc										
1. C.P.	59	1	T.	T.									
49		4	7.4	10.6									
Asthma		8	9.6	10.0									
		12	9.0	10.0	88.0	120.0	.845	1.152	Neg	0			
		24	10.2	12.8	200.0	296.0	1.000	1.480	"	0			
		48	10.6	13.2	196.0	260.0	2.744	3.640	"	0			
		72			117.6	161.6	1.564	2.149	"	0			
											17	4.9	5.8
											29	2.5	4.0
2. N.F.	61	1	T.	T.									
22		4	1.4	2.5									
Bronchitis		8	3.4	3.5									
		12	5.6	5.7	13.2	19.0	.108	.156	"	0			
		25	7.2	7.8	81.6	114.0	.971	1.356	"	0			
		48	9.2	9.6	121.6	176.0	2.918	4.224	"	0			
											16	4.6	5.4
											40	1.5	1.7
3. N.O.	80	1	0	T.									
34		4	3.0	3.7									
Radiculitis		8	4.0	4.1									
		12	5.0	5.1	43.8	45.9	1.092	1.147	"	0			
		24	6.8	7.5	60.6	75.4	1.090	1.357	"	0			
		48*	8.0	8.2	92.8	119.2	2.876	3.695	"	0			
											18	4.3	4.5
											64	F.T.	F.T.
4. S.W.	60	1	0.4	2.7									
27		4	4.4	4.5									

Acute Tonsillitis		8	5.0	5.0								
		12	6.2	6.4	22.5	44.9	.6075	1.212	Neg	0		
		24	7.4	7.6	70.1	74.0	1.402	1.480	”	0		
		48	8.8	9.0	44.8	119.2	.582	1.535	”	0		
											18	4.0	4.1
											40	1.0	1.7
5. L.O.	85	2	2.7	3.5									
50		4	4.2	4.7									
G.C. Arthritis		8	5.6	5.7									
		12	5.8	7.6	117.6	126.8	.705	.761	”	0			
		24	6.7	6.8	168.4	188.0	1.515	1.692	”	0			
6. J.D.	49	1	1.4	1.6									
46		4	2.3	2.3									
Chronic Malaria		8	3.4	3.6									
		12	4.4	4.5	15.0	23.3	.182	.282	”	0			
		24	4.8	5.7	27.0	43.0	.226	.361	”	0			
											24	2.5	4.4
											52	1.0	1.3
7. P.T.	49	1	T.	T.									
40		4	3.5	4.0									
Rheum. heart dis.		8	2.2	3.7									
Inactive, no failure		12	6.4	8.1	75.4	93.0	.629	.776	”	0			
		24	4.4	6.4	29.8	41.2	.278	.385	”	0			
											24	3.0	3.4
8. B.H.	65	1	F.T.	T.									
35		7	4.2	4.3									
G.C. Arthritis		12	3.1	4.1	166.8	236.0	1.735	2.454	”	0			
		24	5.9	8.6	92.0	106.4	.488	.564	”	0			
		48	6.6	7.5	125.0	307.6	2.887	7.105	”	0			
											16	3.8	4.4

*Spinal Fluid at this time = Free, 4.1, Total 4.1 mg%.
F.T. = Faint Trace.
T. = Trace.

52 hours later there is still 1 mg % or over of free drug in the blood. During the first 12 hours, an average of .737 g of free and .254 g of conjugated sulfadiazine was excreted in the urine; during the next 12 hours .859 g of free and .213 g of conjugated, and during the next 24 hours, 2.40 g of free and 1.64 g of conjugated. In 2 cases, the urinary excretion was followed for 3 additional days. In one of these cases (S.W.), a total amount of 10.0 g of free drug and 2.63 g of conjugated drug was recovered out of the total of 16 g of sulfadiazine given during the first 2½ days; in the other case (B.H.), the total recoveries were 6.29 g of free drug and 6.49 of conjugated, the amount of sulfadiazine administered also having been 16 g.

Toxic Reactions. Each urine specimen obtained was tested for occult blood by the benzidine method, and for albumin. No blood or albumin was found in any specimen.

There was no nausea or vomiting in any patient, nor any evidence of kidney, liver, or peripheral nerve damage. The only toxic effect noted was the occurrence of a morbilliform rash in one patient (J.D.). For this reason, the drug was stopped at the end of 24 hours. The patient's face and eyelids were edematous during the next day but the reaction gradually subsided. He had previously had a similar rash after 4 g of sulfapyridine.

Summary. 1. Sulfadiazine was rapidly absorbed into the blood stream and comparatively high levels of total drug were reached. 2. The proportion of conjugated sulfadiazine in the blood was small. 3. The blood level falls rather slowly after the drug is discontinued. 4. Most of the drug is excreted by the kidney. 5. In 4 patients given 2 g of sulfadiazine and in 8 patients given a total of from 7 to 16 g the only toxic reaction noted was a morbilliform rash in one case in the latter group.