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(From the IVth Medical Service of St. Erik's Hospital, Stockholm.)

Absorption, Excretion, Acetylation and Distribution of Sulfaguanidine in Man.[1]

By

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Marshall, Bratton, White and Litchfield (1) recently prepared a new sulfanilamide derivative, sulfaguanidine, which is water soluble but poorly absorbed from the gastrointestinal tract.

Sulfaguanidine (Fig. 1) has a molecular weight of 214 and has a solubility in water of 220 mg per cent at 37.5° C (1), that is more than twice the solubility of sulfathiazole and about four times that of sulfapyridine.

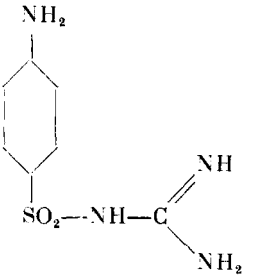

Fig. 1.

The acute toxicity of the drug when given by mouth to animals is very slight, due to poor absorption. On the basis of blood concentration, sulfaguanidine would seem to be more toxic acutely than sulfanilamide in mice and less toxic than sulfapyridine in dogs (1).

[1] I am indebted to the Astra Manufact. Co, Södertälje, Sweden, for supplying sulfaguanidine and sulfadiazine.

Chronic toxicity experiments indicate that very large doses can be given by mouth to mice and dogs without producing symptoms or pathological changes in the tissues. Thus sulfaguanidine when given orally is no more and is probably less toxic than sulfapyridine or sulfathiazole (1).

Marshall et al. (1) found that sulfaguanidine is somewhat less effective against β-hemolytic streptococcus infections in mice than is sulfanilamide, but is equally as effective as sulfapyridine against pneumococcus infection in mice. In vitro studies showed that this drug was equally effective as or more bacteriostatic than sulfanilamide against various bacteria.

In vitro experiments by the writer, using a completely syntethic medium or a sulfanilamide inhibitor-free medium, sulfaguanidine was about as bacteriostatic as sulfanilamide but less effective than sulfapyridine and sulfathiazole against a strain of Escherichia coli communis. Against strains of pneumococcus Type I and III sulfaguanidine was more bacteriostatic than sulfanilamide and equally effective as sulfadiazine (sulfapyrimidine) and sulfapyridine but somewhat less effective than sulfathiazole (2).

Marshall et al. (1) in experiments in animals and man also showed that sulfaguanidine is poorly absorbed from the gastrointestinal tract. In consequence of the pharmacological and chemotherapeutical qualities of sulfaguanidine they suggest that it may prove effective in the treatment of bacterial infections which are localized mainly or entirely in the intestine. Clinical reports (3, 4) lend support to this view. Clinical trials are in progress in this clinic.

In previous papers (5, 6, 7, 8) studies were reported on the absorption, excretion and the distribution of various sulfapyridine and sulfathiazole derivatives. In the present communication, data on the absorption, excretion, acetylation, distribution and renal clearence of sulfaguanidine will be presented.

Methods.

Sulfaguanidine is determined according to the method previously described (5). The drug is quantitatively recovered from blood and urine. The experiments are arranged in the same manner as in previous reports (5, 6, 7, 8).

Table I.

Absorption and Excretion of Sulfaguanidine after Oral Single Dose.

Pat. no.	S—G. Dose in g	Time hours	Blood			Urine				
			Free mg per 100 cm³	Total mg per 100 cm³	Conjugated per cent	Volume cm³	Excretion of drug mg for period		Percent of administered dose excreted Cumulative	
							Free	Total	Free	Total
1.	4.0	1	1.3	2.3	44					
		2	1.9	2.6	27	150	180	195	5	5
		4	2.3	3.0	23	140	163	205	9	10
		6	1.9	2.7	30	230	230	517	16	23
		10	0.9	2.8	68	545	189	403	19	33
		24	—	0.8	100	545	239	555	25	47
		48	—	—		970	118	277	28	53
2.	4.0	1	0.8	1.3	49					
		2	0.8	1.6	50	140	85	101	2	3
		4	1.0	1.7	41	100	62	88	4	5
		6	0.8	1.4	43	90	35	46	5	6
		10	—	0.6	100	265	57	98	6	8
		24	—	—		530	77	145	8	12
		48	—	—		965	57	139	9	15
3.	4.0	1								
		2	1.1	1.7	35	75	57	61	1	2
		4	1.0	1.5	33	125	104	125	4	5
		6	1.1	1.4	22	185	30	30	5	6
		10	1.1	2.2	50	595	302	314	12	14
		24	—	1.1	100	515	278	455	19	25
		48	—	—		1400	164	332	23	33
4.	4.0	1	1.4	2.2	36					
		2	1.5	2.1	29	205	82	101	2	3
		4	0.9	1.3	31	350	197	231	7	8
		6	0.6	1.2	50	100	62	94	9	11
		10	0.6	1.1	45	280	78	134	10	14
		24	—	—		485	109	206	13	19
		48	—	—		1150	86	138	15	23
5.	4.0	1	1.1	1.2	9					
		2	1.8	2.0	10	350	87	90	2	2
		4	2.3	2.8	18	340	185	208	7	7
		6	2.2	2.9	24	280	170	194	11	12
		10	1.3	2.4	46	335	302	405	19	22
		24	0.7	1.2	42	820	345	516	27	35
		48	—	—		2160	213	391	33	45

Experimental.

Blood Concentration, Acetylation and Urinary Excretion after Oral Single Doses of Sulfaguanidine. (Table I).

After a single dose of 4 g of sulfaguanidine the blood concentration attains its maximum within two to four hours. Maximum levels for free sulfaguanidine vary between 1.0 to 2.3 mg per cent, for total between 1.5 to 3.0 mg per cent. The blood concentration then decreases, and after 24 hours the compound as a rule has disappeared from the blood. The acetylation of the drug is rapid about 30 to 40 per cent being present as the conjugated compound. With decreasing bloodconcentration the acetylation of sulfaguanidine increases. The conjugated derivative is the last to disappear from the blood.

The urinary elimination of the drug is rapid, after 24 hours 80 to 90 per cent of the total amount urinary sulfaguanidine have been excreted and after 48 hours the excretion is completed. Of the dose administered 15 to 53 per cent were recovered from the urine as total sulfaguanidine and 9 to 33 per cent as free sulfaguanidine.

Of the sulfaguanidine eliminated 30 to 40 per cent are present as acetylsulfaguanidine. The ratio between free and conjugated sulfaguanidine is practically the same in blood and urine. After oral single dose similar results have been described (1).

Blood Concentration after Repeated Oral Doses of Sulfaguanidine. (Table II, Fig. 2).

Table II shows the blood concentration after repeated doses of sulfaguanidine in twelve patients. The dosage has been: initial dose 2 g, after four hours 2 g, thereafter 1 g every four hours five times daily with the first dose 6 a.m. and the last dose 10 p. m. The blood levels have been determined 9 a. m. every day.

The concentration of total sulfaguinidine in the blood fifteen hours after the onset of the administration varies between 1.9 to 4.1 mg per cent, with a mean value of 2.90 per cent. The corresponding values for free sulfaguanidine are 1.1 to 3.7 mg per cent and 1.83 mg per cent. After 39 hours the bloodlevels are practically the same as after fifteen hours with mean values for total sulfaguanidine 2.84 mg per cent and for free sulfaguanidine 1.68 mg per cent. As a rule 30 to 40 per cent of the sulfaguanidine in the blood are present as the conjugated derivative. Figure 2 is a typical curve of the blood

Table II.

Concentration of Sulfaguanidine in Blood 15 and 39 Hours After Onset of Medication.

Blood Concentration of Sulfaguanidine after 15 Hours			Blood Concentration of Sulfaguanidine after 39 Hours		
Dose in g	Free mg per cent	Total mg per cent	Dose in g	Free mg per cent	Total mg per cent
6	1.9	3.1	11	1.6	3.3
6	1.6	2.3	11	1.6	2.6
6	1.1	1.9	11	1.5	2.1
6	1.9	3.0	11	1.6	2.8
6	1.7	2.4	11	1.7	2.5
6	1.8	3.2	11	1.9	2.7
6	1.7	2.8	11	1.5	2.7
6	2.0	3.1	11	1.7	3.3
6	3.7	4.1	11	2.1	3.5
6	1.1	2.9	11	1.5	3.0
6	2.2	3.5	11	2.1	3.1
6	1.2	2.5	11	1.3	2.5
Mean Value	1.83	2.90	Mean Value	1.68	2.84

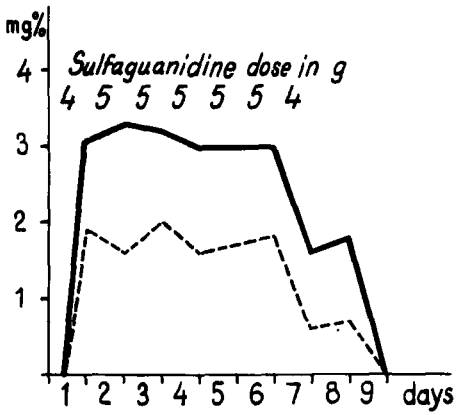

Fig. 2. Daily variations in the sulfaguanidine concentration in the blood. ——— Total _ _ _ _ _ Free

concentration during several days. After a maintenance dose of 0.05 g per kilogram body weight every eigth hours Marshall et al. (3) found a mean bloodlevel for free sulfaguanidine of 2.12 mg per cent and for total sulfaguanidine of 3.16 mg per cent. When the same dose was given every four hours the mean values for free sulfaguanidine were 3.29 mg per cent and for total sulfaguanidine 4.41 mg per cent.

Distribution of Sulfaguanidine in Human Blood, Pleural Effusions and Cerebrospinal Fluid. (Table III).

Table III shows the distribution of sulfaguanidine between corpuscles and plasma, giving whole blood and plasma levels, volumes per cent of plasma and percentage of the drug in plasma, volumes per cent of the corpuscles and percentage of the drug in the red cells, and the ratio of the concentration of the drug in the corpuscles to that in the plasma.

It may be seen that the whole blood values as a rule are somewhat higher than or equal with the plasma levels of total, free and conjugated sulfaguanidine. The total drug is in about the same concentration in plasma and corpuscles. Plasma contains 33 to 60 per cent of the total amount, the red cells between 40 to 67 per cent. The free compound is usually somewhat lower in plasma than in corpuscles, whereas the conjugated derivative as a rule is somewhat higher in plasma than in the red cells. The quantitative difference in the distribution is shown by the ratios of the concentration in the corpuscles to that in the plasma, ranging from 0.89 to 1.90 for total sulfaguanidine, 0.81 to 2.45 for the free and 0.33 to 1.82 for the conjugated compound. The ratio for free sulfaguanidine in twelve cases is higher than 1.0 and usually about 1.50, indicating that the free drug in the red cells is in a higher concentration than in the plasma. The corresponding values for acetylated compound show a greater variation, in seven cases the ratio is higher than 1.0 and in eigth cases the ratio is lower than 1.0. Sulfaguanidine thus resembles sulfanilamide in its distribution between red cells and plasma and differs from the distribution of sulfapyridine, sulfathiazole and sulfamethylthiazole in blood (8).

The data described are in accordance with the results in mice reported by Richardson (9).

Experiments in three patients with pleural effusions show that a

Table III.

Distribution of Free and Conjugated Sulfaguanidine between Corpuscles and Plasma in Blood.

In Whole Blood			In Plasma			Plasma	In Plasma			Corpuscles	In Corpuscles			Ratio Amount in 100 cm³ of Corpuscles		
Total	Free	Conj.	Total	Free	Conj.	Volumes	Total	Free	Conj.	Volumes	Total	Free	Conj.	100 cm³ of Plasma		
Mg per 100 cm³	Mg per 100 cm³	Mg per 100 cm³	Mg per 100 cm³	Mg per 100 cm³	Mg per 100 cm³	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Total	Free	Conj.
2.7	1.6	1.1	2.6	1.2	1.4	56.0	55	50	64	44.0	45	50	36	1.01	1.52	0.65
2.1	1.5	0.6	2.1	1.6	0.5	54.0	52	60	33	46.0	48	40	67	1.03	0.81	1.82
2.8	1.6	1.2	2.6	1.4	1.2	57.0	54	50	58	43.0	46	50	42	1.16	1.33	0.97
2.5	1.7	0.8	2.4	1.1	1.3	51.0	48	35	75	49.0	52	65	25	1.10	2.04	0.33
2.1	1.1	1.0	1.7	0.8	0.9	48.0	38	36	40	52.0	62	64	60	1.47	1.69	1.28
2.7	1.5	1.2	2.4	1.2	1.2	58.5	52	47	58	41.5	48	53	42	1.30	1.61	1.00
1.8	1.0	0.8	1.0	0.7	0.7	54.0	50	50	50	46.0	50	50	50	1.15	1.09	1.27
2.7	1.9	0.8	1.8	1.1	0.7	48.0	33	26	50	52.0	67	74	50	1.90	2.45	1.10
2.5	1.0	1.5	2.5	0.8	1.7	59.0	60	50	67	41.0	40	50	33	0.98	1.91	0.72
3.2	1.7	1.5	3.1	1.9	1.2	55.5	53	65	40	44.5	47	35	60	1.09	0.71	1.68
3.0	1.8	1.2	3.1	1.5	1.6	54.0	57	44	75	46.0	43	56	26	0.91	1.45	0.41
3.2	2.2	1.0	3.2	2.0	1.0	55.5	56	50	70	44.5	44	50	30	0.98	1.24	0.56
3.4	2.0	1.4	3.5	1.7	1.8	54.0	56	45	71	46.0	44	55	29	0.93	1.41	0.48
3.0	1.7	1.3	3.2	1.5	1.7	54.5	57	47	70	45.5	43	53	30	0.89	1.33	0.50
4.2	2.6	1.6	3.9	2.7	1.2	58.0	55	62	44	42.0	45	38	56	1.16	0.88	1.78

free diffusion of sulfaguanidine into pleural fluids takes place (Table IV).

Table IV.

Comparison of Sulfaguanidine Concentrations in Blood and in Pleural Effusions.[1]

Case	Blood		Pleura	
	Free Mg per 100 cm³	Total Mg per 100 cm³	Free Mg per 100 cm³	Total Mg per 100 cm³
6	1.3	2.5	1.2	2.8
7	1.7	2.8	1.2	2.4
8	0.9	1.3	0.9	1.5

[1] Specimens of blood and pleura are taken simultaneously.

Experiments were performed in three patients to determine the penetration of sulfaguanidine into the cerebrospinal fluid. The data are given in table V. The results indicate that only 20 to 25 per cent of the simultaneously determined blood concentration is present in the spinal fluid. The drug thus passes into the spinal fluid less freely than sulfanilamide and sulfapyridine and resembles in this respect the behavior of sulfathiazole (10). Marshall et al. (1) obtained similar results in dog.

The Renal Clearence of Sulfaguanidine. (Table VI).

The clearence values are given in Table VI. An ordinary creatinine clearence was performed simultaneously with the clearence for sulfaguanidine. It may be seen from the table that the clearence values for sulfaguanidine range for the total drug from 55.2 to 103.7 cm³ per minute, for the free compound from 60.5 to 158.5 cm³ per

Table V.

Comparison of Sulfaguanidine Concentrations in Blood and in Cerebrospinal Fluid.[1]

Case	Blood		Cerebrospinal fluid	
	Free Mg per 100 cm³	Total Mg per 100 cm³	Free mg per 100 cm³	Total Mg per 100 cm³
6	1.3	2.5	0.4	0.7
9	1.8	3.4	0.4	0.4
10	1.1	2.9	0.4	0.8

[1] Specimens of blood and cerebrospinal fluid are taken simultaneously.

Table VI.

Renal Clearence of Sulfaguanidine.

Compound	Time in min.	Blood			Urine				Blood cleared cm³ per min.			Creatinine clearence cm³ per min.	Ratio Creatinine clearence / Sulfanilamide clearence		
		Average plasma concentration Mg per 100 cm³			Volume	Mg per 100 cm³									
		Total	Free	Conj.	cm³	Total	Free	Conj.	Total	Free	Conj.		Total	Free	Conj.
S. g.	60	2.6	1.4	1.2	75	136	75	61	65.5	67.4	63.2	173.1	2.63	2.57	2.76
S. g.	60	1.9	1.3	0.6	90	109	64	45	86.1	74.4	111.3	194.7	2.26	2.62	1.75
S. g.	60	2.4	1.2	1.2	240	49	32	17	81.2	106.8	56.8	112.4	1.38	1.05	2.00
S. g.	60	1.8	1.0	0.8	152	65	41	24	92.0	103.6	78.9	169.0	1.84	1.63	2.14
S. g.	60	2.4	1.0	1.4	131	114	73	41	103.7	158.5	64.6	167.1	1.61	1.05	2.58
S. g.	60	3.1	1.7	1.4	215	56	35	21	64.9	73.8	54.1	145.8	2.26	1.98	2.70
S. g.	60	3.3	2.1	1.2	152	72	50	22	55.2	60.5	45.9	155.8	2.82	2.57	3.40
S. g.	60	3.4	1.6	1.9	102	115	66	49	57.5	69.5	44.0	171.9	2.99	2.47	3.91

minute and for the conjugated compound from 44.0 to 111.3 cm^3 per minute. The ratio of creatinine clearence to that of sulfaguanidine varies for the total drug between 1.38 to 2.99 for the free drug between 1.05 to 2.62 and for the conjugated compound between 1.75 and 3.91. These data indicate the total drug clearences usually to be one half of that of creatinine. The free compound in all cases except one is cleared at a higher rate than the acetylated derivative. In two cases the clearences for the free drug was of about the same magnitude as the creatinine clearence. In contrast, the conjugated derivatives of sulfanilamide, sulfapyridine, sulfathiazole and sulfamethylthiazole are cleared at higher rates than the free compounds (8). In dogs (1) the sulfaguanidine clearence is about four times more rapid than the sulfanilamide clearence. Sulfaguanidine is not acetylated in the dog and therefore this behavior is true only for the free drug. By comparing the clearences of free sulfaguanidine described above with the clearences of free sulfanilamide previously reported (8) it will be seen that the clearence rate of sulfaguanidine is two to three times more rapid than that of sulfanilamide.

Discussion and Summary.

The data presented show that sulfaguanidine in spite of higher solubility in water than sulfapyridine and sulfathiazole is absorbed from the gastrointestinal tract to a considerably lesser extent than these drugs. Only 15 to 53 per cent of a single dose of sulfaguanidine are recovered from the urine, whereas the recoveries after the same single doses of sulfapyridine and sulfathiazole are 57 to 78 per cent and 78 to 93 per cent respectively (7). Only 40 to 60 per cent of orally administered guanidine are absorbed (11), this probably being the explanation of the poor absorption of sulfaguanidine.

The absorption of sulfaguanidine is fairly rapid, maximum blood levels after single oral doses are attained within two to four hours. The maximum values are only about one half of the corresponding sulfapyridine values and about one half to one third of the corresponding sulfathiazole levels previously described (7). The acetylation of the drug occurs rapidly, about 30 to 40 per cent being present as the conjugated compound in blood. Sulfaguanidine appears to be acetylated to a greater extent than sulfanilamide and sulfathiazole and to the same degree as sulfapyridine.

The urinary elimination of sulfaguanidine is rapid. Of the drug eliminated 30 to 40 per cent are present in the urine as the acetylated compound. The ratio between free and conjugated sulfaguanidine thus is practically the same in blood and urine. The clearence data indicate that sulfaguanidine is cleared more rapidly than both sulfanilamide and sulfathiazole. The elimination rate of free sulfaguanidine is higher than the clearence rate of the conjugated compound. The acetylated derivatives of sulfanilamide, sulfapyridine and sulfathiazole in contrast hereto are cleared more rapidly than the free compounds (8).

Sulfaguanidine is distributed in blood in such a way that its concentration is somewhat higher in corpuscles than in plasma. It resembles sulfanilamide in its distribution between red cells and plasma and differs from the distribution of sulfapyridine, sulfathiazole and sulfamethylthiazole in blood (8).

Sulfaguanidine passes into the cerebrospinal fluid less freely than sulfanilamide and sulfapyridine and behaves in this respect in the same manner as sulfathiazole (10). Only 20 to 25 per cent of the simultaneously determined blood concentration are present in the spinal fluid. Into pleural effusions there is a free and complete diffusion of sulfaguanidine.

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