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Research Article

RENAL EXCRETION OF SULFAMERAZINE [1]

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Certain advantages might accrue to the use of sulfonamides such as sulfamerazine (2-sulfonamido 4-methyl pyrimidine) that, having essentially the same antibacterial activity as others in common use, are characterized by low rates of renal excretion (1 to 6). These advantages include lower and less frequent dosage and, perhaps, some reduction of the renal hazard incidental to the precipitation of material in the kidneys and urinary tract. It was because of these considerations that it was deemed advisable to study some of the factors concerned with the excretion of sulfamerazine. Observations were also made on the excretion of the N^4—acetyl derivative of sulfamerazine and of sulfadiazine (2-sulfanilamido pyrimidine) for comparative purposes.

The study was conducted in a manner that yields quantitative information on the various discrete processes involved. This was accomplished by the simultaneous measurement of the renal plasma clearance of the drug and the rate of glomerular filtration under different experimental conditions.

Measurements were also made on the extent to which sulfamerazine is bound to the non-diffusable constituents of plasma, presumably plasma albumin, since it is only the unbound drug in the plasma water that is presented to the glomeruli for filtration. The ratio of the unbound drug clearance to the concurrent rate of glomerular filtration (excretion ratio) yields information on the extent to which the filtered material is reabsorbed or excreted by the renal tubules.

MATERIALS AND METHODS [2]

Experimental procedures. The human studies were carried out in young adult patients with normal renal function. Mannitol was used for the measurement of glomerular filtration rate (7). Simultaneous sulfonamide and mannitol clearances were determined at constant plasma concentrations of each during 3 consecutive periods of approximately 15 minutes. Urine was collected by means of an indwelling catheter with bladder washing. Blood samples were obtained at the mid-point of each urine collection period.

The dog experiments were performed on 3 well-trained female mongrels. The glomerular filtration rate was measured by the creatinine clearance (8). The sulfamerazine clearance and glomerular filtration rate were determined simultaneously for several collection periods. Various procedures designed to alter the excretion of the drug were then introduced and the observations continued.

Blood was obtained during each experiment for the estimation of total plasma protein and albumin content so that the concentration of unbound sulfonamide in the plasma water could be determined and its clearance calculated. The proportion of total plasma sulfonamide bound on the non-diffusible constituents of plasma was determined by dialysis across a cellophane membrane against an isotonic phosphate buffer at pH 7.4 and 37° C. Eighteen hours were allowed for the establishment of an equilibrium. All values for plasma binding were corrected to a standard plasma albumin content of 4.0 grams per 100 ml. This correction assumes that the plasma albumins of different individuals have no qualitative differences in their abilities to bind sulfonamides. Each experiment was performed in duplicate, at 4 different concentrations of plasma sulfonamide.

Chemical methods. The concentration of mannitol in the plasma and urine was determined by a modification (9) of (7); creatinine by a modified Folin procedure on tungstic acid filtrates (10); and sulfonamides by the method of (11). Twenty per cent p-toluene sulfonic acid was used as the precipitating and hydrolyzing agent in the determination of the N^4-acetyl sulfamerazine. Chloride in the urine was estimated by a modification of the Volhard method (12). Total plasma protein and albumin were determined by a micro-Kjeldahl method (13) after precipitation by the Howe technic (14).

RESULTS

Plasma binding. The values for plasma binding of the 3 sulfonamides studied (sulfamerazine, N^4-acetyl sulfamerazine, and sulfadiazine) are

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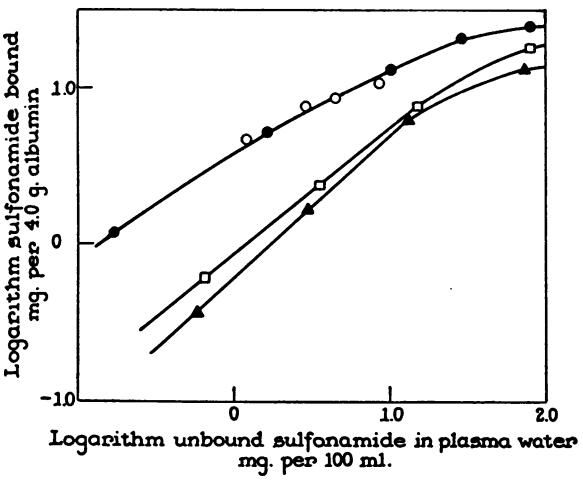

FIG. 1. RELATION BETWEEN BOUND AND FREE FRACTIONS OF SULFAMERAZINE, N^4-ACETYL SULFAMERAZINE, AND SULFADIAZINE IN HUMAN PLASMA AND OF SULFAMERAZINE IN DOG PLASMA

All values are corrected to a standard plasma albumin content of 4.0 grams per 100 ml. The data are recorded logarithmically for the sake of convenient presentation. The actual whole plasma concentrations of the sulfonamides ranged from approximately 1 to 100 mgm. per cent. The sulfamerazine curve for human plasma represents the average of 3 experiments; the other curves are derived from single experiments.

● = Sulfamerazine, human plasma
○ = N^4-acetyl sulfamerazine, human plasma
□ = Sulfadiazine, human plasma
▲ = Sulfamerazine, dog plasma

somewhat lower than previously reported (15). Calculations from the present data (Figure 1) indicate that 63 per cent of the sulfamerazine is bound at a whole plasma concentration of 10 mgm. per cent, whereas only 32 per cent of sulfadiazine is bound at the same concentration. The binding of the N^4-acetyl sulfamerazine is essentially the same as the parent complex. It may also be noted that there is more extensive binding of sulfamerazine in human than in dog plasma.

Renal excretion of sulfonamides by man. The renal excretion of each of the 3 sulfonamides studied was examined in 4 young adults with glomerular filtration rates within normal limits (16). These data are summarized in Table I.

The renal plasma clearance of sulfamerazine in man is very low, the average for the 4 subjects examined being only 3.9 ml. per minute. This is considerably lower than in the dog (No. 1). The clearance of sulfadiazine is higher and more variable, ranging from 11.6 to 33.9 ml. per minute in the 4 subjects studied, while that of N^4-acetyl sulfamerazine is still greater having a mean value of 52.4 ml. per minute.

The data on the excretion ratios (last column, Table I) indicate that an average of 65 per cent of filtered sulfadiazine and 85 per cent of sulfamerazine is reabsorbed by the renal tubules. The N^4-acetyl sulfamerazine, however, would appear to be excreted in part by a process of renal tubular excretion, as is indicated by the high excretion ratio of 2.42.

Renal excretion of sulfamerazine by the dog. The very low excretion rate of sulfamerazine suggests that its reabsorption by the renal tubules is, at least in part, the result of the operation of an active transport system. It was because of this possibility that the study was extended to include observations on the dog which might be expected to yield information on the mechanisms involved. The variables examined include the rates of reabsorption of water and electrolyte by the renal tubules, and plasma drug level. In addition, an attempt was made to block the possible active transport system in the tubule cells with other substances that might compete with the sulfamerazine.

Experiments in which the tubular reabsorption of water was decreased by the intravenous administration of sodium sulfate and increased by the administration of pituitary extract are summarized in Table II. The sodium sulfate experiments are complicated by some increase in glomerular filtration rate (Expts. 1 and 2). However, diuresis in each case was accompanied by proportionately higher increases in sulfamerazine clearance, with consequent increases in its excretion ratio. In contrast, increases in sulfamerazine clearances were also obtained when water diuresis was interrupted by the administration of posterior pituitary extract (Expts. 3 and 4). It is impossible, therefore, to derive a simple relationship between renal tubular reabsorption of water or the rate of urine flow and the excretion ratio of sulfamerazine. Such a circumstance does not preclude the possibility that some sulfamerazine is reabsorbed by a passive process. It does minimize the probable importance of such a process in determining overall excretion since in

this case there should be some correlation with the rate of urine flow.

Diuresis effected by sodium sulfate and antidiuresis by posterior pituitary extract are typically associated with increased electrolyte excretion (Expt.4, Table II). A possible correlation between the reabsorption of electrolyte and the extent of the reabsorption of sulfamerazine was further examined in experiments wherein sodium chloride, potassium chloride, and ammonium chloride were orally administered. These experiments are summarized in Table III. Of these, only sodium chloride administration was accompanied by a dramatic increase in chloride excretion, although there was a general elevation in all, and electrolyte excretion was undoubtedly increased in each instance. There was an observable decrease in reabsorption of sulfamerazine in each experiment, which is also true after sodium bicarbonate (17). However, significant quantities of sulfamerazine were still reabsorbed at the higher chloride excretion rates.

Experiments designed to demonstrate the participation of an active transport system in the tubular reabsorption of sulfamerazine were unsuccessful. Studies on the filtration, excretion, and reabsorption of sulfamerazine over a wide range of plasma drug concentrations (2 to 43 mgm. per cent) gave no evidence of a maximum rate of reabsorption which is a common characteristic of active transport systems. Nor was it possible to block the reabsorption of sulfamerazine to a significant extent by the continuous intravenous administration of maximally tolerated amounts of amino acids (casein hydrolysate) and benzoic acid. These materials were chosen because of possible similarities in chemical structure to sulfamerazine.

DISCUSSION

The addition of a methyl group in the 4-position of the pyrimidine ring of sulfadiazine, to form sulfamerazine, results in a compound that is extensively reabsorbed by the renal tubules and, therefore, has a very low rate of renal excretion. It is somewhat surprising to find that acetylation of sulfamerazine at the N^4-position results in a compound that is excreted rather than reabsorbed by the renal tubular cells.

The low excretion rate of sulfamerazine is the result of two factors. Sulfamerazine is bound in human plasma to such an extent that, at a whole

TABLE I

The renal excretion of sulfamerazine (SM), N^4-acetyl sulfamerazine (ASM), and sulfadiazine (SD)

The clearance values are corrected to a standard surface area of 1.73 sq. m. The clearance and ratio values are the average of 3 consecutive 15-minute periods. The clearance ratio is calculated from the whole drug clearance and the glomerular filtration rate; the excretion ratio, from the unbound drug clearance and the glomerular filtration rate.

Patient	Drug	Range of urine flow	Range of whole plasma drug level	Average glomerular filtration rate	Average whole plasma drug clearance	Average clearance ratio	Average excretion ratio
		ml. per minute	*mgm. per cent*	*ml. per minute*	*ml. per minute*		
Se	SM	3.4 to 3.6	4.0 to 4.9	109	3.61	0.033	0.154
Ch	SM	1.8 to 2.4	10.8 to 11.8	104	4.18	0.040	0.155
Sc	SM	2.5 to 3.0	4.8 to 5.0	110	4.03	0.037	0.164
Ga	SM	2.3 to 2.9	4.5 to 5.2	117	3.63	0.031	0.129
				Average:	3.86	0.037	0.150
Ju	ASM	3.8 to 4.4	2.2 to 2.7	117	53.2	0.455	2.23
Yo	ASM	2.0 to 2.2	1.7 to 1.9	103	59.6	0.580	2.77
Sc	ASM	3.4 to 3.7	2.7 to 2.8	107	33.6	0.314	1.59
De	ASM	2.2 to 2.7	2.2 to 2.2	103	63.0	0.613	3.11
				Average:	53.4	0.490	2.42
Bi	SD	1.8 to 2.4	3.3 to 3.4	148	19.1	0.132	0.265
Mc	SD	8.0 to 8.8	4.5 to 4.5	141	33.9	0.242	0.442
Ma	SD	2.8 to 3.1	3.9 to 4.2	106	29.4	0.276	0.494
Mr	SD	2.0 to 2.1	4.8 to 5.5	108	11.6	0.107	0.189
				Average:	23.5	0.189	0.348

TABLE II

Effect of variation in urine flow on the excretion rate of sulfamerazine (SM) in the dog

The values for the concentration of sulfamerazine free in the plasma water were obtained by correcting the whole plasma concentrations for the amount of drug bound on plasma proteins.

Expt. No.	Dog No.	Urine flow	Glomerular filtration	SM plasma water level	SM plasma water clearance	Excretion ratio	Chloride excretion
		ml. per minute	*ml. per minute*	*mgm. per cent*	*ml. per minute*		*m.eq.* $\times 10^{-3}$ *per minute*
1	1	3.89	66.0	4.06	11.4	0.17	
		1.90	61.1	4.00	10.4	0.17	
		400 ml. 6 per cent sodium sulfate, intravenously					
		13.55	83.4	2.57	32.0	0.38	
		9.00	82.4	2.75	28.2	0.34	
2	2	0.63	55.2	6.70	2.98	0.05	
		0.28	55.4	6.78	4.15	0.08	
		500 ml. 10 per cent sodium sulfate, intravenously					
		9.24	69.0	5.33	16.0	0.23	
		12.34	66.7	4.94	18.0	0.27	
		11.58	65.0	5.14	18.8	0.29	
3	1	6.00	84.7	4.14	11.9	0.14	
		6.70	79.2	4.11	13.4	0.17	
		10 units posterior pituitary extract, subcutaneously					
		0.28	73.1	3.88	12.5	0.17	
		0.53	78.3	3.65	19.5	0.25	
		0.76	76.9	3.64	19.9	0.25	
4	2	5.90	59.0	2.69	15.8	0.27	16.6
		4.95	55.2	2.78	14.9	0.27	10.4
		10 units posterior pituitary extract, subcutaneously					
		1.27	61.4	2.95	24.1	0.39	95
		1.67	60.2	2.86	25.7	0.43	150
		1.42	62.2	2.85	26.6	0.43	119
		1.22	64.4	2.79	29.7	0.46	114

plasma level of 10 mgm. per cent, only 40 per cent is unbound in the plasma water and is available for filtration at the glomeruli and thus for excretion. The reabsorption of sulfamerazine by the renal tubules is equally important, being on the order of 85 per cent of the amount filtered.

The low overall excretion rate of sulfamerazine has two important consequences. First, less frequent and smaller doses of sulfamerazine than of sulfadiazine are required to maintain any given plasma level (2 to 6) since the clearance ratio of sulfamerazine is only one fifth that of sulfadiazine. Also, it would be supposed that the renal hazard incidental to the precipitation of insoluble sulfonamide compounds in the genito-urinary tract would be less as compared to other sulfonamides with higher excretion rates. For example, the urine concentration of sulfamerazine when its plasma concentration is 10 mgm. per cent and the urine flow is 1 ml. per minute may be calculated to be 38.6 mgm. per cent whereas the urine concentration of sulfadiazine in a comparable situation would be 235 mgm. per cent.[3]

[3] Drug clearance (ml. per minute) = UV/P, where U = concentration of drug in urine in mgm. per cent, V = urine flow in ml. per minute, and P = concentration of drug in plasma in mgm. per cent.

TABLE III

Effect of electrolytes on the excretion of sulfamerazine (SM) in the dog

The values for the concentration of sulfamerazine free in the plasma water were obtained by correcting the whole plasma concentrations for the amount of drug bound on plasma proteins.

Expt. No.	Dog No.	Urine flow	Glomerular filtration	SM plasma water level	SM plasma water clearance	Excretion ratio	Chloride excretion
		ml. per minute	*ml. per minute*	*mgm. per cent*	*ml. per minute*		*m.eq.* $\times 10^{-3}$ *per minute*
5	1	7.8	74.5	1.94	16.3	0.22	60
		7.2	65.2	2.20	16.2	0.25	52
		6.3	61.5	2.35	15.2	0.25	42
		200 ml. 1.8 per cent sodium chloride, *per os*					
		2.3	68.7	2.58	27.7	0.40	353
		2.7	71.2	3.05	27.3	0.38	419
		2.4	78.0	2.58	26.5	0.34	420
6	3	6.5	102	2.90	16.1	0.16	41
		5.9	91.8	3.71	15.0	0.16	21
		400 ml. 1 per cent potassium chloride, *per os*					
		7.8	107	3.55	30.9	0.29	36
		7.3	102	3.42	27.4	0.27	59
		7.6	102	3.30	35.5	0.35	176
7	1	4.5	56.3	2.19	14.9	0.26	18
		4.8	59.5	2.50	13.0	0.22	21
		400 ml. per cent ammonium chloride, *per os*					
		3.0	55.0	2.76	20.3	0.37	23
		3.2	55.4	2.66	22.4	0.40	31
		3.4	56.3	2.64	21.4	0.38	42

The somewhat greater solubility of sulfamerazine as compared to sulfadiazine (18) should serve to further decrease the renal hazard. However, no striking differences have been noted in the incidence of renal complications during the therapeutic use of these two drugs in man (3 to 6). A recent report (19 indicates that renal calculi may occur more frequently with sulfamerazine than with sulfadiazine therapy. However, the difference in the incidence of renal complications with the two drugs was not significant at equivalent plasma concentrations. It is possible that more extended clinical observation, when all factors affecting renal excretion are controlled, will reveal a real difference in the renal hazard due to sulfamerazine as compared to sulfadiazine. The extent to which the high excretion rate of the N^4-acetyl derivative of sulfamerazine contributes to the renal hazard is not known but may be significant.

It would be of considerable theoretical interest to define the mechanisms concerned in the renal excretion of sulfonamides such as sulfamerazine. Data are presented which indicate that the reabsorption and excretion of sulfamerazine are not specifically related to the rate of urine flow, but may be in some way related to the renal tubular mechanisms concerned with the reabsorption and excretion of electrolytes. Procedures which increase electrolyte excretion also appear to decrease the tubular reabsorption of sulfamerazine and thus result in an increased rate of drug elimination. The increase may be considerable and occurs in a variety of circumstances. Thus, the administration of posterior pituitary extract, sodium, potassium, and ammonium chloride, and sodium bicarbonate (17) are effective in the dog. It is likely that a similar situation obtains in man, particularly since it has been observed that man excretes sulfadiazine at an increased rate when

given sodium chloride or bicarbonate (20). It has been reported that sulfadiazine excretion is related to the pH of urine (21) but it seems likely that this may be related to the disturbance in electrolyte excretion which accompanies a change in urine pH as well as to the change in pH itself.

The effect of a disturbance in electrolyte excretion on the elimination of sulfamerazine has obvious therapeutic implications. It is common practice to administer sodium bicarbonate to patients receiving sulfonamides to increase their solubility in urine. This procedure will also increase the excretion rate of the drug. Decreased chloride excretion is commonly observed in lobar pneumonia and in severe burns and will be accompanied by diminished rates of sulfonamide excretion. Careful observation of drug plasma levels is indicated in these conditions.

Initial attempts to demonstrate the active renal tubular reabsorption of sulfamerazine in the dogs' kidneys have been unsuccessful. However, there is indirect evidence which suggests that this is the case. It is difficult to understand how passive diffusion across the tubule cells can account for the reabsorption of as much sulfamerazine as indicated by the average excretion ratio of 0.15 (Table I). This view is emphasized when it is considered that such a relatively simple and soluble compound as urea (which is passively reabsorbed) has an excretion ratio of approximately 0.6.

SUMMARY AND CONCLUSIONS

1. The addition of a methyl group to the pyrimidine ring of sulfadiazine to form sulfamerazine results in a compound that has a very low overall renal excretion rate. This is the result of extensive reabsorption by the renal tubules and binding on plasma proteins.

2. The N^4-acetyl derivative of sulfamerazine (which is presumably its conjugated form) is secreted rather than reabsorbed by the renal tubules.

3. The low overall excretion rate of sulfamerazine has two distinct therapeutic advantages. First, relatively infrequent and small doses are required to maintain any given plasma concentration. Second, the urine concentration of the drug at any given plasma level is less than that of other sulfonamides in current use. Such a circumstance should minimize the renal hazard of sulfonamide therapy, but additional factors such as solubility, urine flow, and pH may be expected to operate in this respect.

4. An increase in the excretion rate of sulfamerazine accompanies augmented electrolyte elimination. This occurs when the electrolyte excretion is increased by a variety of means. The renal excretion of sulfamerazine does not appear to be simply related to the rate of urine formation.

5. Indirect evidence suggests that sulfamerazine is reabsorbed by an active transport system in the renal tubules but this has not yet been directly demonstrated.

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