Absorption and Excretion of Sulfachloropyridazine. (23315)

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Interest in the group of sulfapyridazines was stimulated by the finding that one of the derivatives, sulfamethoxypyridazine† (SMP) has unusual properties, the most important of which are: good absorption from the gastrointestinal tract, low degree of acetylation in the blood, very slow urinary excretion, good solubility in the urine, low toxicity and antibacterial activity equal to that of the most active of the sulfonamides in popular use(1-7). In this paper it is shown that sulfachloropyridazine‡ (SCP), which, as seen from Fig. 1, differs only slightly in its structure, is absorbed and excreted quite differently. The methods used were the same as those employed in the study of SMP(1).

Absorption and Excretion of Single Oral Dose of 4 g. Two normal young men were given 4 g of SCP with a glass of water one-half hour before breakfast, after which they were permitted to take food and fluids *ad libitum*. Specimens of oxalated venous blood were taken before and at appropriate intervals after the dose and complete collections of urine were made for 96 hours in one subject and for 24 hours in the other. The concentrations of "free" and "total" SCP in blood, plasma and urines were determined by the method of Bratton and Marshall(8).

Blood levels. The levels of SCP in whole blood are shown in the upper panels of Fig. 2. The peak concentrations were achieved in both subjects at 3 hours; these values for total SCP were 12.1 mg/100 ml in Subject A and 14.6 mg/100 ml in Subject B, and of these amounts, 10.7 and 11.6 mg respectively, were determined as free drug. Peak concentration in the plasma of Subject A was 21.7 mg/100 ml, of which 2.3 mg was conjugated; the corresponding values in Subject B were 28.5 and 4.9, respectively. The proportion of drug found in the plasma in the conjugated form varied between 15 and 31% (average 23%) in Subject A and between 16 and 33% (average 22%) in Subject B.

Diffusion into blood cells. The concentrations of total SCP in whole blood and plasma were determined in the same specimens and concentrations in the cellular elements were calculated from these values and from the hematocrit. The results indicated that little or none of the drug penetrated the blood cells in Subject A and only a small amount (up to 12% of the plasma level) may have gotten into those of some of the specimens of Subject B when the levels in plasma were high.

Renal clearances. The rates at which SCP was cleared from the plasma are shown in the lower panels of Fig. 2. The values were estimated without correction for protein binding and during rather long periods and hence are only crude, but they may be useful for comparisons. The conjugated form was cleared on the average about 2½ times more rapidly than the free form, the latter being cleared at rates varying from about 5 to nearly 30 ml of plasma per min.

Urinary excretion. The rapid renal clearance of SCP is reflected in the very high concentrations achieved in the urine during the first few hours after the dose was ingested. As shown in Fig. 3, the urine of Subject A when excretion was at the maximum rate, contained 608 mg per 100 ml, of which 490 mg was free and 118 mg was in the conjugated form. Maximum excretion in Subject B was observed between 3 and 5 hours after the dose and the urine voided during this period contained 667 mg per 100 ml, 502 mg of which was free and 165 mg conjugated. As shown in the upper panels of Fig. 4 maximum

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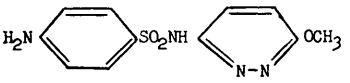
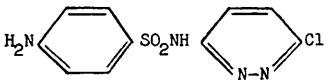
† Supplied under the trademark Kynex by Lederle Laboratories Division, Amer. Cyanamid Co.

‡ Supplied as BA-10370 by Ciba Pharmaceutical Products.



Sulfamethoxypyridazine (Kynex)



Sulfachloropyridazine (BA-10370)

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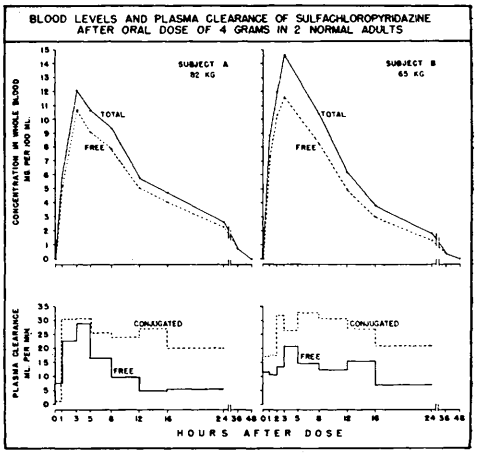

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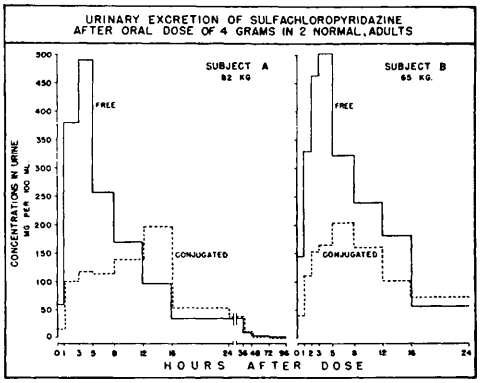

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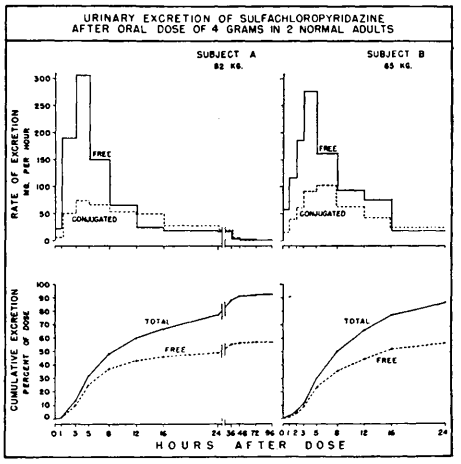

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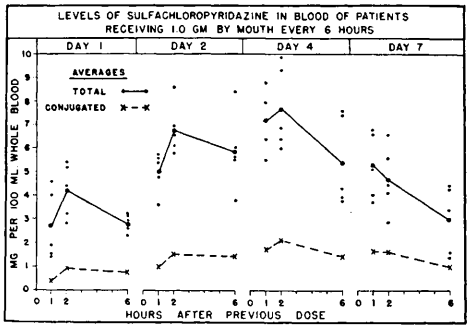

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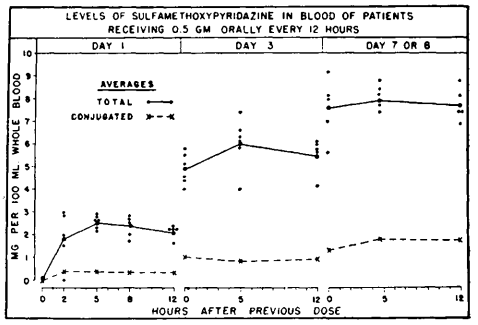

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FIG. 1-6.

TABLE I. Sulfachloropyridazine (SCP) and Sulfamethoxypyridazine (SMP) in Random Specimens of Urine during Continuous Oral Administration.

Drug	Dosage	No. of patients	Day of treatment	Conc. of total sulfonamide in urine, mg % Low	Conc. of total sulfonamide in urine, mg % High	% of drug conjugated Low	% of drug conjugated High
SCP	1.0 g every 6 hr	5	1	26	248	36	60
		5	2	100	360	43	65
		5	4	106	712	39	61
		5	7	100	738	35	73
SMP	.5 g every 12 hr	5	1	8	79	49	85
		2	2	39	298	51	83
		4	3	19	100	56	74
		3	6	56	363	55	86
		5	8	63	152	54	68

rate of excretion for Subject A was 380 mg per hr (306 free and 74 conjugated) and for Subject B 367 mg per hr (276 mg free and 91 mg conjugated). The cumulative excretions in the 2 subjects, shown in the lowest panels of Fig. 4 indicate that 88% of the administered dose was recovered in the urine of Subject A in 24 hours and only 5% more was recovered during the next 3 days; in Subject B, 86% of the administered dose was accounted for in the urine within 24 hours.

Concentrations of SCP in blood and urine during repeated oral doses. Five patients were given doses of 1 g of SCP orally every 6 hours. They ranged in age from 33 to 57 years and in weight from 64 to 82 (Avg 74) kg. They had no known abnormality of renal function. The findings in the blood are shown in Fig. 5, which depicts the individual levels of total SCP in the whole blood as well as average concentrations of both total and conjugated drug. There were wide variations in blood levels among patients at the different times, but there was a general upward trend in the levels from the first through the fourth day; levels on the seventh day, however, were appreciably lower than on the fourth day. In addition, the highest levels on days 1, 2 and 4 were obtained at 2 hours, whereas on the 7th day they were obtained at 1 hour. The proportion of the drug found in the blood in the conjugated form varied in different specimens from 10 to 50% of the total. There was also a tendency of this proportion to increase as administration of the drug was continued; it averaged about 20% on the first day and 32% on the 7th day. The concentrations of drug in random specimens of urine of these patients are listed in the upper part of Table I. Here again there were wide differences in concentration, only part of which were related to the volume of the urine output; the levels of total drug varied from 26 to 738 mg per 100 ml and the proportion of drug found in conjugated form varied from 35 to 73% (Avg 51%).

SMP in blood and urine during continuous oral administration. Six patients were given oral doses of 0.5 g of SMP every 12 hours. These patients ranged in age from 45 to 68 (Avg 52) years and in weight from 60 to 84 (Avg 70) kg; none of them had any recognized abnormality of renal function. Random specimens of urine were also collected from most of these patients. The levels in the whole blood are charted in Fig. 6, which shows the individual levels of the total drug and the average concentrations of both total and conjugated SMP at the various intervals. There was a definite tendency of the drug to cumulate on this dosage during the 7 days of observation, but the levels between doses showed only minor fluctuations. The proportion of drug found in the blood as the conjugated form varied from 12 to 23% of the total and averaged about 17%. The concentration of SMP in random specimens of urine collected from these patients is listed in the lower part of Table I. These levels tended to be considerably lower than those shown for SCP although a concentration as high as 363 mg per 100 ml was noted in one patient. For the most part levels in these urines ranged between 40 and 100 mg per 100

ml for total drug and from 20 to 50 mg per 100 ml of the free form. Conjugation of SMP in the urine occurred to a greater extent than with SCP. The conjugated form accounted for 49 to 86% of the total urinary SMP in different specimens and averaged 62% for all of the specimens.

Discussion. The absorption and excretion of SCP and SMP differ markedly. Both are almost completely absorbed after oral administration of single oral doses, as indicated by the fact that more than 90% of administered doses are accounted for in the urine. The peak concentration of SCP is achieved somewhat sooner (after about 3 hr) than that of SMP (about 5 hr after ingestion of the dose). The half life of a single 4 g oral dose of SCP in the blood, estimated at the time required to achieve one-half the maximum observed concentration in the plasma, is about 11 hours; this is about one-fifth of the half-life of a single 3 or 4 g oral dose of SMP. Whereas one-half of the ingested 4 g dose of SCP can be recovered in the urine within 8 or 9 hours, an average of nearly 60 hours is required to excrete one-half of an oral dose of 3 or 4 g of SMP. These differences are accounted for by the differences in the renal clearance of these drugs, the free SCP being cleared 5 to 20 times faster than free SMP. The conjugated form of SCP is cleared on the average more than twice as fast as its free form, whereas the conjugated SMP is cleared more than 10 times as fast as free SMP. The daily dose required to sustain comparable concentrations of sulfonamide in the blood is about 4 times as great for SCP as for SMP; however, the concentrations of the drugs in the urine from such doses are much greater when SCP is used. Both on 1 g of SCP every 6 hours and on 0.5 g of SMP every 12 hours there was evidence of cumulation of the drugs in the blood after the first few doses. There was less fluctuation of the levels between these doses of SMP than between the doses of SCP. On doses of 4 g of SCP daily some patients achieve concentrations in the urine which may result in crystalluria and irritation of the urinary tract although none was encountered in the present study. On the average, about ⅔ of the SMP and ½ of the SCP recovered in the urine after ingestion of these drugs is found in a conjugated form. No toxic effects were observed from either SCP or SMP in any of the patients in this study.

Summary. Sulfachloropyridazine is rapidly absorbed and rapidly excreted in the urine, in contrast to sulfamethoxypyridazine which is also absorbed fairly rapidly but is excreted much more slowly.

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