Br. J. clin. Pharmac. (1982), **13**, 523–528

THE DISPOSITION AND METABOLISM OF SULPHASALAZINE (SALICYLAZOSULPHAPYRIDINE) IN MAN

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1 We have investigated the disposition and metabolism of sulphasalazine (SASP) in eight adults with and without inflammatory bowel disease.

2 SASP is poorly absorbed (< 12%) and the half-time measured in the serum, 10.2 h, is probably the half-time of absorption and therefore an overestimate of the true half-time. The apparent volume of distribution is low (<9 l). Renal and biliary clearance rates are low (5.5 and 2.1 ml min^{-1} respectively) probably due to a high degree of protein binding. Of the absorbed SASP, two thirds is excreted in the urine and one third in the bile.

3 Most of the SASP reaches the colon and is there split by bacteria, forming sulphapyridine (SP) and 5-aminosalicylic acid (5-ASA).

4 SP is almost completely absorbed and, with its metabolites, is excreted in the urine (SP renal clearance rate 32.1 ml min^{-1}). There is no enterohepatic recirculation.

5 Of the 5-ASA released in the colon at least 25% is absorbed and rapidly eliminated in the urine after acetylation. At least 50% is eliminated in the faeces.

6 There are no differences in disposition characteristics when comparing patients with and without inflammatory bowel disease but the metabolism of SASP is markedly reduced in patients taking antibiotics and after removal of the large bowel.

Introduction

Despite the fact that sulphasalazine (salicylazosulphapyridine, SASP) has been used in the treatment of inflammatory bowel disease for over 40 years, our understanding of its disposition in the body is based on recent work. After an oral dose most of the SASP reaches the colon where its diazo-bond is cleaved by colonic bacteria with the liberation of sulphapyridine (SP) and 5-aminosalicylic acid (5-ASA). Sulphapyridine is almost totally absorbed from the colon and metabolized by acetylation, hydroxylation, and glucuronidation. Some of the 5-ASA is absorbed and excreted in the urine, mostly in the acetylated form, but most of the 5-ASA is excreted in the faeces (Schröder & Campbell, 1972; Das *et al.*, 1973; Peppercorn & Goldman, 1973).

Our aims in this study were to compare the disposition and metabolism of SASP in patients with and without inflammatory bowel disease and to extend our knowledge of its disposition as well as the disposition of its metabolites by measuring their urinary and biliary clearances and apparent volumes of distribution.

Methods

Patients

Eight adults were studied after their consent had been obtained. There were two different groups of patients:

Group I—Four patients with ulcerative colitis or Crohn's disease. These patients took a single oral dose of either 3 or 4 g of SASP in the morning after an overnight fast. No food was allowed for 1 h after administration. Venous blood samples were drawn at 0, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 30 and 36 h and then every 12 h to a total of 96 h. The serum was analysed for SASP and total SP (free SP and metabolites). Urine was collected as 24-h samples for 96 h and analysed for total SP and total 5-ASA (free and acetylated). Two of the patients subsequently underwent ileostomy and were studied again. In one of the subjects with ileocolonic continuity the urine was collected every 4 h for 12 h and then every 12 h to a total of 96 h.

Group II—Four patients who underwent cholecystectomy and bile duct exploration for biliary calculi

0306–5251/82/040523–06 $01.00

Table 1 Disposition characteristics of sulphasalazine (SASP)

Group	$T_{½}$ *(h) calculated from*			*Clearance (ml min^{-1})*		*Total excretion (% of dose)*		*Apparent V_d (l)*
	serum	*urine*	*bile*	*urinary*	*biliary*	*urine*	*bile*	
	7.5 (6.4)*	—	—	5.1 (4.7)*	—	4.6 (4.1)*	—	—
	11.0 (11.4)*	—	—	5.8 (5.5)*	—	2.4 (2.3)*	—	—
I	8.6	—	—	4.4	—	4.3	—	—
	6.5	6.5	—	9.6	—	3.4	—	—
	9.3	9.7	10.1	8.6	2.6	4.9	1.6	9.00
	13.7	15.9	17.7	3.1	1.1	9.0	3.4	4.98
II	11.7	11.4	8.3	7.1	1.7	2.0	0.5	8.97
	16.8	17.5	17.4	4.0	2.4	20.5	12.1	9.40
Median	10.2	11.4	13.8	5.5	2.1	4.5	2.5	8.99

*Figures in brackets are those found after ileostomy

and were left with T-tube drainage of the bile ducts. They were studied starting between the fifth and seventh post-operative days by which time they were eating and their bowel was working normally. They were all taking broad-spectrum antibiotics. They took a single oral dose of 4 g SASP and blood samples were collected and analysed as described for Group I. Urine was collected every 4 h. All the bile draining through the T-tube was collected every 2 h for 4 h, every 4 h for a further 20 h and then every 12 h up to a total of 96 h. All the urine and bile samples were analysed for SASP and total SP.

Analytical methods

SASP, total SP (free SP + N⁴acetyl-SP + SP-O-glucuronide + N⁴acetyl-SP-O-glucuronide) and total 5-ASA (free 5-ASA + acetyl-5-ASA) were measured by standard chemical methods (Hansson, 1973; Hansson & Sandberg, 1973; Sandberg & Hansson, 1973).

Mathematical calculations

The apparent half-times of disposition ($T_{½}$) of SASP and SP were calculated by least-squares linear regression from the terminal log serum-concentration *v* time data. The calculations of disposition half-times from the urinary and biliary data were made by plotting the natural logarithm of the quantity of drug not yet excreted at any time against that time and fitting the terminal exponential by least-squares linear regression.

The area under the serum-concentration *v.* time curve (AUC) was calculated using the trapezoidal rule for the first segment of the curve and integration to infinity of the terminal exponential.

The apparent volume of distribution (V_d) was calculated from the relationship:

$$V_d = \frac{\text{Total (urinary + biliary) excretion}}{\text{AUC} \times k}$$

where $k = 1n2/T_{½}$, and renal or biliary clearance from the relationship:

$$\text{Clearance} = \frac{\text{Total urinary (or biliary) excretion}}{\text{AUC}}$$

The calculation of apparent V_d assumes total recovery of absorbed drug from urine and bile. The kinetics of SASP have been assumed to be first order.

Table 2. Disposition characteristics of sulphapyridine (SP)

Group	$T_{½}$ *(h) calculated from*		*Urinary clearance (ml min^{-1})*	*Total excretion (% of dose)*	
	serum	*urine*		*urine*	*bile*
	9.3	—	37.8	70.1 (3.1)*	—
	10.6	—	44.7	68.7 (4.5)*	—
I	17.8	—	17.7	72.4	—
	9.7	9.1	35.9	54.2	—
	—	—	—	19.4	0.9
	—	—	—	5.2	0.04
II	10.5	11.1	28.2	25.7	0.5
	6.8	14.7	18.3	33.7	0.4
Median	10.1	11.1	32.1	I 69.4	—
				II 22.6	0.45

*Figures in brackets are those found after ileostomy

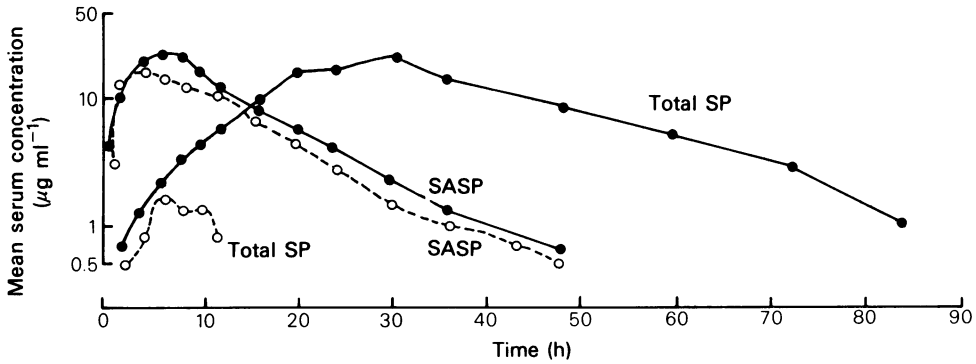

Figure 1 Serum-concentration *v* time curves of SASP and of total SP derived from the mean values in the four patients in Group I and in two of them after ileostomy ●—● before ileostomy, ○—○ after ileostomy.

Separate experiments in 170 patients have shown that the steady-state serum concentrations of SASP are related to the dose of SASP at oral doses of 1 g, 2 g, 3 g and 4 g (Azad Khan, 1977).

Results

The values of the various disposition characteristics of SASP and SP are listed in Tables 1 and 2.

Serum concentrations

1. SASP. In Figure 1 are shown the mean serum-concentration *v* time curves of SASP (a) in the four patients in Group I when they all had ileocolonic continuity and (b) in two of them when they had been treated by ileostomy. For comparison the curve for one of the patients in Group II is shown in Figure 2.

Detectable concentrations of SASP were found within one hour of ingestion in all the patients of Group I and in two patients of Group II. In the other two patients of Group II SASP was not detected until 2 or 4 h after ingestion; both these patients had received morphine shortly before the study. In patients of Group I peak serum concentrations ranged between 15.3 and 30.6 μg/ml and were reached in 4 to 8 h. In patients of Group II similar results were found but the time to peak was longer in the patients who had received morphine (12 to 24 h).

The apparent $T_{\frac{1}{2}}$ of SASP calculated from the serum measurements was slightly longer in the Group II patients, but the difference was not statistically significant. The median $T_{\frac{1}{2}}$ for all the patients was 10.2 h (range 6.5–16.8). The values calculated from urine and bile measurements did not differ significantly from the values calculated from serum measurements (Table 1).

Ileostomy had virtually no effect on the serum concentration of SASP and its apparent half-time (Table 1 and Figure 1).

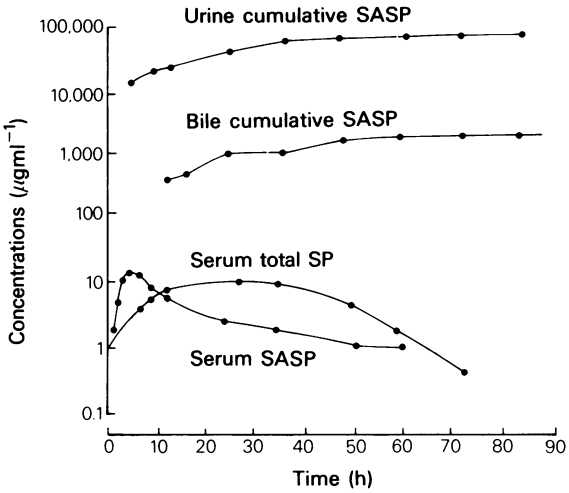

Figure 2 Serum-concentration *v* time curves of SASP and of total SP and the cumulative urinary and biliary recovery of SASP from one patient in Group II for comparison with the data shown in Figure 1.

2. SP. In Figure 1 are also shown the mean serum-concentration *v* time curves of total SP in the patients of Group I when they all had ileo-colonic continuity and in the two who were subsequently treated by ileostomy. In Figure 2 is shown the curve from a patient in Group II for comparison.

Detectable concentrations of SP appeared in the serum of patients in Group I within 2 to 6 h after the ingestion of SASP. Peak serum concentrations were achieved at 20 to 30 h and ranged between 21.6 and 30.9 μg/ml. In both the patients with ileostomy SP appeared in the serum at about the same time as it did

when they had ileo-colonic continuity, rose to a low peak, then rapidly fell and was undetectable by 16 h.

The peak serum SP concentrations occurred at about the same time in the patients of Group II as in those of Group I and were on average slightly lower although not significantly so (range 9.0–44.3 μg/ml). The half-time of SP calculated from the terminal serum concentrations was 10.1 h (6.8–17.8 h) (Table 2).

3. 5-ASA. Serum 5-ASA concentrations are known to be very low after the oral administration of SASP (Das *et al.*, 1973; Peppercorn & Goldman, 1973) and we did not measure them in the serum.

Renal excretion

1. SASP (Table 1 and Figure 2). Total urinary recovery of SASP was the same in the two groups and was 4.5% of the dose (range 2.0–20.5%). It was not affected by ileostomy. There was a positive correlation between peak serum concentration and the percentage urinary recovery ($r = 0.95$, $P < 0.001$). Renal clearance of SASP was very low (5.5 ml min^{-1}, range 4.0–9.6) and was unaffected by ileostomy.

2. SP (Table 2). Total urinary recovery of SP was 69.4% of the dose in patients of Group I before ileostomy and 3.1% and 4.5% in the two patients after ileostomy. In the patients of Group II the total urinary recovery of SP was between 5.2 and 33.7% of the dose. Urinary clearance of SP in the two Groups was 32.1 ml min^{-1} (range 17.7–44.7).

3. 5-ASA. Total urinary recovery of 5-ASA was 26.5% (range 15.1–32.3%) of the dose in the patients of Group I before ileostomy. There was a positive correlation between the total urinary recovery of SP and that of 5-ASA ($r = 0.99$, $P < 0.001$). Total urinary recovery of 5-ASA was markedly diminished in both patients with ileostomy (2.6% and 2.8% of the dose compared with 30.2% and 28.2% respectively before ileostomy).

Biliary excretion (Group II)

1. SASP (Table 1 and Figure 2). SASP first appeared in the bile within 4 to 8 h after having been first detected in the serum at between 1 and 4 h. Peak concentrations occurred in the bile at between 8 and 36 h and ranged between 35 and 1032 μg ml^{-1} (i.e. three to ten times greater than in the serum). Total biliary recovery was 2.5% of the dose (range 0.5–12.1%) (about half the value of urinary recovery). There was a positive correlation between the peak serum concentrations and the percentage of drug recovered in the bile ($r = 0.99$, $P < 0.01$).

2. SP (Table 2). Total biliary recovery of SP was 0.45% of the dose (0.04–0.9%). Biliary concentrations of SP were much lower than those in the serum.

3. 5-ASA. We did not measure 5-ASA concentrations in bile because no satisfactory analytical method was available.

Discussion

1. SASP

We have found no important differences in the disposition of SASP comparing patients with inflammatory bowel disease and those without, apart from the lower urinary recovery of SP in patients taking antibiotics, an observation which is consistent with the inhibitory effect of antibiotics on bacterial metabolism of SASP in the colon. Similarly, although ileostomy did not affect the disposition of SASP which was absorbed intact, it predictably resulted in reduced formation of SP and 5-ASA.

The half-time of SASP was quite variable (6.5–16.8 h) and the values found from calculations using urinary and biliary data were closely similar to those obtained from serum measurements. The true half-time of SASP is not known and, while it may be that the apparent half-time we have measured after oral administration is the true half-time, we believe that it is more likely to represent the half-time of *absorption* of SASP. This view is supported by three observations:

(a) There was a correlation between peak serum concentrations of SASP and its total urinary recovery.

(b) The highest values of SASP half-time were in those patients in whom the time to peak serum concentration was longest.

(c) The two patients whose apparent half-times were longest of all were those who had been given morphine, which would have delayed gastric emptying and thus the rate of absorption.

Thus the median apparent half-time of 10.2 h is probably an *overestimate* of the true disposition half-time.

The apparent volume of distribution of SASP was low and probably overestimated as a result of overestimating the half-time (see section on mathematical calculations). The low apparent volume of distribution is largely attributable to the high degree of protein binding of SASP (> 95%, Azad Khan, unpublished observations). This finding is consistent with the autoradiographic results of Hanngren *et al.* (1963) who demonstrated a high blood:tissue SASP ratio in mice.

The calculations of renal and biliary clearance were independent of half-time. Renal clearance was very low (Table 1), a finding which is entirely attributable to the extensive protein binding of SASP. Passive reabsorption as a mechanism for diminishing the rate of renal clearance is unlikely since Schröder & Campbell (1972), who found similarly low values of

renal clearance, were unable to demonstrate changes in renal clearance with changing urinary pH. Total urinary recovery of SASP was very low (4.5% of the dose) and was unaffected by ileostomy. Biliary recovery was also low (2.5% of the dose) and these observations are consistent with either poor absorption of SASP or a high degree of hepatic metabolism. The results of total urinary and biliary recovery of SP in patients on antibiotics (Table 2) show that, on average, less than 23% of the original dose of SASP excreted in urine and bile as SP could have been formed by metabolism in the small bowel or liver. Furthermore after ileostomy the urinary excretion of total SP fell to about 4% (Table 2) suggesting that the contribution of metabolism in the small bowel or liver is very small, a finding which confirms that of Schröder *et al.* (1973). The low recovery of intact SASP in urine and bile, which amounted to a total of 7% of the original dose, is therefore for the most part attributable to poor absorption.

2. SP

The apparent half-time of SP was 10.1 h as measured from serum concentration data and 11.1 h as measured from urine concentration data. The dis-

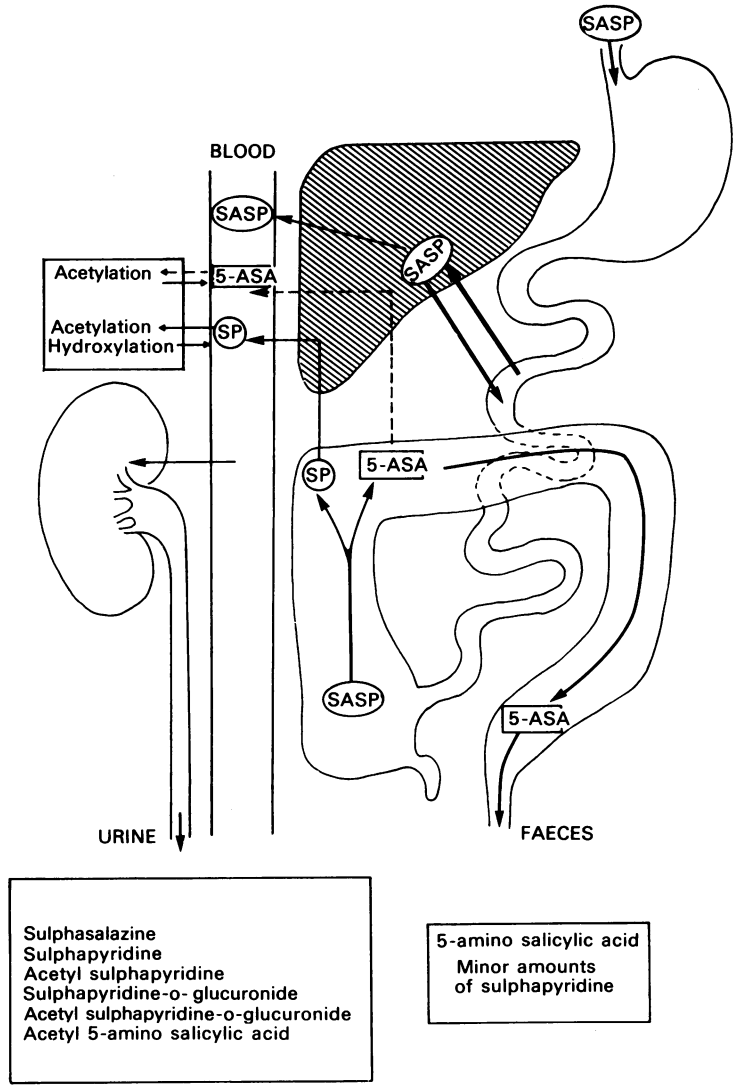

Figure 3 Disposition and metabolism of SASP after oral ingestion.

position half-time measured after oral administration of SP was 5.5 ± 1.2 h in fast acetylators and 15.3 ± 2.2 h in slow acetylators (Fischer & Flotz, 1980). The half-time of absorption was less than 1 h. These data suggest that metabolism of SASP to SP, whether in the gut or in the liver, is not a rate-limiting factor in the subsequent disposition of SP. The values of renal SP clearance of 32.1 ml min^{-1} (17.7–44.7) in our patients are too low simply to be accounted for by the extent of protein binding of SP (49.6%, Fischer & Klotz, 1980) and the clearance of SP must therefore be affected not only by filtration at the glomerulus but also by passive reabsorption in the renal tubules as is the case for other sulphonamides.

Total urinary recovery of SP was 69.4% in patients in Group I compared with 22.6% in patients in Group II ($P < 0.05$, Wilcoxon rank sum test) demonstrating the inhibitory effect of antibiotics on SASP metabolism in the large bowel. Biliary excretion of SP was negligible. In the two patients with ileostomy the total urinary recovery of SP fell from 70.1% and 68.7% to 3.1% and 4.5% respectively, again demonstrating the importance of the large bowel in the metabolism of SASP.

3. 5-ASA

We did not measure 5-ASA concentrations in either serum or bile (see results section). In urine, total recovery in patients in Group I was 26.5% and was predictably reduced in patients with ileostomy. This result is comparable with those of others (Das *et al.*, 1973; Peppercorn & Goldman, 1973; Schröder & Campbell, 1972). The apparent half-time of 5-ASA, in the patient whose urine was collected in sufficient separate aliquots for the calculation to be made, was 4.4 h.

Conclusions

Combining these results with those of others we propose that the disposition of SASP after oral administration is as shown in Figure 3. After ingestion no more than about 12% of the SASP is absorbed intact from the small bowel. Absorption is slow and rate-limiting. Less than 5% is metabolized in the small bowel or liver and of the remainder about two-thirds reaches the systemic circulation, mostly bound to plasma proteins, and is excreted in the urine. The remaining one-third undergoes enterohepatic recirculation. Thus most the SASP reaches the colon where it is metabolized by colonic bacteria to SP and 5-ASA. SP is almost completely absorbed and then undergoes acetylation and hydroxylation followed by glucuronidation. SP and its metabolites are excreted in the urine and there is virtually no enterohepatic recirculation. Of the 5-ASA that is released, at least 25% is absorbed and rapidly excreted by the kidneys after acetylation. About 50% of the 5-ASA is excreted in the faeces and the remaining 25% cannot be accounted for.

We are grateful to our surgical colleagues, Mr M.J. Kettlewell and Mr Emanoel Lee, for their assistance in the study of the enterohepatic circulation of SASP.

J.K.A. is supported by the Wellcome Trust.

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(Received July 10, 1981)