Comparison of the absorption and metabolism of sulphasalazine and acrylic-coated 5-amino salicylic acid in normal subjects and patients with colitis

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Serum levels of 5-amino salicylic acid (5ASA) and acetyl 5ASA have been measured in volunteers after ingestion of sulphasalazine (6 g) and compared with levels after an equivalent dose of acrylic coated 5ASA (2.4 g). The serum levels of both 5ASA and acetyl 5ASA were similar after each preparation apart from an early peak of 5ASA following acrylic coated 5ASA. Serum and urinary levels for 5ASA and acetyl 5ASA have been measured in colitic patients following equivalent doses of sulphasalazine and acrylic coated 5ASA. Serum levels were similar; 25% of the calculated ingested 5ASA was excreted in the urine after sulphasalazine compared with 20% following acrylic coated 5ASA.

Keywords sulphasalazine 5-amino salicylic acid ulcerative colitis

Introduction

5-amino salicylic acid (5ASA) is the active constituent in sulphasalazine. An oral formulation of 5ASA has recently been prepared with an acrylic coating of Eudragit S which releases the drug in the terminal ileum and colon (Dew *et al.*, 1982b). The preparation is as effective as sulphasalazine for the prevention of relapse in ulcerative colitis (Dew *et al.*, 1982a). This study compares the serum levels of 5ASA and its metabolites in human volunteers and patients with colitis after sulphasalazine (SASP) and comparable doses of coated 5ASA.

Methods

Six male volunteers, mean age 35 years (range 27–46 years), took 6 g of SASP while fasting at 08.00 h and 3 weeks later took an equivalent oral dose (2.4 g) of 5ASA coated with Eudragit S (120 μ thickness). On each occasion blood was taken initially and after ingestion at 3, 6, 9, 12, 15, 24, 36 and 48 h.

In a second study six patients with ulcerative colitis in remission (less than three stools per day

without blood and slime confirmed by sigmoidoscopy) three male and three female, mean age 43 years (range 35–56 years) taking SASP (mean 3.8 g/day, range 2–5 g) had serum levels measured 4 h after the last dose and a 24 h urine collection was made. The dose of SASP was then substituted with an equivalent dose of coated 5ASA (mean 1.5 g/day; range 0.8–2 g) and after 2 weeks a further serum level and 24 h urine collection was performed.

Analysis

5ASA and acetyl 5ASA were analysed by high pressure liquid chromatography using a modification of the method of Shaw *et al.* (1980). The analysis was performed on a LiChrosorb 10 RP18 bonded silica reverse phase-column (Merck). The mobile phase was acetonitrile—0.05 M potassium dihydrogen phosphate solution (15:85) pH 7.4 containing 0.1% tetrabutylammonium hydroxide. 5ASA and acetyl 5ASA were detected using a fluorescent spectrometer (excitation 360 nm, emission 425 nm). Serum

samples were treated with an equal volume of acetonitrile to precipitate protein and after centrifugation the supernatant was injected on to the chromatograph. Levels of 5ASA and acetyl 5ASA were read off a calibration curve which was linear over the ranges of 5ASA and acetyl 5ASA measured.

The minimum detectable levels were $0.02 \mu\text{g/ml}$ and $0.1 \mu\text{g/ml}$ for 5ASA and *N*-acetyl 5ASA in subjects taking 5ASA and $0.1 \mu\text{g/ml}$ and $0.25 \mu\text{g/ml}$ in subjects taking SASP.

Results

After oral administration of a single dose of sulphasalazine (6 g), the mean concentration of 5ASA during the subsequent 48 h rose to a peak of $0.36 \mu\text{g/ml}$ at 15 h. With an equivalent dose of 5ASA the serum concentrations reached a maximum of $1.27 \mu\text{g/ml}$ after only 6 h.

Serum *N*-acetyl 5ASA concentrations reached a maximum of $1.7 \mu\text{g/ml}$ 12 h after ingestion of SASP and a maximum of $2.3 \mu\text{g/ml}$ 6 h after the 5ASA (Figure 1). Serum and urine levels of 5ASA and acetyl 5ASA in colitis patients taking sulphasalazine are shown in Table 1.

Discussion

Serum concentrations of 5ASA after 6 g of sulphasalazine or an equivalent dose of 5ASA (2.4 g) were low compared with those of *N*-acetyl 5ASA. Higher peak concentrations of both 5ASA and acetyl 5ASA occurred with the 5ASA preparation compared with SASP; this suggests that more 5ASA was available for earlier absorption with coated 5ASA than sulphasalazine. Sulphasalazine becomes a suspension in the stomach or small intestine and probably reaches the colon in a more gradual way. Metabolism of 5ASA is similar from both preparations, the majority being rapidly acetylated to *N*-acetyl 5ASA.

In patients taking a regular dose of SASP or equivalent dose of 5ASA similar serum levels of 5ASA and acetyl 5ASA were detected. Despite the higher serum levels observed in the volunteer study, urine excretion of 5ASA was a little lower after the coated 5ASA (20% compared with 25% on sulphasalazine).

Acrylic coated 5ASA has several advantages over other methods of administering this drug to patients with colitis. As a carrier molecule is not employed it avoids problems with potential toxicity of both the carrier and also the parent mole-

Figure 1 Mean concentration ($\pm$ s.e. mean) of *N*-acetyl 5ASA in six volunteers. — volunteers on SASP. --- volunteers on 5ASA.

Table 1 Serum and urine levels of 5ASA and Ac 5ASA in colitis patients taking sulphasalazine and subsequently an equivalent dose of coated 5ASA.

	Dose	Serum levels		Urinary excretion		*% 5ASA excreted in urine
		ASA ($\mu\text{g ml}^{-1}$)	Ac 5ASA ($\mu\text{g ml}^{-1}$)	ASA (mg)	Ac 5ASA (day)	
SASP						
Mean	3.8 g	<0.1	0.5	16	317	25
Range	2-5 g	<0.1-0.1	0.4-0.8	2-31	127-504	
5ASA						
Mean	1.4 g	0.1	0.7	19	234	20
Range	0.8-2.0 g	0.30	<0.1-2.7	2-83	36-704	

*Refers to percentage of 5ASA excreted in the urine over 24 h as calculated from the ingested dose.

cule. We have previously demonstrated that the acrylic coated preparation of 5ASA can be taken by patients unable to take SASP (Dew *et al.*, 1983). The higher 5ASA and *N*-acetyl 5ASA levels achieved with coated 5ASA probably reflects the nature of its release in the terminal ileum and colon; similar urinary levels are achieved as with sulphasalazine and we did not note any toxicity from coated 5ASA in our previously reported trial in colitis patients (Dew *et al.*, 1982a).

References

Dew, M. J., Harries, A. D., Evans, B. K. & Rhodes, J. (1983). Treatment of ulcerative colitis with oral 5-amino salicylic acid in patients unable to take sulphasalazine. *Lancet*, **ii**, 801.

Dew, M. J., Hughes, P., Harries, A. D., Williams, G., Evans, B. K. & Rhodes, J. (1982a). Maintenance of remission in ulcerative colitis with oral preparation of 5-amino salicylic acid. *Br. med. J.*, **285**, 1012.

Dew, M. J., Hughes, P. J., Lee, M. G., Evans, B. K. & Rhodes, J. (1982b). An oral preparation to release drugs in the human colon. *Br. J. clin. Pharmac.*, **14**, 405-408.

Shaw, P. N., Aarons, L. & Houston, J. B. (1980). HPLC analyses of sulphasalazine and its metabolites. *J. Pharm. Pharmac.*, **32**, 67.

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