Br. J. clin. Pharmac. (1983), **16**, 738–740

KINETICS OF 5-AMINOSALICYLIC ACID AFTER JEJUNAL INSTILLATION IN MAN

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The human pharmacokinetics of 5-aminosalicylic acid (5-ASA), the active moiety of salazosulphapyridine (SASP), is only known from studies in which rapid absorption has been deliberately avoided. The present investigation demonstrates that pure 5-ASA is absorbed extremely quickly when given as an instillation in the proximal part of the small bowel, and acetylation follows immediately. The metabolite is excreted very rapidly by the liver in small amounts, while the major part is eliminated renally.

Keywords 5-aminosalicylic acid pharmacokinetics jejunal instillation ulcerative colitis Crohn's disease

Introduction

The human pharmacokinetics of 5-aminosalicylic acid (5-ASA) is only known from studies of Salazopyrin® (SASP) (Das *et al.*, 1973, 1979; Peppercorn & Goldman, 1973; Azad *et al.*, 1982) sustained release preparations of 5-ASA (Rasmussen *et al.*, 1982), 5-ASA contained in gelatin capsules (Schröder & Campbell, 1972), azodisalicylate (Willoughby *et al.*, 1982), and 5-ASA given rectally (Fischer *et al.*, 1983). The fate of pure 5-ASA has not previously been traced in man.

Methods

Four healthy subjects (three females, one male, age 34–37 years) consented to volunteer after thorough information about the investigation and its purpose, and the study was approved by the local ethical committee. All persons had fasted for at least 6 h prior to the investigation and no drugs were allowed the preceding week.

Under fluoroscopic control a tube was placed 100 cm distal to the ligament of Treitz and 150 mg purified 5-ASA (recrystallized) in 100 ml 0.1 M phosphate buffer solution adjusted to pH 7.0 with sodium hydroxide was given quickly, followed by an immediate removal of this tube. As the pH in this solution was 7, 5-ASA occurred in ionic form (pK_a 5.8). Subsequently 100 g Complan® (equivalent to 16 g fat, 55 g carbohydrate and 20 g protein) was given perorally. A second tube was thereafter placed approximately 5 cm distal of papilla Vateri, i.e. about 125 cm proximal to the end of the first tube. Blood samples were taken before and 15, 30, 45, 60, 90 min, 2, 3, 4, 5, and 6 h after 5-ASA was given. During the same period continuous vacuum was applied to the tube, and the duodenal aspirate thus removed was divided into 15 min fractions. Urine and faeces were collected for 24 h in two fractions. Methanol (50 ml) was added immediately to the aspirate as well as to the faeces (500 ml). This was done in order to denaturate bacteria which possibly could acetylate 5-ASA.

Determination of 5-ASA and acetylated 5-ASA (ac-5-ASA) was carried out by a previously described h.p.l.c. method (Hansen, 1981). One mol 5-ASA is equivalent to 153.13 g/l and 1 mol ac-5-ASA is equivalent to 195.13 g/l. The following biochemical tests were performed before and after the investigation: haemoglobin, ESR, reticulocytes, thrombocytes, leucocytes, coagulation factors, alanine aminotransferases, creatinine and urea, together with urine analysis for glucose, albumin and sediment—and all were within the limits of normality. A special questionnaire concerning adverse reactions was filled out by each volunteer at the end of the study.

Results

Figure 1 demonstrates both the very rapid absorption and the subsequent fast acetylation of 5-ASA. The parent compound was not detectable in plasma after 4 h and ac-5-ASA not after 6 h. Only a very small fraction (approximately 0.1%) of the 5-ASA dose was recovered in the duodenal aspirate. A high peak

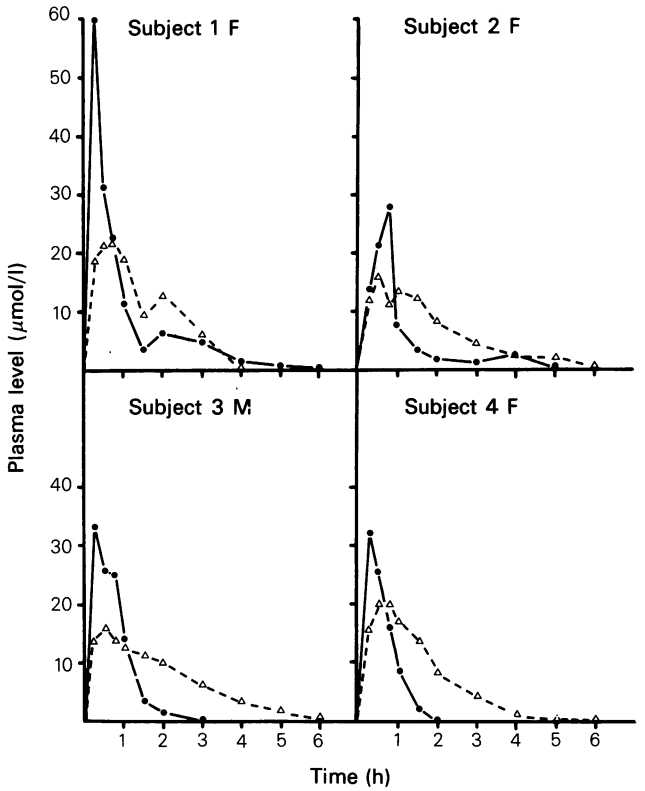

Figure 1 Plasma values of 5-ASA (●) and acetyl-5-ASA (△) for four subjects given 150 mg 5-ASA intrajejunally.

was seen after 60 min, and of the total amount excreted via this route about 1/4 was collected during 1 h, about 1/2 during 2 h and more than 4/5 during 4 h. In the urine about 54% of the dose was recovered, as the acetylated metabolite only (Table 1), and exclusively in the first 24 h period. Less than 2% of the dose was found in faeces also as ac-5-ASA (Table 1). No side effects were observed and all biochemical tests showed normal results, particularly those involving renal function (Calder *et al.*, 1975).

Discussion

5-ASA seems to act locally in the inflamed bowel (Azad *et al.*, 1977; van Hees *et al.*, 1978; Willoughby *et al.*, 1980). Nevertheless, its fate in the body should be known and the present investigation was undertaken to study the kinetic behaviour of pure 5-ASA, when presented in small amounts to the small bowel, as would be the case if given orally as such. The results may not necessarily be representative for the applica-

Table 1 Urinary and faecal excretions of 150 mg 5-ASA given intrajejunally

Subject	*Urinary excretion**		*Faecal excretion**		*Total recovery**	
	mg	*% of dose*	*mg*	*% of dose*	*mg*	*% of dose*
1	74.3	49.5	0.5	0.3	74.8	50
2	103.9	69.3	1.3	0.9	105.2	70
3	74.2	49.5	0	0	74.2	49
4	70.2	46.8	4.6	3.1	74.8	50
Mean						54

* Acetylated 5-ASA given as equimolar amounts of 5-ASA.

tion of higher doses or situations with a somewhat more protracted absorption period.

SASP or other preparations, in which 5-ASA is bound, release 5-ASA slowly giving very low and sometimes undetectable concentrations in plasma, while the concentration of ac-5-ASA is higher (Azad & Truelove, 1980; Rasmussen *et al.*, 1982). In contrast, the present results demonstrate that pure 5-ASA given in an unbound formulation is absorbed rapidly from the proximal part of the gut and thereafter quickly acetylated and eliminated from the bloodstream. Only a tiny fraction of the used 5-ASA dose was recovered from the duodenal aspirate indicating a very limited excretion of 5-ASA (as ac-5-ASA) through the bile at the given dose level. This is in accordance with the results found from patients with biliary T-tube (Fischer *et al.*, 1983). Whether the acetylation takes place in the gut wall or in the liver or both is not known, but the acetylation of 5-ASA is apparently not in accordance with the acetylator phenotype as measured by e.g. sulphadimidine (Rasmussen *et al.*, 1982).

The urinary recovery of ac-5-ASA amounted to about the same fraction as seen in healthy volunteers after much larger doses of 5-ASA in a sustained release form and during steady state conditions (Rasmussen *et al.*, 1982). As the parent compound is not found in the urine, metabolism accounts for the entire elimination of 5-ASA, the dominating pathway being acetylation.

The authors wish to thank pharmacist Steen Honoré Hansen, The Royal Danish School of Pharmacy for performing the 5-ASA analyses. 5-ASA was kindly donated by Ferring Inc.

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(Received June 6, 1983, accepted August 15, 1983)