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Absorption of 5-aminosalicylic acid from colon and rectum

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In order to clarify the characteristics of absorption of 5-aminosalicylic acid (5-ASA) from the colon, a neutral solution was instilled into the right part of the colon and the rectum, respectively, in six volunteers. A laxative (bisacodyl) and liquid meals were given prior to each instillation. No significant difference could be demonstrated between the two parts of the large bowel, but the absorption was considerably restricted compared with previous results obtained from the jejunum. The results confirm in a direct manner earlier observations on 5-ASA released from sulphasalazine.

Keywords pharmacokinetics 5-aminosalicylic acid colonic absorption inflammatory bowel disease

Introduction

Distal ulcerative colitis can be effectively treated with 5-aminosalicylic acid (5-ASA/mesalazine) if applied rectally (Azad Khan *et al.*, 1977; vanHees *et al.*, 1980; Campieri *et al.*, 1981; Danish 5-ASA Group, 1987).

5-ASA is absorbed rapidly and extensively from the small intestine (Nielsen & Bondesen, 1983) if given orally, but little is known about the absorption from the colon. Thus, acidic and neutral 5-ASA solution given rectally resulted in urinary recoveries of 35% and 21%, respectively (Bondesen *et al.*, 1984), but more detailed studies with respect to the absorption pattern as such were not performed. For 5-ASA released from sulphasalazine up to 80% may be recovered from faeces (Schröder & Cambell, 1972). In contrast, the sulphapyridine-moiety is readily absorbed from the colon. The purpose of this study was to clarify the conditions for the absorption of an unbound form of 5-ASA from two different locations in the colon.

Methods

Three male and three female patients (age 32–68 years) consented to participate following hospital admission to colonoscopy on the basis of symptoms of an irritable colon and an X-ray suggesting a colonic polyp. They were all otherwise healthy and took no medicine. The study was approved by the local Ethics Committee.

The study was done by two identical procedures, the only difference being the location of 5-ASA instillation. A laxative (bisacodyl 10 mg) was given at bedtime and only liquid meals were taken during the last 2 days before the investigation. On the study day of colonoscopy 10 mg diazepam was given intravenously for sedation and endoscopy performed. After the exclusion of macroscopic mucosal disease and larger amounts of faeces in the bowel lumen, a 5-ASA solution (see below) was subsequently instillated just proximal to the hepatic flexure (colonic instillation, CI). After a 7 days interval proctoscopy was performed and the 5-ASA solution instillated rectally (rectal instillation, RI). Frequent blood samples were drawn for 8 h and faeces and urine were collected (0–8 h, 8–24 h, 24–48 h) for the analysis of 5-ASA and Ac-5-ASA according to an h.p.l.c. method (Hansen, 1981). For both substances the inter-assay coefficient of variation was <5%.

The solution used for instillation contained 500 mg 5-ASA in 100 ml phosphate buffer, pH 7.4, osmolality 290 mM kg^{-1} (Ferring A/S, Vanløse, Danmark). Statistical comparisons were by the rank sum test.

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Table 1 Median and range for pharmacokinetic variables after colonic or rectal instillation of 500 mg 5-ASA in six healthy subjects

	Colonic instillation		*Rectal instillation*	
	5-ASA	*Ac-5-ASA*	*5-ASA*	*Ac-5-ASA*
n	6		6	
C_{max} (μM)	2.55	8.82	1.90	5.74
range	1.31–3.59	5.49–10.26	0.46–17.52	3.18–22.31
AUC (0–8 h) (μM h)	7.45	53.08	8.17	33.33
range	4.12–16.14	31.28–67.54	1.76–53.20	20.31–118.51
Urinary excretion (% of dose)	24.7		33.1	
range	19.9–44.5		10.6–86.6	

Results

Following CI total faecal output was a median of 134 g 48 h^{-1} (57–295) and following RI 203 g 48 h^{-1} (122–450) (NS). After RI total urinary volume was lower (2160 ml 48 h^{-1}, 1105–3770) than after CI (3027 ml 48 h^{-1}, 1770–4530) ($P < 0.05$). Total recovery of 5-ASA plus Ac-5-ASA in urine and faeces was 33%, (24.5–55.6) after CI and 49.8% (24.7–99.6) after RI (NS).

Bowel retention time (i.e. the period from instillation to first defaecation) was more than 8 h in all patients. After CI two subjects excreted minimal amounts of 5-ASA (< 3%) in faeces during the first 24 h period. The total amount excreted 48 h following CI (mainly as Ac-5-ASA) was a median of 6.5% (1.1–21.4). Following RI all subjects excreted some drug in faeces during the first 24 h period (8.1%, 2.2–36.6). Two subjects excreted 36.6% and 30.0%, respectively, mainly as unmetabolized drug. Total faecal excretion during 48 h was a median of 10.4% (2.2–37.1) (NS).

In the urine practically all the recovered drug appeared during the first 24 h in either situation, after CI 24.7% (19.9–44.5) of the given dose all as Ac-5-ASA and after RI 33.1% (10.6–86.6) mainly as Ac-5-ASA. However, one patient excreted 25% as non-metabolized drug.

The median plasma concentrations (Figure 1) are in both situations low for 5-ASA compared with intrajejunal instillation (Nielsen & Bondesen, 1983). The metabolite was uniformly found to be 4 to 10 times higher. In one patient higher concentrations were found of both 5–ASA and Ac-5-ASA following RI, while in all other subjects concentrations following RI were lower than after CI. Some pharmacokinetic data (median + range) are given in Table 1. Although C_{max} and AUC tended to be higher following CI compared with RI, statistically significant differences were not attained. There was no correlation between AUC of Ac-5-ASA or 5-ASA + Ac-5-ASA and urinary excretion.

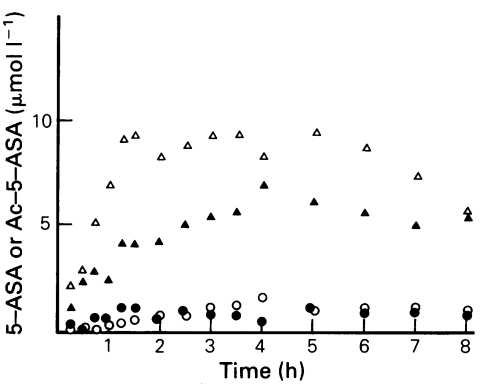

Figure 1 Median plasma concentrations of 5–ASA and its main metabolite in six subjects during an 8 h period after instillation of 500 mg 5-ASA at two different locations in the colon (for details see text). Colonic instillation; 5–ASA: ● Colonic instillation; Ac–5–ASA: △. Rectal instillation: 5–ASA: ○ Rectal instillation: Ac–5–ASA: ▲.

Discussion

5–ASA acts most probably from the luminal side i.e. by penetrating the mucosa at high concentrations (Azad Khan *et al.*, 1977, 1980; vanHees *et al.*, 1980). Several studies on the pharmacokinetics of sulphasalazine have demonstrated that 5–ASA released in the colon by azoreduction is largely (up to 80%) excreted in the faeces (Bondesen *et al.*, 1986) pointing to a limited

permeability of 5-ASA in the colon, while sulphapyridine may be 90% absorbed.

The present results indicate that the absorption of 5-ASA is similar in the right and the left parts of the colon. Absorption of 5-ASA has previously been shown to be influenced by the pH of the solution (Bondesen *et al.*, 1984), and the present results confirm, in a direct manner, earlier observations that 5-ASA (given alone or as sulphasalazine) is poorly absorbed in the colon compared with the small intestine (Schröder & Cambell, 1972; Nielsen & Bondesen, 1983). In the latter study instillation of 250 mg 5-ASA resulted in plasma concentrations of more than 30 μmol l^{-1} and fast urinary excretion of more than 45% of the dose. Thus, the intestinal absorption of 5-ASA seems to be dependent of luminal pH, the concentration gradient as well as the local properties of the mucosa.

The full extent of the drug absorption could not be estimated as not all the drug applied in the colon could be accounted for. Thus, in the present study the total recovery of 5-ASA was lower than expected. Neither incomplete sampling (as reflected in satisfactory urinary and faecal outputs) nor loss of stability of the 5-ASA in the solutions (personal observation) may be held responsible, but incomplete recovery of 5-ASA has been observed earlier (Nielsen & Bondesen, 1983; Bondesen *et al.*, 1984, 1986; van Hogezand *et al.*, 1985), and might partly be explained by the existence of non-detected metabolites in faeces (Bondesen *et al.*, 1984; van Hogezand *et al.*, 1985). The study of other possible metabolites of 5-ASA merits further investigations in the light of 5-ASA being shown to have radical scavenger properties (Ahnfeldt-Rønne & Nielsen, 1987). A major reason for the poor total recovery of 5-ASA must therefore be sought in the low contribution from the faeces, as the urinary recovery is in line with that observed in other studies (Schröder & Cambell, 1972, van Hogezand *et al.*, 1985; Bondesen *et al.*, 1986). In order to estimate the absorption of 5-ASA, emphasis should be placed on the urinary rather than the faecal data. Absolute bioavailability studies concerning various application forms of 5-ASA have not been published. However, unpublished results from our group based on i.v. studies reveal an approximately 40% bioavailability from Pentasa®, an oral, slow release 5-ASA preparation, from which the drug is absorbed equally in the large and the small intestines (Bondesen *et al.*, unpublished).

In conclusion, the results of the present study suggest a restricted absorption of 5-ASA in the large bowel confirming observations with sulphasalazine. The similar permeability pattern in the different areas of the large bowel may support the assumption that increased efficacy towards colitis engaging the right colon may be achieved by therapeutic regimens providing large amounts of 5-ASA to the lumen there, in line with the results after high dose 5-ASA enema treatment in proctosigmoiditis (Azad Khan *et al.*, 1977; Campieri *et al.*, 1981).

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