Oroileal transit of slow release 5-aminosalicylic acid

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Abstract

The predominant active anti-inflammatory moiety in chronic inflammatory bowel disease is 5-aminosalicylic acid (5-ASA). As unprotected 5-ASA is rapidly absorbed in the upper gastrointestinal tract several slow release preparations have been developed to permit passage of 5-ASA to the lower small bowel and to the colon. To investigate luminal kinetics and extent of the release of 5-ASA intraluminal concentrations and loads of this compound together with that of its main metabolite acetyl-5-aminosalicylic acid (ac-5-ASA) were studied, over 15 hours after giving the slow release preparation Salofalk at a dose of 500 mg orally together with a test meal. Plasma concentrations and urinary excretion were also measured. Six healthy volunteers swallowed an 11 lumen oroileal tube, which allowed marker perfusion, aspiration of luminal content from the duodenum, mid-jejunum, and ileum, and recording of intestinal motility. Emptying of 5-ASA into the duodenum started after emptying of the meal, together with the first phase III of interdigestive motility. Mean luminal concentrations of 5-ASA and ac-5-ASA increased continuously from duodenum (both: 15 to 30 µg/ml) to ileum (60 to 110 µg/ml and 80 to 150 µg/ml respectively) over three hours and decreased over the next three hours. During 10 hours after eating, 30% of the total dose passed the ileum in solution and another 10% were excreted in urine. Thus about 60% reached the colon unreleased from tablets and another 30% were in solution. The ratio of 5-ASA and ac-5-ASA in solution was about 1:1 in the duodenum and 1:1.5 to 1:2 in the more distal small intestine. The data suggest that the large quantities of intraluminal ac-5-ASA are generated in the intestinal mucosa and reach the lumen by back diffusion. The results show that most of the 5-ASA from this slow release preparation is delivered into the colon, which explains its effectiveness in ulcerative colitis. The considerable luminal concentrations already present in the distal ileum might justify therapeutic trials in Crohn's disease.

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After giving salazosulphapyridine (SASP) by mouth it is split into 5-aminosalicylic acid (5-ASA) and sulphapyridine by bacteria in the colon. The active moiety to inhibit the inflammation in chronic inflammatory bowel disease has been shown to be 5-ASA.¹ On the other hand, sulphapyridine, used as a carrier molecule for SASP, is responsible for most of the side effects of this compound. Therefore administration of 5-ASA alone seems attractive as a treatment of inflammatory bowel disease. Administration of 5-ASA to the distal intestine

is difficult, however, because of its rapid absorption in the stomach and proximal small bowel; the compound is then acetylated and excreted in urine.²⁻⁴

To overcome this problem, different galenic 5-ASA (mesalazine, mesalamine) preparations have been developed with the aim of slower release of the substance into the gut lumen, which should permit major delivery of 5-ASA to the ileum and the colon: coating with Eudragit S (Asacol) or Eudragit L in combination with sodium carbonate/glycine buffering (Salofalk, Claversal), microgranules coated with ethylcellulose (Pentasa). With another approach, two molecules of 5-ASA are coupled (Dipentum) and released on bacterial cleavage in the colon. Luminal liberation of 5-ASA from these various preparations has been investigated in several studies, generally by measuring urinary or faecal excretion, or plasma appearance and disappearance rates of 5-ASA and its main metabolite acetyl-5-ASA (ac-5-ASA), to estimate kinetics and extent of its intraluminal release.³⁻⁷ Other approaches included radiographic tracings of a barium sulphate marker,^{3,8} scintigraphic tracings of indium-111 released from an Eudragit L coated tablet,⁹ or the recovery of 5-ASA from the ileostomy effluent of patients.^{10,11}

Thus our understanding of the luminal fate of 5-ASA is largely based on indirect estimations.¹²⁻¹⁴ Although it is assumed that liberation of 5-ASA from slow release preparations gradually increases during transit through the small intestine, and although intraluminal concentrations of 5-ASA are of importance for its therapeutic effects, the passage of 5-ASA has not been studied by direct analysis of the luminal contents from different levels of the small intestine.

The aims of this study were to determine the release of 5-ASA and the generation of its main metabolite, ac-5-ASA, from the slow release preparation Salofalk given as a single oral dose with a defined meal into the duodenum, mid-jejunum, and terminal ileum in healthy humans by direct, intraluminal measurements.

Subjects and methods

SUBJECTS

After giving informed consent, six healthy volunteers (men aged 25-35 years) participated in the study. The protocol was approved by the institution's ethics committee.

GASTROINTESTINAL TUBES

After an overnight fast, subjects were intubated with an 11 lumen polyvinyl oroileal tube that was placed with its tip in the distal ileum (240 to 250 cm from the mouth). In this position,

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aspiration ports were in the duodenum (5 to 10 cm proximal to the ligament of Treitz), the mid-jejunum (90 to 100 cm from the pylorus), and the distal ileum (150 to 160 cm from the pylorus). Ports for perfusion of non-absorbed marker and test solutions were at the papilla of Vater. Four additional catheters were perfused with deionised water and served as intestinal pressure recording ports; they were located about 10, 40, 70, and 130 cm from the pylorus. Before the start and after the end of the study, tube position was verified by fluoroscopy.

EXPERIMENTAL PROTOCOL

After the tube had reached its correct position, continuous duodenal perfusion (3 ml/min) of polyethylene glycol 4000 (PEG; 15 mg/ml; pH 7.0) as a luminal dilution marker and continuous recording of intestinal motility was begun. After an equilibration time of three hours, studies were started.

All subjects ingested a standardised semi-liquid 300 ml test meal (138 mg/ml starch; 34 mg/ml triglycerides; 38 mg/ml sodium caseinate) (a gift from Dr Kessler, Fresenius AG, Oberursel, Germany) within 15 minutes. The test meal contained 100 µg/ml of phenolsulphonphthaleine (PSP) as a marker to assess emptying of the meal from the stomach and its transit through the small intestine. Together with the meal, subjects swallowed 500 mg of 5-ASA (Salofalk, 250 mg tablets; a gift from Dr Falk, Pharma GmbH, Freiburg, Germany).

From 30 minutes before up to 15 hours after the meal, 2 to 3 ml aliquots of intraluminal contents were aspirated by hand from each aspiration site at 15 minute intervals and collected into vials that were immersed in ice; when the collectable volume was <1 ml within the 15 minute period, two consecutive samples were pooled to represent a 30 minute aliquot. To ensure rapid removal of fresh intraluminal samples, the tube to each site was flushed with a volume of air equal to its dead space (duodenal = 3 ml, jejunal = 4 ml, ileal = 5 ml) immediately before and after intestinal juice was aspirated. Venous blood samples were drawn at 30 minute intervals and urine was collected at two hour intervals for 14 hours.

ANALYSES AND CALCULATIONS

Gastrointestinal motility was recorded with a low compliance perfusion system (Sensormedics, Essen, Germany) and analysed as described previously.^{15,16} The 5-ASA and ac-5-ASA were measured in intestinal samples, plasma, and urine by high performance liquid chromatography.^{17,18} Concentrations of PEG and PSP and pH were measured and after correction for the amounts removed proximally, were used to calculate intraluminal volume flow rates and delivery rates of 5-ASA and PSP to intestinal sites as described earlier.¹⁹⁻²² Briefly, the perfusion marker was used to compute luminal volume flow rates for each site during each aspiration interval. The 5-ASA and ac-5-ASA delivery rates were calculated at each site from the concentration in the aspirated aliquot sample and the volume flow rate associated with the same sample.

The digestive period was defined as the time between the ingestion of the test meal and occurrence of the first phase III motility in the duodenum; the remainder of the study was defined as the interdigestive period. Gastric emptying time after a meal was defined as the interval between start of the ingestion meal and cumulative delivery of >90% of the meal marker PSP to the duodenal aspiration site, as described earlier.²³ Time intervals between duodenal, jejunal, and ileal delivery of 50% of cumulative PSP recovered were used to calculate duodeno-jejuno-ileal transit times. Cumulative 5-ASA delivery to each aspiration site was defined as the cumulative amount released at this site corrected for cumulative PSP recovery and for the amount of chyme removed proximally. Data are expressed as mean (SD) values unless indicated otherwise.

Results

MOTILITY, GASTRIC EMPTYING, AND SMALL INTESTINAL TRANSIT OF TEST MEAL

Ingestion of the test meal induced a fed motility pattern in all subjects that was terminated by an interdigestive duodenal phase III activity front after 182 to 295 minutes (Fig 1). Cumulative delivery of 90% of the meal marker to the

Figure 1: (A) Intervals between ingestion of the test meal (0 minutes) and 90% cumulative duodenal delivery of meal marker (90% emptying; top bar), occurrence of the first duodenal phase III (middle bar) and first detection of 5-aminosalicylic acid in duodenal samples (bottom bar). Mean (SD) values of $n=6$. (B) Correlation of intervals between eating meal and first duodenal phase III motility and first appearance of 5-aminosalicylic acid in duodenal samples ($p<0.05$).

Figure 2: Delivery to duodenum, jejunum, and ileum of the meal marker phenolsulphonphthalein and release of 5-aminosalicylic acid from Salofalk tablets given with a meal ingested at 0 hours. Mean (SD) values of $n=6$.

duodenal aspiration site, which served as an estimate of gastric emptying of 90% of the meal, was exceeded after about three and a half hours (Figs 1 and 2). Thus at the time of the first duodenal phase III motility, 96.6 (SD 1.8)% of the meal marker had left the stomach. Within this period, no 5-ASA or ac-5-ASA was detected in the small intestinal lumen, blood or urine. Small intestinal (duodenoileal) transit time of the meal marker was 169 (47) minutes and composed of duodenojejunal and jejunoileal transit times of 47 (10) minutes and 122 (51) minutes, respectively (Fig 2).

INTRALUMINAL PH

During the digestive period, mean luminal pH was 6.25 (0.13) in the duodenum, 6.95 (0.12) in the jejunum, and 7.64 (0.16) in the ileum. During the subsequent interdigestive period, mean pH was 6.31 (0.18) in the duodenum, 7.08 (0.18) in the jejunum, and 7.81 (0.12) in the ileum.

DELIVERY OF 5-ASA AND AC-5-ASA TO INTESTINAL SITES

During the digestive period, no 5-ASA was detected in intestinal samples. Measurable quantities were present in duodenal aspirates after 180 to 330 minutes after the meal – that is, in the samples during or immediately after the first duodenal phase III motor pattern (Figs 1 and 2). Thus gastroduodenal delivery and duodenoileal transit of 5-ASA and Salofalk tablets were dissociated from those of the test

meal (Fig 2) and release of 5-ASA occurred exclusively in the interdigestive period. The cumulative quantity of 5-ASA in solution in intestinal fluid at the duodenal aspiration site over the entire study period was 1.5% of the dose administered; cumulative duodenal occurrence of ac-5-ASA was 1.4% (Table I). Cumulative values of dissolved 5-ASA and ac-5-ASA in the jejunum were 5.7% and 11.7% respectively, and in the ileum 12.7% and 17.9% respectively (Table I).

LUMINAL CONCENTRATIONS OF 5-ASA AND AC-5-ASA

Luminal concentrations of 5-ASA increased continuously between proximal and distal aspiration sites within each subject ($p<0.01$). In the duodenum, concentrations of 5-ASA and ac-5-ASA were in the same range, but at the two distal aspiration sites ac-5-ASA concentrations tended to be higher than 5-ASA concentrations: For one to two hours, mean intraduodenal concentrations either compound were 15 to 30 µg/ml. By contrast, mean intrajejunal concentrations of 5-ASA were 30 to 70 µg/ml, and of ac-5-ASA 50 to 130 µg/ml; mean intraileal concentrations of 5-ASA were 60 to 110 µg/ml, and of ac-5-ASA 80 to 150 µg/ml; however, there were large interindividual variations (Fig 3).

Peak concentrations of 5-ASA and ac-5-ASA at the duodenal aspiration site were found after mean intervals of 6.2 (0.4) hours and 6.3 (0.4) hours after the meal, at the jejunal sites after 6.6 (0.4) hours and 6.8 (0.3) hours, and at the ileal site after 7.4 (0.3) hours and 7.5 (0.3) hours, respectively (Fig 2).

5-ASA AND AC-5-ASA IN PLASMA AND URINE

First appearance and the first peak concentration of 5-ASA in the plasma were recorded after a mean interval of four hours and 6.5 (0.2) hours after the meal respectively, and thus paralleled delivery to the duodenum (Fig 3). Up to the end of the seventh postprandial hour, plasma ac-5-ASA and 5-ASA concentrations were similar. By contrast, over the subsequent two hours, plasma 5-ASA concentrations decreased, but ac-5-ASA concentrations increased further and exhibited two distinct, separate peaks, the first after 6.9 (0.2) hours, the second after 8.6 (0.3) hours (Fig 3). Thus the first plasma peak after 6.9 hours occurred during major release of 5-ASA and formation of ac-5-ASA in the distal

TABLE I Cumulative load of 5-aminosalicylic acid (5-ASA) and Acetyl-5-ASA (ac-5-ASA) released during transit through small intestine and delivered to duodenal, jejunal, and ileal aspiration sites, and excreted in urine, during 10 hours after ingestion of 500 mg of 5-ASA as 250 mg Salofalk tablets (mean (SD) values of $n=6$).

	5-ASA		Ac-5-ASA	
	(mg)	(% dose)	(mg)	(% dose)
Duodenum	7.5 (3.2)	1.5	6.9 (1.4)	1.4
Jejunum	28.3 (7.2)	5.7	58.7 (11.5)	11.7
Ileum	63.5 (20.2)	12.7	89.3 (26.5)	17.9
Urine	1.0 (0.5)	0.2	36.5 (17.5)	7.3

Figure 3: Concentration of 5-aminosalicylic acid and acetyl-mesalazine (ac-5-ASA) in duodenal, jejunal, and ileal lumen and plasma, after ingestion of Salofalk 250 tablets (500 mg mesalazine) with a meal at 0 hours. Mean (SD) values of $n=6$.

small intestine, the second peak after the major proportion after 8.6 hours had passed into the colon.

Only small amounts of 5-ASA were excreted in the urine (0.2% of 5-ASA dose). About 7.3% of the administered dose were recovered as ac-5-ASA over the 10 postprandial hours (Table I).

Discussion

Our findings show that 5-ASA tablets with acid resistant coating (Salofalk tablets) given with a meal are emptied into the small intestine not during the digestive period, but with the beginning of the subsequent interdigestive phase III motor activity. During small intestinal transit, intraluminal concentrations of 5-ASA and its main metabolite, ac-5-ASA, gradually increase; at the ileal aspiration site more than 30% of the total dose has been released from the preparation into the gut lumen and could be determined as either 5-ASA or ac-5-ASA. Concentrations of 5-ASA in the plasma parallel those in the proximal small intestine, whereas plasma ac-5-ASA peaks appear later and correspond more to

the 5-ASA release in the terminal ileum and in the colon.

The main site of inflammation in extended ulcerative colitis is the colon up to the caecal region and in Crohn's disease the distal ileum and proximal part of the colon, the ileum being involved in 75%.²⁴ Oral plain 5-ASA is rapidly absorbed in the upper intestine²⁵; therefore, the galenics of an oral 5-ASA preparation have to be modified to deliver sufficient quantities of 5-ASA to the lower small bowel and colon. In Crohn's ileitis, slow delivery of 5-ASA from a slow release preparation has a theoretical advantage over other galenic approaches because it may liberate sufficient quantities of the compound already in the ileum. The fate of a slow release preparation in the small intestinal lumen is determined by gastric emptying and small intestinal transit, intraluminal pH, and the specific coating of the tablet. We studied a preparation that contained 5-ASA in a sodium carbonate-glycine buffering mixture and an acid resistant coating of an acrylic based resin (Eudragit L 100, Salofalk, identical with Claversal). This coating disintegrates and releases 5-ASA at and above pH 6.0, the prevailing pH in the mid and lower small intestine and colon.

Our findings suggest that 5-ASA was not emptied from the stomach with the test meal, but with the first phase III motor complex of the subsequent interdigestive period. Because only particles of <1–2 mm are emptied in the prandial period, this suggests that no intragastric disintegration of tablets occurred. These findings are in agreement with data by Hardy *et al* who used indium-111-labelled 5-ASA containing tablets covered by an Eudragit L film (Claversal = Salofalk) which were emptied from the stomach after four hours when taken with a meal, and after less than one hour when taken in the fasting state.⁹ Meyer *et al* have shown that particles larger than 3 mm are retained in the stomach and emptied postprandially.²⁵ This point has been further established by Ewe *et al*²⁶ who showed that larger particles are retained in the stomach irrespective of the composition of the meal (liquid or solid). Not only gastric emptying, but also small intestinal transit of the test meal and the tablets together with released 5-ASA are thoroughly dissociated. This suggests that even when ingested with a meal, 5-ASA from the tablets may not mix with, or adsorb to, meal components. To avoid discontinuous release of 5-ASA in the gut with several meals over the day, the practical consequence therefore should be to take the tablets about half an hour before a meal in the fasting state. Release of 5-ASA into the lumen began in the duodenum at pH 6 to 7 and increased significantly during small intestinal transit of the tablets, suggesting progressive release due to increasing permeability of the coating. Disintegration of the coating was likely further accelerated by gradually increasing pH between the duodenal and the ileal aspiration site, with a prevailing pH of >7 in the distal lumen. An elegant measurement of the pH-profile in the small and large bowel was published by Evans *et al*, with a radiotelemetry capsule.²⁷ These data show a mean pH of 6.6 (0.5) in the proximal small bowel and of 7.5 (0.4)

in the terminal ileum. Our direct pH measurements in the intestinal fluids are in good agreement with these data. It is interesting that Evans *et al* found a decrease of the pH to 6.4 (0.4) in the cecal region with a final mean pH of 7.0 (0.7) in the left colon. These values would mean that a continuous release of 5-ASA from the tablets can take place also in the colon. Our data suggest that the ileal mucosa was exposed to free 5-ASA concentrations of >50 µg/ml for two hours, whereas concentrations and duration of exposure were lower at proximal intestinal sites.

From the first appearance of 5-ASA in the duodenum, ac-5-ASA was also present in the intestinal fluid. The ratio of 5-ASA to ac-5-ASA was about 1:1 in the duodenum, and 1:1.5 to 1:2 in the distal small intestine. This may be true only for the low dose used in this study. Because acetylation of 5-ASA by intestinal mucosal acetyltransferase follows a saturation kinetic,¹² the 5-ASA to ac-5-ASA ratio might increase after higher doses of 5-ASA.¹⁰ Mardini *et al*²⁸ have reported a proportion of 5-ASA to ac-5-ASA in the colon lumen of 2:4. This might reflect the finding that the absorption rate of 5-ASA is lower in the colon than in the small bowel.²⁹

Initially, concentrations of 5-ASA and ac-5-ASA in the plasma were similar, and their kinetics paralleled those in the duodenal and jejunal lumen. This suggests rapid absorption in the proximal part of the small intestine and rapid metabolism that likely occurs in part pre-systemically. Peak concentrations of 5-ASA were lower and reached earlier than those of ac-5-ASA. Thereafter concentrations of the metabolite were considerably higher than those of the parent drug due to the slower elimination of the metabolite.¹³ After a single oral dose of the same preparation similar mean concentration profiles as measured in our study were found both in healthy subjects and in patients with inflammatory bowel disease^{30,31} in another study initially higher concentrations of the metabolite were reported.³² Considerable interindividual variations in the disposition of 5-ASA have been shown during pharmacokinetic studies with 5-ASA.

The cumulative amount of 5-ASA and ac-5-ASA that was excreted in the urine within 10 hours (that is six to seven hours after the start of 5-ASA emptying into the duodenum) was <10% of the total dose. This value is within the range of other studies; it represents an underestimation because 5-ASA and especially the slowly eliminated ac-5-ASA can be detected in the urine up to 96 hours.⁴ In this study, Rijk *et al* reported a urinary excretion of about 10% within the first eight hours, 20% within 24 hours, and 34% within 96 hours.⁴ In combination, these findings suggest that up to one third of an oral dose of 5-ASA is excreted in urine, and that absorption of the major portion occurs not during small intestinal transit but in the colon.

We found a total ileal cumulative load of 5-ASA and ac-5-ASA of about 30% of the oral dose, and an early urinary excretion of <10%. Thus our data suggest that about 60% of the dose should have reached the colonic lumen still in tablets and another 15% as solubilised 5-ASA (Table II). Our data were obtained from healthy

volunteers. In active inflammatory bowel disease the transit through the small bowel was found to be not different from the healthy state,^{9,30} but the authors had studied only patients with Crohn's disease without a stricture and with ulcerative colitis. It is possible that the transit through the small bowel is changed with the presence of strictures and that tablets could be retained by strictures that could change the pattern of 5-ASA release in the small bowel. In ulcerative colitis it was shown by Rao *et al*³ that transit in the small intestine may be slower than normal. This would mean that more 5-ASA would be acetylated and absorbed before colonic arrival.³⁴ Based on indirect estimates, a colonic availability of 66% has been proposed by Rijk *et al*⁴; the same group has also measured fecal excretion, which was reported to be 37% of the total dose in 96 hours; only 5% was present as 5-ASA and 31% as ac-5-ASA. Measurements of faecal contents may be difficult to interpret, however, because 5-ASA might be degraded by colonic bacteria to ac-5-ASA³⁵ and to unknown products.⁴

It has been shown that 5-ASA is the active anti-inflammatory moiety in chronic inflammatory bowel disease, whereas the acetylated metabolite seems inactive.^{36,37} The uptake of 5-ASA in colonic cell preparations occurs rapidly and is equivalent to the production of ac-5-ASA by the cells, whereas the uptake of acetylated 5-ASA is slower.³⁶⁻³⁸ Not all 5-ASA penetrating the intestinal mucosa is acetylated, however, because our data confirm that a small portion also enters the systemic blood without prior acetylation.

Intestinal acetylation of 5-ASA occurs rapidly within the intestinal mucosa^{17,39} whereas no acetylation was found during incubation in human duodenal, jejunal, and ileal juice (our own unpublished observations); this suggests that intraluminal acetylation does not play a major part in the generation of intraluminal ac-5-ASA in the small intestine. In the colon, the colonic mucosa is also the major site of acetylation of 5-ASA.¹⁷ Allgayer *et al*¹⁷ showed that the colonic mucosa acetylates 370 (20) nmol/g wet weight of tissue per minute. In comparison the acetylation in faecal samples by bacteria was lower (13.0 (3.0) nmol/g). Nevertheless, this means that the luminal colonic content also contributes to the inactivation of 5-ASA. Another factor that influences the availability of 5-ASA to the mucosa in ulcerative colitis is the finding that different 5-ASA preparations show a considerable variation in colonic 5-ASA concentrations.³⁵ Almost double intraluminal concentrations were found with olsalazine compared

TABLE II Overall calculation of the fate of 5-ASA swallowed in a slow release tablet (Salofalk).

5-ASA + ac-5-ASA	
Swallowed in tablet	100%
Solubilised in ileum	30%
Excreted in urine	10%
Unreleased in ileum	60%
After 8 to 10 h	All substance has left the small bowel
Entered into the colon	60% unreleased in tablet 30% in solution (about 15% as 5-ASA; about 15% as ac-5-ASA)
Totally into the colon	90% of the given dose, 75% as 5-ASA
By 8 to 10 h	10% excreted in urine

with equimolar doses of Pentasa and Salofalk. For a positive effect of 5-ASA in ulcerative colitis the concentration in the colonic lumen should be high enough to build up a gradient for absorption into the mucosa. So higher doses of slow release preparations than olsalazine are needed theoretically for therapeutic use in ulcerative colitis. There is no evidence for major entero-biliary recirculation and biliary resecretion of acetyl-5-ASA,⁴⁰ as assessed from kinetics of luminal concentrations at all intestinal aspiration sites as well as in plasma. Thus the considerable intraluminal quantities of ac-5-ASA suggest that 5-ASA may have entered the intestinal mucosa and, after acetylation, have partly back diffused into the lumen. As most of the 5-ASA entering the mucosal cell is acetylated, it seems conceivable that its anti-inflammatory action within the tissue occurs before the acetylation step. We therefore speculate that in the small bowel the intraluminal ac-5-ASA represents the portion that already may have exerted anti-inflammatory action within the tissue and that the free intraluminal 5-ASA represents the portion that has not yet penetrated into the mucosa. Thus it may be misleading to assess the anti-inflammatory potential of 5-ASA based only on its intraluminally available free concentration.

In conclusion this study shows, by direct luminal measurements, that in healthy subjects delayed release of 5-ASA from Salofalk tablets occurs with its major release into the colon. Although the kinetics of this single dose study may differ from those present in patients with chronic treatment, these data might explain the effectiveness of 5-ASA in acute phase and maintenance treatment of ulcerative colitis.^{41,42} Yet the considerable release to the ileal lumen may warrant a trial of its use in Crohn's ileitis. One such trial has been published with promising results in maintaining remission of inactive Crohn's disease.⁴³ This has to be proved in further studies. Evidence is still needed from studies that it also works in active Crohn's disease.

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- 1 Azad Khan AK, Piris J, Truelove SC. An experiment to determine the active therapeutic moiety of sulphasalazine. *Lancet* 1977; 1: 892-5.
- 2 Nielsen OH, Bondesen S. Kinetics of 5-aminosalicylic acid after jejunal instillation in man. *Br J Clin Pharmacol* 1983; 16: 738-40.
- 3 Myers B, Evans DNW, Rhodes J, Evans BK, Hughes BR, Lee MG, et al. Metabolism and urinary excretion of 5-aminosalicylic acid in healthy volunteers when given intravenously or released for absorption at different sites in the gastrointestinal tract. *Gut* 1987; 28: 196-200.
- 4 Rijk MCM, van Schaik A, van Tongeren JHM. Disposition of 5-aminosalicylic acid by 5-aminosalicylic acid-delivering compounds. *Scand J Gastroenterol* 1988; 23: 107-12.
- 5 Rasmussen SN, Bondesen S, Huidberg EF, Hansen SH, Binder U, Halskov S, et al. 5-aminosalicylic acid in a slow release preparation: bioavailability, plasma level and excretion in humans. *Gastroenterology* 1982; 83: 1062-70.
- 6 Klotz U, Maier KE, Fischer C, Bauer KH. A new slow-release form of 5-aminosalicylic acid for the oral treatment of inflammatory bowel disease. Biopharmaceutical and clinical pharmacokinetic characteristics. *Drug Res* 1985; 35: 636-9.
- 7 Klotz U, Seyffert R, Allgayer H, Maier KE. Pharmacokinetic properties of mesalazine (5-aminosalicylic acid). In: McDermott RP, ed. *Inflammatory bowel disease*. New York: Elsevier 1988; 725-9.
- 8 Klotz U. Pharmacokinetic properties of 5-amino-salicylic acid (mesalazine). In: Goebell H, Peskar BM, Malchow H, eds. *Inflammatory bowel diseases - basic research and clinical implications*. Lancaster: MTP Press 1988; 339-47. Falk Symposium No 46.
- 9 Hardy JG, Healey JNC, Lee SW, Reynolds JR. Gastrointestinal transit of an enteric-coated delayed-release 5-aminosalicylic acid tablet. *Aliment Pharmacol Therap* 1987; 1: 209-16.
- 10 Riley SA, Tavares IA, Bennett A, Mani V. Delayed-release mesalazine (5-aminosalicylic acid): coat dissolution and excretion in ileostoma subjects. *Br J Clin Pharmacol* 1988; 26: 173-7.
- 11 Christensen LA, Fallingborg J, Abildgaard K, Jacobsen BA, Sanchez G, Hansen SH, et al. Topical and systemic availability of 5-aminosalicylate: comparisons of three controlled release preparations in man. *Aliment Pharmacol Therap* 1990; 4: 523-33.
- 12 Klotz U. Clinical pharmacokinetics of sulphasalazine, its metabolites and other products of 5-aminosalicylic acid. *Clin Pharmacokinet* 1985; 10: 285-302.
- 13 Brogden RN, Sarkin EM. Mesalazine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in chronic inflammatory bowel disease. *Drugs* 1989; 38: 500-23.
- 14 Jarnerot G. Newer 5-aminosalicylic acid based drugs in chronic inflammatory bowel disease. *Drugs* 1989; 37: 73-86.
- 15 Layer P, Chan ATH, Go VLW, DiMagno EP. Human pancreatic secretion during phase II antral motility of the interdigestive cycle. *Am J Physiol* 1988; 254: G249-53.
- 16 Layer P, Peschel S, Schlesinger T, Goebell H. Human pancreatic secretion and intestinal motility: effects of ileal nutrient perfusion. *Am J Physiol* 1990; 258: G196-G201.
- 17 Allgayer H, Ahnfelt NO, Krus W, Klotz U, Frank-Holmberg K, Söderberg HNA, et al. Colonic N-acetylation of 5-aminosalicylic acid in inflammatory bowel disease. *Gastroenterology* 1989; 97: 38-41.
- 18 Fischer C, Maier K, Klotz U. Simplified high-performance liquid chromatographic method for 5-aminosalicylic acid in plasma and urine. *J Chromatography* 1981; 225: 498-503.
- 19 Go VLW, Hofmann AF, Summerskill WHJ. Simultaneous measurements of total pancreatic, biliary, and gastric outputs in man using a perfusion technique. *Gastroenterology* 1970; 58: 321-8.
- 20 Wingate DL, Sandberg RJ, Phillips SF. A comparison of stable and 14 C-labelled polyethylene glycol as volume indicators in the human jejunum. *Gut* 1972; 13: 812-5.
- 21 Layer P, Zinsmeister AR, DiMagno EP. Effects of decreasing intraluminal amylase activity on starch digestion and postprandial gastrointestinal function in humans. *Gastroenterology* 1986; 91: 41-8.
- 22 Layer P, Jansen JBMJ, Cherian L, Lamers CBHW, Goebell H. Feedback regulation of human pancreatic secretion: effects of protease inhibition on duodenal delivery and small intestinal transit of pancreatic enzymes. *Gastroenterology* 1990; 98: 1311-9.
- 23 Layer P, Go VLW, DiMagno EP. Fate of pancreatic enzymes during aboral small intestinal transit in humans. *Am J Physiol* 1986; 251: G475-80.
- 24 Goebell H, Förster S, Dirks E, Schaarschmidt K, Eigler FW. Crohn's disease: the clinical pattern of the disease in relation to localisation. A prospective analysis of 300 patients. *Med Clin* 1987; 82: 1-8.
- 25 Meyer JH, Elashoff J, Porter-Fink V, Dressman J, Amidon GL. Human postprandial emptying of 1-3 mm spheres. *Gastroenterology* 1988; 94: 1315-20.
- 26 Ewe K, Press AG, Bollen S, Schuhn J. Gastric emptying of indigestible tablets in relation to composition and time of ingestion of meals studied by metal detector. *Dig Dis Sci* 1991; 36: 146-52.
- 27 Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. *Gut* 1988; 29: 1035-41.
- 28 Mardini HAL, Lindsay DC, Deighton CM, Record CO. Effect of polymer coating on faecal recovery of ingested 5-aminosalicylic acid in patients with ulcerative colitis. *Gut* 1987; 28: 1084-9.
- 29 Bondesen S, Bronnum-Schön J, Pedersen V, Rafiolsadat Z, Honore-Hansen S, Huidberg EF. Absorption of 5-aminosalicylic acid from colon and rectum. *Br J Clin Pharmacol* 1988; 25: 269.
- 30 Hardy JG, Healey JNC, Reynolds JR. Evaluation of an enteric-coated delayed-release 5-aminosalicylic acid tablet in patients with inflammatory bowel disease. *Aliment Pharmacol Therap* 1987; 1: 273-80.
- 31 Norlander B, Gotthard R, Ström M. Pharmacokinetics of a 5-aminosalicylic enteric-coated tablet in patients with Crohn's disease or ulcerative colitis and in healthy volunteers. *Aliment Pharmacol Therap* 1990; 4: 497-505.
- 32 Norlander B, Gotthard R, Ström M. Pharmacokinetics of a 5-aminosalicylic acid enteric-coated tablet and suppository dosage form. *Aliment Pharmacol Therap* 1989; 3: 333-42.
- 33 Rao SSC, Read NW, Holdsworth CD. Gastrointestinal transit and stool output in the pathophysiology of diarrhea in ulcerative colitis (UC) [Abstract]. *Clin Sci* 1986; 72 (suppl 15): 41.
- 34 Rijk MCM, van Hogerzand RA, van Schaik A, van Tongeren JHM. Disposition of 5-aminosalicylic acid from 5-aminosalicylic acid delivering drugs during accelerated intestinal transit in healthy volunteers. *Scand J Gastroenterol* 1989; 24: 1179-85.
- 35 Laursen LS, Stokholm M, Bukhave K, Rask-Madsen J, Lauritsen K. Disposition of 5-aminosalicylic acid by olsalazine and three mesalazine preparations in patients with ulcerative colitis: comparison of intraluminal colonic concentrations, serum values, and urinary excretion. *Gut* 1990; 31: 1271-6.

- 36 Binder V, Halskov S, Hvidberg E, Kristensen E, Ruis P, Tongaard L, *et al.* A controlled study of 5-acetyl-aminosalicylic acid (5-Ac-ASA) as enema in ulcerative colitis. *Scand J Gastroenterol* 1981; **16**: 1122.
- 37 van Hogezaand RA, van Hees PAM, van Gorp JPWM, van Lier HJJ, Bakker JH, Wesseling P, *et al.* Double-blind comparison of 5-aminosalicylic acid and acetyl-5-aminosalicylic acid suppositories in patients with idiopathic proctitis. *Aliment Pharmacol Therap* 1988; **2**: 33–40.
- 38 Ireland A, Priddle JD, Jewell DP. A comparison of the uptake of 5-aminosalicylic acid (acetyl-mesalazine) and N-acetyl-aminosalicylic acid (Ac-ASA) into the isolated colonic epithelial cell. *Gastroenterology* 1987; **92**: 1447.
- 39 Ireland A, Priddle JD, Jewell DP. Acetylation of 5-aminosalicylic acid by human colonic epithelial cells. *Gastroenterology* 1986; **90**: 1471.
- 40 Fischer C, Maier K, Klotz U. Specific measurement of 5-aminosalicylic acid and its acetylated metabolite in human bile. *Br J Clin Pharmacol* 1983; **15**: 273–4.
- 41 Riley SA, Mani V, Goodman MJ, Herd ME, Dutt S, Turnberg LA. Comparison of delayed-release 5-aminosalicylic acid (5-ASA) and sulfasalazine as maintenance treatment for patients with ulcerative colitis. *Gastroenterology* 1988; **94**: 1383–9.
- 42 Rachmelewitz D. On behalf of an international study group. Coated 5-ASA versus sulphasalazine in the treatment of active ulcerative colitis: A randomised trial. *B Med J* 1989; **298**: 82–6.
- 43 Thomson ABR and the International Mesalazine Study Group. Coated oral 5-aminosalicylic acid versus placebo in maintaining remission of inactive Crohn's disease. *Aliment Pharmacol Therap* 1990; **4**: 55–64.