Mesalazine release from coated tablets: effect of dietary fibre

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Delayed-release mesalazine formulations rely on pH-dependent coat dissolution to ensure delivery of 5-aminosalicylic acid (5-ASA) to the colon. As dietary fibre acidifies the colonic lumen we have studied the effect of fibre supplementation in 10 patients with quiescent colitis. Greater intake of dietary fibre was associated with a decrease in stool pH and an increase in stool frequency and faecal mass. However, the 24 h faecal and urinary excretion of 5-ASA and *N*-acetyl-5-ASA was unchanged. The percentage of total faecal ASA excreted as *N*-acetyl-5-ASA correlated with whole-gut transit time, suggesting that prolonged transit may be disadvantageous to patients with colitis as *N*-acetyl-5-ASA appears to be inactive.

Keywords ulcerative colitis delayed-release mesalazine whole-gut transit time dietary fibre ispaghula husk

Introduction

Delayed-release mesalazine comprises a formulation of 5-ASA within an acrylic resin coat (Eudragit S). Coat dissolution is pH-dependent, occurring rapidly above pH 7. Radiological studies of barium-containing tablets show that 5-ASA release occurs in the distal ileum or in the proximal colon (Dew *et al.*, 1983). Acidification of the colonic lumen may, therefore, impair 5-ASA release from those tablets that reach the caecum intact. For this reason, lactulose, a laxative that acidifies the colonic lumen and lowers stool pH (Bown *et al.*, 1974), is not recommended for use with delayed-release mesalazine (Data Sheet, 1990).

As changes in dietary fibre also modify intra-colonic and stool pH we have studied the effects of dietary fibre manipulation on the kinetics of delayed-release mesalazine in patients with quiescent colitis.

Methods

Patients

Ten patients with quiescent colitis were studied, six female and four male, aged from 30 to 71 years. All were taking delayed-release mesalazine as sole maintenance treatment. Eight patients were maintained on 800 mg twice daily and two on 1200 mg twice daily. The study protocol was approved by Leigh Infirmary Ethics Committee and each subject gave written informed consent prior to study.

Protocol

Patients were studied over a 28-day period. From day 1 to 14, they consumed a low-fibre diet. From day 15 to 28, they changed to a high-fibre diet together with supplements of ispaghula husk 3.5 g twice daily (Fybogel, Reckitt and Colman, UK). Delayed-release mesalazine treatment was unchanged throughout.

On day 14 and day 28 patients were admitted to hospital. At 09.00 h and 21.00 h patients took their usual dose of delayed-release mesalazine (Asacol, SmithKline Beecham, UK). Blood, urine and stool samples were collected for 24 h. Stool pH was measured using a portable pH meter (Gallenkamp pH stick). Stools were then pooled, weighed, and homogenised with 500 ml methanol in a Colworth Stomacher. All samples were stored at -20°C prior to analysis. Whole-gut transit times were measured on completion of each 14 day study period using a single stool marker technique (Cummings & Wiggins, 1976).

Analytical methods

5-ASA and *N*-acetyl-5-ASA were measured by h.p.l.c. (Waters 6000A pump, Spectra Physics SP8700 automatic injector) with fluorometric detection (Waters 420AC; excitation wavelength 360 nm, emission wavelength 425 nm). After extraction into methanol and dilution with phosphate buffer/tetrabutylammonium hydroxide (1000:2), samples were separated on a 5 μm column (Beckman Ultrasphere, 4.5 mm $\times$ 250 mm) using an elution mixture of 0.1 M phosphate buffer (pH 7.4), methanol and tetrabutylammonium hydroxide (77.5 :

22.5 : 0.1) at a flow rate of 1.0 ml min⁻¹. Calibration curves were linear in the range 0 to 200 ng; detection limits were 5 ng ml⁻¹. Intra- and inter-assay coefficients of variation for 5-ASA and *N*-acetyl-5-ASA were 2.9% and 3.1%, respectively, and 4.3% and 4.0%, respectively, at 100 ng.

Recoveries of 5-ASA and *N*-acetyl-5-ASA added to plasma were 92.7 ± 4.1% and 93.4 ± 2.3%, respectively. There was no loss from urine and recoveries from faeces were 50.4 ± 3.5% and 63.1 ± 4.0%, respectively.

Results

The effects of dietary fibre manipulation on stool parameters and faecal and urinary drug excretion are shown in Table 1.

Changing from a low- to a high-fibre diet was associated with a decrease in stool pH, an increase in stool frequency and faecal weight but no significant change in whole gut transit time. Transit times varied widely between individuals but were correlated on days 14 and 28 ($r = 0.85$, $P < 0.01$). There were no significant correlations between stool pH and transit times. Changes in dietary fibre intake had no effect on either 24 h faecal or urinary drug recovery. Faecal drug recovery varied widely between individuals but was correlated on day 14 and 28 (5-ASA: $r = 0.83$, $P < 0.01$; *N*-acetyl-5-ASA: $r = 0.64$, $P < 0.005$). There were no significant correlations between total faecal drug recovery and either stool pH or whole-gut transit time.

Although faecal drug recovery appeared to be unrelated to whole-gut transit time, the percentage of drug excreted in the stools as *N*-acetyl-5-ASA correlated with transit during periods of both low- and high-fibre intake ($r = 0.77$, $P < 0.01$ and $r = 0.69$, $P < 0.05$ respectively)

Figure 1 The percentage of drug excreted in the stool as *N*-acetyl-5-ASA correlated with whole-gut transit time during periods of both low-fibre intake (day 14, ○) and high-fibre intake (day 28, ●), (day 14, $r = 0.77$, $P < 0.01$; day 28 $r = 0.69$, $P < 0.05$).

(Figure 1). A similar correlation was found between urinary *N*-acetyl-5-ASA excretion and transit time on day 28 ($r = 0.89$, $P < 0.01$).

Plasma concentrations of 5-ASA and *N*-acetyl 5-ASA varied markedly on both study days and were unrelated to dietary fibre intake.

Discussion

It is well recognised that changes in dietary fibre intake modify stool pH (Hillman *et al.*, 1983). Furthermore, Evans *et al.* (1988), using an ingested pH-sensitive radio-telemetry capsule, found that ispaghula supplements reduced both right- and left-sided intra-colonic pH (right colon from pH 6.5 to 5.8; left colon from pH 7.3 to 6.6).

The results of the present study are consistent with these findings, but faecal and urinary excretion of

Table 1 Effects of dietary fibre manipulation on stool parameters and steady-state drug excretion

	Day 14 (Low-fibre)	Day 28 (High-fibre)	Significance
Stool pH	6.9 (6.7–7.6)	6.4 (5.1–7.3)	$P < 0.005$
Stool frequency (per day)	1 (0.5–4)	1 (1–5)	$P < 0.05$
Faecal weight (g 24 h)	165 (121–354)	235 (168–380)	$P < 0.01$
Whole gut transit time (h)	41 (24–72)	47 (29–66)	NS
Faecal 5-ASA excretion (mg 24 h ⁻¹)	275 (64–702)	197 (45–688)	NS
Faecal <i>N</i> -acetyl-5-ASA excretion (mg 24 h ⁻¹)	254 (22–434)	201 (28–324)	NS
Urinary 5-ASA excretion (mg 24 h ⁻¹)	36 (1–195)	34 (4–89)	NS
Urinary <i>N</i> -acetyl-5-ASA excretion (mg 24 h ⁻¹)	209 (53–492)	189 (151–457)	NS

All results expressed as medians with ranges in parentheses. Comparisons were made using Wilcoxin's signed rank test. Drug excretion values are not corrected for analytical recovery losses.

5-ASA and *N*-acetyl-5-ASA were unaffected by fibre supplementation. The magnitude of intracolonic acidification induced by dietary fibre therefore seems insufficient to impair the pH-dependent release of 5-ASA from delayed-release mesalazine. This is reassuring, as a high-fibre diet is often recommended to patients with quiescent colitis (Hawkins, 1983) and ispaghula supplements may be prescribed to a sub-group of patients with distal colitis who tend to constipation (Rao *et al.*, 1987).

Although we could find no relationship between total faecal drug excretion and whole-gut transit time, a clear correlation emerged between the percentage of faecal ASA excreted as *N*-acetyl-5-ASA and transit time. Whether this is related to faecal or mucosal acetylation is not yet clear. However, a prolonged transit time may be disadvantageous to patients with colitis as *N*-acetyl-5-ASA appears to be therapeutically inactive (van Hogezaand *et al.*, 1988).

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