COLONIC RELEASE OF 5-AMINO SALICYLIC ACID FROM AN ORAL PREPARATION IN ACTIVE ULCERATIVE COLITIS

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5-amino salicylic acid coated with acrylic based resin was given orally to eight patients with active ulcerative colitis. Abdominal X-rays confirmed that the preparation released its contents in the terminal ileum and proximal colon. Differences between individuals were marked; the plasma 'concentration-time profile' reflected variations in the time taken for tablets to reach the terminal ileum.

Keywords 5-amino salicylic acid colonic release ulcerative colitis

Introduction

5-amino salicylic acid (5ASA) is the active component of Salazopyrin and probably has a topical effect in ulcerative colitis (Azad-Kahn *et al.*, 1977). We have recently demonstrated that 5ASA coated with an acrylic based resin (Eudragit S) will release the contents in the colon of patients without intestinal disease (Dew *et al.*, 1982b) and is effective in maintaining clinical remission in patients with ulcerative colitis (Dew *et al.*, 1982a). Any enteric coated preparation may fail if the intestinal transit is rapid because of ulcerative colitis causing frequent stools. We have tested our preparation in patients with active colitis to examine the site of breakdown and have measured the serum levels of the drug and its metabolites.

Methods

We studied eight patients, five female and three male, with a mean age of 51 years (range 21–67), all of whom had active ulcerative colitis and passed between 6 to 17 stools/48 h, mean 11. Six had total colitis, one left sided colitis and one proctitis only. Tablets of 5ASA each containing 400 mg 5ASA and 100 mg barium sulphate were coated with acrylic based resin (Eudragit S from Rohm Pharma GMBH) to a thickness of 80 μm . Each patient took eight of these tablets (3.2 g of 5ASA) in the morning after a normal breakfast at 08.00 h. Blood samples were taken initially and after 3, 6, 9, 12, and 24 h. Abdominal radiographs were taken after 6 h in all patients and at 12 and 24 h if any tablets remained intact. Stools were collected for 48 h and were X-rayed to identify any tablets or tablet fragments.

5ASA and acetyl 5ASA were analysed by high pressure liquid chromatography h.p.l.c. using a modification of the method described by Shaw *et al.* (1980). The analysis was performed on a LiChrosorb 10 RP18 bonded silica reversed phase column (Merck). The mobile phase was acetonitrile—0.05 M potassium dihydrogen phosphate solution (15 : 85) pH 7.4 containing 0.1% tetrabutyl ammonium hydroxide. 5ASA and acetyl 5ASA were detected using a fluorescent spectrometer (excitation 360 nm, emission 425 nm). Serum was treated with an equal volume of acetonitrile to precipitate proteins and after centrifugation the supernatant was injected onto 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 assay measured levels of 5ASA to 0.1 $\mu\text{g/ml}$ and acetyl 5ASA to 0.25 $\mu\text{g/ml}$.

Results

Abdominal radiographs show that the rate of tablet transit was very variable in the eight patients; in three most of the tablets remained in the stomach, but intact at 12 h. After 6 h, of the 64 tablets given, 24 remained in the stomach still intact while 40 were either in the terminal ileum or right side of colon and only two of these were intact. At 12 h 20 tablets remained intact in the stomach. We could see speckled barium residue and partly disrupted tablets in the terminal ileum and right colon, but only four tablets remained intact at these sites. At 24 h none remained in the stomach and all tablets were fragmented leaving finely speckled barium throughout the colon in several

Figure 1 (a) Radiograph at 12 h on patient 1 with seven intact tablets in the stomach and one breaking in the ileum. (b) Radiograph at 24 h in patient 1 with no tablets remaining in the stomach.

Figure 2 Serum levels of acetyl 5ASA in eight patients with ulcerative colitis after ingestion of 3.2 g 5ASA in the form of eight acrylic coated tablets.

patients (Figure 1). X-rays of the stools collected over 48 h showed that in three patients there were one or two small tablet fragments in the stool but in none of the other patients were fragments visible.

Blood levels of 5ASA and acetyl 5ASA showed measurable levels in only one subject at the onset of the study (he had taken the preparation 24 h previously). The other patients had either no recordable or very low serum for the first 6 h where the tablets remained intact in the stomach (patients 1, 2 and 7); the levels subsequently rose by the 24 h sample correlating with X-ray appearance of tablet breakdown. Serum levels of acetyl 5ASA are shown in Figure 2. Serum 5ASA levels at 3 h were mean 1.5 µg/ml (range < 0.1–8.3), 6 h mean 2.3 µg/ml (range < 0.1–9.7), 9 h mean 0.4 µg/ml (range < 0.1–0.9), 12 h mean 0.2 µg/ml (range < 0.1–0.5) and 24 h mean 1.1 µg/ml (range < 0.1–5.1). Where there was radiological evidence that the tablets broke early in the right colon or distal ileum, there were correspondingly high serum levels in the 3, 6, and 9 h sample (patients 3, 4, 5, 6, and 8; Figure 2).

Discussion

The observations in our patients with colitis show that the tablets consistently break in the terminal ileum or colon. The study combining radiological and serum measurements shows that information from both sources is important and complementary. Those tablets which remained in the stomach for at least 12 h were still intact (patients 1, 2 and 7) and broken tablets or tablets in the process of breaking are seen only in the terminal ileum and right colon (Figure 1). The tablet transit time varied greatly and was not related to stool frequency. Our colonic delivery system is pH dependent and remains intact below pH 7. Intestinal pH rises above pH 7 in the terminal ileum and colon; consistent with these conditions our

preparation disintegrated at these sites even in patients with severe colitis and rapid bowel transit. The preparation offers a new potential for therapy in ulcerative colitis during periods of relapse and remission. This makes it possible to deliver orally ingested 5ASA or steroids to the diseased colon. Future developments to release drugs in the colon should be supported by radiological observations rather than serum levels alone.

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