J. Pharm. Pharmacol. 1985, 37: 757–758
Communicated March 18, 1985

Absorption of delayed-release prednisolone in ulcerative colitis and Crohn's disease

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The absorption and urinary excretion of [^{3}H]prednisolone after oral ingestion was examined using hard gelatin capsules with and without a coating of Eudragit-S which delayed release of the contents. In 6 patients with ulcerative colitis absorption was delayed until the preparation reached the colon but the total absorption was unchanged. In 6 patients with Crohn's disease and ileal strictures the preparation broke proximal to the stricture and absorption was delayed until this occurred (within 4–12 h). In 5 patients with Crohn's disease and intestinal resections the capsules broke unreliably.

We have previously described a drug delivery system which, following oral administration, releases its contents in the terminal ileum and colon (Dew et al 1982a). It is an effective means of administering 5-aminosalicylic acid to patients with ulcerative colitis (Dew et al 1982b, 1983). Prednisolone could also be given by this system which may improve its therapeutic action with fewer side effects. Patients with Crohn's disease may also benefit from topical release of prednisolone at the site of strictures. This study compares the absorption and urinary excretion of tritiated prednisolone after oral administration on two occasions to examine the effect of the delivery system in patients with ulcerative colitis and Crohn's disease.

Methods

Seventeen patients were studied. Six patients, with a mean age of 49 years (range 23–68), had ulcerative colitis, four with inactive and two with active disease; three had total and three left sided involvement. The remaining eleven patients had Crohn's disease. Five of them, with a mean age of 46 years (range 35–59), had undergone previous bowel resections (4 had a right hemi-colectomy and 1 a terminal ileal resection) and had inactive disease. The other six patients, with a mean age of 29 years (range 20–46), had terminal ileal strictures causing symptoms in three of them.

Each patient, on two separate occasions, was given six capsules containing a total of 5 μCi of tritiated prednisolone ([2,4,6,7-^{3}H]prednisolone, supplied by Amersham, in toluene–ethanol, 9 : 1 solution, spec. act. 75 Ci mmol^{-1}) in 5 mg prednisolone. The capsules were prepared by pipetting 0·08 ml of toluene–ethanol 9 : 1 solution containing 0·83 μCi activity into the lower half of each capsule. These were then placed in a laminar flow cabinet and a forced draft passed over them for 24 h. To the residual powder were added 0·83 mg of 'cold' prednisolone, 200 mg of barium sulphate, 20 mg of starch and 150 mg lactose to ensure dispersion once the coating was breached. The capsules were then sealed.

Uncoated capsules were given first and two weeks later capsules coated with an acrylic based resin (Eudragit S from Rohm Pharma GMBH) 80 μm in thickness. Each patient took the capsules after breakfast at 0900h. Urine samples were then collected at 0–4, 4–12, 12–24 and 24–48 h. Plain abdominal radiographs were obtained at 4, 12 and 24 h following administration of the coated capsules to observe breakdown and release of the contents. The radioactivity in urine samples was quantified by liquid scintillation counting using an LKB Rack Beta liquid scintillation counter. The amount of radioactivity in each capsule was also checked in five capsules from each of two batches.

The study was approved by the Hospital Ethical Committee and each patient gave informed verbal consent. There were no complications during the study.

Results

There was no significant difference in excretion of [^{3}H]prednisolone from the uncoated tablets between the three sets of patients.

In patients with ulcerative colitis the total percentage of the dose of tritiated prednisolone absorbed and excreted in the urine was similar with both the uncoated and the coated preparations (72 and 58%, respectively, $P > 0·05$, Fig. 1). However, maximum urinary excretion of the uncoated preparation was greater over the periods 0–4 and 4–12 h (both $P < 0·05$) whereas that of the coated preparation was greater between 12–24 h and 24–48 h (both $P < 0·05$). From radiological observations 4 h after ingestion, 21 of the 36 coated capsules remained intact and 15 had disrupted in the ileo-caecal region. At 12 h only 7 of the 21 remained intact in the colon, a further 13 had disrupted in the ileo-caecal region and 1 in the duodenum. At 24 h, 3 further capsules had disrupted in the ileo-caecal region (1 patient failed to have a 24 h film).

In patients with Crohn's disease who had ileal

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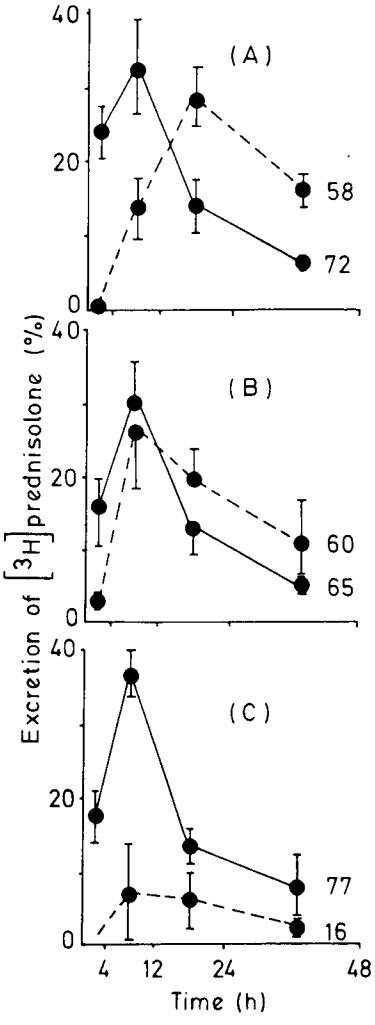

FIG. 1. Urinary excretion of [^{3}H]prednisolone after oral administration during the first 4, 4–12, 12–24 and 24–48 h. Each point represents the mean percentage excretion of the oral dose of [^{3}H]prednisolone (± s.e.m.) (a) in patients with ulcerative colitis (n = 6), (b) Crohn's disease with a small intestinal structure (n = 6), and (c) Crohn's disease after a resection (n = 5). Figures are the means of the total urinary excretion over 48 h. ——● prednisolone in hard gelatin capsules. - - - ● prednisolone capsules coated with Eudragit-S.

strictures, although the total amount of prednisolone excreted in the urine was similar with the uncoated and coated preparations (65 and 60% respectively, $P > 0{\cdot}05$), during the first 4 h less prednisolone was excreted with the coated preparation ($P < 0{\cdot}05$), similar amounts were excreted between 4–12 h and thereafter (Fig. 1). The radiological observations from these patients confirmed that capsules broke in the terminal ileum. At 4 h 12 of the 36 capsules remained intact and at 12 h all capsules had disrupted.

In patients with Crohn's disease who had intestinal resections, the absorption was low with the coated preparation (16% of the oral dose compared with 77% for the uncoated preparation, $P < 0{\cdot}05$) and significantly more of the uncoated preparation was absorbed and excreted in the first 12 h ($P < 0{\cdot}05$). Radiological observation showed that coated capsules broke unreliably. At 4 h all of them remained intact. At 12 h 20 of the 30 capsules remained intact and disruption occurred in the left colon (4) and transverse colon (6). After 24 h 17 of the total remained intact (1 patient failed to have a 24 h film).

The amount of radioactivity which was checked in 5 capsules from each of two batches was 100 ± 1% and 100 ± 2%.

Discussion

In this study the pattern of absorption and excretion of prednisolone from the uncoated preparation was similar in all three groups of patients; excretion occurred earlier than with the coated preparation, was maximal in the first 12 h, and was significantly greater than with the coated preparation at 0–4 h in all three groups and at 4–12 h except in the Crohn's group with strictures. Radiographs were unnecessary for this part of the study since hard gelatin dissolves quickly in the stomach.

In contrast, the maximal excretion of [^{3}H]prednisolone from the coated preparation in patients with ulcerative colitis was delayed to the period 12–24 h, and thereafter excretion from this preparation was significantly greater than from the uncoated preparation, suggesting delayed release. The site of breakdown, from radiographs, was the ileo-caecal region.

Similarly, in patients with Crohn's disease with a terminal ileal stricture, the coated preparation appeared to break at the site of stricture, and, although peak excretion occurred at 4–12 h and was not significantly different from that of the uncoated preparation, higher levels of excretion were found at 12–24 and 24–48 h suggesting delayed release.

This delayed release preparation of prednisolone may be of therapeutic value in patients with ulcerative colitis by producing a topical action in the proximal colon and reducing total absorption of the drug. Patients with Crohn's disease and strictures may also benefit from release of the preparation at the site of the stricture.

Patients who have had a terminal ileal resection for Crohn's disease are unlikely to benefit from the preparation as there was significantly less absorption from the coated preparation during the first 48 h.

REFERENCES

Dew, M. J., Hughes, P. J., Lee, M. G., Evans, B. K., Rhodes, J. (1982a) Br. J. Clin. Pharmacol. 14: 405–408

Dew, M. J., Hughes, P. J., Harries, A. D., Williams, G., Evans, B. K., Rhodes, J. (1982b) Br. Med. J. 285: 1012

Dew. M. J., Ryder, R. E. J., Evans, N., Evans, B. K., Rhodes, J. (1983) Br. J. Clin. Pharmacol. 16: 185–187