Colonic mucosal concentrations of prednisolone following oral administration of a novel formulation of prednisolone metasulphobenzoate (Predocol)

[1]Bell GD, [2]English J, [3]Spiers C, [4]Nylander D, [4]Hancock J, [5]Rowland RS

[1]Sunderland University Medical Sciences Faculty, [2]School of Biological Sciences, University of Surrey, [3]Flexpharm Ltd, Watford, Herts, [4]Department of Gastroenterology, Sunderland Royal Hospital, [5]RMR Systems Ltd, Kirton, Suffolk

Background

Prednisolone metasulphobenzoate (PMSB) is sparingly absorbed, but effective when administered topically, in distal UC [1]. A new oral formulation of PMSB (Predocol) has been developed in which the drug, contained in capsules coated with Eudragit L, is disseminated throughout the large bowel in controlled delivery pellets. Pilot studies suggest there is little systemic absorption of prednisolone from Predocol, and earlier patient studies using a similar formulation were promising [2].

Aims

To measure a) the mucosal concentrations of prednisolone in seven different anatomical locations along the colon following oral administration of Predocol, and b) to see if the pattern of release of the PMSB from the pH dependant Eudragit/controlled delivery pellet formulation along the colon was affected by altering gastric acidity with a PPI.

Methods

Ethical approval has been obtained to study a total of 38 patients with relatively asymptomatic Ulcerative Colitis of greater than 10 years duration who are due to come up for routine surveillance colonoscopy. To date (14th February 2000) we have studied 20 patients. In 10 patients, Predocol was administered in a dose equivalent to 20 mg of prednisolone base BD for 7 days (Predocol 40 group). In a further 7 UC patients, the dose administered was equivalent to 10mg of prednisolone BD for 7 days (Predocol 20 group). In addition, for purposes of comparison, we have studied 3 symptomatic UC patients receiving conventional once daily oral prednisolone in a dose of 20mg mane for at least 7 days prior to colonoscopy. The patients received standard bowel preparation including 2 doses of Picolax on the day prior to colonoscopy. The patients were requested to take the last dose of either Predocol or ordinary prednisolone at 7am on the morning of the surveillance colonoscopy. The examination was scheduled so that the colonic mucosal biopsies could be taken approximately 4-4.5 hours after the last dose of the drug.

All colonoscopies were conducted with the aid of magnetic endoscope imaging to confirm the exact anatomical site of the biopsies [3,4]. Two specimens were taken with standard endoscopy biopsy forceps from each of seven different sites around the colon i.e. 1) Caecum 2) Hepatic flexure 3) Mid Transverse colon 4) splenic flexure 5) descending colon 6) sigmoid colon and 7) Rectum. The saline-washed specimens were stored at minus 40 degrees centigrade for later measurement of tissue prednisolone levels using a radio-immunassay [5].

Results

Total colonoscopies were possible in all 20 patients. No side effects were reported by any of the 17 patients given Predocol. The individual and mean (SEM) mucosal concentration of prednisolone (ng/mg tissue) of the 10 patients in the Predocol 40 group are shown in Table 1 and Figure 1 respectively.

Patient	Caecum	HF	TC	SF	DC	SC	Rectum
1	0.85	1.11	1.56	1.87	3.03	2.29	0.43
2	1.30	1.22	2.71	3.52	5.10	3.76	0.45
3	1.00	1.63	2.10	3.12	4.74	3.57	0.57
4	0.59	0.51	1.31	3.44	4.48	2.46	0.60
5	0.65	0.67	1.41	2.91	3.71	2.58	0.47
6	0.54	1.65	2.07	3.65	3.94	5.88	0.49
7	0.69	0.79	1.96	3.24	4.45	2.7	0.73
8	0.83	1.24	2.12	3.63	5.47	3.13	0.59
9	0.54	0.49	1.72	3.01	5.64	4.15	0.59
10	0.56	0.76	2.08	2.94	4.41	0.94	0.62
Mean	0.78	1.03	1.88	3.15	4.51	3.39	0.55
SD	0.25	0.43	0.41	0.52	0.80	1.32	0.09
SEM	0.08	0.14	0.13	0.17	0.25	0.42	0.03
Max	1.30	1.65	2.71	3.65	5.64	5.88	0.73
Min	0.54	0.49	1.31	1.87	3.03	0.94	0.43

Table 1 - Tissue mucosal concentrations of prednisolone found in the 10 individual UC patients colonoscoped approximately 4 hours after the last dose of Predocol. All received a seven day course of BD predocol equivalent to 40mg of prednisolone per day

As can be seen, the results are remarkably consistent. The relatively low mucosal concentrations of prednisolone found in the caecum gave way to progressively higher levels as one moved across the large intestine from right to left with peak concentrations being found in the descending colon. The levels of prednisolone in the mucosal samples from the sigmoid colon were significantly lower than the descending colon while concentrations in the rectum were similar from those in the caecum.

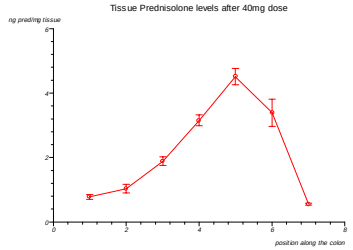

Figure 1 - Mean (SEM) mucosal concentrations of prednisolone (ng/mg tissue) taken at colonoscopy approximately 4 hours after the last dose of a 7 day course of Predocol in a dose equivalent to 40mg of prednisolone base. On the horizontal axis are shown the 7 sites along the length of the colon that biopsies were taken. Sites 1-7 represent the caecum, hepatic flexure, mid transverse colon, splenic flexure, descending colon, sigmoid colon and rectum respectively. Peak concentrations occurred in the descending colon

At all sites along the colon except the rectum, the mucosal concentrations of prednisolone were significantly lower in the Predocol 20 group when compared with the Predocol 40 patients – see Figure 2.

The colonic mucosal concentrations found in the 3 patients (NG, RS, and TR) given 20mg of normal prednisolone are shown in Figure 3 along with the mean(SEM) results for the 7 patients studied to date in the Predocol 20 group.

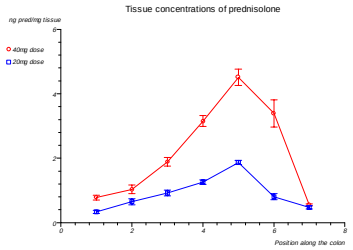

Figure 2 - Mean (SEM) mucosal concentrations of prednisolone (ng/mg tissue) taken at colonoscopy approximately 4 hours after the last dose of a 7 day course of Predocol in a dose equivalent to either 40mg of prednisolone base (red data) or 20mg of prednisolone (blue data). The differences between the mean prednisolone mucosal levels were statistically significant at all sites except the rectum

Conclusions

The magnetic endoscope imaging system [3,4] played a vital role in ensuring that all samples were taken from the correct anatomical segment of the colon. The present results confirm that Predocol capsules delivers high concentrations of PMBS to the left half of the colon in a consistent manner.

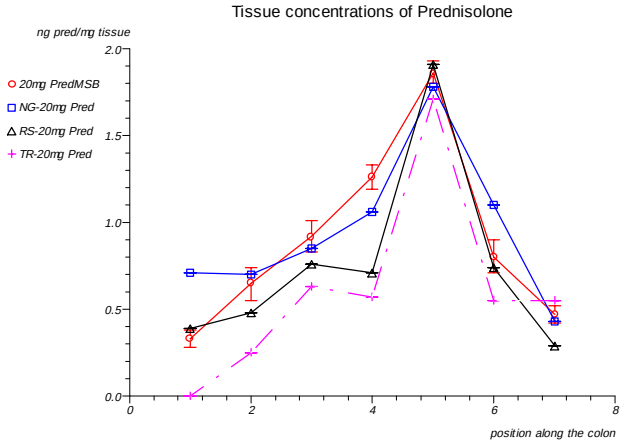

Figure 3 - Mean (SEM) mucosal concentrations of prednisolone (ng/mg tissue) taken at colonoscopy approximately 4 hours after the last dose of a 7 day course of Predocol in a dose equivalent 20mg of prednisolone (orange data points). For comparison the individual data points for three UC patients (NG, RS, and TR) colonoscoped approximately 4 hours after their last dose of 20 mg of prednisolone are shown

The colonic tissue mucosal concentrations of exogenous steroid in the Predocol 20 group are similar to those achieved with 20mg of normal oral prednisolone but without the systemic side effects. Predictably significantly higher concentrations were achieved in the Predocol 40 group. Studies currently in progress will look at both Predocol 60 as well as Predocol 40 plus Lansoprazole to see if even higher colonic mucosal prednisolone levels can be achieved in the right side of the colons of UC patients. A clinical trial evaluating the use of Predocol both for treating acute exacerbations of UC as well as maintaining remission of the disease is due to start in the near future (Dr S Wilkinson – personal communication).

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