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Oral formulation of budesonide for IBD

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SUMMARY

The oral formulation of budesonide for the treatment of inflammatory bowel disease was developed as a continuation of the development of budesonide enema for the treatment of distal ulcerative colitis. An oral formulation of budesonide has been designed with an acid-resistant coating to prevent release in the stomach. This formulation, budesonide CIR (controlled ileal release) capsule, was designed for the treatment of ileocaecal Crohn's disease. Pharmacokinetic studies have shown that the majority of budesonide CIR is absorbed in the terminal ileum and caecum, regardless of the food regimen. The tissue affinity of budesonide for the bowel mucosa has not yet been studied. Clinical trials presently suggest that budesonide CIR is as efficacious as oral prednisolone and causes fewer side effects and less adrenal gland suppression. It remains to be established whether this oral formulation of budesonide will be advantageous in the long-term treatment of active ileocaecal Crohn's disease.

INTRODUCTION

The anti-inflammatory effect of glucocorticosteroids (GCS) in inflammatory bowel disease (IBD), particularly in moderate and severe disease, is unsurpassed by any other type of drug. The clinical response is substantial and usually rapid (within days). Unfortunately, long-term treatment with prednisolone doses of greater than 7.5–10 mg/daily is precluded by the risk of hazardous complications such as osteoporosis, diabetes mellitus and hypertension. Systemic side effects are not uncommon, and may be troublesome, even during short-term treatment. If these systemic problems could be overcome or markedly reduced, GCS may become a more attractive option both for short- and long-term treatment of IBD.

The topically-acting steroid, budesonide, given as an enema, has been proven to be beneficial in mild to moderately active distal ulcerative colitis (UC) and proctitis and causes no, or only limited, depression of endogenous plasma cortisol levels[1,2]. Furthermore, corticosteroid-related side effects associated with treatment with budesonide enema have been rare and mild[1,2]. The enema preparation however, is not suitable for patients with extensive IBD, ie. total UC or Crohn's disease (CD) in the small bowel and/or proximal colon, because the active drug will not spread proximally beyond the splenic flexure. Budesonide, given as a plain tablet, is rapidly and completely absorbed in the proximal small bowel and is extensively metabolised in the liver, *via* the cytochrome-P_{450} 3A system.

involving the small bowel and proximal and transverse colon, provided that it is delivered to the affected bowel segment(s) and at a sufficient dose. Since the intestinal blood flow is predominantly drained *via* the portal vein, the amount of budesonide reaching the systemic circulation would be low due to the high first-pass metabolism in the liver.

DEVELOPMENT OF AN ORAL FORMULATION OF BUDESONIDE

Budesonide was initially developed for use in the airways, but in 1986, an oral formulation for the treatment of extensive IBD was produced. The development of such a formulation took place in parallel with the work on the budesonide enema for the treatment of distal UC. The primary target for the oral formulation was CD, localised to the terminal ileum and proximal colon. The only efficacious treatment for this disease hitherto available, had been either surgery (ie. resection of the diseased bowel segment) or treatment with moderate to high doses of conventional GCS. The topically-acting steroid, budesonide, appeared to offer potential for a better efficacy *versus* side effect ratio.

A primary aim of the oral formulation of budesonide was to deliver most of the active drug to the site of inflammation. The oral formulation of budesonide is therefore acid-resistant to prevent release in the stomach and release should not begin until the formulation had passed into the small bowel. For ileocaecal CD, the active drug ideally should be released in the terminal ileum and the proximal third of the colon.

The gastric emptying of different dosage formulations is variable and dependent upon the type of formulation itself and the type of meal taken at the time of dosing. Heavy meals, high in fat content, increase the time of gastric emptying. Tablets may remain in the stomach for a substantial period of time, ie. several hours, whereas small pellets empty in a more rapid and regular fashion and are not greatly affected by the digestive state of the individual[4]. Pellets also spread into the small intestine. To prevent the release of the active drug in the stomach, pellets are covered with an acid-resistant layer called an enteric coating.

In contrast to gastric emptying, small bowel transit time appears to be constant and independent of the dosage or the calorific content of the concomitant meal[4]. The average small bowel transit time is between 3–4 hours (range: 2–5 hours) for solutions, pellets or single units[5]. The transit time through the small bowel appears to be unchanged following ileocolonic resection[6]. In patients with active CD of the small bowel or with terminal ileal resection, no differences in gastric emptying or small bowel transit time compared with normal controls were detected in a scintigraphic study using ^{111}Indium[7]. It appears that the small bowel transit time of patients with CD confined to the ileocolonic region, with or without previous ileocaecal resection, averages 3.5 hours.

An oral formulation of budesonide destined for use in the treatment of ileocaecal CD was designed to release the main proportion of budesonide approximately three hours after stomach emptying. This formulation consisted of sustained-release pellets with an enteric coating which were called budesonide CIR (controlled ileal release).

COMPOSITION OF BUDESONIDE CIR PELLETS

The CIR pellets are about 1 mm in size and consist of a sugar core over which budesonide and an insoluble polymer is sprayed in a fluid bed dryer. The insoluble polymer serves as rate-control for the release of budesonide. A 10–20 micron thick enteric coating (Eudragit

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