Potential of Loperamide Oxide in the Reduction of Ileostomy and Colostomy Output

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Summary

The effects of a single oral dose of loperamide oxide on stoma output were evaluated in an open trial that included 22 patients - 4 with a colostomy and 18 with an ileostomy, in whom daily stoma output was usually more than 500g. Antidiarrhoeal therapy was stopped from days 2 to 7, and from days 5 to 8 a standardised high-fibre diet was given. Stoma effluent was collected for 24 hours on day 7. On day 8, patients took one dose of loperamide oxide 6mg. In 20 of the 22 patients, stoma output was reduced by 13 to 75% after administration of loperamide oxide. The mean output was reduced by 45% (p = 0.0001). There were no adverse experiences associated with administration of loperamide oxide. The majority of drug recovered in stoma effluent was loperamide, suggesting extensive conversion of loperamide oxide to loperamide. These preliminary findings suggest that a single 6mg dose of loperamide oxide is effective in reducing stoma output in patients with an ileostomy or colostomy.

After intestinal resection surgery, several factors may contribute to water malabsorption and the production of diarrhoea. These factors include loss of absorptive surface area, site of resection, length and functional status of remaining bowel, and bacterial overgrowth. Thus, patients with an ileostomy are more sensitive to diarrhoeal diseases.

Many patients with an ileostomy will at some time complain of an excessive fluid effluent. Ritchie[1] reported that 3% of ileostomy patients followed up over a 12-year period required hospital admission for nonobstructive, noninfective ileostomy diarrhoea. While this type of diarrhoea may be attributable to, for instance, recurrent Crohn’s disease or lactose intolerance, in many cases the cause is not known and symptomatic treatment is all that can be given. Loperamide has been shown to be effective in decreasing water and electrolyte losses in ileostomy patients with diarrhoea.[2,3]

Loperamide oxide is a site-specific prodrug of loperamide targeted more towards the intestinal mucosa than the intestinal muscle layers.[4] It is
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...void of anti diarrhoeal properties itself, but activity is manifested after its gradual reduction to loperamide by anaerobic bacteria, which are scarce in the proximal small bowel but occur with increasing density from the mid small bowel to the caecum. Loperamide oxide effectively acts as a chemically designed sustained-release form of loperamide, the end result being a more even exposure of a greater length of the small and large bowel to active drug. The conditions for absorption are less favourable in the distal as compared with the proximal small bowel, and so plasma levels of loperamide after oral administration of equal doses are 2-fold lower with loperamide oxide than with loperamide.[5,6] Loperamide oxide has been shown to be effective in the treatment of acute diarrhoea in adults at doses of 1 and 2mg.[7,8]

It might be expected that the reduction of loperamide oxide in patients with an ileostomy would be less complete than in normal subjects, depending upon the length of ileum that has been resected. Conversely, one would expect patients with a colostomy to have retained their full potential to reduce loperamide oxide to loperamide. In the study described here, a preliminary evaluation was made of the effect of loperamide oxide on stoma output in patients with a stoma who required anti diarrhoeal treatment. The conversion of loperamide oxide to loperamide was also determined.

**Materials and Methods**

**Patient Selection**

Ambulatory patients who were 18 years or older, who had undergone an ostomy procedure more than 6 weeks before and who had an average ostomy output of greater than 500g per 24 hours, in the absence of antidiarrhoeal treatment, were eligible for the study.

Patients were excluded if they showed signs and symptoms of toxic megacolon or infectious diarrhoea, if they were receiving cytotoxic chemotherapy, if they had significant cardiovascular, renal or hepatic impairment, or if they had significant laboratory screen abnormalities at selection.

Patients were also excluded if they were unwilling to discontinue current antidiarrhoeal treatment or if they were known to be hypersensitive to loperamide.

All subjects provided written informed consent. The protocol was reviewed and approved by the ethics committees of the University of Cape Town Medical School and the Medicines Control Council of South Africa.

**Study Design**

At the selection visit, patients were instructed to discontinue antidiarrhoeal treatment for 6 days. On day 5, at the second visit, patients were prescribed a standard high-fibre diet with foods specified for breakfast, lunch, tea and supper for days 6 through to 8. Stoma effluent was collected on day 7 (i.e. for 24 hours preceding ingestion of loperamide oxide). On day 8, patients took an open dose of 6mg of loperamide oxide (6 tablets of 1mg).

Concomitant use of antidiarrhoeals, including codeine-containing analgesics and anticholinergics, was forbidden. Ostomy output was collected at various time intervals for 24 hours after drug intake while the patients remained in hospital.

Patients kept a diary on days 7 and 8 in which the date and time as well as the weight of output were recorded.

Loperamide and loperamide oxide concentrations were determined in blood samples taken at 0, 0.25, 0.5, 1, 2, 4, 5, 6, 7, 8, 10 and 24 hours after drug administration. Levels were assayed in stoma effluent samples taken at 24 hours predose and in samples of effluent collected at various time intervals after drug administration up to 24 hours for the first 15 subjects and up to 10 hours for the remaining subjects. Separate and specific validated radioimmunoassays for loperamide and loperamide oxide were used.

Stoma effluent samples were extracted using methanol. The limits of detection in plasma were 0.2 ng/ml for loperamide oxide and 0.1 or 0.2 ng/ml (1 and 2ml plasma samples, respectively) for loperamide. For stoma effluent, the limits of detec-