Loperamide for treatment of acute diarrhoea in infants and young children

A double-blind placebo-controlled trial

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High-dose loperamide reduces stool output and shortens the duration of diarrhoea in infants receiving intravenous fluids for rehydration, but may cause potentially harmful side-effects in a small number of patients. This double-blind placebo-controlled study was undertaken to assess whether loperamide would shorten the hospital stay of dehydrated children in a rehydration unit. Ninety-one patients with acute dehydrating diarrhoea received loperamide and 94 received placebo. The groups were clinically indistinguishable on admission to hospital. There was no difference between groups for the duration of rehydration or the number of treatment failures. The use of loperamide is not recommended in the treatment of infants and young children with acute diarrhoea.

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Loperamide in higher than recommended doses reduces stool output and duration of acute diarrhoea in infants receiving intravenous fluids for rehydration.[1] Although there are concerns about the safety of loperamide when given to children,[2-4] particularly those less than 3 months of age,[1] it is a potentially useful agent in developing countries where large numbers of children require admission to rehydration units for treatment of dehydration due to diarrhoeal disease. During the seasonal summer peaks of incidence, these units become seriously overcrowded and any treatment modality that can effectively and safely shorten the time patients have to be kept in the unit would be of benefit.

This study was designed to assess the role of high-dose loperamide in the management of infants and young children with acute diarrhoea associated with mild-to-moderate dehydration. All were rehydrated with enterally administered glucose electrolyte solutions. The effect of loperamide on the duration of admission to the rehydration unit was compared with that of placebo given to a similar group of patients in a double-blind fashion.

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Patients and methods

Patients between 3 and 18 months of age requiring admission to hospital for treatment of acute dehydrating diarrhoeal disease were assessed. Those who were clinically shocked, had an ileus, required antibiotics for other systemic illness (e.g. pneumonia, septicaemia), had dysentery (blood and pus in their stools) or features of kwashiorkor or marasmus were excluded. Informed consent for inclusion in the trial was obtained from the parent or legal guardian. The study was approved by the Ethical Review Committee of the University of Cape Town.

The patients were weighed on admission and at least twice daily thereafter until discharge. Serum acid base status, electrolyte and blood urea nitrogen values were determined on entry into the study and thereafter when clinically indicated. The first stool sample passed after admission was tested for rotavirus and cultured for *Salmonella, Shigella* and *Campylobacter.* Duration of diarrhoea prior to initiation of treatment was recorded, as was the exact time of admission to, and discharge from, the hospital.

Fluid therapy was the same in all cases. Milk feeds were initially withheld and rehydration commenced with continuous nasogastric tube infusion of a glucose electrolyte solution containing Na^+ 64 mmol/l, Cl^- 54 mmol/l, K^+ 20 mmol/l, HCO_3^- 30 mmol/l and glucose 111 mmol/l. The volume of fluid administered during the first 24 hours was that calculated to correct the clinical degree of dehydration (i.e. 50 ml/kg if 5% and 100 ml/kg if 10% dehydrated), plus the amount needed to provide a maintenance volume of 150 ml/kg/day. In children over 12 months the maintenance volume was reduced to 100 ml/kg/day. Patients were reassessed at 4-hourly intervals until fully rehydrated. On each occasion fluid requirements were recalculated based on the clinical signs of dehydration and change in body weight since admission. Provided the patient had improved clinically, full-strength formula milk feeds were reintroduced 6 - 12 hours after admission. The volume of milk given was calculated to provide 100 - 150 ml/kg/day in 8 equally divided amounts depending on age. With the introduction of formula feeds, the volume of glucose electrolyte solution was adjusted accordingly to replace the ongoing abnormal losses in the stools and maintain hydration.

On admission patients were assigned to receive either loperamide or placebo in a double-blind fashion; sequentially numbered bottles were prepared by the manufacturer (Janssen Pharmaceutica). A sealed copy of the code for the numbered bottles was kept by a hospital administrator who was not directly involved in the investigation. In the event of a possible adverse drug reaction to loperamide, the administrator would reveal the contents of only that particular patient's numbered bottle to the investigators. The amount of medication given was designed to provide 0,8 ml/kg/day of loperamide. This was administered in 3 equally divided doses at 8-hourly intervals to a maximum of 6 doses. The infants were deemed fit for discharge not when diarrhoea had ceased but as soon as they were clinically hydrated, were taking oral feeds satisfactorily and were able to maintain their rehydrated body weight without needing additional glucose electrolyte

solution. They were then followed on an outpatient basis to check continuing improvement. If they were discharged before all 6 doses of medication had been administered, the drug was discontinued. Treatment was considered to have failed when children required glucose electrolyte solution to maintain hydration for more than 72 hours or if they developed severe persistent vomiting or an ileus. Thereafter, such patients were managed according to the usual protocol used at Red Cross Children's Hospital.[5]

The actual percentage dehydration on admission was determined in retrospect from the difference between the admission and fully rehydrated weights. The nutritional status of each patient was assessed by expression of the rehydrated weight as a percentage of expected weight-for-age, as per the NCHS centiles. The number of treatment failures in each group was recorded, and the duration of hospitalisation for those who responded to treatment was calculated from the admission and discharge times.

The trial was terminated after 200 patients had been recruited. Thereafter the treatment code was broken and the patients were assigned either to the loperamide or placebo group for comparison. The groups were compared in respect of stool pathogens, age, percentage expected weight-for-age, duration of diarrhoea prior to admission, duration of hospitalisation for those who responded to treatment, the number of doses of medication administered before discharge and the number of treatment failures. The Mann-Whitney U test was used in all comparisons.

Results

Fifteen patients were not included in the final analysis because of incomplete data collection ($N = 5$), incorrect medication dose given ($N = 5$), development of clinically suspected septicaemia ($N = 4$) and febrile seizures ($N = 1$). Of the 185 who completed the study, 91 received loperamide and 94 received placebo. There was no difference between the two groups with regard to stool pathogens. In approximately 50% no pathogen was identified, and in both groups about 25% had rotavirus, 15% had *Campylobacter* and 10% had *Salmonella.* The medians and ranges for age, percentage expected weight for age, duration of diarrhoea prior to admission, calculated percentage dehydration on admission, duration of hospitalisation and number of medication doses administered for both groups are shown in Table I. There were no significant differences between the groups in respect of any of these parameters. Twelve patients in the loperamide group and 10 in the placebo group failed treatment and still required additional fluids to maintain hydration after 72 hours in hospital. Persistent vomiting or ileus did not occur in any patient. Those who failed treatment did not differ from others within their respective groups with regard to age, percentage expected weight for age, duration of diarrhoea prior to admission and calculated percentage dehydration.

Table I. Medians (ranges) of the clinical parameters and duration of hospital stay for patients receiving loperamide or placebo

	Loperamide ($N = 91$)	Placebo ($N = 94$)
Age (months)	8,25 (3 - 18)	7,38 (3 - 18)
Expected weight for age (%)	89 (62 - 150)	89 (62 - 122)
Duration of diarrhoea prior to admission (days)	2 (1 - 7)	2 (1 - 21)
Calculated dehydration (%) on admission	5,7 (0 - 13)	5,5 (4 - 14)
Duration of hospital stay (hrs) for non-failures of treatment	34 (14 - 72)	36 (16 - 72)
Treatment failures (%)	13	10
No. of medication doses given	4 (1 - 6)	4 (1 - 8)

$P > 0,05$ for all comparisons.

Discussion

Acute diarrhoea is usually a self-limiting illness and the use of antidiarrhoeal agents in paediatric practice is controversial. Some have never been shown to be effective while others have unacceptable side-effects.[6-10] Loperamide is an antidiarrhoeal drug that is said to have antisecretory action on the gut and to be relatively free of side-effects.[11-13] Studies using the recommended doses have failed to show any clear benefit of loperamide over placebo,[14,15] but others using much higher doses claimed it was effective for treating both acute and chronic diarrhoea in children[16-18] and that it affected the overall recovery rate beneficially. Recently we demonstrated that loperamide in a dose of 0,8 mg/kg/day (i.e. four times the recommended dose) significantly decreased stool output and duration of diarrhoea in infants with acute diarrhoea who received intravenous fluids for rehydration.[1] The drug may have been the cause of side-effects in a small number of patients, particularly in very young infants. For this reason we cautioned against the indiscriminate use of loperamide and recommended that it be avoided in those with mild diarrhoea who do not need hospitalisation for treatment of dehydration, and in very young infants.

The demonstrated effect of loperamide on stool volume of intravenously rehydrated patients led us to question whether the drug would be a clinically useful adjunct to fluid therapy if used under supervision in a hospital rehydration unit. By decreasing stool output, infants and children might require less additional fluid and a shorter stay in the unit. This in turn would greatly alleviate the problem of overcrowding during the peak of the diarrhoea season.

The sole criterion used in this study was duration of stay in the rehydration unit. Standard procedure is that patients are discharged from the unit once they can be satisfactorily and safely treated as outpatients, i.e. are clinically hydrated, taking oral feeds satisfactorily and are able to maintain their rehydrated body weight without needing additional glucose electrolyte solution. Most still have diarrhoea. Patients receiving loperamide were clinically indistinguishable from

those receiving placebo and the double-blind nature of the trial ensured there was no bias towards one group in decisions about individual patients' discharge. The mean duration of stay for the two groups was almost identical and the majority of children were discharged in less than 72 hours. Treatment failure occured in 13% of the loperamide group and 10% of the placebo group, figures similar to those reported elsewhere for delayed recovery from acute diarrhoea in infants.[19,20] No beneficial effect in shortening of the stay or reduction of numbers of those requiring prolonged treatment in the rehydration unit was noted.

It is not possible to compare the results of this with our previous study[1] as completely different end-points were used as criteria of efficacy of loperamide. No adverse effects were noted in any patient receiving loperamide during this study, but infants under 3 months of age were excluded. It was in this age group that a temporal relationship of drowsiness and loperamide administration was noted in the previous study.[1] However, as no practical beneficial effect could be demonstrated at a unit for the mass rehydration of infants dehydrated due to diarrhoeal disease, and given our and others' previous experience[1-3] of potentially dangerous side-effects, the use of loperamide is not recommended.

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