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ORIGINAL ARTICLE

Macrogol 3350 plus electrolytes for chronic constipation in children: A single-centre, open-label study

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Aim: A Macrogol 3350-based, iso-osmotic laxative has become available for the treatment of chronic constipation in adults. This open-label, non-randomised study aimed to evaluate the safety and efficacy of this preparation in the treatment of chronic constipation in children.

Methods: Seventy-eight children, aged 2–11 years, with chronic constipation for greater than 3 months were enrolled. All children received Macrogol 3350 plus electrolytes for 12 weeks. The primary efficacy variable was the number of spontaneous defaecations per week. Secondary efficacy variables were faecal form, abdominal pain, rectal bleeding, pain on defaecation, straining, soiling, amount of stool, stool withholding and assessments of efficacy by the investigators and parents. Safety and compliance were also assessed.

Results: The mean number of spontaneous defaecations per week increased from 1.4 ± 0.55 (SD) at baseline to 6.8 ± 3.45 after 14 days, and 7.1 ± 3.45 at 12 weeks ($P < 0.001$). Similar improvements were found in the secondary efficacy variables. There was a significant reduction in reported abdominal pain from 53 (69%) children at baseline to 3 (4%) at the final visit ($P < 0.0001$). Similarly, 61 (79%) children had pain on defaecation at baseline, compared with 7 (9%) at the final visit ($P < 0.0001$). Treatment was well tolerated. Of 318 adverse events, 262 (82%) were considered mild, and 241 (76%) were deemed unrelated to treatment. Only 3 (4%) children were withdrawn because of poor compliance.

Conclusions: Macrogol 3350 plus electrolytes is a safe and effective treatment for constipation in children aged 2–11 years.

Key words: child; compliance; constipation; efficacy; polyethylene glycol; safety.

Constipation in children is a common problem that can become chronic if inadequately managed.[1] Five per cent of British children aged 4–11 years are constipated for more than 6 months.[2] This condition is one of the top 10 reasons for a general paediatric outpatient consultation and accounts for a quarter of all referrals to paediatric gastroenterologists.[3] The incidence appears to be increasing, possibly because of changes in diet, reduced fluid intake and lack of exercise.[4]

Key Points

1 The successful management of constipation involves dietary and behavioural interventions, together with long-term laxative treatment.
2 Macrogol 3350-based solutions are a new class of biologically inert laxatives which have been shown to be safe and well tolerated in children.
3 Macrogol 3350 plus electrolytes (Movicol) produced significant improvements in stool frequency and associated symptoms in children with severe constipation.

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The successful management of chronic constipation involves several aspects, including an increase in dietary fibre and fluid intake, the introduction of regular toilet sits after the main meals, and long-term laxative treatment. Laxatives usually need to be continued for several months, at adequate doses to induce and maintain soft stools.[5] Early withdrawal of laxatives is often associated with a relapse in constipation.[6]

Macrogol 3350-based solutions are a relatively new class of laxative, based on a biologically inert polymer with no pharmacological activity. Macrogol 3350 is not absorbed from the gastrointestinal tract and is not metabolised in the body.[7] In solution, macrogol 3350 binds or sequesters water molecules and increases the faecal water content.[8,9] It has a predictable linear dose–response relationship, which means that it is effective in high doses for faecal impaction, and in low doses for constipation.[10]

Macrogol 3350 plus electrolyte preparations have been used successfully in the treatment of severe constipation in adults.[11,12] In children, they appear attractive because of their inert nature. In addition, their balanced electrolyte content implies a reduced risk of adverse effects after long-term or high-dose use. Macrogol 3350 has therefore been investigated in children for lavage of the gastrointestinal tract before colonoscopy,[13,14] as well as for the treatment of faecal impaction[15] or chronic constipation in children, either with or without faecal incontinence.[16]

The aim of the present trial was to assess the safety and efficacy of a Macrogol 3350-based, electrolyte containing preparation in the treatment of chronic constipation in children.

Methods

Patients

Children aged 24 months to 11 years with chronic constipation for at least 6 months were eligible for participation in this study. Chronic constipation was defined as fewer than three complete bowel movements per week over the previous 14 days, in association with either straining or passage of hard stools in at least a quarter of bowel movements. The existing constipation was either untreated or inadequately treated by laxatives.

Children were excluded if they had been treated for faecal impaction with bowel washouts within the previous 2 months, or if they had a past history of intestinal perforation or obstruction, Hirschsprung's disease, paralytic ileus, toxic megacolon, severe inflammation of the intestinal tract, urinary tract infections, uncontrolled renal, hepatic or cardiac diseases, endocrine disorders, or any other severe unstable coexisting disease within the previous 30 days.

Study design

This open-label, non-comparative, non-randomised study was conducted at the Royal Children's Hospital, Melbourne, Australia, between August 2001 and January 2003. The study was approved by the hospital's Ethics in Human Research Committee and conducted according to the Declaration of Helsinki. Written, informed consent was obtained from the parents or guardians of each child.

All participants were assigned to receive the investigational product Macrogol 3350 plus electrolytes (Movicol, Norgine Ltd, Uxbridge, UK) for 12 weeks. Macrogol 3350 plus electrolytes was provided as a powder in sachets containing 6.563 g Macrogol 3350, 175.4 mg sodium chloride, 89.3 mg sodium bicarbonate and 23.3 mg potassium chloride. The contents of each sachet, which also contained acesulfame and lime and lemon flavouring, were dissolved in 62.5 mL of water, providing the following concentrations of electrolyte ions: sodium 65 mmol/L, chloride 53 mmol/L, potassium 5.4 mmol/L and bicarbonate 17 mmol/L.

Children aged 2–6 years received one sachet daily on days 1 and 2, one sachet twice daily on days 3 and 4, and one sachet three times daily on day 5; children aged 7–11 years received one sachet twice daily on days 1 and 2, and two sachets twice daily on days 3, 4 and 5 of the study. Thereafter, until the end of the study, the dosage was titrated according to the faecal form. The dose was increased by one sachet per day in the event of continued hard stools or no bowel movement, and decreased by one to two sachets per day in the event of loose stools or diarrhoea. If the investigator considered it to be clinically necessary, patients could be given another laxative, provided they had failed to respond to the maximum dose for 3 days. No other therapeutic interventions, including an increase in oral fluids or dietary fibre, were instituted. Any child who developed faecal impaction (faecal loading) which required treatment was withdrawn from the study and classified as treatment failure.

Assessments

The primary efficacy variable was the number of spontaneous complete defaecations per week. Secondary efficacy variables were faecal form (assessed using the Bristol stool scale[17]), amount of stool (rated as none, small, moderate or large), abdominal pain, rectal bleeding, pain on defaecation, straining on defaecation and faecal incontinence (all assessed as none, mild, moderate or severe), stool withholding, use of concomitant laxative treatment, investigator assessment of efficacy (on a 5-point scale from very much worse to very much better or cured), and patient or parental assessment of efficacy (on a 5-point scale from very poor to very good). For the assessment of faecal incontinence (soiling), only children who were previously toilet trained were included in the analysis.

Five assessment visits were scheduled. At the first visit (day 0), the participants' bowel movements over the previous 14 days were assessed. Macrogol 3350 plus electrolytes was started on the following day (day 1). During the study, patients were assessed at 14 days (Visit 2), 28 days (Visit 3), 56 days (Visit 4) and 84 days (Visit 5). At each visit, bowel movements over the previous period were assessed by the investigators using a daily diary card, recorded by the participants or their parents or guardians. In addition, a 'final visit' summary included data collected at either Visit 5 or the withdrawal visit.

Safety assessments included adverse events, laboratory tests (full blood examination, urea and electrolytes and liver function tests) and changes in vital signs. Adverse events were monitored throughout the study; venous blood samples for laboratory safety were taken at visits 1, 3 and 5. Vital signs were measured at visits 1 and 5. In addition, investigators assessed compliance on a 4-point scale from very poor (<25% of prescribed dose taken) to very good (>75% of prescribed dose taken).

Statistical analysis

The efficacy analysis included all patients who received at least one dose of study medication and who provided any on-treatment efficacy data. The safety analysis included all patients who received at least one dose of the study medication. Data were summarised as mean ± standard deviation, and statistical comparisons were performed using Student's paired *t*-test, analysis of variance (ANOVA) or χ^2-analysis. Significant differences were accepted for $P < 0.05$.

Results

Eighty-one children were enrolled into the study, of whom 78 received at least one dose of Macrogol 3350 plus electrolytes, and were included in the safety analysis; 77 patients were included in the efficacy analysis (Table 1). The mean age of the children was 4.9 ± 2.6 years, and 34 (44%) were boys. Sixty-five (80%) patients completed the study, and the reasons for premature withdrawal are detailed in Table 1.

Efficacy results

Figure 1 shows the increase in the mean number of successful defaecations per week (primary efficacy variable) over the duration of the study. There was a significant increase in the number of defaecations per week from 1.4 ± 0.54 at Visit 1 to 6.8 ± 3.85 at Visit 2 (paired *t*-test: $P < 0.001$). The stool frequency remained unchanged from Visit 2 until the final visit (ANOVA: $F = 0.81$,

Table 1 Patient recruitment and progress

Patients	*n*	%
Patients enrolled in the study	81	100
Patients included in safety analysis	78	96
Patients included in efficacy analysis	77	95
Patients withdrawn prematurely	16	20
Unable or refused to take medication	6	
Protocol deviation	4	
Poor compliance	3	
Failed to return for final visit	1	
Parent refused to give medication	1	
Serious adverse event	1	
Patients who completed study	65	80

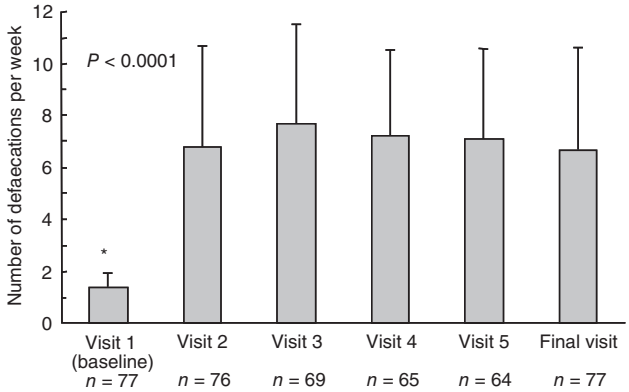

Fig. 1 Mean number of successful defaecations per week from baseline to final visit.

$P = 0.518$). Because the children started on different dosages of Macrogol 3350 plus electrolytes depending on age, a subgroup analysis by age (2–6 vs. 7–11 years) was done. The observed increase in stool frequency was similar for the two subgroups by the final visit (5.6 ± 2.7 vs. 5.6 ± 4.5, not significant).

Results for the secondary efficacy variables showed similar improvements from baseline to final visit. For faecal form, the median score on the Bristol stool form scale changed from 2.0 at Visit 1 (indicating a sausage-shaped, lumpy stool) to 4.0 at the final visit (indicating a smooth, soft stool). The number of children passing large volume stools decreased significantly from baseline 41 children (53%) to the final visit 11 children (14%) ($\chi^2 = 26.13$, $P < 0.0001$).

Changes in severity scores for abdominal pain, rectal bleeding, pain on defaecation, straining on defaecation, and soiling are shown in Figure 2. Improvements from baseline were highly significant for all parameters: abdominal pain ($\chi^2 = 70.15$, $P < 0.0001$), rectal bleeding ($\chi^2 = 28.43$, $P < 0.0001$), pain on defaecation ($\chi^2 = 78.47$, $P < 0.0001$), straining ($\chi^2 = 103.93$, $P < 0.0001$) and soiling in toilet-trained children ($n = 48$, $\chi^2 = 23.47$, $P < 0.0001$). As for the primary efficacy measure, improvements were seen within 14 days of commencing the study medication and were maintained until the final visit.

Stool withholding was reduced significantly from 46 (60%) participants at baseline to 4 (5%) at the final visit; ($\chi^2 = 26.95$, $P < 0.0001$). Throughout the study, 7 children required additional laxatives: 5 (6.5%) patients between baseline and Visit 2, and 2 (2.6%) patients during the remaining time periods.

By the final visit, 65 (84%) children were rated by the investigator as improved, of whom 46 children (60%) were assessed as 'very much better/cured'. Similarly, 62 children or parents (81%) assessed the efficacy as either 'good' or 'very good' by the final visit.

Safety results

Seventy-two (92%) of the 78 patients in the safety population reported a total of 318 adverse events, mostly infections and gastrointestinal complaints. Two hundred and forty-one of 318 (76%) adverse events were assessed as unrelated to the study treatment. Two hundred and sixty-two of 318 (82%) events were mild, and 302 of 318 (95%) had resolved by the end of the study. There were six serious adverse events that occurred in four children. Four adverse events affected the gastrointestinal system. All events were assessed by the investigator as unrelated or unlikely to be related to the study treatment and resolved by the end of the study. One of these serious adverse events (faecal impaction) led to the patient's premature withdrawal from the study as the child was admitted as an inpatient for a bowel washout.

Most patients had normal biochemistry results at baseline and at each visit thereafter. Five sodium values increased from within normal range at baseline to above normal at final visit. However, the baseline mean (SD) value of 143 ± 2 mmol/L did not change during the study, and the range was 139–147 mmol/L at final visit. These values were within clinically acceptable limits. Five potassium values were identified as moving from the normal range to above normal at Final Visit. The mean potassium levels (SD (range)) were 4.3 ± 0.3 mmol/L (3.4–5.2) at baseline, and 4.4 ± 0.4 mmol/L (3.5–5.6) at final visit. These values were not clinically significant.

Overall, only few events (21 events) of haematology value changes from within normal range at Visit 1 to outside normal range at the Final Visit were observed. The majority of these were changes in platelets numbers from within to above the normal range. There was little difference in mean (SD) values from baseline values of $360 \pm 93 \times 10^9$/L to final visit values of $364 \pm 85 \times 10^9$/L. These changes were considered clinically insignificant.

Physical examination and vital signs did not reveal any clinically significant changes as a result of the study medication.

Treatment compliance

The mean duration of treatment was 75.5 days, during which time the participants took an average of 1.3 sachets (6.9 g) of macrogol plus electrolytes per day. At each visit, most children had compliance ratings of 'excellent' (>75% intake of study medication), 86%, 81%, 76% and 79% at visits 2, 3, 4 and 5, respectively. For only few patients the compliance was rated by the investigator as 'poor' or 'very poor', 5%, 1%, 1% and 0%

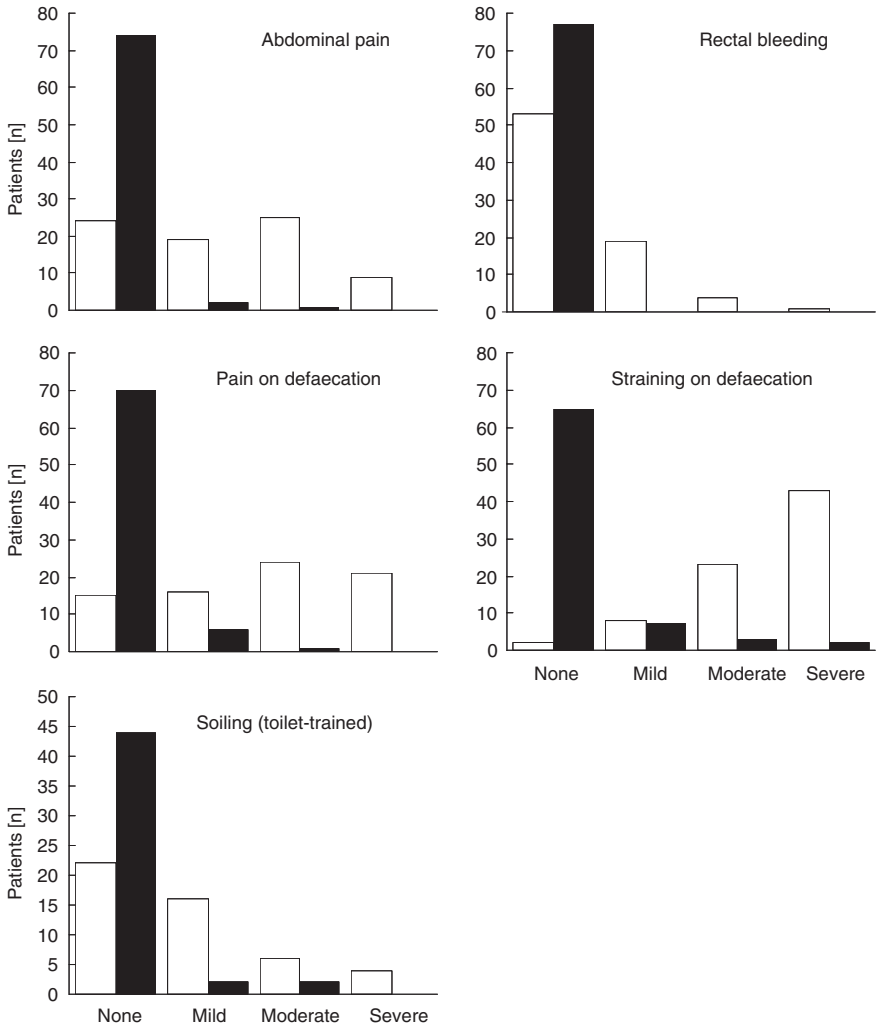

Fig. 2 Changes in severity of secondary efficacy variables from (□) baseline to (■) final visit.

at visits 2, 3, 4 and 5, respectively. Three patients were excluded from the study because of poor compliance.

Discussion

The achievement of at least three comfortable bowel movements per week without associated symptoms such as straining and pain are important aims in the management of constipation in children.[18] In the current study, the number of complete spontaneous defaecations per week (primary efficacy variable) increased significantly from a mean of 1.3 at baseline to 6.7 within 14 days, and 6.9 by the final visit. All associated symptoms including pain, rectal bleeding, and straining also improved significantly. We felt that the rapid relief of symptoms (14 days) in children with a history of chronic constipation encouraged compliance from both the parents and the patient.

The study medication was well tolerated over the 12-week period, and most adverse events were considered to be unrelated to the product. The medication had added electrolytes to make it iso-osmotic with bowel content and prevent any net gain or loss in electrolytes, and there were no significant changes in serum electrolytes in our study population. These findings are in keeping with previous paediatric studies that have not found any safety concerns regarding the short (2–8 weeks),[16,19,20] medium to long-term (3–12 months)[21–23] use of Macrogol 3350 preparations.

Compliance is an important factor in the successful treatment of chronic constipation of children because of the need for long-term treatment.[5] Traditional laxatives are often associated with poor compliance because of their poor palatability or unpleasant side effects. For example, lactulose is fermented by colonic bacteria and can cause gas and acidic stools, which can in turn lead to abdominal discomfort and perianal irritation.[8] Compliance in our study was high, with only three children being withdrawn prematurely because of non-compliance. This is in agreement with other reports that have shown compliance with macrogol 3350 based laxatives to be excellent.[16,23]

This open-label, uncontrolled study did not allow us to distinguish a true treatment effect from spontaneous improvement. However, the study involved children with clinically significant constipation, and it appears unlikely that the improvement seen within 14 days was due to spontaneous recovery or a placebo effect. Open-label studies are potentially subject to bias in assessments of efficacy. However, our findings

are supported by results from several non-randomised[16,21–23] and randomised-controlled studies[19,20] of polyethylene glycol (PEG) 3350-based preparations in children. These studies showed equivalence over 2 weeks[19] and significantly higher success rates over 8 weeks[20] with PEG 3350 preparations (with or without electrolytes), compared with lactulose, in terms of increased defaecation frequency, decreased abdominal pain, as well as decreased straining and pain on defaecation.

Macrogol-based laxatives are widely available as over-the-counter preparations for the treatment of constipation. Our results lend further support to their efficacy and safety in the treatment of childhood constipation. Longitudinal studies are needed to determine the long-term outcome of successful treatment of chronic constipation in childhood.

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