Safety of Polyethylene Glycol 3350 for the Treatment of Chronic Constipation in Children

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Objectives: To assess the clinical and biochemical safety profile of long-term polyethylene glycol 3350 (PEG) therapy in children with chronic constipation and to assess pediatric patient acceptance of PEG therapy.

Design: Prospective observational study.

Setting: Pediatric clinics at a referral center.

Patients: Eighty-three children (44 with chronic constipation, 39 with constipation and encopresis) receiving PEG therapy for more than 3 months.

Main Outcome Measures: Clinical adverse effects related to PEG therapy and acceptance and compliance with PEG therapy. Serum electrolyte levels, osmolality, albumin levels, and liver and renal function test results were measured.

Results: At the time of evaluation, the mean duration of PEG therapy was 8.7 months, and the mean PEG dose was 0.75 g/kg daily. There were no major clinical adverse effects. All blood test results were normal, except for transient minimal alanine aminotransferase elevation unrelated to therapy in 9 patients. All children preferred PEG to previously used laxatives, and daily compliance was measured as good in 90% of children.

Conclusions: Long-term PEG therapy is safe and is well accepted by children with chronic constipation with and without encopresis.

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CONSTIPATION IS a common problem in the pediatric population. This symptom accounts for 3% of outpatient visits to general pediatric clinics and up to 25% of visits to pediatric gastroenterology clinics.1 Treatment regimens vary widely and include dietary and behavioral modification, counseling, and the use of various laxatives and stool softeners.

Polyethylene glycol 3350 (PEG) is a relatively new osmotic laxative. Polyethylene glycol is a component of the PEG-electrolyte lavage solution that has been used in large volume to cleanse the gastrointestinal tract for diagnostic and surgical procedures in children.2 Polyethylene glycol 3350 is a nontoxic and highly soluble compound that is minimally absorbed in the gastrointestinal tract.3,4 Due to these properties, PEG acts as an osmotic agent, increasing fecal water content.5,6 Polyethylene glycol 3350 without electrolytes is supplied as a powder (MiraLax; Braintree Laboratories, Braintree, Mass) that is palatable when dissolved in a beverage such as water or juice.

Recent studies6,7 in adults have reported short-term efficacy of PEG without any major clinical adverse effects. Polyethylene glycol has been approved by the Food and Drug Administration for the short-term treatment of constipation in adults. Three small pediatric studies8-10 have reported short- and long-term efficacy of PEG. Polyethylene glycol is widely used in clinical practice for children with constipation, but, to our knowledge, there are no data on the long-term safety profile of this relatively new laxative in children or in adults. Therefore, the aim of our study was to assess the biochemical and clinical safety profile of long-term PEG treatment in a large cohort of children. We also assessed pediatric patient acceptance of long-term PEG therapy.

METHODS

PATIENTS

All children older than 2 years with chronic constipation who were treated daily with PEG for more than 3 months were eligible for the study. The patients were enrolled at fol-
Following the diagnosis of constipation, PEG therapy was initially prescribed at the dose of 0.8 g/kg per day, based on our previous study, and all other laxative treatments were stopped. Following the diagnosis of constipation, PEG therapy was initiated. The diagnosis of chronic constipation was based on symptoms of at least 3 months’ duration, including at least 2 of the following symptoms: hard stools, painful defecation, encopresis, or fewer than 3 bowel movements per week. Patients with constipation were excluded if they had history of Hirschsprung disease, anorectal malformations, or any systemic illness potentially leading to constipation.

This study was approved by the institutional review board of the University of Iowa College of Medicine, Iowa City. Informed consent was obtained from parents of all patients, and assent was obtained from children older than 7 years.

PEG SAFETY

Clinical adverse effects of PEG therapy were minor and acceptable over the mean duration of 8.7 months (range, 3-30 months) of PEG therapy. Eight patients (10%) reported frequent watery stools sometime during therapy. The diarrhea disappeared with reduction of the dose. Other adverse effects reported were bloating or flatulence in 5 children (6%) and abdominal pain in 2 children (2%). Thirst, fatigue, and nausea after receiving PEG solution on an empty stomach were reported in 1 patient each (1%). None of the patients stopped treatment due to adverse effects, and all were willing to continue PEG therapy. The general physical examination findings revealed no new significant abnormalities compared with the pretreatment examination in all children.

The laboratory evaluation results, including measures of hemoglobin, hematocrit, serum electrolytes, blood urea nitrogen, serum creatinine, serum albumin, and osmolality, were normal in all patients. Ten patients did not have serum osmolality measured. Nine patients (11%) had a slightly elevated ALT level (<1.5 times normal; range, 31-45 U/L). Eight of these patients had ALT levels remeasured within 8 weeks, 7 of whom were still receiving PEG therapy. Seven of these 8 patients had values in the reference range, while 1 had a slightly elevated ALT level (<1.2 times normal; 28 U/L). Three patients (4%) had an elevated aspartate aminotransferase level (<1.5 times normal; range, 42-52 U/L), and all had normal values when remeasured while still receiving PEG therapy. The dose and duration of PEG therapy were not significantly different in the patients with abnormal values compared with those with laboratory values in the reference range.

PATIENT ACCEPTANCE

Polyethylene glycol was mixed in any beverage to suit the child’s preference. Forty-one children used fruit juice (49%);
Chronic constipation is a common problem in children and requires long-term treatment with laxatives. Polyethylene glycol 3350 is a newly available laxative that is widely used in children. Recent studies report efficacy of PEG, but data on its long-term use and safety are lacking.

This study reports a lack of major clinical adverse effects and biochemical abnormalities in a large cohort of children receiving PEG 3350 therapy over the long term. The study also reports good patient acceptance and compliance with PEG therapy. Polyethylene glycol 3350 should be considered as a favorable therapeutic option for children with chronic constipation with or without encopresis because of its safety and efficacy over the long term and good patient acceptance.

11, cow’s milk (13%); 9, water (11%); 8, fruit punch (10%); and other beverages were also used to prepare the PEG solution. All caretakers found it easy to prepare the PEG solution. The PEG solution was liked by 78 children (93%).

All 68 children who had used other therapies preferred PEG to other laxatives. Daily compliance, assessed by parent recall and diary, was good in 75 patients (90%) during the mean duration of 8.7 months of therapy. Seventy-eight (91%) of 83 caretakers reported definite improvement in bowel movement pattern with PEG therapy.

**COMMENT**

Constipation with or without encopresis is often a chronic problem in children. In one long-term study from the United States,11 37% of children continued to have symptoms of constipation 3 to 12 years after initial diagnosis. In another study from Italy,12 constipation persisted in 52% of children 5 years after initial diagnosis. Adequate doses of laxatives and treatment compliance are the most important factors for successful resolution of chronic constipation.11 Long-term treatment is required for children with chronic constipation, as relapse is common after premature discontinuation of laxatives.11 Therefore, there is a need for an ideal laxative that is safe, effective, and acceptable to children over the long term.

In our study, long-term PEG therapy did not have any major clinical adverse effects. The most common clinical adverse effect was excessively loose or frequent stools that resolved with reduction of the PEG dose. Other adverse effects were minimal and acceptable. Polyethylene glycol does not ferment by colonic bacterial flora and, therefore, does not cause excessive gas production that leads to flatulence or bloating. Polyethylene glycol solution—induced acute pancreatitis has been reported in an adult patient with intestinal dysmotility following rapid ingestion of a large volume (4 L) of the solution.13 The mechanism was thought to be due to duodenal distention and reflux of duodenal contents into the pancreatic duct and not the effect of PEG on the pancreas.13 No patient in our study had severe acute abdominal pain or any features suggesting acute pancreatitis.

Although we did not conduct laboratory tests in the patients prior to starting PEG therapy, patients receiving long-term PEG therapy did not have any adverse effects on renal function, electrolyte levels, serum albumin levels, and osmolality. Thus, long-term PEG therapy does not adversely affect fluid and electrolyte balance despite improvement in stool frequency and consistency. Nine patients had minor elevations of ALT levels, and 3 patients had minor elevation of aspartate aminotransferase levels at one point during the study. The elevation was only a few points above the reference range for our laboratory and completely resolved in all but 1 patient when remeasured while still receiving therapy. No symptoms or signs of liver disease were present in these patients. A recent study14 on liver function tests indicates no need for further evaluation if mildly elevated levels of aminotransferase are within the reference range on retesting. Due to these reasons, we believe that the transiently abnormal ALT levels were clinically insignificant and unrelated to PEG treatment. Although we did not see any major adverse effects in our study, the upper limit of the 95% confidence interval of point estimate of zero for adverse effects is approximately 4% in a sample size of 83 patients. Therefore, a study of a larger number of patients followed up for a longer duration of treatment would be required to ensure the absence of rare adverse effects.

Short-term PEG therapy in adults (2 weeks) and children (3 days) has shown no significant change in laboratory evaluation results consisting of electrolyte profile, renal function tests, and serum chemistry analysis.5,15 Postmarketing safety information from the manufacturer reports rare allergic reaction to PEG in the form of rashes, but no other serious adverse effects have been reported in children (John McGowan, BA, Braintree Laboratories, e-mail communication, January 29, 2003). Studies3,5,16 in human volunteers indicate that systemic absorption of PEG is minimal (estimated at 0.06%) and renal excretion is high. Therefore, systemic toxicity of PEG is unlikely.3,5,16

There are several effective medications available for long-term treatment of constipation in children, including milk of magnesia, lactulose, and mineral oil.1 However, these medications have either poor palatability or adverse effects such as abdominal pain, flatulence, or anal leakage, which may limit patient acceptance and compliance.8,9 Most children in our study had tried other laxatives before. They all preferred PEG to other laxatives because of its palatability. Therefore, compliance with PEG and patient acceptance was excellent.

Efficacy of PEG therapy for children with constipation and encopresis has been reported before.8,10 In one study, milk of magnesia was as effective as PEG (67% vs 61%) in children with constipation and encopresis who received these therapies for 12 months.5 However, 33% of children refused to take milk of magnesia, whereas none refused PEG.8 In another crossover study, PEG therapy was as effective as lactulose for the treatment of constipation in children in a 2-week trial, but PEG was preferred by children compared with lactulose.10

In summary, PEG seems to be a safe medication for long-term treatment of constipation in children. It should be considered a favorable option for long-term therapy for children, particularly because of excellent patient acceptance.
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