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A Dose Determination Study of Polyethylene Glycol 4000 in Constipated Children: Factors Influencing the Maintenance Dose

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ABSTRACT

Objectives: To determine the doses of polyethylene glycol (PEG) 4000 without additional salts allowing normal bowel habits in childhood functional constipation.

Methods: This multicenter noncomparative study allocated children to 4 groups: 6–12 months, 13 months–3 years, 4–7 years, and 8–15 years. Constipation was defined as <1 stool/d for more than 1 month in children aged 6–12 months and <3 stools/w for more than 3 months in older children. Children randomly received either a nominal or a double starting dose. Treatment scheduled for 3 months could be adapted. Data were collected daily by the parents and rated at each visit by the investigator.

Results: In the 96 children included, the median (interquartile) effective daily doses were by groups; 3.75 (2.50–5.00) g, 6.00 (4.00–7.43) g, 11.71 (7.00–16.00) g, and 16.00 (16.00–24.00) g, respectively, i.e., around 0.50 g/day/kg with a potential increment of the maintenance dose with higher initial dosages. More children had a final dosage identical to the initial one when started on the nominal dose (73%) than with the double one (42%, $P < 0.003$). More than 90% of children recovered normal bowel habits. Fecal soiling ceased in >60% of children with this symptom at enrolment. Fecal mass in the rectum and abdominal pain were markedly reduced and appetite improved.

Conclusions: A daily dose of PEG 4000 around 0.50 g/day/kg in children aged 6 months to 15 years is effective in more than 90% of constipated children and 60% of those with fecal soiling. ***JPGN 42:178–185, 2006.*** **Key Words:** Constipation—Laxatives—Macrogol—Pediatrics—Dosage. © 2006 Lippincott Williams & Wilkins

INTRODUCTION

Constipation, defined as a delay or difficulty in defecation, is a common pediatric issue, estimated to occur in 5 to 10% of children (1). In about 95% of them, constipation has a functional cause and can result in fecal impaction, fecal soiling and abdominal pain. The treatment of childhood constipation includes fecal disimpaction, suitable diet including fiber consumption and toilet training in preschool children, to prevent future stool impaction and promote regular bowel habits (2). Furthermore, clinical practice guidelines recommend, besides hygiene and nutritional measures, including prokinetic agents or laxatives (3–7).

Among the latter, polyethylene glycols (PEG) laxatives, whose osmotic properties enable softening of stools and promoting bowel transit (8), have clearly demonstrated their efficacy and tolerance for the treatment of chronic constipation, not only in adults (9–12) but also in children (3,5–7,13–18). The ability of a PEG-balanced lavage solution to relieve significant fecal impaction in children with refractory encopresis has been demonstrated in the late 1980s (15). The first clinical studies on PEG-based laxatives in pediatrics (14,16–22) started in 2000. Moreover, a limited number of children were included and treated for a short period and the use of PEG in pediatric practice was still off label (23,24).

Our study aimed at determining the range of effective doses of PEG 4000 for the treatment of functional constipation in children, using a stepwise approach and

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long-term treatment, similar to clinical practice conditions (3,13).

MATERIALS AND METHODS

Study Population and Design

This noncomparative, phase II, dose-ranging study was conducted in 11 secondary and tertiary care centers. The Independent Ethics Committee of Cochin Hospital (Paris, France) approved the study protocol. According to French Law, both parents of the children signed an informed consent before initiating the study.

Eligible for enrolment were ambulatory 6-month to 15-year old children with a history of functional refractory constipation defined according to our own experience as fewer than 1 stool per day for more than 1 month in younger children, and for the older children as fewer than 3 stools per week for more than 3 months. Prior to inclusion in the study, to confirm their need for laxative agents, children had to follow a diet with increased fiber intake for at least 1 month without efficacy. Screening included medical history and physical examination.

Exclusion criteria were organic gastrointestinal diseases (i.e., Hirschsprung's disease) diagnosed by recto-anal manometry and rectal biopsy, previous surgery, intractable fecaloma (i.e., fecal mass, which could not be completely evacuated), severe allergies, known allergy to active substance, history of severe psychiatric disease, and neurologic, endocrine, or metabolic disorders.

Children who fulfilled the selection criteria were allocated to 4 groups according to age: 6–12 months (group I), 13 months–3 years (group II), 4–7 years (group III), and 8–15 years (group IV). In each age group, children were randomly allocated to either a nominal or a double starting dose by means of anonymous numbered sealed envelopes, to begin the treatment with either by the lowest or the highest supposed efficient dose.

The study drug, PEG 4000 (i.e. macrogol 4000 with no added salts) (Forlax®), was supplied to the investigator in sachet form containing either 1.25 g, 2 g, 4 g, or 8 g active drug. According to earlier studies and PEG 4000 off-label use by pediatricians, the starting daily doses were 2.5 g or 5 g, 4 g or 8 g, 8 g or 16 g, and 16 g or 32 g for groups I, II, III, and IV, respectively. The study medication was dissolved in half a glass of tap water before swallowing. When the daily dose included 2 sachets, it was administered once in the morning. Treatment was taken in two doses (morning and evening) when more than 2 sachets were given.

Treatment was scheduled for a 3-month period. Treatment efficacy was evaluated at day 7 (phone contact), day 28 (visit), day 56 (phone contact), and day 84 (final visit). There was no stool from day 1 to day 7, 2 enemas separated by a 2-day interval were allowed after phone contact, but no modification of dosage was allowed before day 14. The administered dose could be increased by 1 sachet in case of persistent constipation at day 28 and day 56 and as soon as day 14 if there has been no stool during the first 14 treatment days despite enemas.

The dose could also be decreased by 1 sachet per day in case of diarrhea, defined as more than 3 stools/d (group I) and more than 2 stools/d (groups II to IV), for at least 2 consecutive days during the study. If necessary, the treatment could be stopped until recovery and then started again at a daily dosage of 1 sachet.

At the study completion, unused sachets were returned to the investigator and counted.

In the absence of literature data, when this study was started, a sample size of 24 children per group was estimated to be adequate for dose determination and performance of nonparametric tests.

Efficacy and Safety Variables

The main criterion was defined as the percentage of children with normal bowel habits for each dose and age group in the last week of treatment period, i.e. experiencing more than 4 bowel movements per week for group I, and at least 3 stools per week and less than 4 stools per day for children in groups II to IV (1,25). The dose allowing those normal bowel habits was considered as effective.

The parents recorded, in a self-evaluation booklet, the administered dose, stool frequency and consistency (hard, normal, loose, liquid); and, for groups II to IV, frequency and intensity of abdominal pain. At each visit, the investigator assessed fecal soiling episodes for groups III and IV, fecal mass in the rectum and appetite on a visual analogue scale (0 mm = none, 100 mm = good). Plain abdominal x-ray for fecal load rating was only performed at day 0 and day 84 for ethical considerations. At the end of the study, three independent readers blinded to the dose and treatment period (i.e. at baseline or after the 3-month treatment period), including two radiologists, were charged to assess the abdominal radiographs together in a spirit of consensus and to rate the abdominal fecal load into 4 grades (normal, mild, moderate, severe), according to Blethyn et al. (26). Results were expressed in terms of ''improvement'' (decrease of at least one grade), ''no change'' and ''worsening'' (increase of at least one grade).

The assessment of safety was based on the onset or worsening of abdominal pain, bloating, nausea, vomiting, and adverse events recorded during each phone conversation and visit. Diarrhea, defined as more than 3 stools per day, was reported as an adverse event.

Statistical Methods

All quantitative parameters were calculated and expressed as median and range values (minimum, maximum). The primary outcome results were expressed as median and interquartile range values (Q1–Q3), and also with range values (minimum, maximum) in the tables.

Qualitative parameters were described by number and percentage of children. Statistical analysis was performed by using TS 020 (AIX) SAS software, release 6.12. According to initial analysis plan, comparisons between qualitative parameters were calculated by the χ^2 test or Fisher's test for description of the 2 starting dose groups per age at baseline. Test of Symmetry or McNemar's test was used for qualitative matched pairs. Comparisons of quantitative parameters were performed using nonparametric Wilcoxon test; P values < 0.05 were considered significant.

Furthermore, complementary post hoc comparisons on primary outcome were performed in the intention to treat population in each age group between the 2 subgroups according to their starting dose.

RESULTS

Children Characteristics

From May 1998 to July 1999, 102 children were enrolled in the study. The intention-to-treat (ITT) population included 96 children (Table 1). Four children withdrew before treatment began, 3 because informed consent was withdrawn or not obtained from the second parent, 1 for a hypoparathyroidism diagnosis, and 2 children were excluded from analysis after an onsite audit revealed to major non compliance to the protocol. The per-protocol (PP) population included 83 children, after the exclusion of 13 children. Three of them experienced a major protocol violation (5 stools/w before start of treatment, use of 14 rectal laxatives during the administration period, and decrease of the dose on the patient's own initiative at day 56), 7 dropped out because of treatment-unrelated abdominal pain (n = 1), moderate but persistent diarrhea (n = 1), concomitant medication (n = 1), move to a foreign country (n = 1), or for personal reasons (n = 3). Finally, 3 children were lost to follow up.

Fecal load was analyzed in 86/96 children. Ten children were excluded from this analysis as they received a rectal laxative before x-ray or because x-ray was performed too late after the end of the treatment period.

Dose Range

The median (interquartile range values) daily effective dose (ITT population) according to statistical analysis was, respectively, for groups I to IV: 3.75 (2.50–5.00) g, 6.00 (4.00–7.43) g, 11.71 (7.00–16.00) g, and 16.00 (16.00–24.00) g (Table 2), corresponding to 0.48 (0.30–0.59), 0.38 (0.32–0.53), 0.50 (0.38–0.73), and 0.51 (0.37–0.76) g per kg of body weight for groups I to IV, respectively. These final dosages were effective in respectively, 100%, 90%, 93%, and 92% of children in groups I to IV.

Moreover a post hoc comparison showed that the median effective dose differed according to the initial dose, nominal or double. The difference seems small in younger children, group I: 2.5 versus 5 g ($P < 0.016$) and group II: 4 versus 6 g (NS). In older children, groups III and IV, the differences are more pronounced: 7 versus 15 g ($P < 0.004$) and 16 versus 27 g ($P < 0.06$), respectively (Table 3). In addition, if 73% versus 42% of children ($P < 0.003$) had a final dosage equal to the starting one when initial dose was 2 and 4 sachets, respectively, more children initially at 4 sachets diminished their dosage (50%) ($P < 0.003$) than children initially on 2 sachets increased it (17%) (Table 4). The daily effective dose was in fact significantly influenced by the initial dose: a lower initial dosage resulted in a lower final one and a higher initial dosage resulted in a higher final dose.

Efficiency on Clinical Signs and Symptoms

Based on the dosage determined above, PEG 4000 showed marked clinical efficacy, with bowel habit normalization compared with baseline in most children in the ITT population at day 84: 100% (n = 15/15, group I) ($P = 0.0001$), 90% (n = 27/30, group II) ($P < 0.0001$), 93% (n = 26/28, group III) ($P < 0.0001$), 91% (n = 21/23, group IV) ($P < 0.0001$). A few patients did not reach an effective dose at final evaluation. In group II: one child was without normal bowel habit at final evaluation as he had at least 1 day with more than 3 stools/d at the dose of 5 sachets/d; 2 children were not assessable for primary outcome. In group III, 2 children had no normal bowel habits at final evaluation, as they both had at least 1 day with more than 3 stools, at the dose of 2 sachets/d. In group IV, two children were without normal bowel

TABLE 1. *Demographic characteristics (intention-to-treat population)*

Age group (n)	6 to 12 months (15)		13 months to 3 years (30)		4 to 7 years (28)		8 to 15 years (23)	
Starting daily dose (g/day)	2.5	5	4	8	8	16	16	32
Gender								
Male (n)	3	5	9	11	9	10	4	4
Female (n)	4	3	4	6	3	6	9	6
Age*, median (min–max)	6.4 (5.8–11.9)	10.2 (5.9–12.0)	2.5 (1.3–3.8)	2.6 (1.1–3.8)	5.3 (4.1–8.0)	5.7 (4.0–8.0)	9.8 (8.2–14.0)	9.5 (7.4–11.9)
Body-weight (kg), median (min–max)								
Male	9.3 (8.4–9.8)	8.4 (7.2–9.8)	13.0 (10.9–17.5)	12.8 (11.3–18.0)	22.0 (15.1–33.0)	18.0 (13.4–27.0)	33.9 (30.0–37.5)	26.0 (23.0–31.4)
Female	6.8 (5.2–8.1)	8.9 (8.7–9.1)	11.4 (10.8–12.0)	12.6 (11.2–17.0)	18.0 (17.0–18.4)	22.3 (16.5–30.5)	29.5 (25.0–52.0)	34.0 (26.2–56.0)
Body-height (cm) median, (min–max)								
Male	70 (68–71)	67.5 (66–75)	92.5 (81–103)	92 (84–104)	121 (100–129)	107.5 (95–128)	141 (133–147)	130 (126–134)
Female	66 (59–70)	72 (66–73)	86 (83–95)	90.2 (74–98)	109 (106–116)	121 (111–130)	138 (132–153)	139.5 (130–153)

*In months for group I, in years for other groups.

TABLE 2. *Effective daily dose of PEG 4000 (g) per age group (intention-to-treat population)*

Age group (N) Daily dose (g/day)	6–12 months (15/15)	13 months–3 years (27/30)	4–7 years (26/28)	8–15 years (21/23)
Minimum	1.25	3.14	3.43	4.57
Q1	2.50	4.00	7.00	16.00
Median	3.75	6.00	11.71	16.00
Q3	5.00	7.43	16.00	24.00
Maximum	6.25	8.57	20.00	32.00

habits, one child who had at least 1 day with more than 3 stools during the first week of treatment at the dose of 2 sachets/d and was dropped at day 7 for diarrhea; one child who had normal bowel habits at day 56 at 3 sachets/d decided by himself to decrease the dose a few days before final evaluation and had only 1 stool/w at final evaluation. The number of children having normal bowel habits per daily dose and per age group is shown in Figure 1. These results were confirmed in the PP population with 100%, 96%, 92%, and 100% of bowel habit normalization obtained in groups I to IV. Bowel habit normalization was already obtained by day 7 in 93%, 70%, 96%, and 82% of children in groups I to IV, respectively. Stool frequency significantly increased after the 3-month treatment period in all groups (Table 5). Stool consistency improved in all groups, with a marked decrease in the number of children with hard stools throughout the study. There were 87%, 90%, 86%, and 83% of children with hard stools at day 0 and 0%, 4%, 0%, and 13.0% at day 84 ($P = 0.0003$, $P = 0.001$, $P < 0.0001$, $P < 0.0001$) in groups I, II, III, and IV, respectively (Table 5).

Concomitantly, fecal soiling discontinued in more than 60% of children who had this symptom at enrollment. Fecal mass and abdominal pain improved with treatment in the 4 age groups, as well as appetite in groups II and III (Table 5).

Abdominal Fecal Load

The pattern of abdominal fecal load assessed by plain abdominal x-ray was variable. Even when bowel habits had normalized at day 84, fecal load did not relate to clinical status. Despite an overall clinical improvement, abdominal fecal load (x-ray) at day 84 was not improved compared with baseline, regardless of age and/or bowel habits at day 84.

Safety Results

The most common adverse effect of medication was diarrhea, reported at least once in 32 children. Considering only clinically relevant episodes requiring reduction or discontinuation of PEG 4000, 14 children experienced 20 episodes of diarrhea, which required discontinuation in 1 case. Abdominal pain was reported in 18 children, usually spontaneous resolved and required permanent discontinuation in only 1 case (onset of diarrhea at the dosage of 32 g per day). Adverse events potentially related to PEG 4000 occurred in 24/45 (53.33%) children initially treated with 2 sachets versus 27/51 (52.94%), in those started on 4 sachets (NS). All these digestive symptoms were expected as they sometimes occur in adults. Furthermore, no unexpected adverse reaction was reported during the study.

DISCUSSION

This is the first large-scale dose determination study of PEG for the treatment of childhood diet-resistant constipation. The results obtained after a 3-month PEG treatment confirmed the clinical efficacy and tolerance already demonstrated in adults (8,9–12,27,28) and in children (14–16,18–22,29).

Independent authors (13,30) and consensus statements (31) suggest that toilet training, dietary advice and

TABLE 3. *Efficient daily dose of PEG 4000 (g) per age group according to initial dose (intention-to-treat population)*

Age group	6–12 months		13 months–3 years		4–7 years		8–15 years	
(n)	7	8	12	15	10	16	12	9
Initial daily dose (g/day)	2.5	5	4	8	8	16	16	32
Minimum	2.50	1.25	4.00	3.14	4.00	3.43	8.00	4.57
Q1	2.50	4.38	4.00	4.00	6.28	11.71	14.86	16.00
Median	2.50	5.00	4.00	6.00	7.21	14.86	16.00	27.43
Q3	2.50	6.25	6.00	8.00	8.00	16.00	16.00	29.71
Maximum	3.75	6.25	8.57	8.00	12.00	20.00	16.00	32.00
P	< 0.016		< 0.20		< 0.004		< 0.06	

TABLE 4. *Evolution of efficient dose of PEG 4000 according to initial dose (% of children)*

	Efficient dose		
Initial dose	Decrease of initial dose	Increase of initial dose	No change of initial dose
2 sachets % (n)	10% (4)	17% (7)	73% (30)
4 sachets % (n)	50% (24)	8% (4)	42% (20)
P	< 0.0001	0.2118	0.0028
< 0.0002			

regular use of laxatives should be combined to prevent future impaction and to ensure a prolonged period of painless defecation, which is essential to provide the confidence necessary for promoting regular bowel habits. Parents must also be reassured that recovery is possible with good toilet training and effective treatments such as laxatives (13,32). Nevertheless, they should be warned that 50% of treated patients experience a relapse within 1 year (33,34).

Short-term administration of PEG in a balanced lavage solution was first shown to relieve fecal impaction in children with refractory encopresis (15,35,36). More recently, different short-term studies and pilot trials used a PEG laxative without added salt at doses from 0.25 to 1.5 g/kg/d (14,17–19,21,22) in constipated children.

The purpose of our study was to define the proper dose range necessary to treat children with refractory functional constipation. In the absence of literature data, when this study was started, a sample size of 24 per age group was estimated a priori to be adequate for doses determination. A post hoc simulation of sample size fully confirmed our initial estimation, as we calculated that with 95% confidence and 2-sided intervals, 19 patients had to be included in each age group to expect at least 85% success.

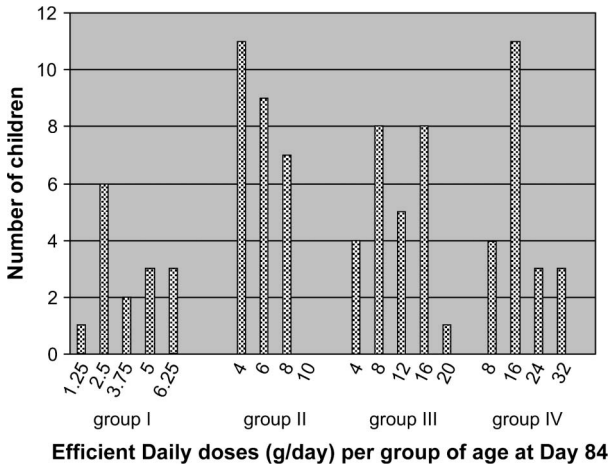

FIG. 1. Number of patients having normal bowel habits at D84 per daily dose and per age group.

When the study was started, the only consensual definition referred to constipation in adults (25). Children eligible for enrolment were therefore defined according to our own experience, as having fewer than 1 stool per day for more than 1 month in group I, and in the other groups, as less than 3 stools per week for more than 3 months. The later definition of functional constipation in infants and preschool children according to 1999 Rome II consensus (31) showed retrospectively that more than 86% of enrolled children in this study strictly fit with these new diagnostic criteria of constipation, i.e., firm stool 2 or fewer times per week, hard stool for a majority of stools, and no evidence of concomitant disorders. Moreover, before enrolment in the study, refractory functional constipation was further assessed by the persistence of symptoms after a 1-month fiber-enriched diet for all children.

Due to the poor absorption of PEG 4000 (37), the extrapolation of the starting dose range in each age group was pragmatically based on results of previous studies in adults and on the coordinator's and investigator's own off-label experience. This choice had a reasonable safety margin due to the lack of absorption, the good tolerance in adults, and careful follow-up, including regular clinic visits and phone contact.

The range of daily dose was determined in more than 90% of included children regardless of the age group. Median dose (interquartile) was 3.75 (2.50–5.00) g, 6.00 (4.00–7.43) g, 11.71 (7.00–16.00) g, and 16.00 (16.00–24.00) g in groups I to IV, respectively. Notably, the median effective dose for group IV was comparable to the daily dosage for the symptomatic treatment of functional constipation in adults (i.e., 10–20 g). A post hoc comparison showed that the median effective dose may differ according to the initial dose, nominal or double. The difference seems low in younger children, group I: 2.5 versus 5 g ($P < 0.02$) and group II: 4 versus 6 g (NS). In older children, groups III and IV, the differences are more pronounced: 7 versus 15 g ($P < 0.004$) and 16 versus 27 g ($P < 0.06$), respectively. In addition, if 73% and 41% of children had a final dosage equal to the starting one when initial dose was 2 and 4 sachets, respectively, more children initially at 4 sachets diminished their dosage (50%) than children initially on 2 sachets increased it (17%). These unexpected results, while providing a good overview of the range of effective dose in each age group, also suggest that low dosages might be as appropriate as higher ones. In addition, these results confirm the wide efficacy and safety margin of PEG 4000.

Conversely, the median dose (min–max) per kg body weight for groups I to IV is, respectively, 0.48 (0.30–0.59), 0.38 (0.32–0.53), 0.50 (0.38–0.73), and 0.51 (0.37–0.76) g and around 0.50 g/Kg regardless of age. The maintenance dose thus depends on the starting dose and the body weight and less specifically on age.

Overall this study showed a marked clinical efficacy with a low median effective daily dose of approximately

TABLE 5. *Efficacy results (intention-to-treat population)*

Efficacy criteria	Age group	Day 0		Day 84		*P*
		n		n		
Number of stools per week, median (min–max)	6–12 months	15	3 (0–5)	15	11 (5–20)	0.0001
	13 months–3 years	30	2 (1–5)	28	7 (3–23)	0.0001
	4–7 years	28	2 (1–3)	28	8 (3–21)	0.0001
	8–15 years	23	2 (1–3)	23	9 (1–37)	0.0001
Hard stools, n (%)	6–12 months	15	13 (87%)	15	0 (0%)	0.0003
	13 months–3 years	30	27 (90%)	28	1 (4%)	0.001
	4–7 years	28	24 (86%)	28	0 (0%)	<0.0001
	8–15 years	23	19 (83%)	23	3 (13%)	<0.0001
Abdominal pain, n (%)	6–12 months		NA		NA	
	13 months–3 years	30	23 (77%)	19*	6 (32%)	
	4–7 years	28	22 (79%)	18*	7 (39%)	
	8–15 years	23	22 (96%)	19*	10 (53%)	
Appetite† (mm), median (min–max)	6–12 months	15	80 (28–100)	15	88 (25–97)	NS
	13 months–3 years	30	45.5 (10–100)	26	67.5 (12–100)	0.0002
	4–7 years	28	41.5 (9–100)	24	66 (22–98)	0.0041
	8–15 years	23	60 (18–93)	19	72 (32–94)	NS
Fecal soiling, n (%)	6–12 months	–	NA	–	NA	
	13 months–3 years	–	NA	–	NA	
	4–7 years	28	9 (32%)	24	2 (8%)	
	8–15 years	23	11 (48%)	20	4 (20%)	
Fecal mass in the rectum, n (%)	6–12 months	15	5 (33%)	15	0 (0%)	
	13 months–3 years	30	14 (47%)	26	1 (4%)	
	4–7 years	28	15 (54%)	24	0 (0%)	
	8–15 years	23	12 (52%)	18	1 (5%)	

NS, not significant; NA, not assessable.
*Number of children having reported abdominal at day 0.
†Assessed on a 100 mm on a visual analogue scale (0 mm = none, 100 mm = good).

0.50 g/kg regardless of the age of the child. More than 90% of the children, regardless of age group, recovered normal bowel habits at the end of the study. The validity of this low dosage was further confirmed by very early normalization of bowel habits, since by day 7, 93% of the 6–12-month children had more than 4 stools per week and 70% to 96% of the 1 to 15 year old children had more than 3 stools per week depending on age. With this dosage of PEG 4000, normalization of bowel habits was accompanied by improved stool consistency in all groups and a significant decrease in the number of children with hard stools throughout the study. Finally, improvement was observed in fecal soiling.

Abdominal pain took slightly longer to disappear than bowel habits to normalize, but its disappearance rate increased over time. Appetite significantly improved at the end of the study compared with the assessment before treatment.

The results of recent pilot studies may be compared with the present one. Pashankar and Bishop (18), found that the mean effective dose of PEG in 20 children aged 2–12.7 years was 0.84 g/kg/d (range, 0.27–1.42 g/kg/d), resulting in a weekly increase in stool frequency of 2.3 ± 0.4 to 16.9 ± 1.6, $P < 0.0001$, and for 9 children with soiling, a decline in weekly soiling events from 10.0 ± 2.4 to 1.3 ± 0.7, $P = 0.003$. Gremse et al. (20) showed that with a dosage of 0.2 to 0.5 g/kg/d for 2 weeks in children aged 2 to 16 years, the decrease of total colonic transit time was greater than with lactulose (47.6 ± 2.7 hours versus 55.3 ± 2.4 hours, $P < 0.04$).

The present study confirmed the preliminary results of these pilot studies. Moreover, by comparison, it has included a large pediatric population, clearly identified into different classes by age and treated for 3 months.

In addition, this study included the assessment of abdominal fecal load by plain abdominal x-ray, before and after the laxative treatment. Radiological assessment of constipation was standardized by a scoring system (26). Inconsistent correlations were found between abdominal fecal load measured by plain x-ray and encopresis (38) or functional constipation (39,40). A recent publication (41) using colonic transit time measurements clearly showed no relation between a radiograph at intake and clinical success after treatment. Our data, evaluating the radiologic fecal load before and after PEG, further confirm these findings: despite the overall clinical improvement and the disappearance of fecal mass in the rectum at the end of treatment, analysis of changes in fecal load via a graded measurement on plain abdominal x-ray failed to demonstrate a significant reduction in the quantity of stools after use of PEG. As a whole, those data underline the lack of correlation between x-ray fecal load and clinical constipation. They suggest that there is little if any utility of such an investigation in the clinical handling of constipated patients.

Compared to bowel habit normalization (42,43), intestinal compliance and sensitivity perturbations (44), such as those observed in some constipated children with a megarectum (43,45), need treatment for longer than 3 months to recover completely. Hence, further exploratory radiologic assessments of long-term constipation relief could be based on measuring changes in rectal volume.

Finally, PEG 4000 was well tolerated in children whatever their age. All the observed digestive symptoms were expected as they sometimes occur in adults. The low incidence of side effects, mainly gastrointestinal as in adults, is remarkable for the treatment duration and the design of such a dose finding study. Moreover, the frequency of adverse events potentially related to PEG 4000 was the same in children whatever their initial dose. Effective daily doses of study drug up to 32 g were administered safely to children in group IV.

In conclusion, this first large-scale dose determination study of PEG in the treatment of refractory functional constipated children for a 3-month period confirms the efficacy and wide safety margin of PEG 4000. Based on this administration schedule, the recommended daily dose of PEG 4000 in children from 6 months to 15 years is approximately 0.50 g/kg/d whatever the age, with a potential influence of the starting dose on the maintenance dose. More than 90% of children recovered normal bowel habits, with an improvement in stool frequency, consistency, appetite, fecal soiling, fecal mass in the rectum, and abdominal pain related to constipation.

ANNEX

List of the multicenter group investigators, working in France in departments of Pediatrics: K. Bargaoui (Sevran), G. Barre (Versailles), D. de Boissieu (Paris 14), F. Gressin (Antony), N. Maamri-Bellaroussi (Boulogne-Billancourt), A. Poujol (Aix-en-Provence), JM. Thiron (Rouen).

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