CME

Long-term Use of Bisacodyl in Pediatric Functional Constipation Refractory to Conventional Therapy

Silvana Bonilla, Samuel Nurko, and Leonel Rodriguez

ABSTRACT

Objectives: Standard therapy for pediatric constipation includes osmotic laxatives with stimulant laxatives use only as rescue therapy. Limited information is available on regular and long-term use of bisacodyl in pediatric population despite its common use in adult and pediatric constipation.

Methods: Retrospective review of patients with functional constipation refractory to conventional therapy (regular use of osmotic laxatives and intermittent use of stimulant laxatives only as a rescue therapy) referred to tertiary care children's hospital (January 2007–December 2014). Patients had a bowel movement (BM) frequency of ≤2 per week and were treated with bisacodyl regularly for longer than 4 weeks. Demographic variables, bisacodyl dose and treatment duration, number of BM/week before and after treatment, side effects, and length of follow-up were recorded. Response to therapy was successful when frequency of BM increased from baseline to ≥3 BM/wk.

Results: A total of 164 patients were included, 52% girls, median age 9.45 years (0.9–21 years). Bisacodyl median dose was 5 mg/day, median duration of treatment was 14 months (1–77 months) with 90% of patients taking the medication for <36 months. Median number of BM/wk doubled after initiation of bisacodyl from 2 to 4 bm/w ($P < 0.001$). Approximately 57% of patients had successful response. At long-term follow-up 55% of patients were successfully weaned off bisacodyl (median time of 18 months). Side effects reported in 9% of patients.

Conclusions: Bisacodyl is effective and well tolerated in the long-term treatment of pediatric functional constipation refractory to conventional therapy. Most of patients with a favorable response were successfully weaned off the medication.

Key Words: chronic childhood constipation, Rome criteria, stimulant laxatives

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What Is Known

- Standard therapy for pediatric constipation includes osmotic laxatives with stimulant laxatives use only as rescue therapy.
- Laxatives such as bisacodyl are commonly used in pediatric and adult population despite the limited information available on its regular and long-term use.

What Is New

- Bisacodyl seems to be effective and well tolerated for the treatment of pediatric functional constipation refractory to conventional therapy.
- Long-term use in children does not seem to be associated with complications or development of tolerance to the medication.
- The majority of patients are able to be weaned off the medication with minimal reported side effects.

Constipation is a common condition encountered in pediatric practice leading to a significant proportion of referrals to pediatric gastroenterology (1). Medical care services and overall healthcare cost are significantly increased in children with constipation (2). If not properly addressed, a fourth of these children continue to experience symptoms as adults (3). Functional constipation is largely the most common etiology of constipation in children (4). The term functional constipation refers to the passage of hard, infrequent bowel movements (BMs) often accompanied by pain without identifiable anatomic abnormality or disease process. The Rome criteria, currently on their fourth iteration, are the most accepted diagnostic criteria for childhood constipation (5).

Standard treatment of functional constipation includes increase fiber intake, osmotic laxatives, suppositories, and enemas, with stimulant laxatives added only as a rescue therapy (4,6). A great percentage of patients will improve with these recommendations (3). Nonetheless, there is a subgroup of patients with poor or no response commonly labeled as refractory or intractable for which other interventions such as surgical procedures (antegrade bowel irrigation, segmental, or total colonic resection) may be considered (7).

Data on effectiveness and safety of short-term treatment with stimulant laxatives in the adult population support their usage (8,9). Less evidence supporting long-term treatment is available (10). Similarly, there is limited information on the regular and long-term use of stimulant laxatives (eg, senna, bisacodyl) in pediatric population. Oral senna appears to be safe and well tolerated in children with constipation (11,12). Bisacodyl is routinely used intraluminally during colonic manometric assessment in pediatric and adult population (13,14). It improves colonic neuromuscular function, and thus helping to rule out true colonic inertia, as well as to better categorize constipated patients. Thus, we conducted a study to

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From the Center for Motility and Functional Gastrointestinal Disorders, Division of Gastroenterology, Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, MA.

Address correspondence and reprint requests to Leonel Rodriguez, MD, MS, Section of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Yale New Haven Children's Hospital, Yale School of Medicine, 333 Cedar St, New Haven, CT 06510 (e-mail: leonel.rodriguez@yale.edu).

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TABLE 1. Factors associated with response to bisacodyl

	Bisacodyl response	*P*
Age		0.940
Sex		
Male	41/78 (53%)	
Female	53/86 (62%)	0.271
Presence of side effects		
Side effects	7/13 (54%)	
No side effects	87/151 (58%)	0.792
Dulcolax dose		<0.001
Follow-up		0.381
Duration of treatment		<0.001

determine the effectiveness and tolerance of regular and long-term use of bisacodyl in pediatric population.

METHODS

We conducted a retrospective study of patients referred to our institution between January 2007 and December 2014 for evaluation and management of constipation refractory to conventional therapy that received bisacodyl for at least 4 weeks.

Patients with a frequency of ≥2 BMs per week and treated regularly with bisacodyl for at least 4 weeks (in addition to osmotic laxatives) were included in the study. Patients with congenital colonic anomalies or colonic surgery were excluded from the study. Institutional review board approval was obtained to conduct this study.

Variables

Demographic data (age and sex), bisacodyl dose (mg/day) and duration of treatment in months, number of BMs per week (bm/w) before and after treatment with bisacodyl, side effects, and length of follow-up in months were recorded.

Definitions

Functional constipation: meet Rome III criteria for functional constipation.

Conventional therapy: Regular use of osmotic laxatives and intermittent use of stimulant laxatives only as a rescue therapy (4).

Refractory constipation: symptoms not responsive to conventional therapy.

Response to therapy: rated as successful when frequency of BMs increased from baseline to 3 or more per week.

Statistical analysis

Medians were compared using nonparametric tests, and proportions using chi square and Fisher exact test as indicated. A binary logistic regression model to determine joint effect of age, sex, indication/diagnosis, and duration of treatments was conducted. Analyses were performed using SPSS software ver. 22.0 (IBM, Armonk, NY).

Frequency of BMs per week at baseline (before therapy) was compared to that recorded after therapy with bisacodyl (for a minimum of 4 weeks). We also evaluated the ability to wean off the bisacodyl in those with a successful response and we also evaluated the rate of side effects and their potential causes.

RESULTS

Demographic Variables, Indication, and Duration of Treatment

A total of 164 patients were included in the study, median age was 9.45 years (range 0.9–21 years) and 52% were girl. Median dose of bisacodyl was 5 mg (range 1–20 mg) with a median duration of treatment of 14 months (range 1–63 months) and 90% of patients taking the medication for less than 36 months. Median duration of follow-up was 18.5 months (range 1–87 months). Data on baseline medications were available in 132 patients. Sixty-eight were on osmotic laxatives (eg, polyethylene glycol, lactulose, milk of magnesia) and stimulant laxatives (eg, sennosides) combined, whereas 64 were on osmotic laxatives only. The remainder of patients was on no medications or data were not available.

Response to Therapy

Median number of BMs per week at baseline (before therapy with bisacodyl) was 2 bm/wk. After therapy, the number doubled to 4 bm/wk ($P < 0.001$). We found no association between response to therapy and age, sex, presence of side effects, or duration of follow-up. We did find an association between response to therapy and bisacodyl dose (median dose in responders was 5 vs 10 mg in nonresponders, $P < 0.001$), and duration of therapy (median of 14 months in responders vs 11 months in nonresponders, $P = 0.002$). (Table 1). Response to therapy (≥3 bm/wk after therapy) was rated as successful in 94 of 164 (57%) patients. A binary logistic regression model to determine joint effect of different factors potentially associated with bisacodyl response demonstrated no association with sex and duration of follow-up but confirmed a lower bisacodyl dose and longer duration of therapy were associated with response to therapy and also showed a trend toward an association with older patient age (Table 2).

TABLE 2. Multivariate analysis of factors associated to bisacodyl response

						95% CI	
	B	SE	Wald	*P*	Exp(*B*)	Lower	Upper
Age*	0.116	0.064	3.249	0.071	1.123	0.990	1.274
Sex	−0.065	0.552	0.014	0.907	0.937	0.318	2.765
Bisacodyl dose	−0.286	0.095	9.115	0.003	0.751	0.624	0.904
Follow-up†	0.004	0.019	0.047	0.828	1.004	0.968	1.042
Duration of Tx†	0.053	0.025	4.437	0.035	1.054	1.004	1.107

*Years.
†Months.

Response to therapy in relationship to baseline medications showed that patients who were on osmotic laxatives only at baseline had a greater response to bisacodyl 39 of 64 (61%) than patients who were on osmotic laxatives and stimulant laxatives combined 28 of 68 (41%), $P = 0.023$.

Ability to Wean Bisacodyl

Bisacodyl was tapered either by decreasing daily dose slowly over 3 to 6 months or by decreasing the daily frequency slowly over the same period of time. We evaluated the ability to wean the bisacodyl on those with a successful response up to the last communication with our center. A total of 94 patients had a successful response to bisacodyl, information in regards to bisacodyl status was available in 71. Of those, 32 (45%) were still taking bisacodyl and 39 (55%) were successfully weaned off. Median time in months to be weaned was 18 months (range 2–48 months). We found no association between ability to wean off the medication and age, sex, bisacodyl dose, or duration of therapy. We, however, found an association with duration of follow-up, median follow-up time in those still taking bisacodyl was 6 versus 29 months on those off bisacodyl $P < 0.001$ Fig. 1).

Side Effects

Side effects were reported in 13 (8%) of patients, primarily self-limited abdominal pain in 8 (62%), diarrhea in 4 (30%), and nausea in 1 (8%). Most side effects subsided with dose adjustment and only 5 required the medication to be stopped due to side effects. We evaluated potential factors associated to the presence of side effects and found no association with age, sex, response to therapy, bisacodyl dose, and duration of therapy. We, however, did find an association with longer length of follow-up (median duration of follow-up in those with side effects of 12 vs 21 months in those without side effects, $P = 0.031$), this association was confirmed in a binary logistic regression model.

DISCUSSION

Although stimulant laxatives are widely use in the treatment of constipation, there is still significant reluctance to its regular use in pediatrics due to potential side effects and concern about developing dependency on the medication. This is understandable given the lack of data in pediatric population. Previous pediatric data on regular use of bisacodyl mostly comes from studies assessing its intraluminal use during colonic manometry and when comparing colonoscopy bowel cleaning regimens (13–15). Our study provides novel data on the tolerance and efficacy of regular and long-term use of bisacodyl in the treatment of pediatric chronic refractory constipation.

Bisacodyl is approved for short-term treatment of constipation and for bowel cleansing regimens in adult population with availability over the counter. The mechanism of action is exerted through the active metabolite, bis-(p-hydroxyphenyl)-pyridyl-2-methane, which both enhances mucosal secretion and has a prokinetic effect in the colonic mucosa (15). Animal studies have shown that it may decrease the expression of aquaporin-3 in the colon via direct activation of colon macrophages, limiting the water transfer from the luminal to the vascular space (16). The resulting effect seems to be to increase water content in the colon lumen causing an acceleration of transit starting in the right colon (17). Long-term colonic effects and possible carcinogenic risk have been a concern though recent studies have failed to find a relationship (18–20).

Data from adult studies has shown bisacodyl to be effective and well tolerated in the treatment of patients with chronic constipation when given orally (8,10). In a recent meta-analysis comparing the efficacy of different pharmacological therapies in the treatment of chronic idiopathic constipation based on comparisons to placebo, bisacodyl was superior to prescription drugs such as prucalopride, lubiprostone, and linaclotide regarding change in baseline number of BMs per week (9). Our study findings are in line with this observation with the median number of BMs per week doubling after initiation of bisacodyl.

In regards to bisacodyl dose, we found an association between lower dose of bisacodyl and response to therapy. This

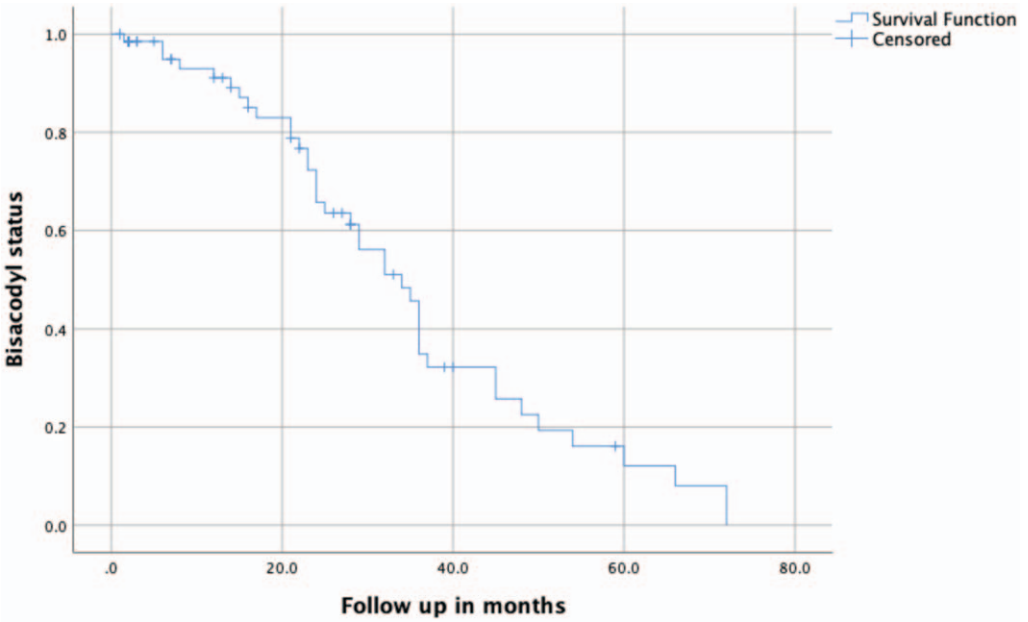

FIGURE 1. Kaplan-Meier graph depicting the ability of wean off bisacodyl over time.

could be explained by the fact that one is inclined to keep increasing the dose when the desired effect is not achieved, even if at the end is not successful. Alternatively, it is important to mention that higher starting or ending doses may be required and be effective in some patients. In regards to duration of therapy, we found an association between longer duration of therapy and response to therapy, probably due to the fact that we were only continuing the medication for a longer period on those patients with a favorable response.

The concern about development of dependence on the medication is an important limiting factor for the use of bisacodyl in clinical practice. We did observe that at long-term follow-up a total of 55% of those with a successful response were able to stop the medication. The average time to come off bisacodyl was 18 months. We observed that those still taking the medication had a shorter follow-up compared to those that were off (were weaned off), suggesting that it is a matter of time before those with a favorable response can come off the medication. Available data on baseline medications showed that patients who were on single therapy with osmotic laxatives only had a greater response to bisacodyl than patients on combined therapy with osmotic laxatives and stimulant laxatives. These results suggest that nonresponse to a stimulant laxative decreases the likelihood to respond to a second stimulant laxative agent.

A recent study reviewed the clinical trial evidence for safety and efficacy of long-term treatment (4 weeks) with bisacodyl, sodium picosulfate, and pyridostigmine in adult patients diagnosed with constipation (10). Adverse effects were common, from 3% to 72%, although all mild, including predominantly diarrhea and abdominal pain. In contrast, side effects in our population were also mild but relatively infrequent (9%). A possible explanation for this finding is the relative lower doses of medication we used in the children included in our study. It is also likely that the adult studies referenced above had a stricter and prospective data collection, whereas ours was limited because it was collected retrospectively.

This study has important limitations. The most relevant is that this is an open-label study with retrospective data collection, with all the potential biases associated to that, and the lack of a placebo arm to properly evaluate bisacodyl's efficacy. Because our study did not systematically follow patients due to its retrospective nature, it is certainly possible adverse events occurred that we were unable to assess. In addition, we were not able to control for the administration of other laxatives.

In conclusion, bisacodyl appears to be effective and well tolerated for the treatment of pediatric functional constipation refractory to conventional therapy. The majority of patients are able to be weaned off the medication and side effects seem to be mild; we observed no long-term complications with its long-term use in children. Larger prospective studies are needed to further evaluate the safety and efficacy of bisacodyl.

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