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Are *Senna* based laxatives safe when used as long term treatment for constipation in children?

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ABSTRACT

Background and aim: Senna is a stimulant laxative commonly used by pediatricians, pediatric gastroenterologists, and pediatric surgeons. Many clinicians avoid *Senna* for reasons such as tolerance or side effects but this has little scientific justification. We recently found several patients we were caring for developed perineal blistering during the course of *Senna* treatment. Because of this we chose to review the literature to identify side effects in children taking this medication as well as to analyze our Center's experience with *Senna*'s secondary effects.
Methods: We performed a literature review (MEDLINE, PUBMED) using the keywords of *Senna*, sen, sennosides and children, and pediatric and functional (idiopathic) constipation. We looked for articles with information regarding perineal blisters related to *Senna* as well as other secondary effects of *Senna* laxatives in children when used on a long-term basis. We also reviewed the charts of our patients who had previously taken *Senna* or are currently taking *Senna*, looking for adverse reactions.
Results: Eight articles in the literature reported perineal blisters after administration of *Senna* laxatives in 28 patients. Of those occurrences, 18 patients (64%) had accidental administration of *Senna* and 10 (36%) had *Senna* prescribed as a long term treatment. All of the blistering episodes were related to high dose, night-time accidents, or intense diarrhea with a long period of stool to skin contact. At our institution, from 2014 to 2017, we prescribed *Senna* and have recorded data to 640 patients. During the study period, 17 patients (2.2%) developed blisters during their treatment. Patients who developed blisters had higher doses 60 mg/day; 60 [12–100] vs. 17.5 [1.7–150] ($p < 0.001$).
All of the blistering episodes were related to night-time accidents, with a long period of stool to skin contact. 83 (13%) patients presented minor side effects such as abdominal cramping, vomiting or diarrhea which resolved once the type of laxatives were changed or enemas were started. The doses of *Senna* was not significantly different in these patients 15 mg/day [4.4–150] vs. 17.5 mg/day [1.5–150]. There were no other long-term side effects from *Senna* found in the pediatric literature for long-term treatment besides abdominal cramping or diarrhea during the first weeks of administration. We found no evidence of tolerance to *Senna* in our review.
Conclusion: There is a paucity of information in the literature regarding side effects of sennosides as a long-term therapy, and to our knowledge, this is the first review of *Senna* side effects in children. *Senna* induced dermatitis is rare, but may occur when patients need a higher dose. All of the cases described had a long period of exposure of the skin to stool. Besides the perineal rash with blisters, we could find no other described major side effect with *Senna* administration in the pediatric population or evidence of the frequently mentioned concern of the development of tolerance to *Senna*. Pediatric caregivers should advise families of the rare side effect of skin blistering and educate them to change the diaper frequently in children who are not toilet- trained to reduce stool to skin exposure. We can conclude from this review that *Senna* is a safe treatment option for constipation in children.
Level of evidence: IV.

Senna (found in leaves and pods) is an anthraquinone stimulant laxative and is the main constituent of sennosides [1,2]. Sennosides A and B are homodianthrone diglucosides of rhein, (the active component of *Senna*), or heterodianthrone diglucosides [3]. Anthraquinone derivatives show a wide array of pharmacological activities including laxative, anti-neoplastic, anti-inflammatory, anti-arthritic, anti-fungal, anti-bacterial, anti-viral, anti-platelet, and neuroprotective effects [4]. The primary mechanism of action of *Senna* is selective action at the nerve plexus of intestinal smooth muscle which increases intestinal motility [5]. Due to its natural origin, apparent low oral toxicity, effectiveness,

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and accessibility without a medical prescription, *Senna* is popular for the treatment of constipation. There is an important need for clinicians caring for children who might need this treatment to characterize the potential harmful and/or toxic effects of *Senna* which is lacking in the literature. Currently, the major reported side effects of *Senna* include abdominal cramping, electrolyte and fluid deficiencies, and malabsorption [5].

Recently, we observed a group of our Center's patients who developed a severe perineal rash with blisters while they were taking *Senna* to treat constipation. We decided to perform a literature review in order to find and describe all potential secondary effects with the use of this very common medication in children, and to review our own experience.

1. Methods

1.1. Literature review

We performed a literature review to April 2017 (MEDLINE, PUBMED) using the keywords of *Senna*, sen, Senna *alexandrina*, sennosides and safety, toxic effects, children, pediatric, functional constipation, and idiopathic constipation, excluding those references related to bowel preparation. Articles with information regarding adverse effects from *Senna* laxatives in children when used on a long-term basis were considered.

1.2. Our patient's review

We performed chart reviews on patients seen at our Center from April 2014 to April 2017 who previously received *Senna* or are currently taking *Senna* to identify potential *Senna*-related side effects. We used our pharmacy prescriptions to track down the length of treatment, change in the doses, and discontinuity. We analyzed the patient's disease, age, dose, length of the treatment, the type of side effect, the involvement of social services, and the treatment received for the side effect.

1.3. Statistical analysis

We compared dose, length of treatment, and type of *Senna* between patients who had side effects and patients who did not using non parametric test with unpaired data (Mann Whitney test). Analyses were conducted GraphPad Prism v6 (GraphPad Software; La Jolla, CA), with a two-sided p-value <0.05 considered statistically significant.

2. Results

2.1. Literature review to April 2017

We found 8 articles in the literature that mentioned perineal blisters after administration of *Senna* laxatives in a total of 28 patients. In 18 of these patients (64.3%) a single accidental high dose administration of *Senna* occurred (median dose 141 mg, 4–8 times the recommended pediatric dose (range 32.5 mg- 400 mg)). All cases of accidental ingestion of the product were in the form of chocolates squares. There were 10 patients of the 28 (35.7%) who had *Senna* prescribed as long-term treatment for diagnoses including: functional constipation [8], anorectal malformation [1], and constipation associated with spinal injury [1]. The age of these patients ranged from 23 months to 10 years. Four patients (15%) reported being diapered day and night and 24 (85%) patients had lesions evident the following morning, found when the caregiver was changing the diaper.

All of the patients reported the same type of lesion, characterized as large blisters around the perineal area that resemble a second-degree burn and associated with a severe diaper rash. In some of the patients the genital area was affected as well. There was no noted association between the skin lesion and the age of the patient, length of treatment, gender, underlying condition, or type of *Senna* administered. However, all of the patients had a long period of contact of the skin with the stool. All lesions were treated with topical creams or ointments and none required surgical intervention. Social services were involved in 9 cases (32%) because of the concern of an intentional scald (Table 1).

There were no additional references in the literature with any other safety concerns during long-term use in children, including no references to a development of tolerance.

2.2. Our Center's data from April 2014 to April 2017

Since the initiation of our Colorectal Center in April 2014, we have treated 796 patients with *Senna*. We could access dosage data and length of treatment in 640 patients. 230 (36%) were patient with functional/idiopathic constipation, 265 (41.5%) had anorectal malformation, 85 (13%) patients had Hirschsprung Disease, 53(8.2%) had spinal abnormality, and 7 patients had other colorectal diseases (1%). In 340/640 (53%) patients the dose of *Senna* was adjusted over time. 241/640 (37%) had an increase in the dose over the last 3 years. 110/640 (17.1%) needed a decrease in the dose. We did not find any patient who needed to stop the treatment due to lack of effectiveness because of tolerance.

We did not find any side effects in 540 (84.3%) patients. The median length of treatment in patients who did not have any side effects recorded in their medical charts was 338 days [1–1050]. The median dose in this cohort was 17.5 mg/day [1.7–150]. 430 (80%) of them are currently taking *Senna*, 110 (20%) have switched to an alternate therapy (rectal enema or antegrade option) or did not need laxatives anymore.

We found side effects related to *Senna* administration in 100/640 patients (15.6%). 83/640 patients (13%) presented abdominal pain/abdominal cramps or diarrhea after administration of *Senna*. The median dose for this cohort was 15.5 mg/day [4.4–120]. These effects appeared within the first week of administration. 40/83 (48%) of them resolved spontaneously after 2 weeks of treatment, 20/83 (24%) changed the type of laxative or form of *Senna*, and 23/83 (28%) switched to rectal enemas. In all of them the symptoms resolved after changing the laxative, type of *Senna*, or started on rectal enemas. The doses of *Senna* was not significantly different in patients who developed abdominal pain, cramping or vomiting compared with those who did not have any side effect 15 mg/day [4.4–150] vs 17.5 mg/day [1.5–150]($p = 0.66$).

We also found an unexpected side effect in 17/640 (2.2%) patients who developed blisters during treatment (Fig. 1). The patients' ages ranged from 2 to 7 years with a mean age of 4 years old. The lesions appeared from 2 days to 3 years after treatment. Seven patients (41%) experienced an increase in the dose days prior to the appearance of the blisters (Table 2). The doses of *Senna* prescribed ranged from 12 mg/day to 100 mg/day per day with a median of 60 mg/day [12–100]. In 11 of the 17 patients (64%), *Senna* was discontinued after the lesions developed and bisacodyl, another type of stimulant laxative, was initiated. The blisters resolved within days (Fig. 2). In six patients, the *Senna* dosage form was changed (from squares to liquid or from squares to tablets). Of these six patients, the lesions did not redevelop in 3 of them, but in the other 3 a new severe perineal rash with blisters recurred within the next 3 weeks. The decision was made at this point to transition from *Senna* to bisacodyl. All of the patients who developed blisters were diapered or wearing toilet training underwear overnight. None of the lesions occurred in patients who were in normal underwear or did not have accidents. All patients were treated successfully with topical creams and none of the cases required surgical grafts or further intervention. There were 2 patients (12%) in our series that were referred to social work due to concerns of an intentional perineal scald. Once our Center was contacted and we explained this side effect, social work concerns were dismissed.

We found significantly higher doses in patients with blisters with median of 60 mg/day [12–100] vs 17.5 mg/day [1.5–150] ($p < 0.001$). However, the length of treatment was significantly longer in patients who did not develop the blisters with a median of 338 days [1–1095] vs 120 days [1–720]($p < 0.002$). There was no significant difference between the age of those patient who developed blisters compared with

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Table 1
Cases described in the literature related to *Senna* blisters.

Article	Number of patients	Disease	Ingestion	Age	Diaper Usage	Dose	Type of *Senna*	Length	When	Social Services Involvement	Treatment
Cogley et al. Pediatric Dermatology	8	6 IC 1 ARM 1 Spinal	long term treatment	1 to 10 yo	yes	32,5 mg −150 mg	unknown	6 days to 18 months	overnight	no	topical cream
Spiller et al. The Annals of Pharmacotherapy	10	healthy	accidental	mean 2.4 yo	yes	100–117 mg	chocolate tablets and liquid *Senna*	single ingestion	overnight diaper related	30% cases	topical cream
Smith WA et al. Arch Dermatol.	2	1 healthy 1 HD	accidental long-term treatment	14mo 3 yo	yes yes	unknown 2.1 ml/day	chocolate tablets liquid	single ingestion long-term treatment	overnight diaper related overnight diaper related	no	topical cream and discontinue treatment
Leventhal et al. Pediatrics	4	healthy	accidental	23 mo 27 mo 29 mo 42 mo	yes	400 mg	chocolate tablets	single ingestion	overnight	75% cases	topical cream
MacDuff et al. Pediatric Emergency Care	1	IC	long-term treatment	33 mo	yes	unknown	unknown	long term	related to diarrhea	yes	topical cream
Durani. et al. Journal of Plastic, Reconstructive & Esthetic Surgery	1	healthy	accidental	3 yo	no	200 mg	chocolate tablets	single ingestion	related to diarrhea	no	topical cream
Cherilyn C. et al. The Journal of Emergency Medicine	1	healthy	accidental	4 yo	no	270 mg	, chocolate tablets	single ingestion	related to diarrhea and overnight	yes	topical cream
McManus et al. Journal of pediatric Child health	1	healthy	accidental	2 yo.	yes	15 mg	chocolate tablets	single ingestion	overnight	yes	topical cream

IC: idiopathic constipation.
ARM: anorectal malformation.
yo: years old.
mo: months old.
HD: Hirschsprung Disease.

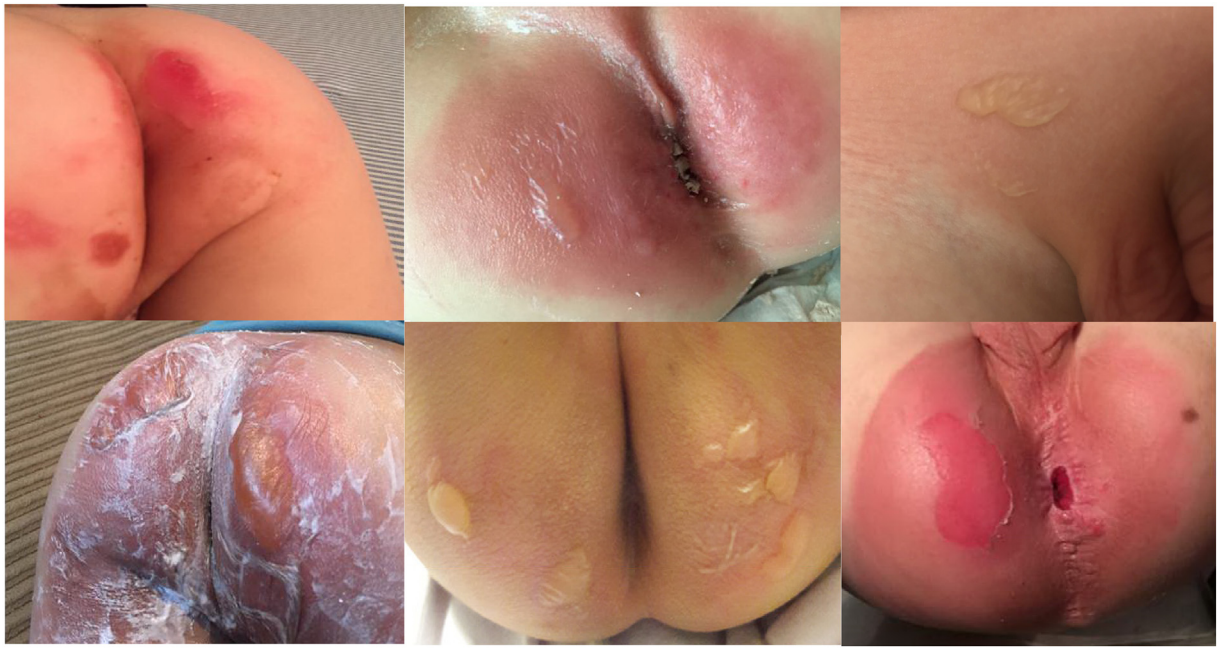

Fig. 1. Blisters associated with *Senna* usage.

those who did not, with median age 5 years [0.8–23] vs 4 years [2–7] ($p = 0.2$).

3. Discussion

In this manuscript we present a literature review on *Senna* based laxatives in children looking for side effects. We also present our experience in a pediatric Colorectal Center with the same laxative usage. We found an unexpected side effect in the literature; There are 8 papers in the literature referencing a perineal blisters and severe perineal rash after accidental administration of *Senna*. We also found this unexpected side effect in the 2.2% of our patient population. We found a strong correlation between higher doses of *Senna* and the blisters, however we did not found correlation between the length of treatment, or age. All the patients who developed the blisters reported in the literature and in our cohort had a long period of contact of stool to skin. Regarding other side effects in our population abdominal cramps, vomiting, and diarrhea were found in 83 patients; 53% of our patients needed an adjustment in the dose of *Senna* during the study period; 241 patients (37%) increased the dose in the last 3 years and 110/640 (17.1%) needed a decrease in the dose. We think the increase in the dose may be due to normal child growth and not related to tolerance. We did not find any patient who increased the dose and needed to stop the treatment due to tolerance.

From its introduction in the 19th century, anthranoid laxatives have been widely used throughout the world. Among the plants that contain anthranoid glycosides laxatives, *Senna* (*Senna alexandrina* or *Cassia angustifolia*) is the most used [6]. The onset of action generally occurs within 6–8 h after consumption. The products are easily accessible to consumers in many different dosages and forms (liquid, tablet, chewable tablet, syrup, etc.). The anthranoid glycosides are generally well tolerated as they are not absorbed in the small intestine, and instead, are maintained as prodrugs until they reach the large intestine, where they are metabolized to the active form [7].

Recently, a randomized trial studying the effectiveness of *Senna* vs. Poly-ethylene glycol (PEG) in patients with functional constipation or anorectal malformations concluded, with a level A evidence, that *Senna* laxatives should be the treatment of choice in this patient population due to its helpful stimulant characteristics [8]. There are only 2 prospective trials comparing mineral oil and lactulose with *Senna* for the treatment of chronic constipation in children [9,10]. In these reviews the only side effects described with *Senna* were abdominal cramps in the first weeks of administration; no other side effects were described. Limitations of these studies included a lack of description of randomization methods, the studies were unblinded, and exclusions from the studies were not described [9,10]. Additional studies have found *Senna* based laxatives to be well tolerated and safe when used as a bowel preparation before colonoscopy in the pediatric population but these studies referred only to short term treatment results [11,12].

Of the stimulant laxatives, *Senna* compounds and bisacodyl are the most commonly used in adults. Although there is some data to support the neoplastic potential of this class of drugs in vitro studies, epidemiologic data in humans thus far have not established such a link [13]. Additionally, the link between stimulant laxatives and structural changes, such as the "cathartic colon", enteric nerve damage, or habituation is not well established either [14].

In 2009, a systematic literature review to identify the potentially harmful or toxic effects of the anthranoid laxatives (*Senna*) analyzed 50 basic science articles with animal experimentation and human clinical research, however, none of the studies analyzed *Senna* use in the pediatric population [6]. This review concluded that there was no convincing evidence that the chronic use of *Senna* has any structural or functional alteration of the enteric nerves or on the intestinal smooth muscle. It also affirmed that there is no relationship between the long-term administration of *Senna* extract, the appearance of gastrointestinal tumors, or of any other tumor in rat experimental models. *Senna* was not found to be carcinogenic in rats even after a daily administration for 2 years in doses up to 300 mg/kg/day, and the evidence currently available does not show that there is a risk of genotoxicity for patients who consume *Senna*-based laxatives [15].

In 2011 an evidence-based systematic review of *Senna* demonstrated that its most common side effects in humans included: abdominal pain, cramping, flatulence, nausea, bloating, diarrhea, vomiting, and incontinence. [16]. We found the same minor side effects in 10% of patients in our cohort. Chronic liver damage, portal vein thrombosis and hepatitis have been reported following the use of *Senna* alkaloids in the elderly with underlying conditions [17,18]. Loss of haustral folds in the colon and pigmentation of the colon (melanosis coli) has been reported as a result of chronic *Senna* use in adults [16]. In severe melanosis coli, apoptosis seems to be delayed, causing longer crypts but without a

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Table 2
Characteristics of patients who developed *Senna* blisters in our center.

Patient	Disease	Age	Diaper	Dose	Type of *Senna*	Length	When	Type of lesion	Social services	Treatment
1	IC	7yo	no	75 mg/day (5/kg)	squares	3 months	Overnight	Blister	no	Switch to bisacodyl
2	IC	5yo	yes	60 mg/day (3.5/kg)	squares	7 days	Overnight	Multiple blister	no	Switch to bisacodyl
3	ARM	4yo	yes	20 mg/day (3/kg)	squares	1 week	Overnight	Multiple blisters	no	Switch to bisacodyl, barrier cream
4	IC	4yo	yes	62.5 mg/day (3,4/kg)	squares	3 months	Overnight	Big blisters	yes	Switch to bisacodyl
5	IC	5yo	no	75 mg/day (3.75/kg)	squares	4 days	Overnight	Big blisters perineal and penile	no	Switch to bisacodyl
6	IC	4yo	no	45 mg/day (1.5/kg)	squares	3 days	Overnight	Small blisters perineal and penile	no	Switch to *Senna* tablets but blister reappeared. Then bisacodyl
7	ARM	3yo	yes	45 mg/day (3/kg)	squares	3 weeks	Overnight	Big blisters	no	Squares to *Senna* tablets
8	HD	3yo	yes	22.5 mg/day (1.5/kg)	squares	1 years	Overnight (symptoms of enterocolitis)	Small blisters	no	Switch to liquid *Senna* but blister reappeared. Then bisacodyl
9	ARM	4yo	yes	82.5 mg/day (4.5 mg/kg)	squares	3 months	Overnight	Small blisters	no	Bisacodyl
10	ARM	4yo	no	60 mg/day (3.5/kg)	squares	1.5 years	Viral diarrhea, overnight	Big blisters	yes	Polyethylene Glycol suppository
11	HD	2yo.	yes	30 mg/day (3 mg/kg)	liquid	2 years	Overnight	Small blisters	no	Switch to *Senna* tablets, barrier cream
12	HD	3yo.	yes	12 mg/day (1 mg/kg)	liquid	8 months	Overnight	Big blisters	no	Switch to bisacodyl, barrier cream
13	ARM	5yo	yes	70 mg/day (4.6/Kg)	liquid	6 months	overnight	Small blisters	no	Switch to *Senna* tablets
14	IC	5yo	yes	97.5 mg/day (5 mg/kg)	squares	4 months	overnight	Big blisters	no	Switch to liquid *Senna* but blister reappeared. Then Bisacodyl
15	SCT	4yo	yes	100 mg/day (? mg/Kg)	squares	7 days	overnight	Big blisters	no	Switch to bisacodyl
16	HD	2yo	yes	15 mg/day (1.5 mg/Kg)	squares	1 day	After stool accident	Big blisters	no	Switch to bisacodyl
17	HD	5yo	yes	30 mg/day (1.5/kg)	liquid	1 year	After stool accident	Small blisters	no	Switch to bisacodyl

IC: idiopathic constipation.
ARM: Anorectal malformation.
HD: Hirschsprung Disease.
yo: years old.
mg: milligrams.

rise in proliferative activity. This escape from a presumably protective mechanism may enhance the risk of carcinogenesis [13]. A retrospective analysis of 2229 adults who used anthraquinone laxatives was carried out in search of a relation between melanosis coli and the use of *Senna*-based laxative with the development of colorectal cancer. Although colorectal adenomas were found with a greater frequency in patients with melanosis coli than those without, the presence of colorectal cancer was not associated with melanosis coli or the use of laxatives [19,20]. A cause–effect relationship between melanosis coli and colon cancer remains only speculative [21].

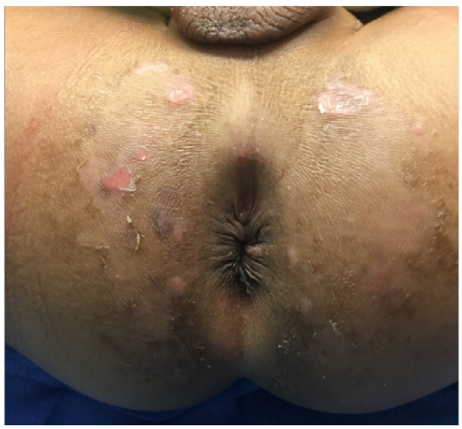

Fig. 2. Appearance of the perineum 2 weeks after *Senna* was discontinued.

There are some lesser known side effects related to *Senna* use in children. A total of 8 articles to date report the same skin lesions we have described here [22–29]. These lesions appear to be unrelated to the length of exposure, age, type of *Senna* administered, or gender. They do seem to be clearly related to length of time of skin contact with stool and the doses were high. We also found statistical correlation between the dose of *Senna* and the development of *Senna* blisters. In a high percentage of cases, social services was involved because the location and severity of the lesions can be suspicious for nonaccidental trauma. All of the accidental ingestions were related to the chocolate form of this medication. This attractive formulation is helpful to entice children to take their medication, but can also confuse the drug with chocolate candy. It is very important to alert all pediatric specialists that this a rare skin lesion associated with a laxative that could mimic intentional submersive scalding. Lesions can range from a mild perineal rash to a second degree burn with blisters around the perineal area [22–29].

The pathogenesis of the skin reaction to *Senna* overdose is unclear. It may be that the high concentration of digestive enzymes in the diarrheal stool due to the increased gut transit time may cause a chemical contact burn to the skin [26]. However, this theory does not explain the skin lesions in children that are on chronic treatment and do not have diarrhea. There have been a few reports of sennoside eruptions in adults, including Erythema multiforme (2 cases), fixed drug eruption (2 cases), lichenoid reaction (2 cases), toxic epidermal necrolysis

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(1 case), urticaria (1 case), photosensitivity (2 cases), and contact dermatitis (3 cases) [30–35].

Despite an extensive search of both the medical and lay literature we did not find any reference to long term tolerance due to treatment which we find is a frequently mentioned concern by families and clinicians.

It has been proposed that patients who are not toilet trained should take *Senna* at a time that allows for bowel movements to occur during the day and not overnight [28]. This avoids contact between the stools and the skin for a long period of time. We agree with this recommendation and would also advise that the caregiver protect the skin with a barrier cream in those patients who are diapered and taking *Senna*. We also suggest that *Senna* be stopped and the laxative type switched to an alternative stimulant laxative, to avoid this secondary effect from happening again, as we had two recurrences in patients who only changed the dosage form of *Senna*.

We found some important limitations to our study. This is a retrospective review of our cohort of patients taking *Senna*. We obtained the data from the medical charts of our patients. Although, *Senna* based laxatives is a medication which could be obtained over the counter and the doses can be modified by parents without a medical prescription. Parents managed the doses depending on daily basis bowel pattern, and this could be affected by age, food or concomitant conditions. Therefore we acknowledge some bias in the data.

We conclude that despite its common usage, there is a lack of information regarding the safety of *Senna* in children. A trial and long-term analysis would be needed to clarify its consequences when used as long-term treatment for functional constipation, or other conditions in children. We can conclude that there is a low risk of developing adverse side effects associated with its use and it is safe when used as directed or under the supervision of a healthcare provider. Perineal blisters may occur associated with *Senna* based laxatives and are more likely in diapered children. This adverse effect is self-limited if the *Senna* is discontinued and can be managed with topical creams. Parental and clinician education and counseling to recognize this complication is mandatory when prescribing this treatment in children. Improved awareness of this side effect can prevent inappropriate social service consults. Moreover, the often mentioned concern for tolerance to laxative therapy has no scientific basis.

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