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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