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Are all stimulant laxatives the same? A comparative perspective on bisacodyl, sodium picosulfate (SPS) and senna

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Stimulant laxatives, such as bisacodyl, sodium picosulfate (SPS), and senna, are recommended to treat constipation, based on the recent AGA/ACG guideline [1], with different levels of recommendation and evidence. They all stimulate intestinal motility, as well as water and electrolyte secretion, and accelerate intestinal transit time [2, 3]. Herbal laxatives cannot be generalized to be gentler compared other to synthetic laxatives [1]. A retrospective observational study demonstrated that bisacodyl can be used safely even for prolonged treatment duration [3]. Long-term use of bisacodyl and SPS during pregnancy and use during breastfeeding has shown no evidence of undesirable or harmful effects [4].

Natural laxatives are not necessarily safer to use

There is a general misconception that natural and herbal drugs are better and/or safer for our health compared to synthetic medicines. Not all natural products have been proven to be effective and additionally, some have been associated with serious safety concerns [5]. The aim of this review was to summarise and compare the current evidence on three stimulant laxatives commonly used in clinical practice: SPS and bisacodyl (both of synthetic origin) and senna (natural origin).

Commonalities and differences in the mechanism of action of stimulants

The global prevalence of constipation is estimated at 14% [2, 3]. The pharmacological treatments for constipation include fibre (e.g. psyllium), osmotic laxatives (e.g. polyethylene glycol, PEG), stimulant laxatives (e.g. bisacodyl, senna, SPS), secretagogues (e.g. linaclotide) and serotonin agonists (e.g. prucalopride) [1]. In the case of stimulant laxatives, they can be subdivided into two categories: diphenylmethane derivatives (e.g., bisacodyl and SPS) and plant-based anthraquinones (e.g., senna, aloe, and cascara) [2, 3]. In this review, we will focus on bisacodyl, SPS and senna, which are commonly used stimulant laxatives.

All stimulant laxatives have been shown to have both, prokinetic and secretory effects on the colon, by stimulating both, intestinal motility as well as water and electrolyte secretion, and therefore, accelerate gut transit time (**Fig. 1**) [2, 3].

Bisacodyl and SPS are both prodrugs and are converted in the gut into the same active metabolite bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM), responsible for the laxative effect. While bisacodyl is converted to BHPM by endogenous enzymes of the intestinal mucosa, the conversion of SPS to BHPM is dependent on colonic bacteria (**Fig. 2**) [2].

Senna is a derivate from the senna plant and contains sennoside A and B, which require being metabolized by gut bacteria into the active metabolites rhein anthrone and rhein (**Fig. 2**) [3].

Therefore, both SPS and senna depend on bacterial activity to obtain a laxative effect. If the intestinal microbiome is altered, for example due to antibiotic treatment, the effect of these laxatives may be impaired, suggesting bisacodyl owns a more consistent effect [2], though this notion awaits confirmation.

The guideline highly recommends bisacodyl and sodium picosulfate

When it comes to clinical evidence, studies on bisacodyl and SPS have been conducted since the 50's and since the introduction of good clinical practice three major clinical trials have been performed [2]. Based on evidence from trials, the AGA/ACG recently published a clinical practice guideline for the pharmacological management of chronic idiopathic constipation where both bisacodyl and SPS have been categorized as strongly recommended for short-term treatment (daily use for 4 weeks or less) or

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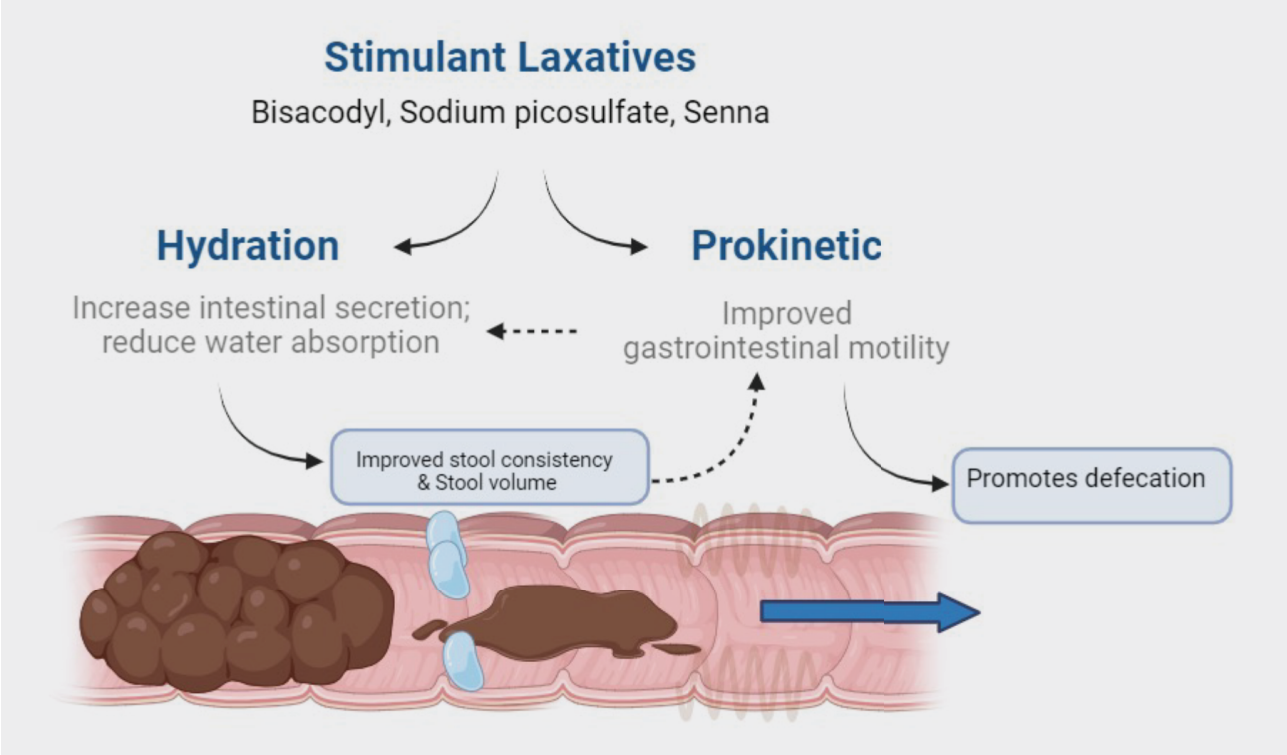

Fig. 1. Mechanism of action of stimulant laxatives [2].

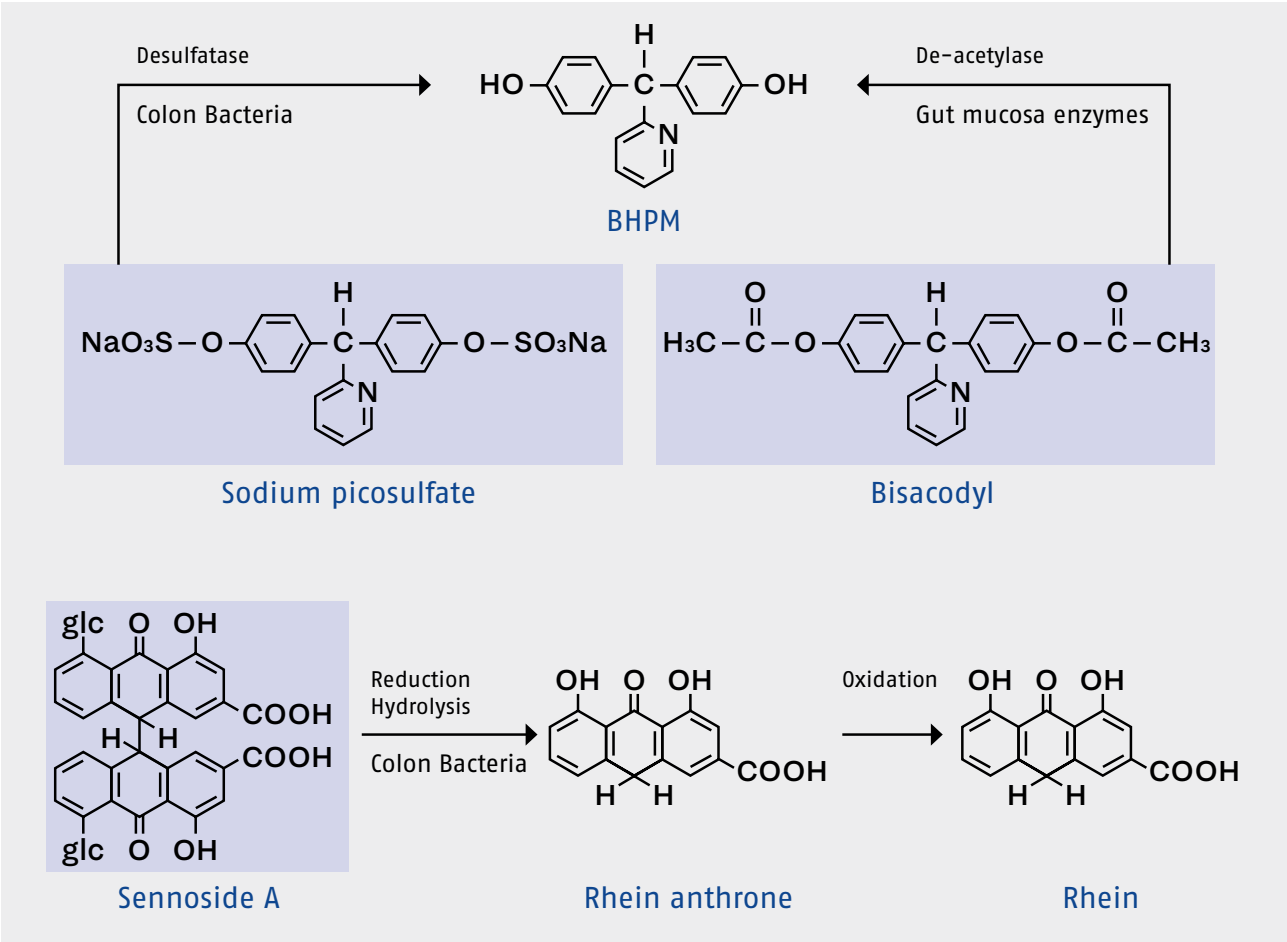

Fig. 2. Metabolism of bisacodyl and sodium picosulfate and senna. BHPM = bis-(p-hydroxyphenyl)-pyridyl-2-methane. Adapted from [6].

as rescue medication. This classification is the highest level of recommendation and certainty of evidence among the different laxatives included in the AGA/ACG guideline [1]. Furthermore, the fact that bisacodyl and SPS are recommended as rescue medication for clinical trials investigating new compounds suggests that there is no doubt on their effectiveness [2]. In published RCTs, the initial daily dose was 10 mg orally for both SPS and bisacodyl allowing a down-titration during the treatment period. The percentage of patients with drug-related AEs (diarrhea or abdominal pain) decreased markedly when reducing the dose, suggesting the treatment was better tolerated once patients established their individual dose [2, 3]. In addition, the AGA/ACG guideline recommends starting at a lower dose and increase it if tolerated and needed, being in line with previous findings for a better constipation management [2, 3].

Patients occasionally express a desire for a natural laxative such as senna, based on the conviction that a natural laxative might be more gentle and more tolerable. However, when looking into the literature, large, randomized, controlled trials on senna are lacking [2]. In a recent systematic review and meta-analysis, senna supplementation did not show better results than placebo in terms of improving constipation symptoms [7]. In addition, the AGA/ACG guideline rated senna with conditional strength of recommendation and low certainty of evidence [1]. The authors of the guideline highlight the fact that the available studies use higher doses compared to those commonly used (1 g daily vs. 6–17 mg daily), which implicates that further studies are necessary [1, 7].

Therefore, based on available evidence and supported by international guidelines, bisacodyl and SPS show more robust data than senna in the management of chronic idiopathic constipation, which is the reason for their higher level of recommendation.

Safety considerations for up to 28 days and long-term use

In contrast to PEG and more recent approved drugs, the available evidence on long-term use of bisacodyl, SPS and senna is limited [3]. Nevertheless, concerns on dependency, habituation/tolerance or damage to the gut are continuously raised. These are based on unsubstantiated assumptions and experience with other laxatives and can be refuted by recent studies investigating bisacodyl [2].

From a pharmacological perspective, the active metabolite BHPM (from bisacodyl and SPS) is not absorbed and cannot cross the blood-brain barrier and therefore cannot cause dependency of any kind, regardless of the duration of use [2, 3, 8].

Given the fact that there is limited information on long-term use, a recent retrospective observational study may be helpful to supplement clinical data [3]. In this study, the authors assessed changes in dosing of bisacodyl during continuous use for at least 28 days.

Throughout the follow-up period, 94.0% of patients maintained their initial dose of bisacodyl. Only seven patients (4.2%) of those taking bisacodyl 5 mg increased their dose, while four patients (10.8%) in the 7.5 mg group and two patients (13.3%) in the 10 mg group decreased their dose during this period (**Fig. 3**). These results suggest that bisacodyl can be prescribed in a stable dose and, in line with previous studies, there were no signs indicating a potential habituation [3].

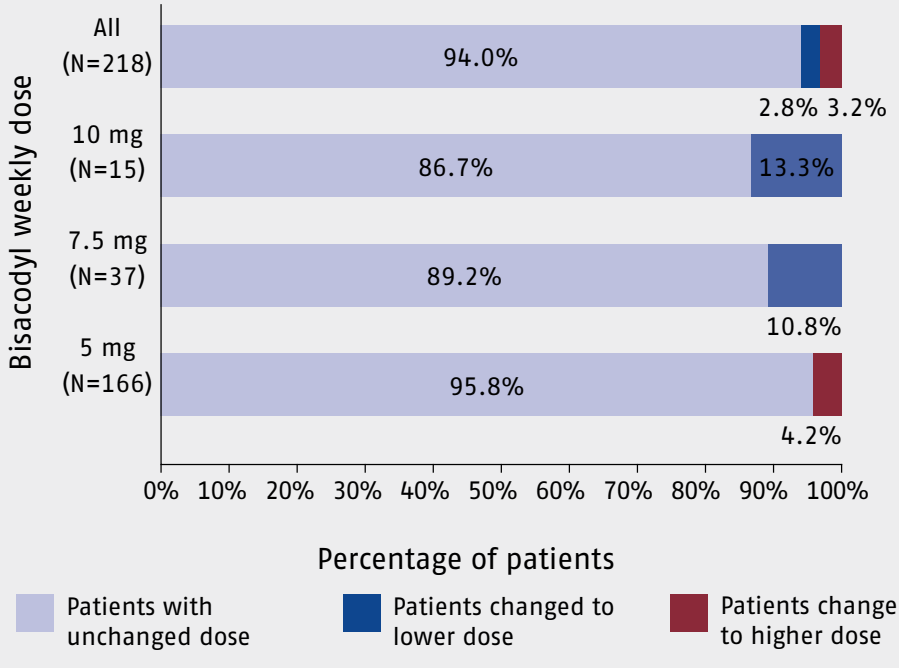

Fig. 3. Proportion of patients with dose changes during the follow-up period in the long-term cohort. Adapted from [3].

On senna side, a systematic review reported that two-thirds of individuals suffering from chronic constipation discontinued senna-based treatments due to insufficient relief of bowel symptoms and due to side effect. The two studies analysed included 254 participants taking between 15 mg and 1 g of senna daily [7].

Safety of use during pregnancy and lactation

The compounds bisacodyl and SPS have been used to treat constipation since the 50's and the 60's, respectively. There are no adequate and well-controlled studies conducted in pregnant women. However, there has been no evidence over the last 70 years regarding undesirable or damaging effects during pregnancy [2].

A study with eight lactating mothers showed that no active ingredient was excreted in breast milk even after multiple administrations of bisacodyl [2]. The Embryotox database concludes that breastfeeding is possible without restriction during bisacodyl therapy [9].

The assessment of the use of SPS during pregnancy and lactation is consistent with that of bisacodyl [10]. In contrast, there are reasons not to use senna in pregnant women, as chemically comparable substances have shown weak genotoxic effects in animals [1].

Summary

The natural or synthetic origin of laxative medications does not define whether one is safer or more effective than another. Both are medicines and must prove their effectiveness and safety in clinical trials. The most recent guideline from AGA/ACG recommends using natural and synthetic stimulants to treat chronic idiopathic constipation but grants different levels of recommendation and evidence. The authors criticize the lack of trial data and the fact that unusually high doses were used in the available studies.

Bisacodyl and SPS are locally acting laxatives with effects on intestinal secretion and motility and are considered being standard treatments for constipation. Treatment should be initiated at a low dose and increased as needed. Since chronic idiopathic constipation often occurs over long periods of time, a safe and clinically effective treatment is needed. Available studies indicate that long-term intake of bisacodyl is not associated with habituation or dependence.

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