

Diphenyl methane laxatives do not induce electrolyte imbalance

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ABSTRACT

Aim: To analyse whether there are changes in sodium and potassium serum levels during chronic treatment with the diphenyl methanes bisacodyl and sodium picosulfate. **Methods:** A literature search was done using PubMed, and the reference lists of pertinent papers were screened for additional studies. Only studies of at least 4 weeks duration were considered for further analysis. **Results:** Four relevant studies were identified. In three randomised controlled trials with 5 to 10 mg daily of bisacodyl or sodium picosulfate, respectively, over four weeks no electrolyte losses were found. Hypokalemia was also not a problem in a group of patients with paraplegia using bisacodyl suppositories for 2 to 34 years. **Conclusions:** Electrolyte losses, particularly hypokalemia, are not a problem when bisacodyl or sodium picosulfate are used long-term.

Keywords: Laxative; Bisacodyl; Sodium Picosulfate; Hyponatremia; Hypokalemia

1. INTRODUCTION

Consumer reports, whether printed or in the internet, often contain warnings of side effects of laxatives, particularly of the so-called stimulant laxatives. These comprise the anthraquinones (e.g. sennosides) and the diphenyl methane derivatives (bisacodyl and sodium picosulfate) and exert a dual, namely a secretory and a prokinetic action [1,2]. These warnings read e.g. “confusion, irregular heartbeat, muscle cramps, and unusual tiredness or weakness” [3-6].

Similar concerns have, to my knowledge, not been expressed regarding water binding laxatives (salinic laxatives, sugars such as lactulose, and macrogol). Nor have they been expressed for pure prokinetics such as prucalopride and the new secretory stimulants lubiprostone and linaclotide, potentially because the manufacturers

were hitherto successful in avoiding the term “laxative” for these products.

If these side effects would occur they would occur with almost certainty be due to electrolyte losses, particularly of potassium. It is well known that induction of diarrhea by these laxatives may lead to hypokalemia [7-9], but this does not allow the conclusion that such losses may also occur when the laxatives are used in the proper dose.

The purpose of the present paper is to present the available data of sodium and potassium serum levels during chronic treatment of chronic constipation with diphenyl methanes.

2. METHODS

A literature search was done using PubMed with the terms (diphenyl methanes OR bisacodyl OR sodium picosulfate) AND (electrolytes OR sodium OR potassium) and the available respective MeSH terms (“picosulfate sodium” [Supplementary Concept]) AND (“Hypokalemia” [Mesh] OR “Water-Electrolyte Imbalance” [Mesh]). In addition the reference lists of the papers were screened for additional studies. Only studies of at least 4 weeks duration were considered for further analysis. The manufacturer of bisacodyl and sodium picosulfate was then asked to provide the original data on electrolytes from the respective trials.

3. RESULTS

The oldest paper on the subject reports long-term data from 101 patients with spinal cord injury using bisacodyl over a period of 2 to 34 years. Patients used bisacodyl suppositories, predominantly one to two suppositories two or three times weekly [10]. Only two patients had potassium levels slightly below the lower limit of normality and without clinical relevance (**Figure 1**). However, no information is available regarding intake of other drugs affecting serum electrolytes such as diuretics.

There are three randomised controlled trials with

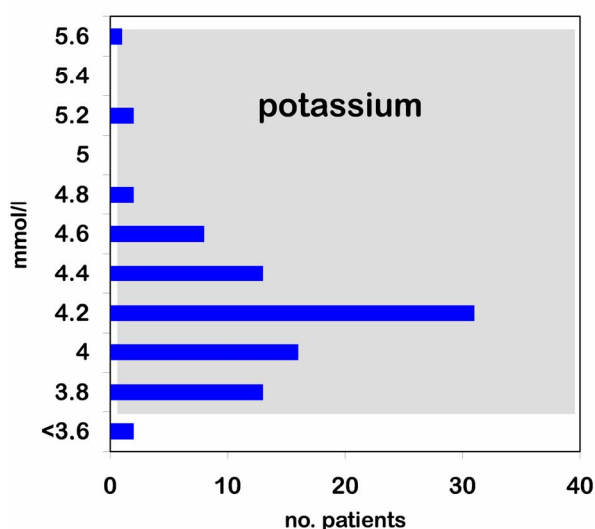


Figure 1. Serum potassium levels in 88 paraplegic patients chronically using bisacodyl suppositories. More than 80% of the patients used bisacodyl for more than 5 years. Shaded area: normal range. Data from 10.

orally administered diphenyl methanes over 4 weeks each in patients with chronic constipation according to the Rome II and Rome III criteria, respectively [11,12]. After a one to two weeks baseline period, patients were randomized to one of two arms.

In the first open-label study, bisacodyl 5 to 10 mg was compared to 5 to 10 mg sodium picosulfate daily in 144 patients [13]. There was no difference regarding efficacy between both drugs, and there were no losses of electrolytes as shown in **Figure 2(A)**.

The second study compared bisacodyl 5 to 10 mg to placebo in 368 patients [14], and the third study compared sodium picosulfate 5 to 10 mg to placebo in 367 patients [15]. As expected, active treatments were largely superior to placebo. **Figures 2(B)** and **(C)** show the time course of serum sodium and potassium in these double-blind trials. Again, hypokalemia or hyponatremia did not occur.

The designs of these trials are summarized in **Table 1**, baseline characteristics of their patients are given in **Table 2**.

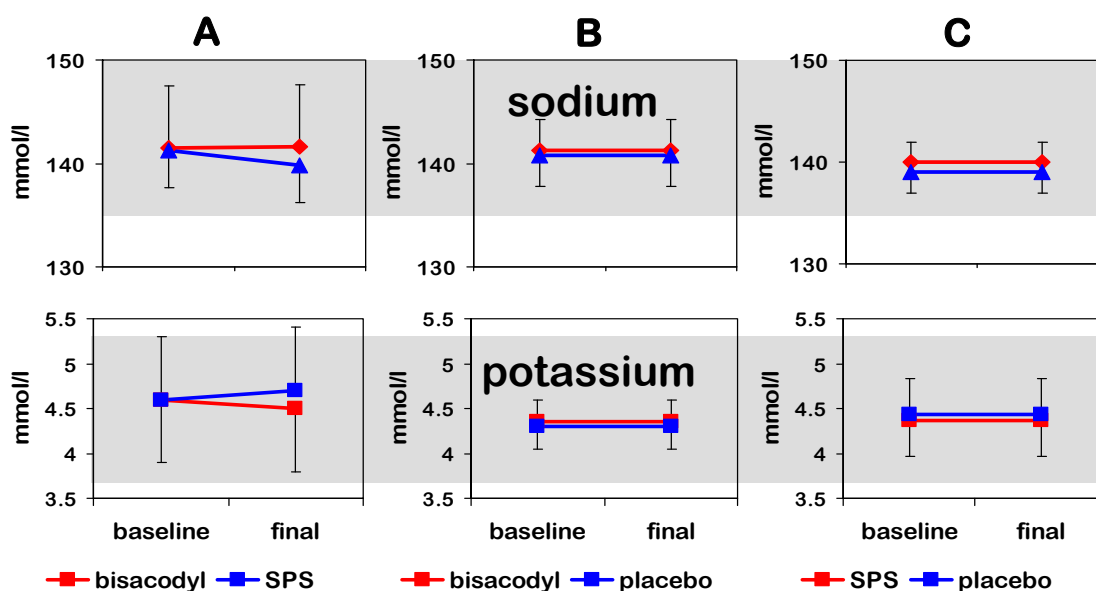


Figure 2. Serum levels of sodium and potassium at the beginning and end of treatment with bisacodyl, sodium picosulfate (SPS), and placebo, respectively, for 4 weeks (means \pm SD). Shaded area: normal range. (A) from Ref. [13]; (B) from Ref. [14]; (C) from Ref. [15].

Table 1. Characteristics of published studies with bisacodyl or sodium picosulfate in chronically constipated patients giving details on serum electrolytes. SPS: sodium picosulfate.

Number of patients	Treatment arm 1	Treatment arm 2	Duration	Reference
88	1 to 2 bisacodyl suppositories 2 to 3 times weekly	None	2 to 34 years	[10]
144	Bisacodyl 5 to 10 mg daily	5 to 10 mg SPS daily	4 weeks	[13]
368	Bisacodyl 5 to 10 mg daily	Placebo	4 weeks	[14]
367	SPS 5 to 10 mg daily	placebo	4 weeks	[15]

Table 2. Baseline data from studies with bisacodyl or sodium picosulfate in chronically constipated patients giving details on serum electrolytes. SPS: sodium picosulfate.

Reference	[13]	[14]	[15]
Number of patients on bisacodyl	70	247	-
Number of patients on SPS	74	-	233
Number of patients on placebo	-	121	134
Number of females (n, %)	104 (67.5)	275 (74.7)	285 (77.7)
Age (years, s.d.)	62.7 (18.3)	55.4 (15.6)	50.8 (16.9)
Duration of constipation (years, s.d.)	>6 months	21.2 (19.2)	13.2 (14.0)
Baseline stool frequency (per week, s.d.)	3.2 (1.2)	4.2 (1.1)	3.1 (1.1)

There were no differences regarding sex distribution, age, duration of constipation, and baseline stool frequency between the treatment groups within the three trials.

4. DISCUSSION

The role of the colon is threefold, namely absorbing water from intestinal contents, retaining, mixing and propelling feces, and allowing bacterial degradation of undigested nutrients such as dietary fiber. The latter considerably contributes to the energy balance of species with a large cecum such as rodents but is of minor importance in man. About 2 liters of small intestinal juice enter the colon each day being reduced to around 200 ml of more or less solid feces. However, in diarrheal states large amounts of fluids may be excreted. This fluid contains electrolytes in concentrations isoosmotic to serum. This holds true for both osmotic and secretory diarrhea. Both anthraquinones and diphenyl methanes may induce diarrhea when given in too high doses. This is a well known effect in psychiatric patients abusing laxatives such as anorexia nervosa or Munchhausen's syndrome [7-9,16]. Under these circumstances hypokalemia is the most prominent and dangerous laboratory abnormality potentially causing muscle weakness and kidney injury. However, these psychiatric conditions definitely differ from chronic laxative intake for constipation, e.g. since the laxative intake is concealed by the users.

Diarrhea is the desired effect if laxatives are used in bowel cleansing protocols. However, such protocols today usually contain macrogol alone or in combination with another laxative such as bisacodyl. Macrogol preparations for bowel cleansing contain however electrolytes in isoosmotic concentration in order to prevent electrolyte from shifting from blood to the colonic lumen. Therefore, data from studies on bowel preparation are not likely to show potential electrolyte losses induced by bisacodyl and are not suited to refute such a side effect. Rather the analysis had to focus on trials with one secretory laxative only.

Since chronic constipation usually requires long-term laxative intake, only studies of several weeks duration were considered for further analysis. In addition, it is already known that short time treatment with bisacodyl or

sodium picosulfate does not affect serum electrolytes [17].

Regarding longer treatment, the available data clearly show that bisacodyl and sodium picosulfate as used both in controlled trials and in open observations do not have untoward effects on the electrolyte balance. This holds true for trials over four weeks and for observations over years and decades. On one hand, this is not surprising since laxatives should be used by constipated patients in doses not leading to diarrhea but to a soft formed stool. However, as reported in nearly all trials with laxatives diarrhea sometimes does occur although not intended. This is reflected in the recent trials with bisacodyl and sodium picosulfate, respectively, where patients were allowed to lower the daily dose [14,15]. The fact that about half of the patients on verum did so suggests some diarrhea occurring with the full dose. However, these days were obviously irrelevant with regard to serum electrolytes.

Can the compliance with the dose be extrapolated from controlled trials to the real life situation? From an observational study in constipated patients taking sodium picosulfate, it is known that nearly all users adhere to the recommendation regarding interval of intake and dose [18]. This makes it highly unlikely that the use of diphenyl methanes in daily practice will expose the users at risk for electrolyte losses.

In summary, there is not only no indication that chronic use of diphenyl methanes in recommended doses may lead to electrolyte imbalance, particularly hypokalemia, but controlled trials have specifically refuted this side effect.

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