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Randomised, placebo-controlled, double-blind study to investigate the efficacy and safety of the acute use of sodium picosulphate in patients with chronic constipation

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Disclosures
Vix, Schuijt and Peil are employees of Boehringer Ingelheim. Wulkow, Kamm and Jordan acted as consultants to Boehringer Ingelheim.

SUMMARY

There are few studies supporting the effective and safe use of laxatives for constipation. This study examined the short-term efficacy and safety of sodium picosulphate in patients with chronic constipation. Patients with a history of chronic constipation for at least 3 months were randomised to receive 7 mg sodium picosulphate or placebo for three consecutive nights. Patients recorded stool frequency and consistency, straining, bloating, and pain at baseline and during treatment. Vital signs, haematocrit, serum creatinine and electrolytes were monitored. Primary end-point for efficacy was the occurrence of a response to treatment, defined as improvement in stool frequency and occurrence of straining. All 57 randomised patients (sodium picosulphate n = 29, placebo n = 28; mean age 54.8 and 54.1 years) completed the study. Sodium picosulphate produced a treatment response (improved stool frequency and straining) in 82.8% compared with 50% in the placebo group ($p = 0.010$) and reduced bloating more often than placebo. There were no serious adverse events and one patient with diarrhoea and another with abdominal pain in each treatment group. There were no cardiovascular effects, changes in serum haematocrit, creatinine or electrolytes in either group. This study confirmed that sodium picosulphate is an effective, well-tolerated and safe laxative in the acute treatment of constipation.

What's known
Sodium picosulphate has been developed as laxative for the treatment of constipation. Since then it has been used by many patients as safe and effective stimulant or contact laxative; in most countries as non-prescription drug. Most clinical trials have been performed in the time before Good Clinical Practice was introduced.

What's new
This study provides clinical efficacy and tolerability data for acute treatment of constipation obtained in a clinical trial performed under GCP conditions.

Introduction

Given the high prevalence of chronic idiopathic constipation (up to 28% of the population in the developed world) and its impact on both genders at all ages, there is a need for simple, low-cost, safe and effective treatments (1–6). Where changes in diet, such as increased intake of fibre, have failed to provide adequate relief from symptoms, laxatives are generally viewed as a first-line pharmacological treatment (7). These may be prescribed by the physician or self-prescribed and obtained as over-the-counter preparations. Surprisingly, however, there are relatively few placebo-controlled studies evaluating their efficacy and safety (8,9).

Laxatives act through a number of different mechanisms, as osmotic agents, as lubricants or surfactants, or as stimulants, the latter including polyphenolic and anthraquinone compounds. All of these modify net intestinal water absorption, which has an indirect effect on gut motility, but the stimulant laxatives also have a direct action on gut motor function. Sodium picosulphate is one of polyphenolic group of stimulant laxatives. It is converted to the active diphenol form through the action of bacterial enzymes in the colon (10). As a result, its effects are directed principally at the target organ, namely the colon.

Although they may improve large bowel motor function, laxatives, by virtue of their effects on water reabsorption and transit in the gastrointestinal tract, also have the potential to cause changes in electrolyte and fluid balance. Thus, a key consideration in evaluating safety relates to their potential effects on plasma electrolytes. We report here a multi-centre, randomised, placebo-controlled trial of the safety and efficacy of sodium picosulphate in the short-term treatment of patients with chronic constipation in an outpatient setting. The study was designed to establish the effectiveness of sodium picosulphate in

improving the symptoms in patients with chronic constipation, and to determine its safety in terms of adverse events and effects on electrolyte balance.

Methods

This study aimed to determine the safety and efficacy of sodium picosulphate over a 3-day treatment period in patients with chronic constipation. It was conducted in five general practitioner clinics in Germany and was a phase IV, double-blind, randomised, placebo-controlled, parallel group design trial.

Patient population

Male and female patients aged 18 years or older, having a history of chronic constipation for at least 3 months and who were able to give their informed, written consent, were eligible for the study. Chronic constipation was defined as the need for straining during 25% or more of bowel movements, and/or a stool frequency of < 3 bowel movements per week (11,12).

Patients were excluded if there was evidence of organic gastrointestinal disease, if they had undergone abdominal surgery within the previous 4 weeks, or had undergone any surgery involving the colon or small intestine (other than appendectomy) within the past 12 months. Other exclusions were: severe hepatic, renal, cardiac, metabolic or haematological disease, a history of malignancy or chronic spinal injury. Female patients who were pregnant or breast-feeding were also excluded.

Patients were excluded if they were a chronic user of any drug likely to affect the gastrointestinal tract or electrolyte balance, were currently taking antibiotics, had received a study drug during the last 4 weeks, or had a history of alcohol or other drug abuse. A washout phase of at least 1 week was required following any recent treatment with laxatives.

Ethics approval

The study was approved by the Innovex (Biodesign) GmbH Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki. All patients provided written, informed consent.

Trial design

On day 1 of the study, patients underwent a physical examination and provided information on their demographic details, medical history, concomitant medication and bowel function in relation to stool frequency and consistency, straining, bloating and abdominal pain. In addition, on days 1 and 5 (or 6), blood pressure and heart rate were recorded and blood samples were taken for determination of haematocrit, creatinine and serum electrolytes to provide baseline and end of treatment values. Where significant deviations of laboratory values from the normal range for the investigator site were detected, they were followed up until normalisation had been achieved through standard medical practices.

The study medication was taken once daily in the evening, before going to bed, on days 1, 2 and 3 of the study.

Patients were required to complete a daily diary card for days 1–5. In addition to filling a check box to confirm that study drug had been taken, stool frequency and stool consistency, occurrence of straining, bloating and abdominal pain were recorded. Daily frequency of stool was categorised as 'no stool', '1 per day' or 'several times'. Where the latter category was ticked, multiple entries in the fields for stool consistency and straining were possible. Patients recorded stool consistency according to one of four descriptions: 'liquid', 'pasty', 'well-formed' or 'hard'. The occurrence each day of straining, bloating and abdominal pain was recorded as 'yes' or 'no'. The diary also provided space to record adverse events and intake of any concomitant medication.

At the final study visit, the diary entries were reviewed to provide overall assessments of the respective symptom patterns for the full treatment period using the same categories as those employed at baseline.

In a pilot phase of the study, 11 patients were randomised to receive either sodium picosulphate (Dulcolax®, Laxoberal®; Boehringer Ingelheim, Ingelheim, Germany), or corresponding placebo, as 20 drops (equivalent to 10 mg sodium picosulphate per day) orally, in the evening, prior to going to bed, on three consecutive days. Two patients experienced moderate-to-severe diarrhoea. As a result, the study protocol was amended and the dose was reduced to 14 drops (equivalent to 7 mg) sodium picosulphate (or corresponding placebo solution) per day. All patients on the study reported here received the 7 mg dose or corresponding placebo.

The randomisation ratio was 1 : 1 (sodium picosulphate or placebo) and allocation of treatments was made double-blind, by centre, according to a randomised block design, with block size of 4. The investigators were not made aware of the block size. Study drug containers were collected at the conclusion of the study for checking.

Primary end-point

The primary end-point was the occurrence of a response to treatment with the randomised study medication. A patient responding positively in both

efficacy parameters, frequency of stools and occurrence of straining, was defined as a responder.

For assessment of stool frequency, results were categorised as 'several times per day', 'once daily', 'every 2–3 days per week' or 'once per week', based on the diary entries during the treatment period. A stool frequency of once or several times per day was defined as a treatment success.

For assessment of occurrence of straining, a four-point scale was adopted as follows: 'never', 'rarely', 'frequently' or 'constantly', again based on the diary entries during the treatment period. Occurrence of straining assessed as 'never' or 'rarely' was defined as treatment success.

Secondary efficacy end-points

The secondary efficacy end-points were the frequency of stools, occurrence of straining, consistency of stools, occurrence of abdominal pain and bloating as assessed at the end of the treatment period. The scale adopted for consistency of stools was as per the diary, 'liquid', 'pasty', 'well-formed' or 'hard'. The occurrence of abdominal pain was assessed on a four-point scale as 'never', 'rarely', 'frequently' or 'constantly', based on the entries in the patient's diary during the treatment period. The occurrence of bloating was assessed using the same scale.

Safety assessment

The principal variables relating to safety were haematocrit, serum creatinine, and serum levels of the electrolytes potassium, sodium and chloride. Abnormalities of blood pressure and heart rate were also recorded. Adverse events were reported as mild, moderate or severe and assessment of the likelihood of a relationship to study drug as 'yes' or 'no'.

Statistical analysis

Demographic and baseline values were assessed for homogeneity. The primary end-point was evaluated by the Cochran–Mantel–Haenszel test stratifying by centre. Secondary variables were evaluated by descriptive statistics. The primary efficacy analysis was based on all patients who had received at least one dose of study medication (full analysis set). Safety data were analysed descriptively, with all randomised patients included.

Sample size estimation

A response rate of 10% was anticipated in patients receiving placebo. For the purpose of sample size estimation, an overall response rate of 50% was assumed in the sodium picosulphate-treated group. To detect a difference of 40% between the two treatment groups, the minimum required number of patients per group was calculated as 24 (two-tailed test on proportions; significance level $\alpha = 0.05$; power $1\text{-}\beta = 0.8$).

Results

Patients

A total of 57 patients in five centres were randomised to receive a dose of 7 mg sodium picosulphate per day ($n = 29$) or matching placebo ($n = 28$). All patients completed the study. The age range in the placebo group was 19–89 years (mean 54.1 years) and 19–85 years (mean 54.8 years) in the sodium picosulphate group. There was a predominance of female patients in the study. The number of male patients was higher in the sodium picosulphate group (female: male 26 : 2 in placebo group; 20 : 9 in sodium picosulphate group). In all other respects, the two groups were well-matched in terms of baseline characteristics contributing to the primary and secondary measures of efficacy (Table 1).

The majority of patients had concomitant diagnoses and associated therapies (cardiovascular 21%, musculoskeletal 19% and gastrointestinal disorders 12%), but these were distributed between the treatment groups and were not considered to be confounding factors.

All randomised patients took at least one dose of study drug and so all participating subjects were included in the full analysis set. There were no protocol violations requiring exclusion from the per protocol population and so the full analysis and per protocol sets were identical.

Primary end-point for efficacy

For the primary end-point of efficacy, that is the number of 'treatment responders' (defined as those patients who had a stool frequency of 'daily' or 'several times daily' and a straining score of 'rarely' or 'never'), there was a statistically significant difference between the two treatment groups ($p = 0.010$, Table 2). The proportion of patients classed as responders in the sodium picosulphate treatment group was 82.8% compared with 50% in the placebo group.

Analysis of response rates in female and male patients in the two treatment groups revealed that the majority (19/20) of female patients in the sodium picosulphate group had a positive response compared with 5/9 of the male patients. In the placebo group, there were equal numbers of responders and non-responders for female and male patients (13 : 13 and 1 : 1 respectively). Although this might suggest a somewhat greater response rate in female patients, the small numbers of male patients in the study

Table 1 Demographics and baseline characteristics of chronic constipation

	Sodium picosulphate	Placebo
Number of patients	29	28
Age (years)		
Mean (SD)	54.8 (18.8)	54.1 (17.0)
Range	19–85	19–89
Sex [n (%)]		
Male	9 (31.0)	2 (7.1)
Female	20 (69.0)	26 (92.9)
Frequency of stools [n (%)]		
Several times per day	0 (0.0)	0 (0.0)
Once daily	0 (0.0)	0 (0.0)
Every 2–3 days	26 (89.7)	22 (78.6)
Once per week	3 (10.3)	6 (21.4)
Occurrence of straining [n (%)]		
Never	0 (0.0)	0 (0.0)
Rarely	3 (10.3)	4 (14.3)
Frequently	20 (69.0)	17 (60.7)
Constantly	6 (20.7)	7 (25.0)
Consistency of stools [n (%)]		
Liquid	0 (0.0)	0 (0.0)
Pasty	0 (0.0)	0 (0.0)
Well-formed	13 (44.8)	9 (32.1)
Hard	16 (55.2)	19 (67.9)
Occurrence of bloating [n (%)]		
Never	1 (3.5)	1 (3.6)
Rarely	11 (37.9)	10 (35.7)
Frequently	16 (55.1)	16 (57.1)
Constantly	1 (3.5)	1 (3.6)
Occurrence of abdominal pain [n (%)]		
Never	7 (24.1)	5 (17.9)
Rarely	17 (58.6)	16 (57.1)
Frequently	4 (13.8)	7 (25.0)
Constantly	1 (3.5)	0 (0.0)

Table 2 Primary efficacy analysis – Descriptive statistics, 95% confidence interval and p-value for the comparison of sodium picosulphate and placebo in terms of the number of responders during the three treatment days (all patients treated)

	Sodium picosulphate	Placebo
Number of patients	29	28
Responder [n (%)]	24 (82.8)	14 (50.0)
Comparison to placebo (%)		
Difference	32.8	
95% confidence interval	9.7–55.8	
p-value	0.010	

preclude any conclusions as regards possible equivalence or differences in responses between sexes.

Secondary end-points for efficacy

When viewed as the individual components of frequency of stools and occurrence of straining, there was a clear trend towards an increase in stool frequency and a reduction in the occurrence of straining in the sodium picosulphate group (Table 3). 24/29 (82.8%) of patients receiving sodium picosulphate reported stool frequencies of one or more per day compared with 17/28 (60.7%) in the placebo-treated group. Similarly, straining was reported in 24/29 (82.8%) of sodium picosulphate-treated patients as 'never' or 'rarely' compared with 14/28 (50%) in the placebo-treated group.

Assessments of the further secondary end-points of stool consistency, bloating and abdominal pain reinforced the observation of a favourable clinical response to sodium picosulphate (Table 3). There was a trend towards softening of the stool, with

Table 3 Global assessment of frequency of stools, occurrence of straining, consistency of stools, and occurrence of bloating and abdominal pain after 3 days of treatment (all patients treated)

	Sodium picosulphate	Placebo
Number of patients	29	28
Frequency of stools [n (%)]		
Several times per day	8 (27.6)	3 (10.7)
Once daily	16 (55.2)	14 (50.0)
Every 2–3 days	5 (17.2)	8 (28.6)
Once per week	0 (0.0)	3 (10.7)
Occurrence of straining [n (%)]		
Never	9 (31.0)	6 (21.4)
Rarely	15 (51.7)	8 (28.6)
Frequently	4 (13.8)	9 (32.1)
Constantly	1 (3.4)	5 (17.9)
Consistency of stools [n (%)]		
Liquid	1 (3.4)	0 (0.0)
Pasty	11 (37.9)	5 (17.9)
Well-formed	14 (48.3)	11 (39.3)
Hard	3 (10.3)	12 (42.9)
Occurrence of bloating [n (%)]		
Never	16 (55.2)	9 (32.1)
Rarely	11 (37.9)	11 (39.3)
Frequently	2 (6.9)	5 (17.9)
Constantly	0 (0.0)	3 (10.7)
Occurrence of abdominal pain [n (%)]		
Never	16 (55.2)	12 (42.9)
Rarely	9 (31.0)	13 (46.4)
Frequently	4 (13.8)	3 (10.7)
Constantly	0 (0.0)	0 (0.0)

12/29 (41.4%) of patients reporting pasty or liquid stools in the sodium picosulphate group compared with 5/28 (17.9%) in the placebo group. In the assessment of bloating at baseline, 17 patients in each group reported bloating occurring frequently or constantly. Following the treatment period, 27/29 (93.1%) patients receiving sodium picosulphate experienced this symptom rarely or never, compared with 20/28 (71.4%) of the placebo-treated patients. There was little difference between the two treatment groups as regards the numbers experiencing abdominal pain, although there was a slight numerical superiority for the sodium picosulphate group in terms of patients experiencing no abdominal pain (16/29: 55.2% vs. 12/28: 42.9%).

Safety assessment

All patients ($n = 57$) were included in the safety assessment.

Adverse events

The adverse events reported during the course of the study are summarised in Table 4. There were no deaths or serious adverse events. Two patients in the placebo group and five in the sodium picosulphate group experienced adverse events. Of the potentially drug-related gastrointestinal disorders reported, there was one patient with diarrhoea and another with abdominal pain in each of the treatment groups.

Laboratory variables

Values for the laboratory measures of haematocrit and creatinine, together with the electrolytes, potassium, sodium and chloride, were generally within the normal ranges and remained stable over the 5-day study period in the majority of individuals. There were no relevant differences between the two treatment groups with respect to any of these measures.

Vital signs

The two treatment groups were similar in terms of pulse rate, systolic and diastolic blood pressures measured at baseline and exhibited no significant differences at the end of the treatment period.

Discussion

This study has demonstrated that sodium picosulphate is an effective and safe laxative for the short-term treatment of patients with constipation. At a dose of 7 mg per day, the drug is effective in improving the symptoms of constipation, while being well tolerated and without significant adverse effects.

Sodium picosulphate is a well-established laxative which has been the subject of extensive evaluation in comparative studies, either alone or in combination with other agents, for bowel preparation prior to colonoscopy (13,14), CT colonography (15) and other radiological diagnostic procedures (16). It has been less well evaluated in formal trials for the treatment of constipation. A retrospective study of the use of sodium picosulphate for the treatment of chronic constipation in patients aged 18–65 years old concluded that no significant adverse effects emerged during long-term use and that patients used the drug because alternatives were less effective (17).

In a meta-analysis of studies on a range of laxatives, Jones et al. (2002) concluded that there are few examples of formal studies demonstrating a significant clinical benefit of any laxative preparations over placebo in the treatment of constipation (8). Similarly, Ramkumar & Rao (2005) (9) concluded that there is a paucity of clinical trial data to support for the use of many commonly used agents . This is at variance with the view developed by clinicians and patients in their clinical experience of the use of laxatives over many years. Nevertheless, it highlights the

Table 4 Adverse events in both treatment groups

Treatment	Patient no.	Adverse event	Intensity	Assessment of relation to study drug
Placebo	10	Abdominal pain	Moderate	Yes
	46	Diarrhoea	Moderate	Yes
Sodium picosulphate	27	Abdominal pain	Moderate	Yes
	62	Diarrhoea	Mild	Yes
	48	Migraine	Moderate	No
	7	Dysuria	Moderate	No
		Frequent micturition	Moderate	No
	11	Increased sweating	Moderate	Yes
		Dizziness	Mild	Yes

importance of providing clear evidence from clinical trials to confirm or reject the proposition that a given drug and dosing regimen is effective and safe. Against this background, it was appropriate to re-examine the safety and effectiveness of sodium picosulphate in the double-blind, placebo-controlled, randomised trial in patients with chronic constipation reported here.

In routine use, patients frequently titrate the dose of laxatives to establish the dose that is most effective and best tolerated for them. Selection of the fixed dose in the present study was guided by clinical experience of the likely most effective but well-tolerated dose, together with the observation of a single case of severe diarrhoea in a pilot phase in which patients received 10 mg sodium picosulphate per day. In the light of this observation, the lower dose of 7 mg was selected and this proved to be well-tolerated. This latter dose would appear to be effective in terms of achieving the desired clinical effect, while minimising side effects.

In the assessment of the primary efficacy measure (number of complete responders), the placebo response (50%) was higher than anticipated. Nevertheless, the sodium picosulphate-treated group exhibited a clear superiority over placebo, with only five of the 29 patients in the treatment group being classified as non-responders. Assessment of the component measures of stool frequency and straining confirmed a clear shift towards a majority of patients having a stool frequency of at least one per day and an absence or rare occurrence of the need to strain when treated with sodium picosulphate.

The overall clinical improvement in bowel habit exhibited in the primary efficacy measures was reflected also in stool consistency and bloating. The numbers of reports of absence or rare occurrence of abdominal pain were also in favour of sodium picosulphate, although both groups had only small numbers reporting frequent pain and none reporting it as occurring constantly.

The safety profile of sodium picosulphate was reassuring in this short-term study. One patient in each treatment group experienced diarrhoea and one in each group experienced abdominal pain. As noted from the pilot study and the broader experience with sodium picosulphate, diarrhoea may occur as a predictable adverse effect; titration of the dose could have resolved the problem. Of the other adverse events reported, the single report of dizziness was considered to be a possible treatment-related effect, perhaps consequent upon the gastrointestinal effects. The same patient reported an increase in sweating. No patient withdrew from the study for any reason and there was no significant effect on haematocrit, creatinine or, importantly, on electrolyte balance. Thus, the treatment was well-tolerated and provided no significant concerns with regard to safety.

This study was based on a relatively small number of patients and was conducted over a short treatment period of 3 days. Nevertheless, it has provided a clear demonstration of the efficacy of the compound in the acute treatment of patients with a history of chronic constipation and it has raised no concerns with regard to safety or electrolyte balance. A recent report made a retrospective analysis of the use of sodium picosulphate in 35 patients over a median period of 10 years (range 3 months to more than 20 years). This concluded that, while patients may adjust the dose to optimise the effect, there were no apparent untoward effects, even over an extended period (17).

In conclusion, sodium picosulphate is an effective, well-tolerated and safe laxative when treating constipation acutely. Given its liquid formulation, it has the advantage of being easily titrated to achieve the optimal combination of efficacy with minimal side effects.

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