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ORIGINAL RESEARCH

Efficacy and tolerability of Laxatan® Granulat in patients with chronic constipation

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Background: On average 12% of the population worldwide suffer from acute or chronic constipation. Pathological intestine alterations, an unhealthy diet with reduced liquid intake, and little exercise are potential reasons. Often the motility of the intestine is disturbed. Changing nutrition habits or lifestyle is not always successful. In such cases, laxatives containing macrogol and inulin are highly effective.

Methodology: The efficacy and tolerability of Laxatan® Granulat, a laxative containing macrogol, inulin, and mineral salts, was assessed in a drug-monitoring study of 105 patients for four weeks.

Results: At the end of this study, a highly significant reduction of the constipation symptoms in 98.1% of the patients was observed. No adverse events were reported during this drug-monitoring study. The overall efficacy was rated as being "very good" or "good" for 96% and the overall tolerability was rated as being "very good" or "good" for 99% of patients.

Conclusion: The combination of macrogol, inulin, and mineral salts is highly effective in the treatment of chronic constipation. Due to its prebiotic activity, inulin probably leads to proliferation of lactic acid-producing bacteria. The lowered pH and increased water content probably increases the peristaltic action and therefore reduces constipation.

Keywords: Laxatan®, macrogol, inulin, constipation

Introduction

Constipation is defined by infrequent bowel movements, typically only every three to four days a week, difficulties during defecation, and is associated with hard stool, pain, strong pressing, and the sensation of incomplete bowel evacuation. When these symptoms last for more than three months, the condition is called chronic constipation. The reasons for constipation are manifold. In some cases it is caused by a low fiber diet, dehydration, or a lack of exercise. Other reasons are intestinal disorders, treatment with medication, or disturbances in the water and electrolyte balance. Changing nutrition habits, such as a high fiber diet and higher liquid intake, or a change of the lifestyle such as an increased level of exercises are not always effective.[1,2] In these cases laxatives are useful. However, long-term administration of pharmaceutical laxatives could result in habituation and a reduced efficacy of the laxative. Laxatives containing macrogol and inulin can be used over a long time without causing habituation. Macrogol consists of polyethylene glycol (PEG). PEG is a nontoxic and highly soluble component, which is not absorbed by the gastrointestinal tract.[3,4] PEG acts as an osmotic agent by increasing fecal water content.[5] The increased stool volume dilates the bowel wall and triggers the defecation reflex. The efficacy and safety has

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been shown in several clinical studies.[6–8] PEG has been accepted as a substance generally recognized as safe (GRAS) by the US Food and Drug Administration (FDA). Inulin has no or only minor laxative properties, but pronounced prebiotic activity.[9,10] In contrast to probiotics, which are defined as viable microbials, prebiotics are nondigestible for humans, but selectively stimulate the growth and activity of bifidobacteria and lactobacilli.[11] These microorganisms are well known because of their positive effect on the intestinal health by producing lactic acid which lowers the pH in the colon and leads to an increased peristaltic activity.[12]

The primary objective of this drug-monitoring study was to assess the efficacy and tolerability of Laxatan® Granulat, a combination of macrogol, inulin, and mineral salts, in symptoms of chronic constipation. To the best of our knowledge, this is the first study to investigate the effect of a combination of macrogol and the prebiotic inulin on patients with chronic constipation.

Patients and methods

In total 105 patients (86 women; 19 men) with chronic constipation and at least three constipation symptoms of moderate intensity were enrolled into this drug monitoring study. Additionally, all patients were at least 18 years old and long-term user of laxatives. Exclusion criteria consisted of anaphylaxis against one of the ingredients of the medication, simultaneous intake of other laxatives, dubious pain in the abdominal cavity, possibility of intestinal perforation, intestinal obstruction, inflammatory colon disease (such as Crohn's disease, colitis ulcerosa), acute toxic megacolon, serious organ or systemic disease, alcohol abuse, drug or medication abuse, or pregnancy or lactation. The patients had an average age of 64.3 years (22 to 94 years), an average height of 164.7 cm (141 to 187 cm), and an average weight of 74.8 kg (50 to 162 kg). During the first two weeks the patients took 2 × 2 packages of Laxatan® Granulat (dissolved in 125 ml water) daily. In the following two weeks the dosage was reduced to 2 × 1 package of Laxatan® Granulat per day. One package of Laxatan® Granulat contains 13.125 g macrogol 4000, 0.25 g magnesium citrate, 0.125 g calcium citrate, 0.015 g potassium chloride, and 1.0 g inulin. During the course of the study, a total of three examinations were performed for each patient: a baseline assessment at the start of the study, a control examination after about two weeks, and a final examination after about four weeks at the end of the study.

At each examination, the following constipation symptoms were rated by means of a four-point rating scale: infrequent defecation, firm stool, painful defecation, strong pressing during defecation, stomachache, sensation of fullness, and flatulence. Rome criteria were not used to diagnose constipation. At the end of the study the sum score of all constipation symptoms was calculated for each examination and the change of the sum score at study end compared to baseline was assessed. The sum score was calculated based on the average score of each symptom (0 to 3 points) and could reach a value between 0 and 21 for all seven symptoms. The efficacy criteria were the decrease of the sum score for the constipation symptoms and a global assessment of the efficacy conducted by the physicians and patients at the end of the study. The tolerability was evaluated based on the occurrence of adverse events and by a global assessment of the tolerability by the physicians and patients at the end of therapy.

The study was performed according to the recommendations of German Federal Institute for Drugs and Medical Devices (BfArM), The German Society for Phytotherapy (GPHY), as well as the German Society for Medical Computer Science Biometry and Epidemiology (GMDS).[13–15]

Statistical analysis

The results of this study are presented descriptively, with efficacy evaluated by means of a pretreatment versus post-treatment comparison. A Wilcoxon test for paired values was used for changes in the sum score of the constipation symptoms and Pearson's chi-squared test was used to calculate the level of significance.

Results

Data were analyzed for all 105 patients. To evaluate the efficacy of the Laxatan® Granulat, the seven constipation symptoms (infrequent defecation, firm stool, painful defecation, strong pressing during defecation, stomachache, feeling of fullness, flatulence) were assessed at three examinations by the physician. Each constipation symptom was rated on a four-point rating scale (0 = none, 1 = minor, 2 = moderate, and 3 = severe) resulting in an average score for each symptom at each examination between 0 and 3. The frequency distribution of the seven constipation symptoms at each examination is summarized in Table 1.

For all examined symptoms an improvement could be demonstrated by a comparison before and after treatment.

Before treatment

Infrequent defecation

At the first examination, all patients (100%) complained of moderate or severe infrequent defecation. By the end of the therapy (third examination) 82.7% showed no or

Table 1 Frequency distribution of constipation symptoms at the first, second, and third examinations

Symptoms	Examination	N	Assessment of intensity							
			None		Minor		Moderate		Severe	
			Patients	[%]	Patients	[%]	Patients	[%]	Patients	[%]
Infrequent defecation	1	105	0	0	0	0	44	41.9	61	58.1
	2	105	31	29.5	45	42.9	27	25.7	2	1.9
	3	105	43	41.0	49	46.7	11	10.5	2	1.9
Firm stool	1	105	0	0	1	1.0	28	26.7	76	72.4
	2	105	37	35.2	40	38.1	26	24.8	2	1.9
	3	105	48	45.7	48	45.7	8	7.6	1	1.0
Painful defecation	1	105	19	18.1	13	12.4	44	41.9	29	27.6
	2	105	58	55.2	31	29.5	13	12.4	3	2.9
	3	105	73	69.5	23	21.9	8	7.6	1	1.0
Strong pressing	1	105	4	3.8	7	6.7	40	38.1	54	51.4
	2	105	42	40.0	36	34.3	22	21.0	5	4.8
	3	105	60	57.1	30	28.6	13	12.4	2	1.9
Stomachache	1	104	38	36.5	21	20.2	34	32.7	11	10.6
	2	105	64	61.0	29	27.6	11	10.5	1	1.0
	3	105	68	64.8	30	28.6	7	6.7	0	0
Feeling of fullness	1	105	4	3.8	20	19.0	49	46.7	32	30.5
	2	105	33	31.4	43	41.0	25	23.8	4	3.8
	3	105	48	45.7	35	33.3	20	19.0	2	1.9
Flatulence	1	105	5	4.8	30	28.6	44	41.9	26	24.8
	2	105	17	16.2	50	47.6	31	29.5	7	6.7
	3	105	24	22.9	55	52.4	22	21.0	4	3.8

minor complaints of this symptom, and only 12.4% of the patients still suffered from moderate or strong infrequent defecation.

Firm stool

At the beginning of therapy, 104 patients were afflicted by firm stool (26.7% moderate, 72.4% severe). After about two weeks (second examination), 73.3% were either free of this symptom or had only minor complaints. At the end of the study only one patient had severe problems with firm stool.

Painful defecation

Moderate or severe pain during defecation was reported by 69.5% of patients at the first examination. At the end of the observation, 91.4% of patients were either free of pain or reported tolerable (minor) pain during defecation.

Strong pressing during defecation

Like all other symptoms the strong pressing during defecation symptom was significantly reduced from the first to third examinations. At the beginning of the study, defecation was associated with severe or moderate pressing for 89.5% of the patients. Only 14.3% rated this symptom as severe or moderate after about four weeks at the third examination.

Stomachache

In 43.3% of patients, constipation was associated with moderate or severe stomachache. At the end of the study, 68 of 105 patients (64%) were free of stomachache and none of the patients complained about severe stomachache.

Feeling of fullness

At the first examination, 77.2% of the patients complained about a moderate or severe feeling of fullness. By the end of the therapy (third examination), 79.0% had no or minor complaints of this symptom and only 20.9% still suffered from moderate or strong feeling of fullness.

Flatulence

Flatulence was reported as moderate or severe by 66.7% of the patients at the first examination. At the end of the study, 26 of 105 patients (24.8%) still suffered from moderate or severe flatulence. 52.4% complained about minor flatulence and 22.9% of the patients were symptom free.

After treatment

The improvement of chronic constipation could also be demonstrated by the decrease of the average scores of the individual constipation symptoms. The decrease of these scores is shown in Figure 1.

Infrequent defecation

The average score for the symptom infrequent defecation was 2.58 ± 0.5 at the beginning of the therapy and dropped down to 0.73 ± 0.73 at the last examination. The improvement rate of 71.1% is statistically highly significant ($P < 0.001$).

Firm stool

The average score for this symptom was 2.71 ± 0.48 at the first examination and decreased to 0.64 ± 0.67 at the third examination. The improvement rate of 76.4% by the end of the study is statistically highly significant ($P < 0.001$).

Painful defecation

The average score for painful defecation had a value of 1.79 ± 1.04 at the beginning of the study and a value of 0.40 ± 0.67 by the end of the study. The improvement rate of 77.6% is statistically highly significant ($P < 0.001$).

Strong pressing during defecation

The average score for the symptom of strong pressing during defecation was 2.37 ± 0.78 at the beginning of the therapy and dropped down to 0.59 ± 0.78 at the last examination. The improvement rate of 75.1% is statistically highly significant ($P < 0.001$).

Stomachache

The average score for this symptom was reduced from 1.17 ± 1.05 at the first examination to 0.42 ± 0.62 by the end of the study. The improvement rate of 64.1% is highly statistically highly significant ($P < 0.001$).

Feeling of fullness

The average score for "feeling of fullness" had at the beginning of the study a value of 2.04 ± 0.81 which decreased to 0.77 ± 0.82 at the last examination. The reduction of the symptom by 62.3% is statistically highly significant ($P < 0.001$).

Flatulence

The reduction of the average score of this symptom was statistically highly significant. The average score decreased from 1.87 ± 0.84 at the first examination to 1.06 ± 0.77 at the third examination, which represents a statistically highly significant ($P < 0.001$) improvement rate of 43.3%.

Summation of the average scores of the seven individual symptoms resulted in the sum score for all symptoms as shown in Figure 2. This sum score clearly demonstrates a strong reduction of the constipation symptoms between the first, second, and third assessment. The value dropped from 14.5 ± 2.9 points at the beginning of the study to 4.6 ± 3.9 points by the end of the study, which represents an

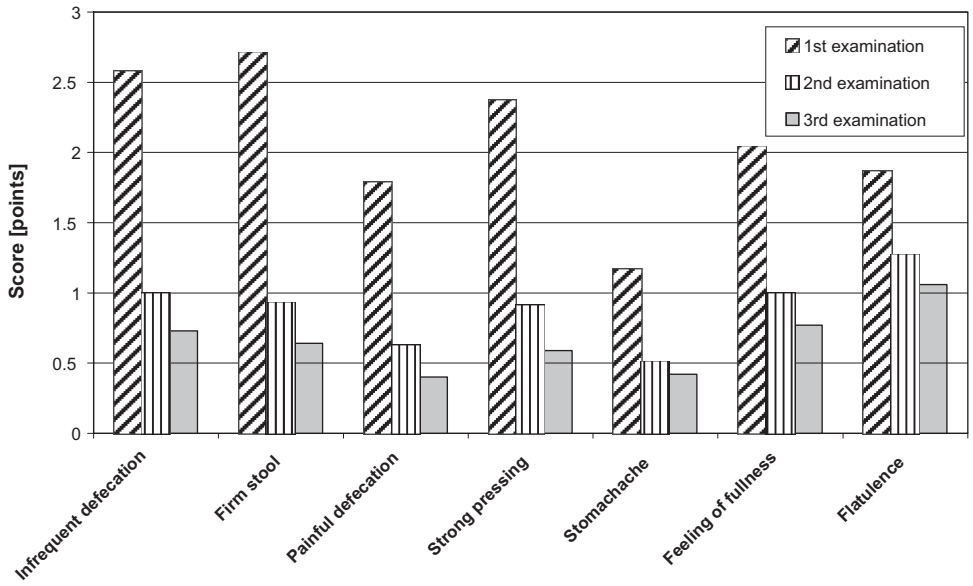

Figure 1 Average score of the individual constipation symptoms.

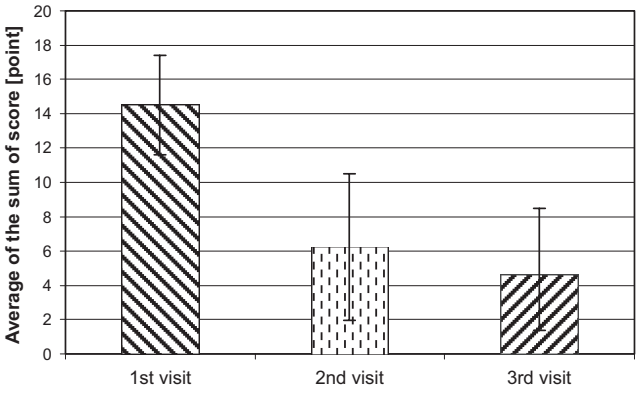

Figure 2 Scores at the first, second, and third examination.

improvement rate of 68%. This result was statistically highly significant ($P < 0.001$)

Global assessment of efficacy

At the end of the observation period the efficacy of Laxatan® Granulat was rated both by the physicians and the patients. The categories were "very good", "good", "moderate", and "insufficient". 96.1% of the physicians and the patients rated the efficacy as being "very good" or "good". 91.3% of the patients reported that Laxatan® Granulat had a better effect than the laxatives used previously.

Global assessment of tolerability

An evaluation of the tolerability of Laxatan® Granulat was performed by the patients and the physicians. The product was reported as being "very good" or "good" by 98.0% of the patients and 99.0% of the physicians, respectively. There were no adverse events during the course of the study.

Global assessment of compliance

Compliance was judged by the physicians as being "very good" or "good" for 96.1% of patients.

Discussion

The term chronic constipation is used if there is no defecation for periods of four days for longer than three months, when strong pressure is necessary for defecation and if there is a feeling of incomplete defecation. The objective of treatment of constipation is the increase in intestinal motility. Macrogols are polymeric macromolecules (PEG), which are not adsorbed by the digestive system. Due to their osmotic activity and the ability to bind water, they hydrate hardened stool and increase the stool volume, leading to expansion of the intestinal wall. This provokes the defecation reflex.[16] In contrast to lactulose, a commonly used osmotic-acting laxative, PEG is more effective[17] with fewer side effects. The use of lactulose may lead to habituation, which has not been observed with PEG.[18]

The safety and efficacy of PEG preparations in treatment of chronic constipation has been shown in several short-[19,20] and long-term clinical studies[21–23] and are summarized in several reviews.[6,24,25] The safety of PEG has also been demonstrated in toxicity studies, where PEG neither showed mutagenic nor carcinogenic effects.[26,27]

The efficacy and safety has even been demonstrated in children. Eighty-three children received the PEG therapy on average for 8.7 months. The medication was well tolerated and did not cause major clinical adverse effects.[22] The use of macrogol is nowadays the first choice for treatment of chronic constipation.

However, it has been shown that PEG 4000 may inhibit the metabolic activities of the fecal flora.[19] Inulin on the other hand is a prebiotic. Prebiotics are not laxatives. They have a positive influence on the composition of intestinal flora and move the bacterial colonies in the direction of the desired bifidobacteria and lactobacilli. These bacteria build lactic acid and lower the pH in the colon, which increases the peristaltic of the intestine.[12] Therefore, the new combination product of both PEG and inulin will be beneficial for patients suffering from constipation.

Conclusion

To our knowledge this is the first drug-monitoring study to investigate the efficacy and safety of a combination product of macrogol, inulin, and mineral salt in patients with chronic constipation. This study has demonstrated very good efficacy and safety in the combination product of macrogol and inulin. Upon conclusion of the drug-monitoring study, 98.1% of the patients showed an improvement of the symptoms of chronic constipation. The sum score for the constipation symptoms calculated from the average scores of the individual symptoms at the conclusion of the study (after 32.2 days) showed a statistically highly significant ($P < 0.001$) improvement of 68.3% and a clinically relevant reduction of the symptoms. The average scores of the individual symptoms (infrequent defecation, hard defecation, painful defecation, strong pressure necessary for defecation, stomachache, feeling of fullness, and flatulence) showed a statistically highly significant decrease ($P < 0.001$) between the first and third examinations. The improvement rates for the individual symptoms lay between 43.3% and 77.6% (before/after comparison).

At the end of the observation period, 96.1% of the physicians and patients rated the efficacy of the treatment as being "very good" or "good". 91.3% of the patients stated that Laxatan® Granulat had a better effect than the laxative used previously.

The tolerability of the product was rated as being "very good" or "good" by 98.0% of the patients and 99.0% of the physicians, respectively. No adverse events occurred during the course of the study. Compliance was judged by the physicians as being "very good" or "good" for 96.1% of patients.

The results of this drug-monitoring study demonstrate a very good efficacy and tolerability of the combination product containing macrogol, the prebiotic inulin, and mineral salts with statistically highly significant and clinically relevant improvements of the symptoms of chronic constipation. We have shown that the combination is highly effective. However, we don't know to which extent the individual components influence the result. Further double-blind, placebo-controlled clinical trials should be performed to distinguish between the different components and to confirm these promising findings.

Disclosures

The authors report no conflicts of interest in this work.

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