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Effects of bisacodyl on ascending colon emptying and overall colonic transit in healthy volunteers

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Abstract

Background and Aim—The mechanism of action of bisacodyl in the unprepared human colon is unclear. Our aim was to evaluate the effect of oral bisacodyl on the overall and regional colonic transit in humans. \

Methods—In a double-blind, randomized, placebo-controlled study of 25 healthy participants, effects of oral bisacodyl (5mg p.o. per day) and placebo on colonic transit were compared. Validated scintigraphy using ¹¹¹In-charcoal delivered to the ileocolonic region in a delayed-release capsule was used to measure colonic transit. The primary transit endpoints, ascending colon emptying (AC) $t_{1/2}$ and geometric center (GC) of colon isotope at 24 hours (overall transit), were compared (Wilcoxon rank sum test).

Results—There were significant treatment effects on AC $t_{1/2}$, with the bisacodyl group demonstrating accelerated emptying [median 6.5 h, interquartile range (IQR) 5.0 – 8.0 h] relative to the placebo group [11.0 h (7.0 – 17.1)], $P=0.03$]. Numerical differences in colonic GC 24 hours [bisacodyl median 3.0 (2.2 – 3.8), placebo 4.0 (3.1 – 4.6)] were not significant ($P=0.19$). There were no significant differences observed in GC 4 hours.

Conclusion—Oral 5mg bisacodyl accelerates AC in the unprepared colon in healthy adults; this action may contribute to the drug's efficacy in constipation.

Keywords

bisacodyl; ascending colon emptying; overall colonic transit

INTRODUCTION

Bisacodyl is a diphenyl methane laxative that has been used for the treatment of constipation since its introduction into the market in 1952 and, more recently, in facilitating bowel evacuation before investigational procedures (e.g. colonoscopy, barium enema) or surgery. Its action appears to be mainly in the large intestine, and it is usually effective within 6 to 12 hours following administration by mouth and within 15 to 60 minutes following rectal administration.

The Physician's Desk Reference¹ indicates that, for constipation, bisacodyl is given in usual doses of 5 to 10 mg daily as enteric-coated tablets administered at night or 10 mg as a suppository or enema administered in the morning. Doses of 10 to 20 mg are given by

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STATEMENT OF INTERESTS

Authors Personal Interests None.

mouth for complete bowel evacuation, followed by 10 mg as a suppository the next morning.

After both oral and rectal administration in humans, bisacodyl is hydrolyzed by intestinal and bacterial enzymes to a deacetylated active metabolite which is responsible for the laxative action. Absorption from the gastrointestinal tract is minimal with enteric-coated tablets or suppositories; the small amount that is absorbed is excreted in the urine as the glucuronide. Bisacodyl is mainly excreted in the feces. In fact, Roth et al.² have shown that only 16% of the orally administered formulation is absorbed, the laxative effect started 7.7 ± 1.7 hours after intake, and there was no apparent relationship between laxative effect and plasma level. Rectal suppository administration of bisacodyl resulted in undetectable or low plasma levels, despite prompt laxative effect after 20 ± 10 minutes. Flig et al.³ confirmed these findings and concluded that the laxative effect of the suppository results from a local effect in the rectum. The rapidity of this action of bisacodyl suggests that an effect on small intestinal secretion is unlikely to be the only mechanism that leads to laxation.

Thus, bisacodyl's laxative action is based on two modes of action: stimulation of myoelectrical and motor activity in the colon⁴⁻⁷ and stimulation of intestinal secretion.² However, the reported effects on motor functions focused on the prepared or cleansed distal colon, except for a study which evaluated the transit of a single metallic marker through the entire colon⁷ and a study using radiopaque markers which was compromised by a low number of radiographs.⁸ The mechanism of action of oral bisacodyl in the unprepared colon, particularly the proximal or ascending colon, is unclear.

The aim of this study was to compare the effects of bisacodyl, 5 mg p.o., and placebo on overall colonic transit and the emptying time of the ascending colon.

METHODS

Trial Design and Participants

We conducted a randomized, double-blind, placebo-controlled study of the effects of bisacodyl, 5 mg p.o., on colonic transit in 25 healthy male and non-pregnant, non-breastfeeding female participants, aged 18–52 years old. The study was approved by Mayo Clinic Institutional Review Board, and all participants signed informed consent. Participants were allowed to continue low, stable doses of thyroid replacement, estrogen replacement, and birth control pills or depot estrogen injection.

Exclusion criteria included the use of medications within 48 hours of dose initiation, structural or metabolic diseases/conditions that affect the gastrointestinal system, and functional gastrointestinal disorders. Participants with previous abdominal surgery other than appendectomy, cholecystectomy, hysterectomy, or hernia repair, or other known illnesses such as diabetes, cardiovascular or lung disease were excluded. For screening, the shortened version of the Bowel Disease Questionnaire⁹ was used to exclude subjects with dyspepsia, irritable bowel syndrome, or significant gastrointestinal symptoms. Of the 16 questions, participants had to have 3 or less positive responses (ranked as mild to worst) to be eligible to participate. Subjects who had participated in another clinical study within the prior 30 days were ineligible.

Colonic Transit Measurements

To evaluate colonic transit, an adaptation of our established scintigraphic methods was used.¹⁰⁻¹² Briefly, ¹¹¹In adsorbed on activated charcoal particles were delivered to the colon by a methacrylate-coated, delayed-release capsule.¹² All participants ingested the capsule containing ¹¹¹In charcoal at 6:00 a.m. after an overnight fast (last meal prior to 9:00 p.m. on

the previous day). When the capsule had been demonstrated to have emptied from the stomach (with images obtained every 30 minutes while the patient remained fasting), all participants received the study medication and standard breakfast (218 kcal egg meal) at time 0 and two standardized meals at 4 hours (530 kcal chicken meal) and 8 hours (750 kcal steak dinner) after the medication was administered.

A variable region of interest program was used to measure transit, as in previous studies.^{10–12} Time 0 was the time of ingestion of the study medication. We obtained abdominal images every 30 minutes for the first 10 hours after administration of the study medication, with scans being increased to every 15 minutes for the first 2 hours after meals. A final scan was obtained 24 hours after ingestion of the study medication. The performance characteristics of this test are summarized elsewhere.¹³

Transit Data Analysis

The geometric center (GC) is the weighted average of counts in the different colonic regions [ascending colon (AC), transverse colon (TC), descending colon (DC), rectosigmoid (RS)] and stool, respectively 1 to 5. Thus, at any time, the proportion of colonic counts in each colonic region is multiplied by its weighting factor as follows: $(\%AC \times 1 + \%TC \times 2 + \%DC \times 3 + \%RS \times 4 + \%stool \times 5)/100 = GC$. Thus, a higher GC reflects a faster colonic transit.

AC emptying was summarized by the $t_{1/2}$ calculated by linear interpolation of values on the AC emptying curve. The demonstration of either acceleration or delay of transit (using the same assessment parameters) appears to predict the efficacy of the respective agents on bowel dysfunction in prior studies with prucalopride, tegaserod, alosetron, and recombinant human neurotrophin 3.^{14–17} The primary efficacy parameters were AC $t_{1/2}$ and GC at 24 hours. Secondary endpoint was GC at 4 hours.

Statistical Analysis

Data are expressed as the median and interquartile range (IQR), with full range and outliers shown on box and whisker plots. Wilcoxon Rank Sum Test was used to compare transit profiles in response to bisacodyl and placebo (SigmaStat, SPSS, Chicago, IL, USA). P value <0.05 was deemed significant.

Sample Size Assessment

The primary assessment measures (GC at 4 and 24 hours and AC $t_{1/2}$) have coefficients of variation [(CV) %] of 44%, 40%, and 51%, respectively, based on data for healthy volunteers studied using the previous methods in the same laboratory (Table 1).^{14–17} The table indicates the ‘effect sizes’ (difference in mean values as a percentage of the overall groups mean value) that could be detected with 80% power at an α level of 0.05 using a simple two-sample z-test between the two groups (N=12 per group).

RESULTS

Participants

All participants completed the study. As a result of randomization, 13 subjects received the placebo and 12 subjects received bisacodyl. Mean age of the bisacodyl group was 34.1 ± 3.8 years old, and that of placebo group was 30.9 ± 2.0 years old. The female to male ratio of the bisacodyl group was 7/6 and that of placebo group was 7/5. The mean body mass index of the bisacodyl group was 26.8 ± 1.2 kg/m² and that of the placebo group was 26.4 ± 1.3 kg/m². There was no significant difference in these parameters between the two groups.

Effect of Bisacodyl on Overall Colonic Transit

The colonic GC at 4 hours of the placebo group was 1.0 (IQR; 1.0–1.2), and that of bisacodyl group was 1.2 (IQR; 1.0–1.2). There was no significant difference between the two groups (Figure 1). The colonic GC at 24 hours of placebo group was 3.0 (IQR; 2.2 – 3.8), and that of bisacodyl group was 4.0 [(IQR; 3.1–4.6), $P = 0.19$, Figure 1].

Effect of Bisacodyl on Ascending Colon Emptying

Figure 2 shows examples of sequential scintiscans in participants randomized to bisacodyl or placebo. The AC $t_{1/2}$ was 11.0 (IQR; 7.0 – 17.1) hours in the placebo group, and that of the bisacodyl group was 6.5 [(IQR; 5.0 – 8.0), Figure 1]. The bisacodyl group had significantly accelerated AC emptying compared to the placebo group ($P = 0.03$). Figure 1 also shows the progression for each participant from ascending colon emptying $t_{1/2}$ (where lower numbers reflect faster emptying) to overall colonic geometric center at 24 hours (where higher numbers reflect faster transit). The figure shows erratic progression with placebo. In contrast, for all except 3 participants receiving bisacodyl, there appears to be a relatively fast ascending colon emptying $t_{1/2}$, but there is relatively little effect on overall colonic transit.

DISCUSSION

This double-blind, randomized, placebo-controlled study has demonstrated that low-dose oral bisacodyl accelerates emptying of the unprepared ascending colon in healthy subjects.

Bisacodyl has been used as a first-line laxative for many years, and clinical experience suggests that it is effective, yet only a few controlled studies are available to examine its mechanism of action.^{18,19} Previous studies showed that bisacodyl was a hydragogue, that is, it induced intestinal water secretion.²⁰ Bisacodyl stimulates other mechanisms that may result in laxation and secretion, including stimulation of nitric oxide synthase,²¹ mucin secretion²² and increasing mucosal permeability.²³ Other agents that cause intestinal secretion, such as lubiprostone and linaclotide, also accelerate colonic transit.^{24,25}

There is also evidence that bisacodyl acts locally in the large bowel by directly enhancing motility, reducing overall colonic transit^{7,26,27} and increasing the water content of the stool.²⁸ However, there are few studies to evaluate its mechanisms under the more physiological condition in the unprepared colon. Ewe et al.⁷ demonstrated impressive acceleration of overall colonic transit of radiopaque markers [7 ± 8 (SD) hours for bisacodyl versus 31 ± 14 hours for controls). Bisacodyl, 10 mg per day for three days, also accelerated overall colonic transit.²⁹ However, it is unclear from prior studies whether this was due to effects on proximal or distal colonic transit.

In general, noninvasive techniques are required to evaluate regional colonic transit in greater detail. Radiopaque marker techniques, widely used for colonic transit assessments by individual images at 4 or 5 days after marker ingestion, would require high radiation doses to assess AC emptying. Furthermore, larger non-digestible markers may be less physiological when compared with the 1–2 mm or smaller markers used in scintigraphy.³⁰

Significantly accelerated emptying of the unprepared proximal colon with 5 mg bisacodyl p.o. is likely to be relevant to the mechanism of the drug's benefit in inducing laxation. Thus, the significant acceleration of AC emptying may reduce the time for fluid absorption in a colonic region that is known for its high capacity for fluid absorption.³¹ Acceleration of AC emptying may change stool consistency, complementing the secretory effects of the medication. Ratnaike et al.³² demonstrated that bisacodyl impairs fluid absorption by activating adenylate cyclase in enterocytes, increasing cyclic AMP, and causing active

secretion of Cl^- and HCO_3^- , passive efflux of Na^+ , K^+ and water and inhibition of Na^+ and Cl^- absorption into the enterocyte. It is also reasonable to hypothesize that the effects of bisacodyl on small intestinal and colonic secretion of water and electrolytes contribute to accelerated emptying of the AC or colonic transit, as observed with other secretory agents activating chloride channels (lubiprostone)³³ or the guanylate cyclase-C receptor that induces chloride secretion through the cystic fibrosis transmembrane regulator.²⁴

Another example is carcinoid diarrhea that causes both secretory and motor diarrhea.³³ The effects of locally delivered bisacodyl on motor functions have been demonstrated in the left or distal colon. Bisacodyl may act locally in the AC to directly enhance proximal colonic motility. Kamm et al.⁶ infused 5.5 mg bisacodyl into the splenic flexure and documented the induction of high amplitude propagated contractions in the distal colon. Bassotti et al.²⁷ investigated the effect of a 10 mg bisacodyl solution and found that about 90% of patients with slow transit constipation showed motor response characterized by one or more high amplitude propagated contractions. However, motor effects in the proximal colon were not previously documented.

The current study revealed that oral bisacodyl, 5 mg, did not significantly accelerate overall colonic transit, which is not consistent with previous studies.^{27,34} Two possible explanations are that, in previous studies,^{27,34} bisacodyl was administered directly to the distal colon and doses of bisacodyl were higher than the 5 mg used in this study. It is conceivable that oral bisacodyl, 5 mg, did not reach sufficient levels through the colon to affect overall colonic transit. A medication delivery system that releases the bisacodyl to the colon in a single bolus without dilution during its transit through the small intestine may accelerate overall or distal colonic transit.

We considered the possibility of a type II error due to the relatively small number of subjects (n=12) treated with bisacodyl. However, the observed pooled CV for GC at 24 hours was 31%, which was lower than the 40% used to estimate the required sample for the study. We believe that there may be inter-individual differences in efficacy (as illustrated in 3 participants in Figure 1) in stimulation of overall colonic transit. Further studies would be needed to explore the reason(s) for the lack of efficacy in nonresponders.

There are some potential limitations in this study. First, we did not evaluate the plasma level of the active metabolite of bisacodyl, deacetyl-bisacodyl. However, the effects of bisacodyl are mediated through a direct action in the gastrointestinal mucosa, and previous study¹⁸ showed that there was no apparent relationship between the plasma level of the metabolite and the laxative effect, suggesting that systemic absorption was not required for the laxative action. Second, we did not evaluate intestinal secretion in this study. Further mechanistic studies of effects of bisacodyl on colon motility, mucosal permeability and secretion will enhance our understanding of the pharmacological effects of oral bisacodyl in the human gastrointestinal tract.

In summary, bisacodyl has been previously shown to be efficacious in the treatment of chronic idiopathic constipation.³⁵ Our study shows that accelerating AC emptying is likely to be an important mechanism of oral bisacodyl's action in healthy subjects. The current data provide further support for the potential use of bisacodyl for the occasional treatment of patients with idiopathic constipation.

Acknowledgments

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Abbreviations used in this paper

GC	geometric center
AC	ascending colon
TC	transverse colon
DC	descending colon
RS	rectosigmoid
AC $t_{1/2}$	ascending colon emptying time
IQR	interquartile range
CV	coefficient of variation

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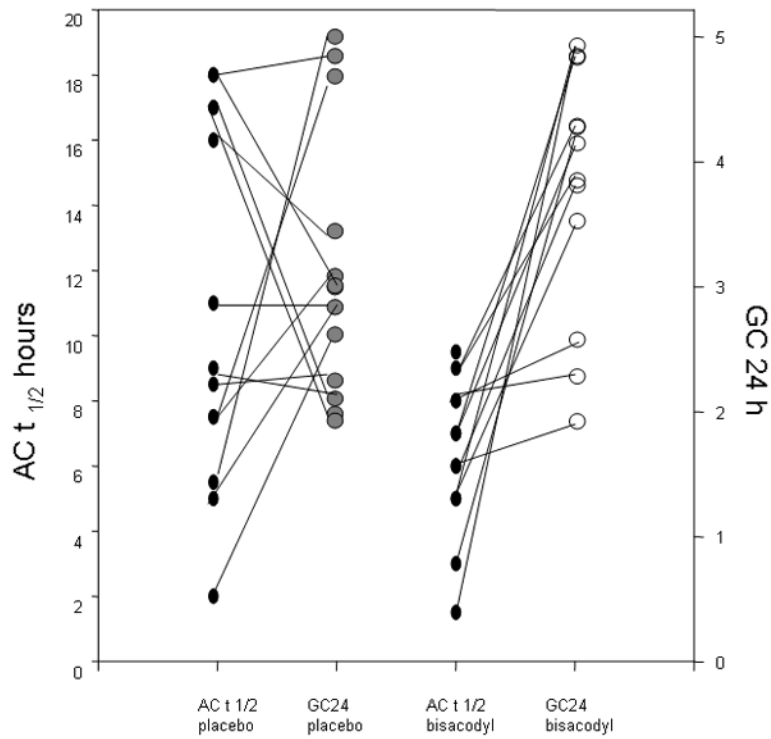


Figure 1.

Effect of bisacodyl on ascending colon emptying $t_{1/2}$ and on overall colonic transit at 24 hours. The bisacodyl group had significantly accelerated ascending colon emptying compared to the placebo group ($p=0.03$). Note that, in response to placebo, the progression from ascending colon to overall transit at 24 hours is highly variable; in contrast, there is a consistent progression for ascending colon to overall colonic transit in the bisacodyl group in all but three participants. Thus, although overall colonic geometric center was not significant in bisacodyl vs. placebo ($p=0.19$), 9 of the 12 participants appear to show substantial progression from ascending to overall colonic transit.

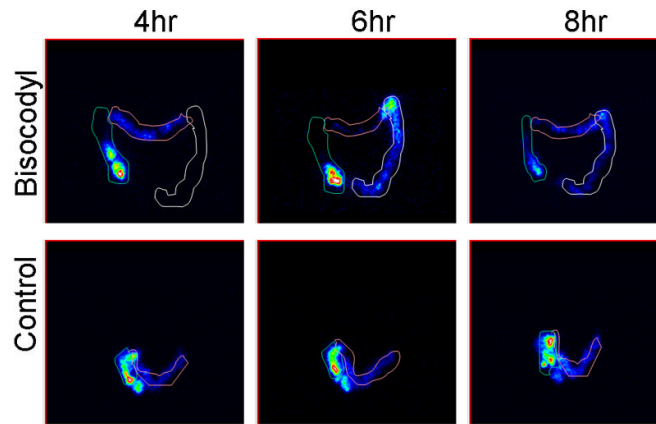


Figure 2. Colonic transit scintiscans at 4, 6 and 8 hours in patients receiving bisacodyl or placebo. Intensity of image reflects the concentration of counts in each region. Variable regions of interest are drawn around isotope in ascending, transverse, and descending regions. Note that bisacodyl accelerates ascending colon emptying relative to placebo.

Table 1

Statistical power atatement

Colonic Transit Response Variable	CV (%) in Healthy Subjects	Effect Size (%) Detectable with 80% Power (n = 12/group)
Geometric Center (at 4 hours)	44%	50%
Geometric Center (at 24 hours)	40%	46%
Ascending Colon T _{1/2}	51%	58%

CV, coefficients of variation.