Adverse Effects of Laxatives

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Laxatives are among the most commonly used drugs or additives. Most are quite safe when used judiciously, intermittently when possible, and in the absence of contraindications. Bulking agents and nonabsorbable compounds such as lactulose can cause bloating but have very few serious adverse effects except for the allergic reaction to psyllium preparations. Osmotic laxatives containing poorly absorbable ions such as magnesium or phosphate can cause metabolic disturbances, particularly in the presence of renal impairment. However, if taken intermittently, in the absence of conditions such as ileus or bowel obstruction, they have few adverse effects. Polyethylene glycol solutions are emerging as an effective and safe mode of treatment for chronic constipation. Of stimulant laxatives, senna compounds and bisacodyl are the most commonly used. Although there are data to support the neoplastic potential of this class of drugs in *in vitro* studies, epidemiologic data in humans so far has not established a clear link between these laxatives and colonic neoplasia. The link between stimulant laxatives and structural changes, such as the "cathartic colon" or enteric nerve damage, is not well established either. Danthron compounds should be avoided because of hepatotoxicity. [Key words: Constipation; Bulking agents; Osmotics; Lubricants; Stimulant laxatives; Anthranoids; Adverse effects]

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Laxatives are among the most widely used medications. Many factors, including aging of the population, low fiber diets, misconceptions about the normal (and desirable) frequency of bowel movements, fear of the consequences of constipation, and the availability of laxatives over the counter, have resulted in the widespread use of laxatives. At the same time, fears of side effects of laxatives may result in underuse by patients who depend on laxatives for regulation of bowel habits. To obtain a comprehensive assessment of adverse effects of laxatives, we conducted a literature search using MEDLINE from 1965 through the present. We have reviewed all classes of laxatives: 1) bulking or hydrophilic agents; 2) osmotic agents; 3) lubricants; and 4) stimulants (Table 1).

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BULKING AGENTS

This category includes agents of dietary or processed natural fibers (bran and psyllium), chemically modified cellulose (methylcellulose) and synthetic polymers such as polycarbophil. These organic polymers have various water-holding capacities. The increase in intraluminal volume because of water retention stimulates motility and speeds the transit of luminal contents through the colon, thus resulting in softer, more bulky stool.[1] In addition, once in the colon, these agents are subjected to bacterial fermentation that produces short chain fatty acids that may increase luminal osmolarity and water retention in the lumen, thus potentiating their laxative effect.

Mechanical Obstruction

Sporadic cases of acute esophageal obstruction have been reported after ingestion of bulk laxatives in patients with episodic mild dysphagia,[2] Parkinson's disease,[3] and even in patients without esophageal diseases.[4,5] An excessive dose or possibly inadequate fluid intake may cause intestinal obstruction.[6] Large-bowel obstruction has been reported after excess bran ingestion[7] and in patients taking ispaghula during the immediate postoperative period after major colonic surgery.[8] Thus, fecal impaction is a potential complication in patients with severe colonic inertia.

Anaphylaxis

It has been repeatedly reported that psyllium-containing laxatives can cause life-threatening anaphylaxis, asthma, and other allergic reactions in patients ingesting or exposed to these agents.[9–15] An epidemiologic study showed that of the 743 surveyed health care workers who prepared psyllium laxatives for patients, 136 (18 percent) reported allergic events, and 5 percent of them reported shortness of breath, wheezing, or hives within 30 minutes after preparing

Table 1.
General Classification of Laxatives and Some of Their Trade Names

Agents	Trade Names
Bulk-forming agents	
Psyllium	Konsyl, Mucilloid; Metamucil; Fiberall
Polycarbophil	Fibercon Caplets; Mitrolan; Equalactin
Methylcellulose	Cologel; Citrucel Orange
Lubricants	
Mineral oil	Milkinol; Fleet Mineral Oil
Osmotic agents	
Magnesium citrate	Citroma
Magnesium hydroxide	Phillips' Milk of Magnesia
Magnesium sulfate	Epsom Salts
Sodium phosphates	Fleet's Phospho-Soda
Lactulose	Chronulac; Duphalac
Sorbitol	
Polyethylene glycol	Miralax
Stimulants	
Sennosides	Correctol Herbal Tea; Senokot; Senolax; Ex-Lax Gentle Nature Pills; Herbal Laxative
Casanthranol	Constiban; Black Draught
Danthron	Doxidan; Modane; Unilax
Cascara	Stimulax
Castor oil	Neoloid; Castor Oil
Bisacodyl	Correctol; Dulcolax
Emollients/Stimulants	
Docusate sodium	Colace; Doctate; Regutrol
Docusate calcium	Surfak
Docusate potassium	Dialose

psyllium laxatives.[12] Psyllium hypersensitivity may be a more prevalent phenomenon than is currently realized by physicians and other health-care providers. In healthy subjects psyllium can significantly reduce hunger feelings, increase the sensation of satiety, and delay gastric emptying.[16,17] Bloating and flatulence may be experienced with these compounds because of the byproducts of fermentation, including gases such as carbon dioxide and hydrogen.

LUBRICANTS

Liquid paraffin, also known as mineral oil, is the major lubricant laxative. Seed oils from croton and arachis are also in use. These agents act when given orally or rectally by decreasing water absorption and softening the stool, thereby allowing easier passage. It is not chemically active, and serious adverse effects are uncommon. Anal seepage of oily material is the most common problem. Lipoid pneumonia may occur as a result of mineral oil aspiration.[18,19] Hence it should not be used in patients with a tendency for aspiration, regurgitation, or just before bedtime. The long-term oral administration of lubricants may conceivably interfere with the absorption of fat-soluble substances, including fat-soluble vitamins (A, D, E, and K), and may result in deficiencies of these substances. However, this adverse effect has not been clearly documented.

OSMOTICS

Osmotic laxatives include salts of poorly absorbable cations (magnesium); anions (phosphate, sulfate); molecules that are not absorbed in the small bowel but metabolized in the colon, such as lactulose and sorbitol; and metabolically inert compounds such as polyethylene glycol. The presence of these molecules in the lumen results in water retention to maintain normal osmolality of the stool. The laxative effect of these agents depends on the extent to which they remain in the lumen. Absorption by the mucosa, precipitation by other chemicals, and metabolism by luminal bacteria can reduce the osmotic effect. The metabolism of agents such as lactulose and sorbitol is responsible for such side effects as excessive flatulence and abdominal pain. Because the ions contained in such laxatives can be partially absorbed, the serious adverse effects are related primarily to metabolic disturbances caused by excessive ion absorption.

Hypermagnesemia

Many reports indicate that overdose or repetitive ingestion of magnesium-containing cathartics can cause hypermagnesemia, which can be fatal,[20–26] even in patients with normal renal function.[20,24,26] The diagnosis of hypermagnesemia should be considered in patients who present with symptoms of hyporeflexia, lethargy, refractory hypotension, shock, prolonged QT interval, or respiratory depression, and they need immediate attention. The use of this laxative should best be avoided in patients with renal insufficiency.

Hyperphosphatemia and Hypercalcemia

Sodium phosphate is commonly used to prepare patients for various gastrointestinal procedures. Both oral forms and rectal application have been reported to

cause acute and severe hyperphosphatemia,[27–35] especially in the elderly[33] and in patients with abnormal renal function.[27,31,32] Patients with hyperphosphatemia may present with nausea, vomiting, dehydration, and fatal hypercalcemia.[29,30,35] Administration of phosphate cathartics in conventional doses could result in a striking increase in serum phosphorus and significant decline in serum calcium levels even in healthy subjects.[36]

Bowel phosphate absorption from laxatives seems to be linearly related to enema retention time.[37] Hence, the use of phosphate cathartics, and chronic administration in particular, should be avoided in patients with the potential for prolonged luminal retention, such as those with fecal impaction, paralytic ileus, bowel obstruction, or congenital megacolon, and those with a preexisting fluid-electrolyte disturbance.[34,38]

Hypernatremia

Hypernatremia was described after the oral administration of osmotic cathartics such as lactulose[39,40] and activated charcoal-sorbitol suspension.[41,42] These agents can cause substantial water loss from the gastrointestinal tract. This may happen because the active absorption of sodium is not accompanied by equal absorption of water, kept in the lumen by the osmotically active laxative. Hypernatremia was also described after use of sodium-containing laxatives such as sodium phosphate.[43]

Hypokalemia

Hypokalemia is a common metabolic disturbance induced by osmotic laxation.[44] The loss of potassium in the watery feces is aggravated by further loss of potassium from the kidney[45] and gut,[46,47] because of activation of renin and secretion of aldosterone, after volume depletion.

Hypoalbuminemia

Few reports have linked the use of laxatives to the occurrence of hypoalbuminemia.[48,49] A cross-sectional, population-based study among elderly persons found that increasing age and laxative use were independently associated with hypoalbuminemia.[49]

Polyethylene glycol is a metabolically inert polymer that cannot be degraded by colonic bacteria and thus exerts osmotic activity. It is in use in lavage solutions for bowel preparation before colonoscopy. It was shown to be effective in the short-term treatment of constipation, when taken daily in small doses.[50] In a recent study patients with functional constipation were treated with either polyethylene glycol solution (average of 17.5 grams/day) or placebo, for a period of six months. A significant improvement was observed in patients taking the medication, whereas side effects and laboratory values did not differ between the two groups.[51]

STIMULANT LAXATIVES

Drugs in this category stimulate intestinal motility and/or affect epithelial transport of water and electrolytes. Most of these agents belong to the following groups: diphenylmethane derivatives (phenolphthalein, bisacodyl, and sodium picosulfate), anthranoids (senna and cascara), ricinoleic acid (castor oil), and surface-acting agents (docusates). Phenolphthalein was among the most commonly used agents in over-the-counter laxatives in the United States and is still widely used in many other countries. It was banned from use in the United States because of animal studies suggesting that it might have a carcinogenic effect.[52,53]

Castor oil is hydrolyzed in the small intestine to release glycerol and the active component, ricinoleic acid. Ricinoleic acid induces laxation by altering intestinal absorption[54,55] and enhancing colonic motility.[56,57] It is an effective cathartic, but may cause cramping abdominal pain in some patients. Thus, it is usually reserved for bowel preparation before diagnostic and surgical procedures.

Docusates are surface-active agents with emulsifying and detergent properties that allow water to interact more effectively with fecal mass and thus produce looser stool. They also have relatively subtle stimulatory effects on gut mucosa.[58,59] One potential side effect is that docusates may enhance the gastrointestinal or hepatic uptake of other drugs and thus increase their potential hepatotoxicity.[60] The underlying mechanism for this phenomenon is still not clear. There is also some evidence showing that docusates (dioctyl sodium sulfosuccinate) can significantly damage and ablate ganglion cells in the myenteric plexus[61] and produce structural changes in the gut mucosa of humans.[59] The clinical significance of this is still not known.

Anthraquinones are a group of plant-derived compounds. Their basic structure is a tricyclic anthracene ring. The rings are substituted with hydroxyl, methyl,

or carboxyl groups to form various anthraquinones, which vary in their laxative effect. After ingestion, anthraquinones are passed unchanged to the colon and undergo bacterial metabolism there with release of the active forms, which induce net fluid secretion and increased colonic motility. Besides abdominal pain, electrolyte imbalances, allergic reaction,[62] and potential hepatotoxicity,[63] abnormalities such as melanosis coli, cathartic colon, and neoplastic changes have also been linked to anthraquinones derivatives.

Pseudomelanosis Coli

Stimulant laxatives, especially anthranoids, exert direct toxic effects on colonic mucosa, which can facilitate the infiltration with inflammatory cells and the formation of apoptotic bodies in the tissue.[64] Increased numbers of apoptotic bodies have been found in the surface epithelium and lamina propria of the colon in patients with pseudomelanosis coli.[65]

Melanosis can occur in any part of the gastrointestinal tract. The nature and composition of pigments may vary with location. In pseudomelanosis coli the pigment granules contain lipofuscin.[66] The formation of lipofuscin is mainly caused by degradation of the apoptotic bodies of colonic epithelial cells within macrophages. The precursors of the melanic substance are derived from anthranoids free radicals.[67,68] Experimentally induced pseudomelanosis coli with dextran sulfate sodium and senna was mainly limited to the cecum and proximal colon.[69] In humans pseudomelanosis coli is also more common in the proximal part of the colon.[70]

The link between pseudomelanosis coli and the occurrence of colorectal cancer is controversial. In a large retrospective/prospective study Siegers *et al.*[71] found that the incidence of pseudomelanosis coli was much higher in patients with colorectal adenomas and carcinomas than those without colonic pathology, suggestive that patients taking anthranoid laxatives are possibly at a higher risk of developing colorectal neoplasia. However, a recent prospective study failed to document such an association.[72]

Cathartic Colon

"Cathartic colon" is a radiologic term, based on barium enema features such as loss of haustration, dilated lumen, dilated terminal ileum, and gaping of ileocecal valve.[73] The presence of this entity has been recently questioned, given the small number of reported cases in the literature.[74] A recent study showed that 45 percent of patients using bisacodyl, phenolphthalein, senna, and casanthranol more than three times per week for one year or longer had subsequent radiographic changes of colonic redundancy and dilation with loss of haustral markings that were not seen in the control groups.[75] Furthermore, reversal of these radiologic features after discontinuation of laxatives was observed.[76]

Enteric Changes

Long-term use of stimulant laxatives has been linked to substantial pathologic changes in the neurons in the myenteric plexus and smooth muscles in the colon. These changes included loss of neurons, replacement of ganglia by Schwann cells, and shrinkage and clubbing of the remaining argyrophilic cells.[77,78] Electron microscopy studies showed a range of lesions, from ballooning of axons, reduction of nerve-specific cell structures, and increase in lysosomes to a total degeneration of whole nerve fibers.[79] These findings, however, may not be specific to laxatives and have been reported in patients with diabetic autonomic neuropathy and chronic inflammatory bowel disease.[79]

Laxatives and Neoplasm

The data linking laxatives with carcinogenesis were derived from *in vitro* and *in vivo* studies in both animals and humans.

In Vitro *Studies*. A variety of studies indicate that stimulant laxatives have genotoxic and mutagenic effects. Most studies linking these effects were performed in a bacterial test system with *Salmonella typhimurium* strains. The results show that some anthraquinone derivatives, especially those with hydroxyl substitutes, were frameshift mutagens.[80–84] Danthron,[85] aloe-emodin,[86] emodin,[81,85] physcion,[85] emodic acid,[81] senna glycosides,[87] or extracts of senna[87] all had genotoxic and tumorigenic effects, although of different severity, in *Salmonella typhimurium* strains.

Anthraquinones also seem to be mutagenic in malignant mammalian cell lines.[88,89] However, anthraquinones did not affect normal colorectal epithelial cells *in vitro*,[89] and an ethanol extract of crude senna and emodin could inhibit mutations in the *Salmonella typhimurium* tester strain TA98.[90,91]

Animal Studies. Phenolphthalein has been shown to be a multisite/multispecies carcinogen in animal studies.[52,53] When administered continuously in the feed for 2 years to rats and mice, malignant neoplasms developed in different organ systems.[52] Short-term exposure to phenolphthalein may also potentiate the carcinogenic process when there is a genetic predisposition to cancer. In genetically altered mouse model systems carrying one wild-type p53 gene and one p53 null allele, treatment-related atypical hyperplasia and malignant lymphomas were seen after only four months of phenolphthalein exposure.[53] Dietary supplementation with bisacodyl was found to induce epithelial proliferative lesions, including a transitional-cell carcinoma, but only in the urinary bladder epithelium of rats.[92]

Certain anthraquinones have been clearly shown to be carcinogenic in animals. Hydroxyanthraquinone and chrysazin (danthron), added at different concentrations to the diet of mice and rats, resulted in adenomas and carcinomas developing in the colon of the treated animals.[93–95] However, some anthranoids did not show any gastrointestinal carcinogenic action in animals despite their clear mutagenic activity *in vitro*.[87,89] Dietary exposure to high doses of senna and cascara for 56 successive days did not cause aberrant crypt foci (ACF) in the rat colon mucosa.[96] A daily administration of senna pod extract by mouth for 13 to 28 weeks, which produced a weak laxative effect, did not cause increased incidence of ACF or tumors in the rat colon.[97] Prolonged exposure of a purified senna extract *via* the drinking water for two years also did not cause gastrointestinal, liver, kidney, or adrenal tumors in rats.[98]

It has been speculated that some of these anthranoids might function as tumor promoters in experimental carcinogenesis. This concept is supported by data derived from animal studies with senna or its extracts.[96,97] These substances were not carcinogenic alone at concentrations that produced light laxative effects. However, when given at high doses along with other mutagens, many more ACF, considered to be preneoplastic lesions, were observed compared with the rats treated with the mutagens alone.[96,97]

Human Studies. The colonic epithelium in humans undergoes marked transformation after exposure to anthranoids, with marked mucosal cell loss, significantly increased cell proliferation, and inhibition of apoptosis.[99,100] However, the results of epidemiologic studies evaluating the possible carcinogenic effects of stimulant laxatives in humans are inconclusive.

Several studies have suggested an association between laxative use and colonic neoplasia. Jacobs *et al.*[101] found that cumulative lifetime use of commercial laxatives was associated with increased risk of colon cancer in middle-aged males and females. A meta-analysis of 14 previously published case-control studies revealed a significantly increased risk of colorectal cancer associated with both constipation and the use of cathartics.[102] Nusko *et al.*[103] reported that a statistically significant association existed between the occurrence of colorectal adenomas and laxative use, although it could not be ascertained whether the increased risk was associated with anthranoid-containing laxatives. A recent study showed that habitual intake of laxatives may significantly contribute to the development of urinary cancer, especially of the renal pelvis and ureter.[104]

However, not all studies support the neoplastic potential of stimulant laxatives. In an epidemiologic study conducted in Australia, the authors found no difference in previous laxative intake pattern between 685 colorectal cancer patients and 723 age-matched and gender-matched controls. Previous use of anthraquinone laxatives and of phenolphthalein-containing laxatives was not associated with the risk of colorectal cancer.[105] Longnecker *et al.*[106] reviewed the data from three case-control human studies, which included 866 cases and 1,066 controls, and found that the use of phenolphthalein laxatives did not increase risk of adenomatous colorectal polyps in humans. Finally, the long-term use of anthranoid laxatives was not associated with an increased risk for the development of colorectal adenoma or carcinoma,[72] and in a large, prospective, epidemiologic study involving 84,577 females, no association was found between infrequent bowel movements, laxative use, and risk of colorectal cancer.[107]

As such, while *in vitro* data from both animals and humans support the potential carcinogenic effect of stimulant laxatives, the results of epidemiologic studies in humans are in conflict. Given the widespread use of stimulant laxatives, more research is needed to determine conclusively whether a link between stimulant laxatives and colorectal neoplasia does exist.

SUMMARY

Most laxatives, if used judiciously and in the absence of contraindications, are generally well tolerated and are quite safe. Most stimulant laxatives are safe even when taken chronically. The persistent and

common reluctance by practitioners to prolonged use of stimulant laxatives, even in the face of considerable symptoms related to constipation, is in contrast to the frequency of over-the-counter use of these agents by the general population. The association between stimulant laxatives and colorectal neoplasm in humans remains inconclusive. In patients who respond poorly to other types of laxatives, the alternatives to stimulant laxatives need to be considered before advocating cessation of this class of drugs.

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