SAFETY ISSUES AFFECTING HERBS

How Long can Stimulant Laxatives be Used?

BACKGROUND

Ingestion of laxatives is one of the primary self-treatment methods in the West. Laxatives are readily available as over-the-counter drug products and as dietary supplements. They are used for two purposes: to treat constipation and to aid in weight loss. Most health authorities discourage the use of laxatives for weight loss, saying that they do not significantly reduce absorption of food calories (26). Even so, senna leaf teas (or preparations in capsule or tablet form) are widely used for this purpose and are a major import from China and Europe. In the treatment of constipation, there are three basic types of laxatives:

- stimulants: these induce intestinal peristalsis and are the ones taken for weight control;
- bulking agents, mainly fiber, but also other polymers; and
- softeners (emollient laxatives): they either add oily material, increase water retention in the intestine, or aid mixing of water and oil components in the fecal material.

With the exception of taking fiber supplements to replace dietary fiber that is consumed in insufficient quantities, laxatives are indicated for short-term use. Nonetheless, many people with chronic constipation use them routinely.

Abuse of laxatives, including misuse in treatment of obesity and persistent use in treatment of chronic constipation, is a significant problem that has been mentioned in the medical literature. Laxative abuse is particularly prevalent with stimulant purgatives, for which several concerns have been raised: laxative dependence (that is, stimulated peristalsis begins to replace natural peristalsis), potassium imbalance, and potential damage to the intestinal tract after years of relying on them. The California Department of Health, Food and Drug Branch, now requires products with stimulant laxatives to warn about taking them during pregnancy, nursing, while taking medications, or if the user has a “medical condition,” as well as warning about potential diarrhea, loose stools, or abdominal pain (21, 27).

The nature of laxative dependence is a controversial matter (1). It may result, in part, from degeneration of the nerves in the intestines, dulling the natural responses that stimulate peristalsis; however, laxative dependence may simply be a psychological dependence. The link between use of stimulant laxatives and colon nerve damage or other structural changes is not well established but is an active area of investigations (25). Potassium imbalance, from long-term use of laxatives, especially at excessive dosage, has been blamed for deaths of apparently otherwise healthy women (21). Laxatives are always mentioned in discussions of drug interactions because of the concern that they will exacerbate potassium losses that may be an otherwise minor side effect of drug therapies.

ANTHRAQUINONES

The naturally occurring stimulant laxatives that are sufficiently safe and gentle for general use involve one basic category of chemical compounds, known as anthraquinones. (fig.1)

These include both the simple anthrones and the bianthrones, also called dianthrones, comprised of two anthrones linked together (see fig.2). The anthraquinones often occur in plants in the form of glycosides. These compounds are found in rhubarb root (the prominent Chinese laxative), senna leaf and pod (a Middle Eastern laxative), cascara sagrada (a North American laxative), buckthorn (also known as frangula; a European laxative), and aloe (known worldwide). The anthraquinones are colorful, in the spectrum of yellow to orange to red, evident in certain varieties of rhubarb, sometimes called “painted rhubarb” because the colors appear as beautiful striations across the sliced root surface. The colors of rhubarb result mainly from its content of emodin (orange), chrysophanol (yellow), rhein (yellow-orange), and physcion (brick-red).
Emodin is the most widely occurring anthraquinone in medicinal herbs. Among Chinese herbs, it is found in several species of Rheum, Rumex, Polygonum, and Cassia. Valuable medicinal aspects of emodin have been proclaimed on the basis of laboratory research, including: potential cancer prevention activity (blocking the growth of newly transformed cells); antiviral activity; antioxidant properties; gastric ulcer protection; liver protection; promoting blood circulation; inhibiting autoimmune attack; and benefiting the kidneys (inhibiting undesired proliferation of cells).

Rhubarb root is a dominant herbal therapy in China for treatment of nephritis and prevention of renal failure.

Anthraquinones are also found in other herbs, usually in small quantities, most notably in species of Polygonum. There are anthraquinones in vegetables, such as cabbage and lettuce, being particularly high in beans (36 mg/kg fresh weight). Physcion is the dominant anthraquinone in foods. Purpurin, an anthraquinone from madder root (Rubia tinctorium), is a component of an approved red food coloring.

In relation to the laxative effects, it is understood that anthraquinones act directly on the intestinal wall (in the colon region) to produce the desired result. They are poorly absorbed, and bianthrones are virtually unabsorbed; rather, they are degraded in the colon to produce more active metabolites, mainly anthrones (2). Anthraquinone laxatives increase fluid electrolyte accumulation in the distal ileum and colon (change in absorption and secretion of water; retention of potassium) through unknown actions, possibly via an irritation of the intestinal mucosa and endothelial cells. There may also be a direct stimulation of peristaltic activity. The bianthrones, especially sennosides, as found in rhubarb and senna, appear to be more active as laxatives than the simple anthraquinones. In single-dose treatment of constipation, the effects of the anthraquinones are noted in about 6-8 hours, the time it takes for them to reach the colon.

TRADITIONAL USE OF PURGATIVE THERAPY

The use of laxatives to treat acute constipation has been mentioned throughout the literature of the world’s various herbal traditions. Acute constipation may occur as the result of a disease or a change of diet. It is usually resolved by taking the laxative preparation once or twice; perhaps the treatment will need repeating for a few days. In the history of Chinese medicine, use of rhubarb for acute constipation is firmly established in relation to the “yangming” phase of a disease; this is where the body fluids become dry as the result of a febrile condition; the intestines become dry, and the person suffers from constipation. Mirabilium (Epsom salt; magnesium sulfate) is often used along with rhubarb in the Chinese treatments for acute constipation. Compared to rhubarb, it causes peristalsis higher in the intestinal tract (small intestine region), produces a quicker action (within 2-3 hours, even more quickly with higher dosage), and retains more water in the intestinal tract.

Purgation was also adopted worldwide as a therapy for diseases. The idea behind this broad application was that something in the body, the entity or toxin that caused the disease, needed to be flushed out. The elimination of this pathological influence was thought to be accomplished by either sweating it out through the pores, vomiting it out...
through the mouth, or disposing of it through the intestines or urinary tract. In the ancient Chinese system of therapy prevalent during the Han Dynasty, the three methods of diaphoresis, emesis, and purgation were widely used for this purpose. Although the reliance on such approaches to treating diseases faded at times (some medical authorities considered the methods too drastic, debilitating the patient), they were later revived. For example, these methods were again promoted during the Jin-Yuan medical reform (12th-13th century) by proponents of the Purgation school (or Attacking school). In America, treatment of numerous diseases by elimination techniques, especially purgation, has become a hallmark of the natural healing profession since the 19th century and is still deemed an important component by its practitioners, including use of such questionable therapies as colonics (intestinal cleansing with water).

CHRONIC CONSTIPATION AND ITS RESOLUTION

During the 20th century, chronic constipation had become a common health problem, particularly of the elderly. This disorder, known also as idiopathic constipation, is not widely discussed in the medical literature. Rather, the main focus of medical investigations and discussions has been on constipation that is secondary to a specific disease process, bowel malformation, or a side effect of drugs. While commercial advertisements and labeling for over-the-counter laxative products mention that the products are intended for treatment of “occasional irregularity,” the fact is that many people experience constipation that is so regular that they treat it persistently. Constipation does not necessarily involve infrequent or irregular elimination; the term has been used by people to describe difficult bowel movements (straining) or a sensation of incomplete bowel movements.

Studies on the etiology of chronic constipation have not been reported, but several lines of information converge on two key contributors. One is the sedentary lifestyle that has become increasingly prevalent. The absence of physical labor, or compensating vigorous exercise, results in laxness of the abdominal muscles, as well as other muscles. Current recommendations for exercise that are given to those who do little or no exercise are rarely helpful for overcoming the abdominal weakness. For example, it is commonly stated in the popular literature that walking just 20 minutes per day will improve health. While this is undoubtedly a benefit compared to no exercise, unless the walking is on an uneven path (e.g., a hilly natural path with numerous irregularities), there is essentially no exercise of the abdominal muscles involved. Further, 20 minutes of exercise represents activity during only 2% of the waking day, with 98% of the daily routine potentially being virtually inactive. Such a low level of activity was probably never experienced before in human history, except by the few who held the highest offices of the land and by those debilitated from disease or injury. Abdominal muscle laxity not only contributes to inability to move the bowels, but also may lead to prolapse and expansion of the lower intestinal tract, making it possible for the fecal matter to stagnate in masses that are difficult to pass. Lack of exercise also contributes to obesity, osteoporosis, heart disease, and depression, to mention a few well-known adverse consequences; it is associated with higher rates of colon cancer.

A second contributor to chronic constipation is insufficient bulk in the intestines as the result of low intake of fiber and water. The pressure of this bulk of material against the intestinal walls is a stimulus to natural peristalsis. Health authorities repeatedly emphasize the value of fruits and vegetables, many of which are high in fiber and water, and they recommend consumption of large amounts of additional fluids, mostly in the form of water. A standard recommendation is to consume two quarts of water (equivalent to 8 servings of one cup each) per day. Fiber is also obtained via ingestion of whole grains and fiber supplements; however, this dry fiber is not a satisfactory solution in the absence of adequate water ingestion. Even with a diet that em-
phasizes fibrous foods, inadequate total intake of food can contribute to constipation. In particular, those who are sedentary may consume less than the 2,000-calorie daily intake that is normally expected, and the amount of food material may be low enough, despite its fiber content, that the intestines are not stimulated to move it through in a normal manner.

Practitioners involved with natural health-care therapies often recommend various dietary supplements, including herbs, which will have a laxative effect. While these supplements can be quite helpful, it is important to put them into proper context and to be aware of potential problems from extended use of stimulant purgatives. Relying on laxatives to permanently replace exercise, fibrous foods, and water is inappropriate except in extreme cases where there are no other options (such as elderly patients with limited capabilities). While use of the laxatives as part of a changing lifestyle may be a valuable component of therapy leading towards alleviation of chronic constipation, it is inconsistent with the tenets of natural healing to recommend use of supplements only, particularly without a reasonable limit of duration.

**BLACK INTESTINES**

Colonoscopy was developed as a routine diagnostic tool during the 1970s and it was soon found that many people had a black or dark brown intestinal wall; the condition was named melanosis coli. Normally, the intestinal wall has a healthy pink appearance. This darkened intestinal wall was found to be associated with chronic use of anthraquinone laxatives. Histological study of colon biopsies in chronic laxative users showed an increased number of macrophages in the connective tissue of the colon mucosa (3). The anthraquinones and their metabolites are retained in the macrophages, where they yield the dark color. Melanosis coli could also arise more rarely from serious diseases of the intestine, the blackening coming from areas of cell necrosis. Thus, the laxative-related condition is sometimes called pseudomelanosis coli, to indicate that the darkening of the intestinal wall is believed to be due only to discoloration rather than a physiological disorder.

A debate over the significance of melanosis coli in relation to anthraquinone use soon arose, and it persists to this day. On the one side, many doctors have interpreted this condition as one of simple staining of the intestinal wall by anthraquinone residues, and viewed it as a harmless and reversible condition (1, 4, 16, 17). Other doctors have seen it as more than just staining, as possibly involving significant damage to the colon wall, and considered that it might be a precursor to more serious intestinal problems, such as colon cancer (15, 18). The majority of articles written about melanosis coli indicate that the condition arises after years of frequent use of anthraquinone laxatives and is not associated with harm. Nonetheless, there are worries that the changes in colon macrophage content and possible changes in colon wall structure that appear to accompany persistent anthraquinone use represent potential harm.

Some patients with melanosis coli have obvious damage to the colon wall (epithelium plus mucosa), which may or may not have been induced by the persistent ingestion of anthraquinones. It is possible that the laxative ingredients have caused cumulative damage in persons whose intestinal repair mechanisms are weak (the intestinal wall cells are among the fastest replicating in the body). In one study (5), 45 patients with prolonged use of anthraquinone laxatives were found to have abnormalities in the absorptive epithelial cells of the colon and autonomic nerve fibers were in various stages of degeneration. A Scandinavian study indicated the presence of nerve damage that might correlate with reduced motility of the intestines (10) in chronic laxative users. In a recent study carried out in Argentina (6), it was reported that the colon cells in patients with melanosis coli had a larger proportion of dead cells, and that the discoloration may have been a combination of anthraquinone residues plus saccharides from the dying cells. After administration of a single dose of sennosides,
it was shown that there was an increase in apoptosis (cell death) of colon epithelial cells (18). One implication is that the anthraquinones may have been inducing premature cell death, with potential for colon wall damage.

On the other hand, the chronic constipation may have been associated with or a causative factor in intestinal damage, and the anthraquinones may have simply darkened the cells but not contributed to the damage nor provided any additional threat to the health of the colon. Repeated damage to cells, especially rapidly replicating cells as found in the intestinal wall, might be expected to increase the rate of cancer formation. A retrospective study in Germany with more than 2,200 patients suggested that there was no increase in colorectal cancer incidence in persons with melanosis coli compared to those without the condition (4). There was a more frequent finding of adenomas in these patients, but this was attributed to easier detection not higher incidence, since the adenomas do not incorporate the pigment and show up as white spots on a black colon wall background. A case report of a woman with melanosis coli after 20 years of laxative use showed no colon abnormalities (16). In a series of over 1,000 rectoscopies conducted in Germany, 10% of the patients were found to have melanosis coli; accompanying inflammation of the colon mucosa was seldom found (17); mild inflammation was attributed to an increased turnover of mucosa cells, which is not necessarily harmful.

In relation to potential carcinogenic action, anthraquinones have been tested for mutagenic potential. Purpurin (7) and the anthraquinones of rhubarb (8) were shown to have antimitogenic effects in laboratory studies. The anthraquinone chrysophanol did not cause chromosomal aberrations when tested in laboratory animals (9). While some laboratory screening tests indicate a genotoxic activity of emodin and aloe-emodin, human clinical trials and animal studies do not support concerns that senna laxatives (the ones most commonly used) pose a genotoxic risk to humans when consumed as normally prescribed (19).

**RECOMMENDATIONS: DOSAGE AND DURATION OF USE**

Use of anthraquinones should probably be limited in dosage and duration to avoid any potential adverse health consequences related to melanosis coli. In one study of colon submucosal nerves in patients with chronic abuse of laxatives, it appeared that nerve fiber damage was related to both dosage and duration of laxative use (10). Pseudomelanosis coli is usually found after a minimum of 9-12 months of regular stimulant laxative use (15). Presumably, after a break in the use of anthraquinones for several weeks, the colon will return to normal and a course of laxative therapy could be safely repeated if deemed necessary. During the break from use of the anthraquinone-containing preparations, lactulose preparations or polyethylene glycol preparations (the newest therapies to show good results) may be used instead. These bulking agents are taken in a dose of about 10 grams each time, twice daily, and have relatively quick effects: normal stool within one to four weeks (11, 12). Their use is becoming prevalent; in a study of more than 3,200 elderly patients in Italy, it was found that lactulose was the most frequently used laxative, followed by anthraquinone laxatives; the use of anthraquinones declined, in favor of lactulose, during hospitalization (13).

In a small study in France of elderly patients (average age 81 years) with chronic constipation (14), 20 mg sennosides daily was administered for six months. This treatment was shown to be without adverse effects: there were no abnormal losses of either protein or potassium; no testing was done for melanosis coli, which would not be expected to occur in six months. Little is known about the dosage that causes melanosis coli or that might cause a more severe form of the condition with intestinal damage. A limiting daily dosage corresponding to 20-30 mg of anthraquinones from senna leaf has been recommended in the herbal literature based on European suggestions for safe use (20). Over-the-counter stimulant laxative drug products are deemed safe and effective when administered in amounts of 12 to 50 mg of sen-
nosides per dose, once or twice per day (21).

In order to evaluate the dosage of various herbal preparations, it is necessary to know the content of anthraquinones in the crude dried herbs and in the prepared teas. A study of rhubarb constituents revealed that the dried root contained 1.2% anthraquinones for R. tanguticum and 3.4% for R. palmatum, with lower amounts in processed roots (22). To get a 20-mg daily dose of anthraquinones (comparable to the dose of sennosides used in the above study), one would consume about 600 mg of rhubarb root derived from R. palmatum. Senna leaf (from S. alexandrina) is reported to contain a similar level of 1.5-3.0% anthraquinones and senna pod contains about 1.4-3.5% (20). Therefore, daily doses of about 500 to 1,000 mg of senna leaf appear to be in the safe range. In a study carried out in California (21), senna teas were tested for sennoside content: teas (in teabag form) labeled as laxatives contained 7-10 mg of sennosides per cup; a dieter's tea yielded 19 mg per cup. In a report from China, patients with addiction to senna leaf tea as a laxative, were reported to suffer from symptoms of fidgetiness, sleeplessness, dilated pupils, and loss of appetite when consuming 5-9 grams of senna daily (24). This is 10 times the range mentioned above that would be deemed safe (based on an estimate of sennoside content for Chinese senna leaf at 1%). About half the people who showed these symptoms of regular senna ingestion had lost weight, indicating the potential modest success rate for long-term overdose of laxatives in a weight loss regimen. Cases of rare hepatic inflammation possibly induced by anthraquinone derivatives have been reported (28, 29, 30, 31) and may be dose related. It is suggested that the anthraquinone may be metabolized in the intestines to form a hepatotoxic compound that some people are sensitive to, resulting in reversible liver damage. Herbs that have been associated with the liver reaction include senna, ho-shou-wu (Polygonum multiflorum; being used as a blood tonic to prevent graying of hair, not as a laxative), and cascara sagrada. In the reported case involving senna ingestion, the dosage was very high, corresponding to 100 mg sennosides per day in addition to twice per week ingestion of a tea made with 10 grams of senna leaves (31). These reactions appear to be so rare that they are not considered cause for warnings or alerts. Limiting the daily intake of anthraquinones to 20-30 mg per day, and limiting duration of continual use to 9-12 months may be a reasonable means of avoiding any of the potential problems associated with stimulant laxatives. If, after this course of therapy, constipation cannot be alleviated by exercise, diet, and physical therapies (e.g., acupuncture, abdominal massage), then anthraquinone use could be continued after an interval of a few weeks while relying on bulking agents as a substitute.

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