TREATMENT FOR INTESTINAL GAS, BLOATING, MICROSCOPIC COLITIS, INFLAMMATORY BOWEL DISEASE AND TRAVELER’S DIARRHEA USING COLLOIDAL BISMUTH SUBCITRATE

Inventor: Eli Ehrenpreis, Skokie, IL (US)

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ABSTRACT

A method of treatment for intestinal gas bloating, microscopic colitis, traveler’s diarrhea and inflammatory bowel disease, said method comprising ingesting an effective quantity of a composition comprising colloidal bismuth subsalicylate to eliminate gastrointestinal discomfort.
TREATMENT FOR INTESTINAL GAS, BLOATING, MICROSCOPIC COLITIS, INFLAMMATORY BOWEL DISEASE AND TRAVELER'S DIARRHEA USING COLLOIDAL BISMUTH SUBCARTRATE

CLAIM FOR PRIORITY/RELATED APPLICATIONS

This application claims priority from U.S. Provisional Application Ser. No. 60/869,003 filed Dec. 7, 2006 entitled TREATMENT FOR INTESTINAL GAS, BLOATING, MICROSCOPIC COLITIS, INFLAMMATORY BOWEL DISEASE AND TRAVELER'S DIARRHEA USING COLLOIDAL BISMUTH SUBCARTRATE, which application is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The invention is directed to compositions and methods for the treatment of intestinal gas and other gastrointestinal disorders. More particularly, the invention relates to methods and compositions for treating intestinal gas, bloating, microscopic colitis, inflammatory bowel disease and traveler’s diarrhea using colloidal bismuth subcartrate (CBS).

BACKGROUND OF THE INVENTION

Gas production normally occurs in the human colon, also known as the large intestine. Colonic gas production takes place when bacteria residing normally in the colon metabolize undigested or partially digested substances. This fermentative process results in the formation of hydrogen (H2), methane (CH4), and CO2. Incomplete upper intestinal digestion and absorption of some food-based carbohydrates is a normal occurrence. Sometimes these substances do not undergo breakdown and absorption across the mucosa (also called the lining) of the small intestine. Unabsorbed carbohydrates are passed by normal intestinal muscular contraction towards the colon. Ultimately, these substances enter the colon in their original form.

Bacterial metabolism of these unabsorbed carbohydrates and some amino acids results in gas production within the colon. Undigested poly saccharides from fruits and vegetables are also sources of intestinal gas formation. Intestinal gas is eliminated from the gastrointestinal tract in several ways. Belching, or forced evacuation of gas from the stomach, is utilized primarily for the removal of swallowed air and ingested CO2 from carbonated beverages. Some gas diffuses from the intestinal lumen into the bloodstream. Ultimately, the lungs excrete these gases. Additionally, specialized colonic bacteria may utilize gas produced by fermentation by other bacteria as a source of fuel. These methods of gas elimination make up only a small portion of the methods of colonic gas removal. The majority of intestinal gas is eliminated by passage out of the colon through the anus as flatus.

In patients with intestinal malabsorption, disaccharidase deficiencies, small intestinal and pancreatic diseases and other more poorly characterized conditions, large quantities of disaccharides enter the colon where they are fermented by colonic bacteria. These individuals are prone to the production of large volumes of intestinal gas. Excessive intestinal gas results in the symptoms of excessive flatus, bloating, diarrhea and abdominal distension. Of interest, passage of voluminous or noxious flatus also appears to be a common complaint in normal persons.

Patients with irritable bowel syndrome and other functional gastrointestinal disorders frequently complain of abdominal bloating, cramping and flatulence. However, clinical studies have generally failed to demonstrate excessive gas production in these individuals. Elderly patients with decreased digestive function, persons with lactose or fructose intolerance and many other patients commonly complain of excessive gas. If diminished anal sphincter function is present, (as occurs in the elderly as well as persons with prior anal sphincter injury or surgery), excessive gas production may result in gas incontinence, an embarrassing condition that may result in diminished quality of life. At present, patients with difficulty with excessive gas production, abdominal bloating or control of colonic gas have few readily available treatment options.

Simethicone is an over-the-counter product marketed for the relief of abdominal discomfort secondary to gas buildup. It acts as emulsifying agent and changes the surface tension of gas bubbles in the stomach and intestines. However, simethicone causes small gas bubbles to join together into larger bubbles. It is thought that these larger gas bubbles are more easily eliminated from the body by belching or passing flatus. Unfortunately, this proposed mechanism has not been proven to be beneficial to patients. Additionally, it may be hypothesized that easier passage of large gas bubbles may result in adverse effects of simethicone in patients with excessive intestinal gas production or those with gas incontinence.

Lactase enzyme supplements such as Lactaid and DairyEase improve dairy digestion in patients with lactose intolerance. Patients that are lactase deficient will incompletely absorb milk products when they ingest dietary substances that contain dairy. These products will reduce the formation of gas in many patients that have the symptoms of lactose intolerance.

Activated charcoal has been shown to absorb a variety of organic and inorganic compounds. This includes absorption of hydrogen and nitrogen gasses, which in theory could reduce the volume of flatus in persons complaining of excessive gas passage. Additionally, binding of the sulfur containing gasses (hydrogen sulfide and methanethiol) by charcoal could potentially reduce the unpleasant odor of gasses in these patients. Although some clinical trials have demonstrated benefits of activated charcoal in reducing gas passage, other studies have failed to demonstrate this positive effect. Activated charcoal ingestion may also predispose to vitamin deficiencies and malabsorption of drugs.

Although laboratory studies have demonstrated that bismuth subsalicylate may decrease overall bacterial production of noxious gasses such as hydrogen sulfite, no clinical studies have demonstrated effectiveness of this compound for the treatment or prevention of excessive intestinal gas. No formal studies of bismuth citrate have been performed to determine its efficacy in the treatment of excessive gas or abdominal bloating.

Microscopic colitis is a form of chronic diarrheal illness that appears to be increasing in prevalence in the United States. This condition, which is characterized by the daily occurrence of frequent watery diarrhea, is most commonly seen in women over the age of fifty. Diagnosis of microscopic colitis is made by the performance of colonoscopy with multiple biopsies of the mucosal lining throughout the colon. Generally, the colonic mucosa is normal by endoscopic appearance. However biopsies reveal chronic inflammation of the colonic mucosa. Two characteristic patterns of mucosal inflammation are seen in microscopic colitis. In collagenous colitis, thickening of the lamina propria collagen layer is seen in association with infiltration of chronic inflammatory cells. In lymphocytic colitis, marked lamina propria infiltration of lymphocytes, with associated intra-epithelial
lymphocytes are seen. A variety of treatments have been recommended for microscopic colitis. These include systemic corticosteroids, which may resolve symptoms without histologic improvement, topical 5-aminosalicylic acid containing drugs and a variety of miscellaneous treatments.

Recently, randomized, controlled trials have shown that the topical steroid, enteric-coated budesonide (Entocort) appears to be a highly effective treatment for microscopic colitis. An open-label study of chronic, high dose bismuth subsalicylate (8 chewable Pepto-Bismol daily for 8 weeks) resulted in improvement of symptoms in 11 of 12 patients studied. Each tablet contains Bismuth subsalicylate 262 mg. In the study, nine patients (75%) had complete resolution of colitis on examination of colonic biopsies. A very small randomized, controlled trial of bismuth subsalicylate appeared to confirm these initial findings. By definition, subjects in these studies were excluded if they were allergic to aspirin. Most clinicians are unable to duplicate the success rates of these studies in treating the symptoms and eradicating microscopic colitis due to patient's inability to tolerate these doses of bismuth subsalicylate.

Traveller's diarrhoea occurs as an acute illness in persons visiting countries with poor sanitary conditions. The condition develops as a form of food poisoning after consumption of food or water containing pathogenic bacteria, viruses or parasitic organisms. The majority of cases of traveller's diarrhoea are due to the E. coli bacteria strains that secrete enterotoxins.

Bismuth subsalicylate is commonly used for the prevention of traveller's diarrhoea and has been FDA approved for the control of traveller's diarrhoea. As with other conditions mentioned, a relatively high dose of bismuth subsalicylate is required for this indication. Current recommended doses of bismuth subsalicylate to prevent traveller's diarrhoea are 2 chewable tablets (containing Bismuth subsalicylate 262 mg.) four times daily. A 66% reduction in the occurrence of diarrhoea is achieved with this dosage. Unfortunately, this dose will not be tolerated by a significant number of individuals using bismuth subsalicylate to prevent traveller's diarrhoea, particularly if the common and unpleasant side effects of these doses of bismuth subsalicylate develop during travel.

Bismuth subsalicylate is also a commonly used over-the-counter treatment for benign forms of infectious diarrhoea in adults and children. It is also prescribed for upset stomach (dyspepsia).

Antibiotics, particularly metronidazole and ciprofloxacin, are used as adjunctive pharmacotherapy for the treatment of acute episodes and maintenance therapy for ulcerative colitis and Crohn's disease (collectively known as inflammatory bowel disease, or IBD). The mechanisms by which antibiotics are effective for these conditions are not known, but alteration of gastrointestinal flora and direct anti-inflammatory activity appear to be an important factors. The short and long term use of antibiotics in these conditions can be problematic. Antibiotics may cause diarrhoea, thus worsening these conditions. Additionally, these drugs may wipe out beneficial bacteria and cause overgrowth of resistant organisms. Long term use of metronidazole may result in injury to the nerves of the hands and feet. In some patients, this form of nerve injury, termed neuropathy, may be permanent.

SUMMARY OF THE INVENTION

The invention involves the oral administration of colloidal bismuth subcitrate (CBS), and other forms and alterations of bismuth citrate. Reference to CBS or colloidal bismuth subcitrate should be understood to include ranitidine bismuth citrate and other forms and alterations of bismuth citrate. CBS has many advantages over the currently available bismuth subsalicylate because of decreased side effects and better tolerability of the medications at the doses required to treat appropriate conditions. The compounds according to the present invention may also be used for individuals that are allergic to aspirin. These substances may be used for the treatment of excessive gas production. These compounds may also be used for the prevention and treatment of traveler's diarrhoea. These compounds may also be used to reduce the symptoms of microscopic colitis and to induce remission of this condition. Additionally, these compounds may be used for the medical management of abdominal bloating and diarrhoea associated with functional bowel disorders such as irritable bowel syndrome. These compounds may also be used as adjunctive initial or maintenance therapy for IBD.

A therapeutic dosage of CBS or salts of bismuth subcitrate according to the present invention is a dosage of up to 2700 mg daily. This dosage may be utilized for up to eight weeks for the treatment of microscopic colitis. Doses of ranitidine bismuth citrate would be 800 mg three times daily.

Doses of two to eight capsules CBS (up to 2700 mg) daily may be administered to prevent traveler's diarrhoea in persons going to endemic areas. Doses of two to eight CBS capsules daily in divided doses may be utilized for the management of excessive gas production for up to 12 weeks duration. Subsequently, up to 2700 mg/day bismuth citrate may be used on an as needed basis for these conditions. Doses of ranitidine bismuth citrate would be up to 800 mg three times daily.

According to one aspect of the present invention for the treatment of intestinal gas bloating, microscopic colitis and traveller's diarrhoea, comprises ingesting an effective quantity of a composition comprising bismuth citrate (or colloidal bismuth subcitrate) for gastrointestinal discomfort. The composition of the aforementioned method may contain between 125 and 900 mg of bismuth subcitrate. Moreover, the composition may be administered once, twice or up to six times daily. The daily dose of ranitidine bismuth citrate would be 400-800 mg daily or up to three times per day.

The composition may be administered in a form selected from the group consisting of chewing gums, lozenges, troches, and combinations thereof.

DETAILED DESCRIPTION OF THE INVENTION

Bismuth compounds have been used since the 1700s as treatments for a variety of medical conditions. The most common uses of bismuth-containing compounds are for the treatment of diarrhoea and dyspepsia. A variety of bismuth salts have been administered as remedies for gastrointestinal disorders via the oral route. The only commercially available form of bismuth in the United States at present is bismuth subsalicylate (Pepto-Bismol; Procter & Gamble Co., Cincinnati Ohio).

More recently, ranitidine bismuth citrate (Trilice, Glaxo Pharmaceuticals) was FDA approved as a component of treatment for the Helicobacter pylori infection. Trilice was marketed as a portion of triple antibiotic therapy for Helicobacter pylori infection. The advantage of adding a bismuth-containing compound to antibiotic therapy for Helicobacter pylori infection is that bismuth limits the production of antibiotic-resistant organisms. This is particularly important in European countries, where strains of Helicobacter pylori that are resistant to erythromycin and metronidazole had been identified. Despite its ease-of-use, very low side effect profile, and potential advantage in prevention of antibiotic-resistant Helicobacter pylori organisms, the use of Trilice never
became popular in the United States and is no longer commercially manufactured or available in this country. Bismuth subsalicylate is commonly used over-the-counter form of bismuth used for the treatment for non-specific gastrointestinal symptoms and diarrhea. A single clinical trial has been published suggesting that bismuth subsalicylate, administered as 8 chewable 262 mg tablets daily for eight weeks resulted in the diminution of the symptoms of collagenous colitis. The complete resolution of diarrhea and colitis occurred in nine of twelve patients that completed that open-label clinical trial.

A randomized, placebo-controlled trial of bismuth subsalicylate, three 262 mg tablets orally three times a day for eight weeks was performed in nine patients. Four of nine patients received bismuth subsalicylate and all of these demonstrated clinical and histologic improvement, in contrast to no effect seen in the placebo group. Unfortunately, this study was never published in a peer-reviewed journal and only appeared abstract form.

The FDA has approved the use for bismuth subsalicylate for the prevention and treatment of traveler’s diarrhea an acute diarrhea illness often produced by infection with a strain of E. coli that secretes enterotoxin chemical compounds. Bismuth subsalicylate administered in the doses used in the studies (8-9 262 mg chewable capsules three times/day) for the treatment of microscopic colitis and for the prevention of traveler’s diarrhea. At these doses, bismuth subsalicylate has the significant disadvantage of producing a number of side effects. These side effects include a metallic taste in the mouth, ringing in the ears (tinnitus) and other effects of the salicylate portion of the drug. Nonetheless, in the clinical trials of bismuth subsalicylate for microscopic colitis, no patient reported developed toxic side effects of bismuth subsalicylate and measured serum bismuth levels remained well within the safe range in all study patients. Clinical experience with these doses of bismuth subsalicylate for the treatment of microscopic colitis has generally not been as successful as the published trials. Most patients are unable to complete an 8 to 12 week course of treatment due to the large number of side effects with these doses of bismuth subsalicylate.

Colloidal bismuth subcitrate (CBS) has never been utilized as a stand-alone treatment for gastric and duodenal ulcers, Helicobacter pylori infection and nonulcer dyspepsia. Applicant has discovered that Bismuth citrate offers many advantages over bismuth subsalicylate and may be useful for the treatment of a variety of conditions. Since bismuth citrate does not contain salicylates, potential side effects from the use of salicylates including gastrointestinal mucosal inflammation, salicum (tinnitus, dizziness and possibly kidney damage), taste disturbances and other central nervous system (CNS) side effects would not be expected to occur. Allergic reactions would be exceptionally rare and patients that are allergic to aspirin could take the drug.

The consistent safety of this compound was emphasized in a review of 20 clinical studies of ranitidine bismuth citrate including a total of more than 5000 patients performed by Pgp et al. They found that the side effects of ranitidine bismuth citrate were no different than those seen with ranitidine alone. The authors concluded that like ranitidine alone, the combination drug ranitidine bismuth citrate had a well-documented safety profile for clinical use. Like bismuth subsalicylate, colloidal bismuth subcitrate (CBS) is a poorly absorbed substance that achieves very low peak levels when orally administered over a prolonged duration at therapeutic doses. CBS works at the gastrointestinal mucosal level where it has both an antibacterial effect and mucosal protective effect. In addition, CBS binds bile salts and to epithelial growth factor. Unlike bismuth subsalicylate, CBS increases endogenous prostaglandin and alkali secretion. This results in improved gastrointestinal blood flow and enhancement of gastrointestinal mucosal protection. A number of studies have demonstrated that safe serum bismuth levels occur when these levels are measured after the ingestion of up to 480 mg per day of CBS for more than 4 weeks.

Other studies demonstrated the safe use of 480 mg of CBS daily for 8 weeks for nonulcer dyspepsia. The only episodes of acute reversible renal failure demonstrated after the ingestion of bismuth subcitrate were seen in with an overdose of the drug. Chronic encephalopathy, a central nervous system disease seen with other forms of bismuth salts has been occasionally described in patients consuming bismuth subsalicylate. It is only been reported once in a patient with renal impantment consuming prolonged high doses of bismuth subcitrate. In fact in a review of the pharmacology of bismuth containing compounds, published in the journal Reviews of Infectious Diseases, Lambert has stated that bismuth compounds “administered for short duration to subjects with normal renal and hepatic function are rarely toxic. Toxicity has mainly resulted from unsupervised and indiscriminate use of these compounds”. Lambert also stated that both the clinical effects and pharmacokinetics of CBS has been carefully analyzed scientifically.

The inventor has specific clinical experience with the use of CBS. Six patients who had episode both severe fatus passage and gastrointestinal discomfort after the consumption of large quantities of nonabsorbable carbohydrates were treated with CBS obtained from a compounding pharmacy. In all six patients, CBS 125 mg, 1 or 2 capsules per day or twice a day for one to two days completely eliminated all of acute symptoms of excess of gas passage. No toxic effects were noted in these individuals. A single dose of CBS 125 mg was administered to a dog with excessive and bothersome gas following a large meal including table food. Complete session of flatus occurred following administration of this single dose. One patient with symptomatic microscopic colitis had complete resolution of symptoms after one month of CBS 600 mg three times daily.

Because of the well-established safety of CBS, its positive effect on gastrointestinal function, poor absorption and limited risk for toxicity and allergic reactions, CBS is an ideal compound for the treatment of a variety of gastrointestinal disorders. It appears to be effective for the treatment of excessive gas at low doses that would not be expected to result in toxicity, even when administered on a chronic basis. It is proposed that this substance can be utilized for the treatment of excess of gas production, gastrointestinal bloating, and irritable bowel syndrome with excessive of diarrhea, and microscopic colitis including collagenous colitis and lymphocytic colitis. It may also be useful as replacement for conventional antibiotic therapy for IBD.

It may also be used for dyspepsia or the aforementioned indications in patients that are allergic to aspirin. All of these treatments would be administered daily for limited time (8 weeks or less) with subsequent on an as needed basis.

According to another aspect of the invention, CBS may be administered in combination with one or more additional compositions or products such as simethicone at a dosage such as 50-200 mg/capsule, up to 1000 mg/day. The simethicone may be replaced with activated charcoal at a dosage of 100-500 mg/capsule, up to 3000 mg/day.

CBS may further be administered in combination with a steroid or other anti-inflammatory such as budesonide 1-5 mg per capsule, up to 9 mg/day; anti-inflammatory
mesalamine (5-ASA) 100-500 mg/capsule, up to 2500 mg/day; or a steroid, anti-inflammatory or antibiotic such as Rifaximin for inflammatory bowel disease. For example, combination of CBS 125-600 mg and 5-ASA 400-800 mg in a delayed release capsule such as Eudragit-S would be suitable for treating microscopic colitis. Dosage range would be 3-12 capsules per day.

Alternatively, 5-ASA could be complexed to CBS as a compound or mixture for the same purpose. This treatment could also be used for ulcerative colitis or Crohn’s disease. This complex could also be delivered as a standard or delayed-release tablet or standard or delayed release capsule.

Combination or CBS with a steroid could include CBS 125-600 mg plus budesonide 1-3 mg or prednisone 1-20 mg. These may be in a standard tablet or capsule, or delayed release tablet or capsule. Combination therapy with an antibiotic could include a combination of CBS 125-600 mg with ciprofloxacin. In addition, these doses of CBS may be combined with Rifaximin 100 or 200 mg in standard or delayed release capsules or amoxicillin 250-500 mg in standard or delayed-release capsules.

For treatment of intractable gas, CBS 125-600 mg may be combined with simethicone 10 to 750 mg, peppermint oil 100-1000 mg, chamomile 10-1000 mg activated charcoal 10-1000 mg, ginger 10-1000 mg, and/or chlorophyll 10-1000 mg. Essential oils of these herbal preparations may be used as well. For the treatment of irritable bowel syndrome, CBS may be combined with hyoscyamine 0.125-0.375 mg or dicyclomine 5-20 mg, chloridiazepoxide 1-10 mg and clindamycin 1-10 mg or any of the above combinations.

Colloidal bismuth subsalicylate, alone or in combination with other ingredients, may also be administered in enema or suppository form. In addition, an ointment or paste containing these compounds may be utilized.

According to another aspect of the invention, CBS may be used to treat microscopic colitis by administering CBS in combination with one or more of 5-ASA (mesalamine), budesonide, azathioprine, or bromolaine.

According to another aspect of the invention, CBS may be used to treat traveler’s diarrhea by administering CBS in combination with one or more of ciprofloxacin, amoxicillin (with or without clavulanate), trimethoprim/sulfamethoxazole, levaquin, Rifaximin, or metronidazole.

According to another aspect of the invention, CBS may be used to treat dyspepsia by administering CBS in combination with one or more of PPI, sucralfate, guar gum, ginger, or chlorophyll.

According to another aspect of the invention, CBS may be used to treat dyspepsia by administering CBS in combination with one or more of PPI, sucralfate, guar gum, ginger, or chlorophyll.

According to another aspect of the invention, CBS may be used to treat dyspepsia by administering CBS in combination with one or more of PPI, sucralfate, guar gum, ginger, or chlorophyll.

It should be noted that each of the drug combinations disclosed herein may be mixtures, compounds or salts. Moreover, the CBS alone or in combination with one of the additional ingredients disclosed above may be administered using capsules or tablets, pH sensitive capsules (such as Eudragit L, S or N), or other delayed release tablets or capsules.

The foregoing description of the invention is illustrative only, and is not intended to limit the scope of the invention to the precise terms set forth. Further, although the invention has been described in detail with reference to certain illustrative embodiments, variations and modifications exist within the scope and spirit of the invention as described and defined in the following claims.

1. A method of treatment for intestinal gas bloating, microscopic colitis and traveler’s diarrhea, said method comprising ingesting an effective quantity of a composition comprising colloidal bismuth subcitrate to eliminate gastrointestinal discomfort.

2. The method according to claim 1, wherein the composition contains at least 125 mg of colloidal bismuth subcitrate.

3. The method according to claim 2, wherein the composition is administered once daily.

4. The method according to claim 2, wherein the composition is administered twice daily.

5. The method according to claim 2, wherein the composition is administered up to six times a day.

6. The method according to claim 1, wherein the composition contains between 125 mg and 900 mg of colloidal bismuth subcitrate.

7. A topical oral dosage form selected from the group consisting of chewing gums, lozenges, troches, and combinations thereof, wherein the topical oral dosage form comprises a pharmaceutically active agent effective against intestinal gas bloating, microscopic colitis and traveler’s diarrhea, wherein the pharmaceutically active agent comprises colloidal bismuth subcitrate.

8. The topical oral dosage of claim 7 wherein the dosage form is a chewing gum.

9. The topical oral dosage of claim 7 wherein the dosage form is a lozenge.

10. The topical oral dosage of claim 7 wherein the dosage form is a troche.

11. The topical dosage of claim 7 wherein the topical dosage form is chewing gum.

12. The topical dosage of claim 11 wherein the chewing gum comprises between about 125 mg and about 900 mg of colloidal bismuth subcitrate.

13. The method according to claim 1, wherein the composition contains ranitidine bismuth citrate at a dose of 400 mg, administered daily or up to three times per day.

14. The method according to claim 1, wherein the composition contains ranitidine bismuth citrate at a dose of 800 mg, administered daily or up to three times per day.

15. The method according to claim 1, wherein the composition further contains one or more of the following simethicone, a steroid, an anti-inflammatory, and an antibiotic.

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