Recent Advances in Pharmacotherapy

Gastrointestinal gas

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Complaints related to gastrointestinal gas are commonly encountered in clinical practice. Various therapies have been proposed, yet none has appeared to be extremely effective. A review of the literature revealed little hard evidence to support the use of simethicone, pancreatic enzymes, anticholinergic agents or antibiotics. Evidence supporting the use of prokinetic agents has been the strongest, and there may be a pathophysiologic basis for the use of these agents if the complaints are related to abnormal intestinal motility. The use of activated charcoal for adsorbing intestinal gas has been effective in healthy subjects but has not been properly investigated in patients with gas complaints. Dietary modification may be beneficial in certain cases. Additional controlled trials are necessary to clarify the issues in the treatment of this common problem.

En pratique quotidienne on entend souvent les clients se plaindre de flatulence gastro-intestinale. Des nombreux remèdes proposés, aucun ne semble très efficace. La revue de la littérature apporte peu de preuves solides en faveur de la siméthicone, des ferments pancréatiques, des anticholinergiques et des antibiotiques. Les stimulants du péristaltisme s'en tirent mieux; du point de vue physiopathologique leur emploi se justifierait en présence d'anomalies de la motilité intestinale. L'adsorption des gaz intestinaux par le charbon activé, efficace chez le sujet bien portant, n'a pas été étudiée comme il le faudrait chez celui qui se plaint de flatulence. Le traitement diététique peut être efficace dans certains cas. Pour éclaircir cette question il faudrait plus d'essais comparatifs.

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Patients frequently complain of gas. Various therapies have been suggested, yet none appears to be extremely effective. We did a computer-assisted search of the English-language literature for relevant articles and then cross-checked the references of those articles. We reviewed all the articles in a systematic manner to determine whether there was evidence to support the use of the various therapies.

Symptoms

The symptoms of gaseousness can be divided into three groups.[1] The first, excessive eructation, is the easiest to treat. The cause is simply the repetitive swallowing or aspiration of air, followed by its eructation. There is no specific therapy other than a search for its cause (e.g., anxiety, dry mouth, poorly fitting dentures and gum chewing) and an explanation and reassurance for the patient.

Excessive rectal gas, the second type of symptom, depends mostly on the amount of unabsorbed carbohydrate that reaches the colon, the nature of the colonic flora and the speed at which the gas reaches the rectum. Antibiotics have been used in an attempt to change the colonic flora, but they have had variable results and may even increase gas production.[2] The amount of undigested carbohydrate can be modified through changes in diet; lactose intolerance and sorbitol or mannitol ingestion should be considered in patients presenting with excessive rectal gas. However, even in the absence of a true state of malabsorption, other food components may be incompletely absorbed in healthy subjects.[3-9]

The third and most difficult group of symptoms to treat comprises pain and bloating, which do not appear to be related to an increased volume of intestinal gas. Lasser, Levitt and Bond[10] found that patients with these symptoms had volumes of intraluminal gas similar to those of asymptomatic control subjects; however, the symptomatic patients had delayed transit of gas. This suggests that the symptoms were caused by disordered intestinal

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motility and an abnormal pain response to distension instead of by the volume of gas. The same group also studied patients after a standard meal and found that "gaseous" patients did not have an excessive volume or production of intestinal gas postprandially.[11] Again, the symptomatic patients had delayed transit of gas that was associated with pain and bloating.

Drug therapy

Simethicone

Silicone compounds were initially used as defoaming liquids and then as prevention against the appearance of bubbles during gastroscopy. They were also found to be useful in the treatment of bloating in ruminants. Silicones were eventually used to treat gas in humans and have since found their way into a number of antacid preparations.

Rider[12] carried out what appears to be the first clinical trial of silicones in humans. Of 117 patients with complaints of intestinal gas and bloating who were treated with methylpolysiloxane, 84 reported good or excellent results. However, only 20 of the patients received a placebo, which was given after successful treatment with methylpolysiloxane; of these, 18 reported a return of symptoms within 24 hours after the placebo regimen had been started. The fact that the placebo was lactose might explain the recurrences. A follow-up report published later the same year showed similar results;[13] the group had grown to 200 patients, but there was still no proper control group.

In 1961 Oswald[14] reported the results of a placebo-controlled double-blind study in patients with functional symptoms such as abdominal distension and discomfort, belching, excessive flatus and heartburn. The patients were treated with tablets that contained either methylpolysiloxane or an unspecified placebo. However, the adequacy of the blinding and the randomization is questionable, because more patients received the drug than the placebo (40 v. 14). Of the 40 patients in the treatment group 26 had good or excellent results, as compared with 5 of the 14 in the placebo group. This difference was not statistically significant.

In 1965 Marks, Band and Groll[15] reported the results of a randomized, double-blind study in which 32 patients with functional gastrointestinal complaints received methylpolysiloxane (either alone or in combination with atropine methylbromide, magnesium oxide and magnesium carbonate) or placebo; each patient received the active treatment for 1 week and the placebo for the alternative week. The placebo used in the group given methylpolysiloxane alone consisted of lactose, and the one used in the group given the combined preparation comprised magnesium carbonate, aluminum hydroxide and dextrose. Twenty of the patients preferred the drug over the placebo for relief of abdominal distension. Only one patient preferred the placebo. The results are impressive but difficult to interpret, because the lactose-containing placebo might have worsened the symptoms. In addition, some of the patients were treated with a bulk purgative, which might also have affected the symptoms. The authors did not specify how many of the patients in the drug-treated group received methylpolysiloxane alone.

In 1966 Cohen and Belsky,[16] from an uncontrolled study, reported good responses to simethicone combined with butabarbital sodium and belladonna alkaloids in a group of patients with functional complaints and organic disease. In a randomized, double-blind, placebo-controlled trial of simethicone combined with butabarbital and belladonna alkaloids published in 1968 Bobruff[17] found that the drug therapy was more effective than the placebo in relieving gas in 31 patients ($p < 0.01$). However, this study lasted only 4 weeks and used a lactose placebo and combination therapy, all of which make the effect of simethicone alone difficult to interpret.

Bernstein and Schwartz,[18] in a double-blind, randomized, placebo-controlled trial of the effect of simethicone on symptoms after a test meal, found that the drug was more effective than the placebo in relieving postprandial gas ($p < 0.05$). Bernstein and Kasich[19] reported the results of a double-blind, randomized 10-day trial in which 41 patients with various upper gastrointestinal complaints such as gas, abdominal distension and bloating were treated with either simethicone or placebo. The drug was significantly better than the placebo in relieving gas ($p < 0.001$). In neither of the two studies did the authors define what they meant by gas, nor were the ingredients of the placebo identified.

A report published in 1985 highlighted the problems involved with carbohydrate-containing placebos in the assessment of gas.[20] The effect of a simethicone-containing tablet on the elimination of intestinal hydrogen in the breath, which is a measure of colonic gas production, was studied in subjects given lactulose alone, simethicone and lactulose or placebo and lactulose. Lactulose increased the amount of hydrogen, which was decreased by simethicone but actually increased by the placebo. The placebo tablet, like the simethicone tablet, contained unabsorbable pentasaccharides; this explains the placebo's effect on the hydrogen level. The authors concluded that the effect of simethicone was reduced because of hydrogen production from the unabsorbable carbohydrate in the tablet.

Enzyme preparations

The use of simethicone in combination with pancreatic enzymes (Phazyme; Reed and Carnrick, Kenilworth, New Jersey) has been found to be effective in uncontrolled studies.[21,22] In a prospective, double-blind, placebo-controlled trial[23] 108

patients with various gastrointestinal problems, of whom approximately 50% had organic disease, were treated with either Phazyme or placebo for 2 weeks and then with the alternative substance for another 2 weeks. In one subgroup of 43 patients with irritable bowel syndrome 27 responded well to the drug, as compared with only 11 to the placebo ($p < 0.001$). Unfortunately, the type of placebo was not specified, the study was not randomized and lasted only 4 weeks, and there was no time allowed for the substance to clear before the regimens were changed. In 1985 pancreatin was removed from Phazyme.

Pancreatic enzymes have been used in combination with bile acids (Doxegest; G.A. Breon Co., New York). In one uncontrolled trial all of the 22 patients showed some benefit from this combination, but they were also taking phenobarbital and belladonna.[24]

Prokinetic agents

Prokinetic agents, such as metoclopramide and domperidone, have also been used in the treatment of gas. In a double-blind, crossover study 42 patients with flatulent dyspepsia were treated for 4 weeks with either metoclopramide or placebo;[25] 17 of the 29 patients who had not undergone gastrointestinal surgery preferred metoclopramide, and 6 preferred the placebo ($p < 0.01$). The study did not separate the responses according to symptoms of gas and of gastroesophageal reflux, although it did state that all the symptoms were equally affected. When these results were republished in 1973 the symptoms were looked at more closely:[26] those of gas and of gastroesophageal reflux were significantly decreased after metoclopramide therapy ($p < 0.01$); however, in that analysis the author did not separate the postoperative patients from those with functional dyspepsia.

Another study compared the effects of metoclopramide, antacid alone and antacid containing simethicone on dyspeptic symptoms such as gas and on those suggestive of gastroesophageal reflux.[27] Sixty-nine patients completed the 12-week study, each type of therapy lasting 4 weeks. None of the patients received a placebo. Metoclopramide was found to be superior, although the difference was small.

Domperidone, a newer prokinetic agent, has been suggested for the treatment of gas. In a double-blind, placebo-controlled trial it was given to 10 of 20 patients who had symptoms of gas and those suggestive of gastroesophageal reflux;[28] 16 had irritable bowel syndrome, and 4 had gastritis. Eight patients reported good or excellent results, as compared with only 1 placebo-treated patient. However, the effect on the target symptoms was not specified, and the study was published only in abstract form. In a second randomized, double-blind study of the effect of domperidone in 66 patients with irritable bowel syndrome 34 patients were treated with domperidone and 32 with placebo for 4 weeks.[29] Thirteen target symptoms were assessed, including a group of symptoms termed "postprandial flatulence". Domperidone significantly decreased the latter ($p < 0.01$).

The results of these studies suggest that prokinetic agents may be useful in the management of gas. Certainly the evidence is stronger than that for simethicone.

Activated charcoal

A number of recent studies have examined the effect of activated charcoal on intestinal gas. Activated charcoal is supposed to adsorb intestinal gas, as it is known to be an excellent adsorbent of many chemical substances, including gases. Two placebo-controlled studies examined its effect on hydrogen levels in the breath after a gas-producing stimulus had been taken by healthy, asymptomatic adults.[30,31] The first study showed a decrease in the number of flatus events and in the levels of hydrogen in the breath after a bean meal in the treated group.[30] The second study showed similar results after lactulose administration in the treated group.[31]

Another study compared the effects of simethicone, activated charcoal and placebo after a bean meal in healthy adults and found that the activated charcoal reduced the levels of hydrogen in the breath and the severity of the symptoms and that simethicone was no better than the placebo.[32] The most recently published study again confirmed the ability of activated charcoal to decrease hydrogen levels in the breath of healthy asymptomatic adults after a bean meal.[33] This study was carried out mainly because a previous one had failed to demonstrate such decreases in healthy asymptomatic adults treated with activated charcoal or placebo.[34]

The results of these studies suggest that activated charcoal can decrease the severity of symptoms, the number of flatus events and the level of hydrogen in the breath in healthy adults after a gas-producing stimulus has been given. However, these results cannot be extrapolated to patients who actually present with complaints of intestinal gas. Obviously, the next step is a properly designed study in symptomatic patients.

Miscellaneous drugs

Various other drugs have been suggested for the treatment of gas. Antibiotics have had variable effects and can increase or decrease gas production.[2,7] Anticholinergic agents have also been suggested because of their ability to inhibit postprandial colonic contractions and cramping — the gastrocolic response.[35] The effects of anticholinergic agents on gas production have varied,[7,36] but

we could find no trial of these drugs in patients with symptoms of gas.

Carminatives have been used for centuries to treat postprandial gas and bloating. They essentially consist of aromatic, volatile oils that induce eructation.[37] Experimental evidence has suggested that these preparations do this by relaxing the lower esophageal sphincter.[38] No controlled trials of their use in patients with gas have been carried out. Kinloch[37] stated that "the effectiveness of these preparations in giving symptomatic relief is directly proportional to the faith the patient and physician have in them".

Diet

The effect of diet on rectal gas has been mentioned, but diet can also affect such symptoms as bloating and abdominal discomfort. As in the case of excessive flatus, the amount of unabsorbed carbohydrate that reaches the colon appears to be the culprit. A number of studies have shown that carbohydrates in a normal diet may not be totally absorbed and may thus cause increased gas production by colonic flora as well as such symptoms as gas, bloating, abdominal cramps and diarrhea.[3-9] These carbohydrates include lactose, sorbitol, mannitol, fructose, carbohydrates in all-purpose wheat flour and, perhaps the most infamous, the oligosaccharides in many beans.

In a recent review Bond[39] suggested that certain foods stimulate abnormal motility and cause symptoms by that mechanism rather than by "their tendency to gassify in the gut". This was based on the findings of normal volumes of gas in patients with gas complaints after both fasting and eating and on pain in response to the presence of gas at volumes well tolerated by healthy control subjects.

Summary

Dietary factors seem to play an important role in intestinal gas complaints, and modifications in diet may benefit some patients. In particular, an attempt should be made to identify dietary carbohydrates, such as lactose and sorbitol, that may be incompletely absorbed and thus lead to symptoms.

Effective pharmacologic therapy for intestinal gas has been limited. Prokinetic agents have had the best effect and provide a rational approach to therapy.[1,10,11] New prokinetic agents (e.g., cisapride, which acts throughout the gastrointestinal tract) are becoming available and may be useful in patients with complaints of intestinal gas. Evidence supporting the use of simethicone, enzymes, anticholinergic agents and antibiotics has not been convincing.[1,40-45] Activated charcoal appears to be promising, but a controlled trial in symptomatic patients is needed to prove its efficacy.

Although the complaint of gas is quite common, it is surprising that we could not find one large, long-term, prospective, randomized, double-blind, inert-placebo-controlled study that showed any pharmacologic agent to be effective in treating gas.

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Additional comments on gastrointestinal gas

Gastrointestinal gas is part of the human condition. It is only the extent to which it enters a person's consciousness that it becomes a problem. As Fardy and Sullivan make clear, repetitive burping and belching require no more than an explanation and reassurance. Although the average daily number of flatus events is 14, this number varies greatly between people, and there is little evidence that any therapy will consistently reduce gas production.[1] The organisms that produce the gas need substrate, so starvation may help. However, this solution offers no future for the host. None the less, foods such as beans and cabbage that contain nonabsorbable carbohydrate can be proscribed[2] and those such as rice that have efficient absorption characteristics encouraged.[3] There is no rationale for the use of simethicone or prokinetic agents here, and, as pointed out, antibiotics may make matters worse. The adsorbant powers of activated charcoal have been promising, but charcoal is messy, unavailable in pharmaceutical form and not yet proven effective in symptomatic patients. Perhaps increased tolerance of flatus would be a better solution, for we tamper with harmless natural phenomena at our peril.

The symptoms of bloating, distension, borborygmus and just "gas" are quite a different matter. These symptoms occur in 30% of apparently healthy people[4] and are an integral component of the irritable bowel syndrome.[5] Studies have shown that the volume of gas is the same in complainers and noncomplainers, although the motility may differ.[6] In such patients we should be wary of the use of any drug with possible side effects, because the condition is benign and often lifelong. Metoclopramide should not be used, because of its neurologic effects.[7] Although more expensive the other prokinetic agents — domperidone and cisapride — are safer, but do we really know what we are trying to accomplish here? There is no evidence that distension or the irritable bowel syndrome is due to a sluggish gut. The symptoms are usually chronic, so when does one stop the drug?

The notion that there is a pill for every ill is a pervasive but dangerous concept. For some symptoms (e.g., bloating) an explanation, reassurance and compassion with no drug therapy is the best medicine.

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Intestinal gas, flatulent dyspepsia and the "gas-bloat" syndrome are all terms used to describe a