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The Problem of Gas in Irritable Bowel Syndrome

Patients with irritable bowel syndrome (IBS) complain of a constellation of symptoms (1), of which abdominal pain is not necessarily the most intrusive (2, 3). Recognition of this fact is important from a therapeutic point of view, as successful management is dependent on targeting the features that the patient finds most troublesome. It is becoming increasingly recognized that abdominal distension is very distressing for many patients (3), but the pathophysiology of this symptom is poorly understood, although the obvious explanation of excessive gas is unlikely to be the whole answer (4, 5). Thus, although patients often attribute bloating to gas, this is not always the case.

It has been shown that some normal subjects consistently pass more gas than others (6), but the passage of excessive gas seems to be a particular problem for many patients with IBS. However, they are often reluctant to admit to it and it is seldom referred to in the literature. In our tertiary referral clinic, it is not uncommon to see IBS patients who avoid relationships because of this problem and many other sufferers find it incapacitating both socially and in the workplace. Not surprisingly, the problem is further compounded if the gas consistently smells offensive.

With the notable exception of the work of Dr. Michael Levitt there has, until recently, been remarkably little interest in intestinal gas, especially in relation to IBS. On balance, what evidence there is points to a considerable proportion of patients with IBS having excessive intestinal gas. The study by Koide *et al*. (7) in this issue of the *Journal*, using a radiological technique, confirms this view. An interesting additional observation highlighted in their paper was that individual gas volume scores were remarkably consistent from day to day.

The accumulation of gas within the gut of IBS patients can only result from a limited number of mechanisms such as excessive swallowing, over production, changes in tone/motility, or impaired release. There is evidence to support all of these possibilities in IBS patients (8–11), but it remains to be determined how much these abnormalities overlap in a particular individual and whether they are additive. It is important to realize that if air swallowing is suspected, that this can be subconscious and is not necessarily indicative of psychopathology. If intestinal gas analysis is available, this problem should be suspected if nitrogen is the predominant constituent (12).

Another extremely important consideration in all of this is the problem of perception. It is now generally accepted that a significant proportion of patients with IBS seem to have disordered perception (13), which could appreciably affect how they report the sensation of gaseousness or even the passage of flatus.

The treatment of IBS patients who complain of passing excessive gas is notoriously unrewarding and largely empirical, with agents such as peppermint preparations worth trying. The traditional remedy of activated charcoal has not stood up to scrutiny either for reducing volume of gas or odor (14). The best we can do at present is to consider the different possible mechanisms and, for instance, use dietary manipulation with the aim of minimizing the intake of flatogenic foods and additives or reducing fermentation. Alternatively, if excessive swallowing is suspected, then a behavioral technique may be worth considering. Antibiotics are not practicable as they cannot be used long term, sometimes exacerbate other symptoms of IBS, and, on cessation, the bacterial flora frequently revert to pretreatment patterns. No other pharmacological approaches are currently available, although it has recently been suggested that in patients with a motility component to their gas retention, drug treatment may have a role (15). Lastly, the whole concept of perception has to be borne in mind, because if this happens to play a part in a patient's symptomatology, then a completely different therapeutic approach may be required.

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Long-Term Treatment of Crohn's Disease With Methotrexate, or, Why's a Nice Drug Like You Still a Wannabe in the Treatment of Inflammatory Bowel Disease?

Despite the widespread use of immunosuppressives in steroid-refractory or steroid-resistant inflammatory bowel disease (IBD), methotrexate use remains limited 10 years after the initial report suggesting short-term efficacy for both Crohn's disease and chronic ulcerative colitis (1). Reasons for this are complex but include a paucity of controlled trials (2), concern about toxicity (3), uncertainty as to whether the drug maintains clinical remission (4), and its ill-defined place in relation to 6-mercaptopurine (6-MP), azathioprine, or even cyclosporin-A (5). Couple this with the introduction or study of targeted cytokine modulators such as infliximab, and its application has become even muddier (6).

As such, the manuscript by Lémann *et al*. (7) in this issue of the *American Journal of Gastroenterology* is a welcome addition to the literature. In it, the authors review 49 Crohn's patients treated for ≥6 months with methotrexate. Of these, 27 (40%) were on active steroids and 42 (86%) had either failure or intolerance to previous azathioprine. Of 49, 41 (84%) achieved complete remission and, in this latter group, 20 of 22 (91%) could discontinue steroids. The latter figures are comparable to those of our uncontrolled trial but significantly higher than the 39.4% complete remission achieved by the North American Crohn's Study Group (2). Nevertheless, these data compare favorably to the 25% and 55% rates of steroid elimination, respectively, in trials by O'Brien *et al*. (8) and Present *et al*. (8) using either 6-MP or azathioprine for refractory Crohn's.

Previous data by our group reported that 51% of IBD patients started on methotrexate continued the drug at 69 wk, although long-term efficacy seemed higher in patients with Crohn's disease than in those with chronic ulcerative colitis (4). The current article expands our knowledge about both long-term efficacy and toxicity. The probabilities of relapse at 1, 2, and 3 years, respectively, were 29%, 41%, and 48%. Relapse rates were comparable whether the medication was given parenterally or orally, and dosages were comparable and approximated 15 mg weekly for both relapsing patients and those maintaining a remission. These relapse rates seem to be higher than the 11% and 32% at 1 and 5 years, respectively, reported by the same authors upon review of their Crohn's patients treated with azathioprine or 6-MP (10). However, the groups were not strictly comparable and may have been preselected for refractory disease, as the majority of the patients had either failed (53%) or been intolerant (32%) of these latter medications.

The current article also enlarges our database about long-term methotrexate toxicity in Crohn's disease. As such, adverse reactions occurred in approximately one-half of the patients but necessitated drug discontinuation in only 10%. Hepatotoxicity, in particular, seemed minor and was comparable to that in our own previous report and ongoing prospective evaluation (11). In contrast, significant interstitial pneumonitis was a problem in one patient and must always be considered in methotrexate-treated patients who develop a chronic, nonproductive cough or shortness of breath.

With the above as a background, what role should methotrexate play in the acute and chronic treatment of inflammatory bowel disease? I believe there are clear data to suggest efficacy in the acute treatment of refractory Crohn's disease and there are nonrandomized, nonblinded data, including our own and those in the current publication, suggesting long-term efficacy in this disease process. In our own institution, we use methotrexate interchangeably with 6-MP/azathioprine, although there are no head-to-head studies looking either at efficacy or at side effect profile. Nor would I quibble with those practitioners who use the drug as a "back-up" to those who are intolerant or unresponsive to more conventional immunotherapy. From the standpoint of ulcerative colitis, I remain convinced of short-term, and skeptical of long-term benefit (12). Nevertheless, there are a number of chronic ulcerative colitis patients in my practice who have been in remission >5 years on methotrexate alone. Clearly, additional work is needed to define a subset