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An antiemetic for irritable bowel syndrome?

A drug used for cancer patients may provide some relief to patients with IBS.

PRACTICE CHANGER

Consider prescribing ondansetron up to 24 mg/d for patients who have irritable bowel syndrome with diarrhea (IBS-D).[1]

STRENGTH OF RECOMMENDATION

B: Based on a well-done double-blind, placebo-controlled randomized controlled trial (RCT).

Garsed K, Chernova J, Hastings M, et al. A randomised trial of ondansetron for the treatment of irritable bowel syndrome with diarrhoea. *Gut.* 2014;63:1617-1625.

ILLUSTRATIVE CASE

A 23-year-old woman who was diagnosed with irritable bowel syndrome (IBS) comes to your clinic with complaints of increased frequency of defecation with watery stools and generalized, cramping abdominal pain. She also notes increased passage of mucus and a sensation of incomplete evacuation. She says the only thing that relieves her pain is defecation. She has tried loperamide, acetaminophen, and ibuprofen without relief. She does not have Crohn's disease or ulcerative colitis. What else can you offer her that is safe and effective?

IBS is a chronic, episodic functional gastrointestinal disorder characterized by abdominal pain or discomfort and altered bowel habits (constipation [IBS-C], diarrhea [IBS-D], or alternating periods of both—mixed [IBS-M]).[2] It is diagnosed based on Rome III criteria—recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with ≥2 of the following: improvement with defecation, onset associated with a change in frequency of stool, and onset associated with a change in form (appearance) of stool.[3] IBS often is unrecognized or untreated, and as few as 25% of patients with IBS seek care.[4]

IBS-D affects approximately 5% of the general population in North America.[5,6] IBS-D is associated with a considerably decreased quality of life and is a common cause of work absenteeism.[7,8] Because many conditions can cause diarrhea, patients typically undergo numerous tests before receiving an accurate diagnosis, which creates a financial burden.[9]

For many patients, current IBS treatments, which include fiber supplements, laxatives, antidiarrheal medications, antispasmodics, and antidepressants such as tricyclics and selective serotonin reuptake inhibitors, are unsatisfactory.[10] Alosetron, a 5-hydroxytryptamine 3 (5HT3) receptor antagonist, has been used to treat IBS-D,[11] but this medication was voluntarily withdrawn from the US market in 2000 due to concerns of ischemic colitis and severe constipation.[12] It was reintroduced in 2002, but can be prescribed only by physicians who enroll in a prescribing program provided by the manufacturer, and the drug has restrictions on its use.

Ondansetron—a different 5HT3 receptor antagonist used to treat nausea and vomiting caused by chemotherapy—may be another option for treating IBS-D. Garsed et al[1] recently conducted a RCT to evaluate the efficacy of ondansetron for patients with IBS-D.

STUDY SUMMARY

Ondansetron improves stool consistency, severity of IBS symptoms

In a 5-week, double-blind crossover RCT, Garsed et al[1] compared ondansetron vs placebo for symptom relief in 120 patients who met Rome III criteria for IBS-D. All patients were ages 18 to 75 and had no evidence of inflammatory bowel disease. Exclusion criteria were pregnancy or breastfeeding, unwillingness to stop antidiarrheal medication, prior abdominal surgery other than appendectomy or cholecystectomy, or being in another trial. Patients were started on ondansetron 4 mg/d with dose titration up to 24 mg/d based on response; no dose adjustments were allowed during the last 2 weeks of the study. There was a 2- to 3-week washout between treatment periods.

The primary endpoint was average stool consistency in the last 2 weeks of treatment, as measured by the Bristol Stool Form (BSF) scale.[13] The BSF is a visual scale that depicts stool as hard (Type 1) to watery (Type 7); types 3 and 4 describe normal stools. The study also looked at urgency and frequency of defecation, bowel transit time, and pain scores.

Treatment with ondansetron resulted in a small but statistically significant improvement in stool consistency. The mean difference in BSF score between ondansetron and placebo was -0.9 (95% confidence interval [CI], -1.1 to -0.6; $P<.001$), indicating slightly more formed stool with use of ondansetron. The IBS Severity Scoring System score (maximum score 500 points, with mild, moderate, and severe cases indicated by scores of 75-175, 175-300, and >300, respectively) was reduced by more points with ondansetron than placebo (83 ± 9.8 vs 37 ± 9.7; $P=.001$). Although this mean difference of 46 points fell just short of the 50-point threshold that is considered clinically significant, many patients exceeded this threshold.

Compared to those who received placebo, patients who took ondansetron also had less frequent defecation ($P=.002$) and lower urgency scores ($P<.001$). Gut transit time was lengthened in the ondansetron group by 10 hours more than in the placebo group (95% CI, 6-14 hours; $P<.001$). Pain scores did not change significantly for patients taking ondansetron, although they experienced significantly fewer days of urgency and bloating. Symptoms typically improved in as little as 7 days but returned after stopping ondansetron, typically within 2 weeks. Sixty-five percent of patients reported adequate relief with ondansetron, compared to 14% with placebo.

Patients whose diarrhea was more severe at baseline didn't respond as well to ondansetron as did those whose diarrhea was less severe. The only frequent adverse effect was constipation, which occurred in 9% of patients receiving ondansetron and 2% of those on placebo.

WHAT'S NEW

Another option for IBS patients with diarrhea

A prior, smaller study of ondansetron that used a lower dosage (12 mg/d) suggested benefit in IBS-D.[14] In that study, ondansetron decreased diarrhea and functional dyspepsia. The study by Garsed et al[1] is the first large RCT to show significantly improved stool consistency, less frequent defecation, and less urgency and bloating from using ondansetron to treat IBS-D.

CAVEATS

Ondansetron doesn't appear to reduce pain

In Garsed et al,[1] patients who received ondansetron did not experience relief from pain, which is one of the main complaints of IBS. However, this study did find slight improvement in formed stools, symptom relief that approached—but did not quite reach—clinical significance, fewer days with urgency and bloating, and less frequent defecation. This study did not evaluate the long-term effects of ondansetron use. However, ondansetron has been used for other indications for more than 25 years and has been reported to have a low risk of adverse effects.[15]

CHALLENGES TO IMPLEMENTATION

Remember ondansetron is not for IBS patients with constipation

Proper use of this drug among patients with IBS is key. The primary benefits of ondansetron are limited to IBS patients who suffer from diarrhea, and not constipation. Ondan-

For patients with IBS-D, ondansetron reduced frequency of defecation and bloating, but did not relieve pain.

setron should not be prescribed to IBS patients who experience constipation, or those with mixed symptoms. JFP

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Probiotics for colic? A PURL update

In "Colicky baby? Here's a surprising remedy" (*J Fam Pract*. 2011;60:34-36), we summarized a 2010 double-blind randomized controlled trial (RCT) that found the probiotic *Lactobacillus reuteri* DSM 17938 reduced daily crying time in colicky, exclusively breastfed infants.[1]

A recently published RCT of the same probiotic by Sung et al[2] adds to the body of evidence and suggests that the jury may still be out as to the value of probiotics for colicky babies.

The newer study (which also measured colic using modified Wessel's criteria) included babies who were formula-fed as well as those who were breastfed. When researchers looked at all babies as a single group, those who received probiotics fussed significantly more than those who received placebo at nearly all of the postintervention time points. However, when they delved deeper, the researchers noted that an increase in fussing occurred only among infants on formula. On the other hand, the time that breastfed infants spent crying or fussing did not vary significantly between those who received probiotics and those who received placebo.

Both the 2010 and 2014 studies used valid RCT methods with low risk for bias, so we're not clear why the results (especially for breastfed infants) differed. The 2010 study was done in Italy and required breastfeeding moms to avoid cow's milk, while the 2014 Sung et al[2] study was conducted in Australia and did not have this requirement, so environmental factors may have played a role. The reporting method in the Sung et al[2] study—a well-validated, detailed diary of infant behaviors—may have led to less parent recall error than the diary used in the 2010 study. All in all, we can only conclude that it is unclear whether probiotics work to reduce crying in colicky infants.

A safe bet may be to avoid recommending probiotics for colicky formula-fed infants, since no study of this population has shown probiotics are effective, and in the Sung et al[2] study, they appeared to worsen symptoms. For breastfed babies, there is no evidence of harm, and mixed evidence on whether probiotics help.

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