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Alosetron

A Viewpoint by Douglas A. Drossman

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The irritable bowel syndrome (IBS) is rapidly gaining the attention of clinicians, investigators and the general public.[1] In part, this relates to the recent and projected release of new therapeutic medications: agents active at 5-HT receptors. Alosetron, the first of these to become available, is a peripherally acting 5-HT_3 receptor antagonist that increases colonic compliance and decreases colonic transit time in healthy volunteers and patients with IBS. Results of clinical trials of alosetron show adequate relief of symptoms of abdominal discomfort/pain and also significant improvement in symptoms of diarrhoea and rectal urgency, particularly in female patients with non-constipation (diarrhoea or mixed type) IBS. So what is the therapeutic role for alosetron in the treatment of IBS?

The studies reviewed in the Alosetron New Drug Profile were carefully designed to optimise a treatment effect. Patients with infrequent (<2/week), very mild or severe symptoms, or with symptoms of constipation were not included in the these trials. Furthermore, the selective benefit of the drug for female patients was a post-hoc observation that is currently being re-evaluated.

From these data we can say with some confidence that female patients with frequent symptoms of diarrhoea-predominant or mixed IBS of moderate intensity are likely to benefit. Fortunately, this is the most common group of patients with IBS seen by physicians.

However, this may only be a starting point, since these data also raise important clinical questions that are amenable to further study:

1. Is the effect in males an artifact of early studies or is this a true gender difference in the targeted actions of the drug?

2. Can patients with constipation-predominant IBS benefit if alosetron is also prescribed with an osmotically active laxative (e.g. sorbitol) or with polyethylene glycol (PEG)? Or should we wait for the release of new 5-HT_4 receptor agonists that have prokinetic effects?

3. Can the drug be taken 'when required' by patients with mild or occasional symptoms? Steady-state concentrations of the drug are reached in 1 day, but the clinical trials were designed only to look at clinical effects beginning at 1 week.

4. Would patients with more severe and painful symptoms benefit from a combination of peripherally acting alosetron with a low dose tricyclic antidepressant (TCA). This combination may enhance the clinical effects of alosetron via the TCA's central analgesic and antidiarrhoeal action.

All of these questions go beyond the current US Food and Drug Administration indications for the drug, but they open the door to future investigation. For the moment, it is likely that alosetron and possibly the other agents active at 5-HT receptors will have an important and much-need role in the care of patients with IBS. ▲

Reference

1. D.A. Drossman. The functional gastrointestinal disorders and the Rome II process. Gut 1999 45: II1-II5