Letter: Therapeutic potential of ketotifen in irritable bowel syndrome (IBS) may involve changes in mast cells at sites beyond the rectum: Reply

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Therapeutic potential of ketotifen in irritable bowel syndrome (IBS) may involve changes in mast cells at sites beyond the rectum

The recent study published in Gut by Klooker and coworkers1 reported very early work4 we studied mast cells across where the biopsy tissue is taken. In our design,2,3 mast cell stabiliser ketotifen did not alter mast cell numbers or mediator release in the rectal biopsy tissue investigated in this study. It is this latter finding that is more challenging to explain.

The absence of changes in mucosal mast cell numbers and in histamine or tryptase release would seem to suggest that the effects of ketotifen therapy occur independently of mast cell stabilisation. This may, as the authors suggest, be through H1 receptor antagonism effects of the drug. However, based on the evidence presented in this paper, one cannot rule out the possibility that some of the effects may indeed be attributable to direct effects on either mast cell numbers or activation that simply were not detectable in the study. Changes in mast cell parameters were not found based on the tissue investigated by Klooker et al (ie, in rectal tissue). Mast cell stabilisation may have occurred elsewhere in the gut at other sites beyond the scope of detection in this study—for example, in the small intestine, caecum or other locations in the colon. Indeed, rectal tissue may not be an optimal marker for detecting the mechanism of effects of ketotifen on mast cell activation in IBS.

Similarly, at baseline this study2 found no increase in mast cell numbers in IBS rectal tissue compared with controls. As the authors highlight, increases in mast cells have not been reported by all studies and some have failed to find any increases. There is generally reasonably consistent evidence of increased mast cell numbers in patients with IBS, bearing in mind the heterogeneity of the disease and study designs.4

Mast cell counts may vary depending on the IBS subtype, gender or psychological factors, and also on the site where the biopsy tissue is taken. In our early work2 we studied mast cells across a range of sites in IBS (caecum, ascending and descending colon, rectum) and could not detect mast cell changes in the rectum—the most consistent results tended to be at the proximal colon. Although differences in mast cell numbers in IBS at baseline were not documented in rectal tissue in the current paper,1 differences at other sites may still be plausible.

In short, it could equally be concluded that changes in mast cell stabilisation at sites beyond the rectum may underlie the therapeutic effect of ketotifen on visceral hypersensitivity or IBS symptoms in this study. This stimulating paper highlights the complexity and contradictions in understanding the mechanisms by which mast cells may contribute to the pathogenesis and/or optimal therapeutic strategies for this disease.

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REFERENCES


The Authors’ reply We would like to thank Dr O’Sullivan for her positive comments on our paper recently published in Gut.2 We agree that the exact mechanism of action of ketotifen, either through mast cell stabilisation or H1 receptor blockade, needs further study. We tend to disagree, however, that we may have missed differences between patients with irritable bowel syndrome (IBS) and healthy subjects by studying the rectum. Concerning the number of mast cells, as illustrated in figure 2A of our paper, similar findings were obtained in the colon descents of patients with IBS and healthy subjects as in the rectum. In line with our data, Cenac et al also reported similar results in rectal and ascending colon biopsies. Obviously, depending on the patient population studied, mast cell numbers may vary along the gastrointestinal tract as described by Dr O’Sullivan but, in our study, rectal and colonic biopsies yielded similar results, making it less likely (but not excluding the possibility) that, in our patient population, rectal tissue is an inappropriate marker. In the same way, in preliminary experiments we compared the release of both histamine and tryptase in the supernatant of rectal and descending colon biopsies and found similar results. Also, proteolytic activity in the supernatant and tissue mRNA levels of trypsin and tryptase are comparable in the rectum and ascending colon, as recently reported by Cenac et al. Nevertheless, as pointed out in our discussion, our results do not rule out the possibility that ketotifen stabilises mast cells in the gastrointestinal tract, particularly as we feel that the mediator release detected in the supernatant, independent of the region where the biopsies are taken, may not actually reflect physiological release. We agree with Dr O’Sullivan that we need to continue our search for better and more optimal markers in order to better evaluate the mechanism of action of drugs in general on mucosal mast cells.

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REFERENCES

1. O’Sullivan M. Therapeutic potential of ketotifen in irritable bowel syndrome (IBS) may involve changes in mast cells at sites beyond the rectum. Gut 2011;60:423.

Seasonal variations of immunochemical and gaiac faecal occult blood tests

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The Authors' reply
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