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Word of caution before implementing ketotifen for gastrointestinal transit improvement

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Abstract

The therapeutic potential of long-term ketotifen in irritable bowel syndrome and postoperative ileus is currently under investigation. Ambiguous results of prolonged postoperative ketotifen use on gastrointestinal passage have been found. The current data point at a hampered gastrointestinal transit after prolonged postoperative ketotifen use in a rodent ileus induction model. Therefore, caution should be taken when administering ketotifen in the perioperative phase.

Key words: Ketotifen; Gastrointestinal transit; Postoperative ileus

Core tip: Prolonged postoperative ketotifen impairs gastrointestinal transit in a rodent ileus induction model.

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TO THE EDITOR

Postoperative ileus has a major impact on length of hospital stay after bowel resection[1]. Currently, the therapeutic potential of long-term ketotifen in postoperative ileus and irritable bowel syndrome is under investigation[2,3]. The underlying mechanism, however, remains unclear as ketotifen exerts both mast cell stabilizing and H1 receptor blocking effects. Furthermore, the long-term effects on gastrointestinal (GI) transit deserve definition. The and colleagues showed that ketotifen improved gastric emptying at 24 h follow-up; however continuing treatment up to 48 h postoperatively produced ambiguous results on GI passage[2]. Therefore, we performed a rat study to assess the influence of prolonged use of ketotifen on GI transit time at 5 d follow-up after ileus induction.

The same postoperative ileus induction model was used as previously described[4]. Male Wistar rats (250-300 g) were anesthetized using buprenorphine 0.1 mg/kg *sc* and anesthesia was maintained using 2.5% isoflurane. Subsequently, rats underwent a laparotomy *via* a midline abdominal incision under aseptic conditions. The small intestine was placed on moist gauze pads outside the abdomen, manipulated with moist cotton swab sticks for 5 min and kept moist at all times. After manipulation, the small intestine was placed back in the abdomen and the abdomen closed in 2 layers with continuous sutures. Rats (6 in each group) received either ketotifen in a high-dose (1 mg/kg) or low-dose (0.1 mg/kg), mast cell stabilizer cromoglicic acid (50 mg/kg) or vehicle (saline). The high dose of ketotifen is comparable to doses prescribed for humans. Cromoglicic acid prevents the release of mediators from mast cells through a non-H1/2-receptor pathway. Doses were administered twice daily in a volume of 1.5 mL *via*

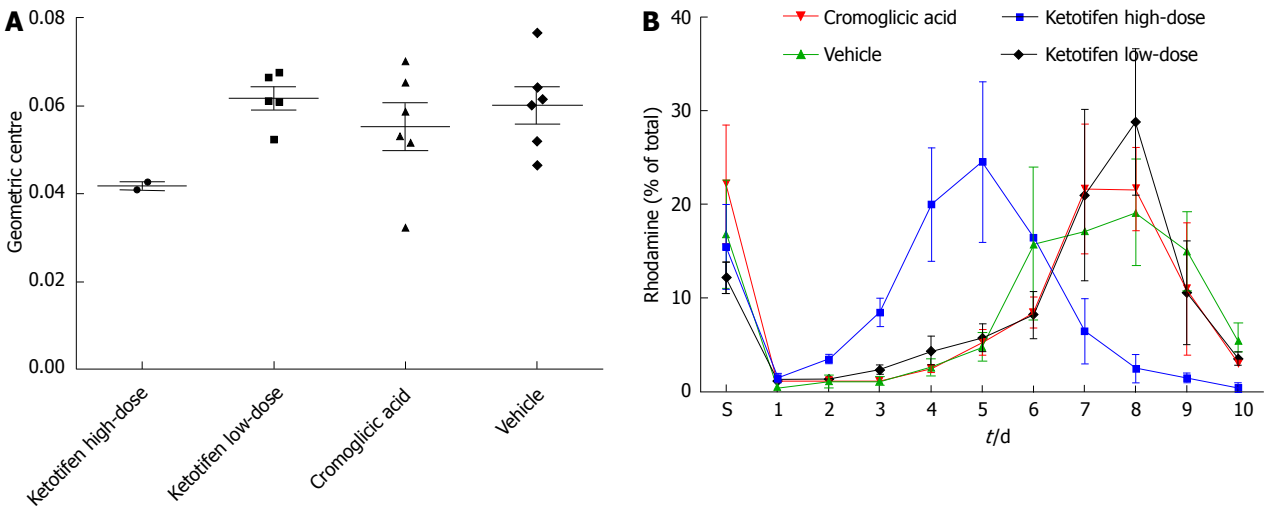

Figure 1 Geometric centre of recovered rhodamine, calculated as (Σ% fluorescence per segment × segment number)/100 (A), and amount of recovered rhodamine per bowel segment (ketotifen high-dose, *n* = 2; all other groups, *n* = 6) (B).

oral gavage starting at 2 d preoperatively until sacrifice. GI transit time was measured at the time of sacrifice (5 d postoperatively, by cervical dislocation after anesthesia with 4% isoflurane) by evaluating the GI distribution of rhodamine-B-labeled dextran (Sigma-Aldrich, St. Louis, MO, United States). Rhodamine [200 μL of 6.25 mg/mL in phosphate buffered saline (PBS)] was administered *via* oral gavage. One hour after administration the animals were sacrificed, the small bowel divided in 10 equal parts (part 1: beginning at jejunum, part 10: ending at the transition of ileum to coecum) and resected together with the stomach. A fluorescence reader was used to quantify the rhodamine-containing gut content in the supernatant after vigorous mixing and centrifuging of the gastric and bowel contents in 2 mL PBS. A histogram of fluorescence distribution per segment (% of total recovered rhodamine) was plotted for transit analysis and expressed as geometric center for statistical analysis. Geometric centers were calculated for each animal as (Σ% fluorescence per segment × segment number)/100.

In the high-dose ketotifen group, 4 out of 6 rats died before reaching 5 d follow-up with an extremely distended stomach at necropsy. The geometric centers of the surviving animals were also markedly lower than the other groups, but numbers ($n = 2$) were too low to allow for statistical analysis (Figure 1). However, GI transit times in the low-dose group were comparable with the control group ($P = 0.66$, Mann-Whitney U test) implying that the beneficial ketotifen effects after postoperative ileus are dose-dependent and probably restricted to the very early postoperative period, *i.e.*, less than 5 d. GI transit in the cromoglicic acid group was comparable to control ($P = 0.70$, Mann-Whitney U test). These results suggest that the effects of ketotifen on GI transit may indeed not, or not fully, depend on mast cell stabilization but rather a H1 receptor pathway.

As stated earlier by The *et al*[2], caution should be taken when administering ketotifen in the perioperative phase as prolonged postoperative treatment may have an inhibitory effect on enteric smooth muscle contraction. Indeed, the current data point at a hampered GI transit after prolonged postoperative ketotifen use. A careful treatment regimen as proposed by de Jonge *et al*[5], *i.e.*, preoperative treatment only, is therefore mandatory.

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