EVALUATION OF COLONIC VASCULAR REACTIVITY FOLLOWING CHRONIC LOPERAMIDE AND ALOSETRON TREATMENT IN RATS

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Introduction

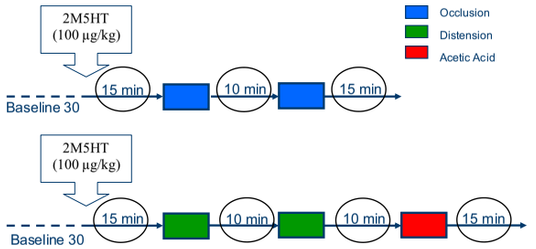
Alosetron is an effective treatment in female diarrhea-predominant IBS patients (Camilleri et al. 1999). Despite the marked symptom improvement the use of alosetron has been limited because of a small number of cases of ischemic colitis in patients receiving treatment (Friedel et al. 2001). Potential contributing factors include altered blood flow regulation secondary to constipation, or pre-disposition of the patient group. To date there have been no studies on the long term effect of 5-HT_3 receptor blockade on colonic haemodynamics. Our aim was to investigate the effects of 5 day treatment with alosetron on baseline haemodynamics and vascular responses to reactive- and reflex-induced vasodilatation in comparison to treatment with loperamide as a constipation control.

Methods

Three groups of animals were treated twice daily for 5 days with alosetron (0.5mg/kg s.c.), loperamide (5mg/kg s.c.) or vehicle (5%EtOH/Miglyol s.c.). Experiments were performed in pentobarbitol (60-80 mg/kg) anaesthetised rats following institutional animal care guidelines. The following parameters were measured:

- Mesenteric Blood flow (MBF) using a Transonic ultrasonic transit time flowmeter.
- Serosal vascular perfusion (P[s]) using a laser Doppler probe (Perimed).
- Tissue oxygen content (pO_2) from a serosal polarographic oxygen electrode.
- Mean arterial pressure (MAP) from the carotid artery and heart rate derived from the triggered pressure pulses.
- Intraluminal pressure (LP) in some experiments.
- Data are presented as mean ± SEM and were analyzed statistically using Student's t-test or ANOVA with post-hoc Tukey's tests as appropriate (n ≥6).

Experimental protocols



- Haemodynamic responses to 2m5HT were absent after alosetron.
- Occlusion (5min) was achieved by clamping the superior mesenteric artery immediately proximal to the arterial flow meter. The reperfusion response followed removal of the clamp.
- Isovolumetric distension was achieved by rapid instillation of saline to a peak pressure of ~25 mmHg. Distension was maintained for 3 min over which time pressure adapted to a constant plateau pressure of ~14 mmHg, which was similar in all 3 groups of animals.
- 1.0 ml of 4% acetic acid was instilled into the colon and then 15s later flushed out with 5 ml isotonic saline.

Results

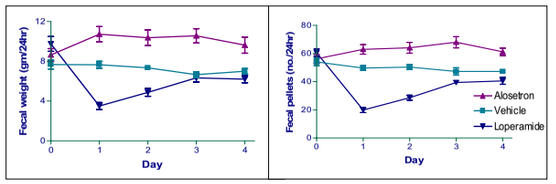


Figure 1 - Fecal Output - Loperamide caused a reduction in fecal output which returned towards baseline levels during the 5 day treatment period. Surprisingly, alosetron did not cause constipation despite a treatment regime designed on the basis of pharmocodynamic data to provide 24 hour 5-HT_3 receptor blockade.

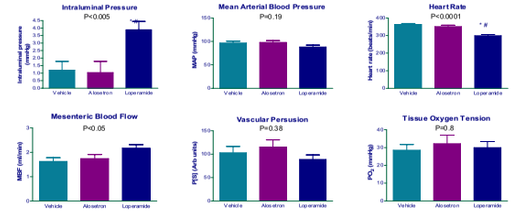


Figure 2 - Baseline Parameters - Baseline colonic haemodynamics were unchanged following chronic dosing with alosetron.

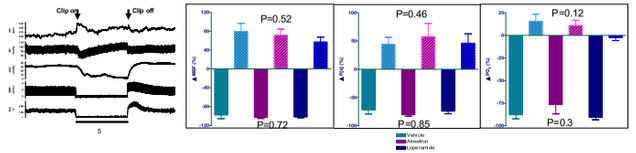


Figure 3 - Response to occlusion and reperfusion - Occlusion effectively blocked mesenteric blood flow, with ~80% reduction in vascular perfusion and pO_2 levels. Reperfusion evoked a rebound increase in all parameters. These changes (expressed as % of baseline) were unaltered in either alosetron or loperamide treated animals.

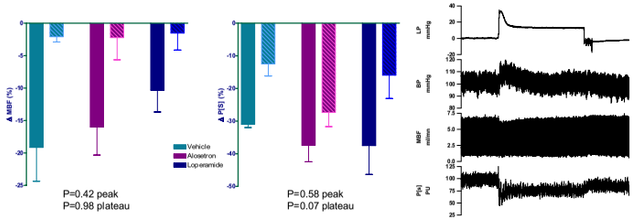


Figure 4 - Response to colonic distension - Blood flow and vascular perfusion are reduced at the peak of distension (left bars) and return during the distension plateau (right bars). The magnitude of these changes (expressed as % of baseline) were unchanged in either alosetron or loperamide treated animals. The plateau phase of the vascular perfusion response was somewhat attenuated in the alosetron group (P=0.07), but this was not reflected in the mesenteric blood flow.

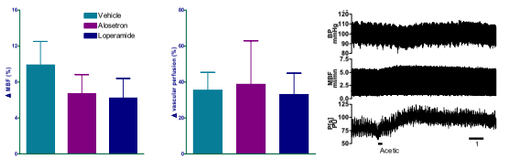


Figure 5 - Acetic acid effects - Blood flow and vascular perfusion are increased following intraluminal administration of acetic acid into the colon. The magnitude of these changes (expressed as a % of baseline) was unchanged in either alosetron or loperamide treated animals.

Summary

- Chronic alosetron dosing had no effect on fecal output.
- Baseline colonic haemodynamics were unaffected by chronic alosetron.
- Colonic occlusion and reperfusion haemodynamic responses were unchanged after chronic alosetron.
- Chronic alosetron had no effect on the reduction in blood flow elicited by colonic distension.
- Chronic alosetron had no effect on the reflex hyperaemia induced by intraluminal acetic acid.

Conclusions

Chronic 5-HT_3 receptor blockade with alosetron does not alter haemodynamic responses to local colonic stimuli designed to assess vascular reactivity.

References: Camilleri M, et al. Aliment Pharmacol Ther 1999; 13: 1149-59. Friedel D, Thomas R, Fisher RS. Gastroenterol 2001; 120: 557-560.

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