Effect of a 5-HT$_3$ antagonist on small bowel water content

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Introduction:

We have recently developed and validated magnetic resonance imaging (MRI) methods, based on MR cholangiopancreatography, to measure regional intestinal water volumes serially and non-invasively [1,2]. We have observed a significant decrease in fasting small bowel water content (SBWC) in Irritable Bowel Syndrome patients with diarrhoea (IBS-D) [2]. 5-HT$_3$ antagonists inhibit secretions, propulsion and the frequency of the migrating motor complex (MMC) which clears fasting fluid from the small bowel into the colon. Since these drugs are effective in IBS-D we hypothesized they could reverse the observed decrease in fasting SBWC. Before undertaking a clinical study we first examined the effect of a 5-HT$_3$ antagonist (Ondansetron) in healthy volunteers.

Aim:

To assess the effect of Ondansetron on small bowel water content in healthy volunteers using MRI.

Methods:

This was a placebo controlled, double-blind, randomised, 2-way cross-over study. 16 healthy volunteers were administered either a placebo or 8mg Ondansetron syrup tds on the day prior to the study. On the study day, after overnight fasting, they received either placebo or 16mg Ondansetron syrup one hour before the MRI study. After baseline MRI scans the subjects ate a standard 320 kcal meal and underwent serial imaging at 45 min intervals for 5 h. The MRI study was carried out on a 1.5 T Philips Achieva scanner. Figure 1 shows examples of the images that were acquired for this study: (a) shows an axial Balanced Turbo Field Echo image acquired across the full stomach (indicated by the white arrows) of a volunteer, used to measure gastric emptying. (b) shows a coronal dual-echo Fast Field Echo image through the transverse colon of a volunteer, used to measure colonic volumes. (c) shows a coronal magnetic resonance cholangiopancreatography (Coronal Turbo Spin Echo or MRCP) image acquired across the small bowel of a volunteer, used to measure SBWC and ascending colon water content. The volume of fluid in the bowel at each time point was calculated by integrating all image pixels containing water signal above a given threshold as validated previously [1]. The subjects filled symptoms questionnaires during the study and a Bristol Stool Diary for a week on each occasion.

Results:

(mean±SEM) Ondansetron was well tolerated with no adverse events. All subjects completed the trial and tolerated the test meal and serial MRI scanning without difficulty. High quality images as shown in Figure 1 were obtained in all subjects and no images were rejected during the analysis. The fasting SBWC was higher for Ondansetron (266±26 ml) than for placebo (165±22 ml, $p<0.0001$) as shown in Figure 2. After feeding the SBWC rapidly reduced with a concomitant increase in the ascending colon water content. The volume of the right colon increased from 300±23 ml at fasting baseline to 349±24ml at t=0 after feeding ($p<0.001$), with no difference between drug and placebo (2 way ANOVA $p<0.7$). The volume of the colon returned to baseline after t=45 min.

Conclusion:

Ondansetron markedly increased fasting SBWC. This may reflect reduction in fasting small bowel migrating motor complex (MMC) frequency or inhibition of resting secretions. We have also been able to visualise the ileo-colonic reflex induced by feeding and to measure an increase in right colonic volume in response to feeding. Our new method to assess SBWC has potential important clinical application in understanding the role of 5-HT$_3$ antagonists in controlling SBWC and transit, and how these mediate gastrointestinal symptoms in IBS-D.

References:

1. Hoad C.L. et al. *Phys Med Biol* 2007, *in press*.

2. Marciani L. et al. *Gastroenterology* 130(4):A743, 2006.

Fig. 1

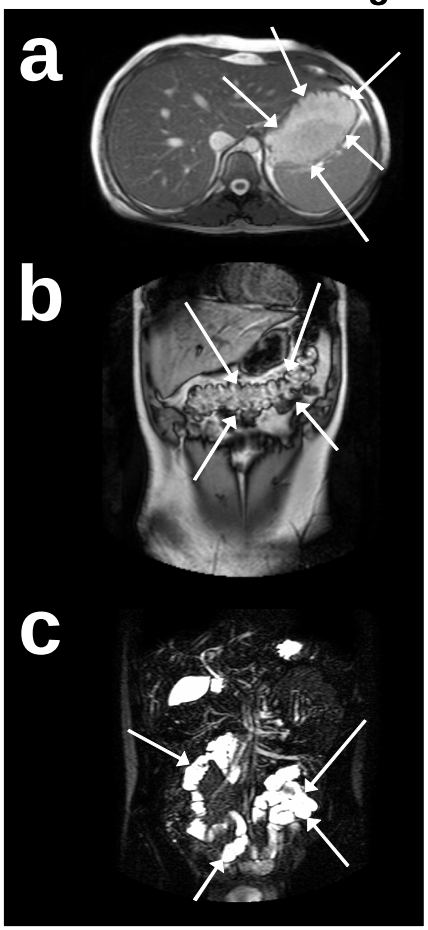

Fig. 2