Defining the mode of action of Loperamide and Loperamide plus Simethicone using an MRI model of acute diarrhoea

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Introduction

Loperamide (LOP) is a widely used anti-diarrhoeal agent which is believed to act largely by slowing transit with an uncertain effect on secretion. Adding simethicone (SIM) to LOP seems to improve its efficacy [1] but the mechanism of interaction is unclear. We have recently validated a novel MRI technique to assess small bowel water content (SBWC) [2] and have thus shown that mannitol solutions markedly increase SBWC [3]. We aimed to use quantitative MRI techniques to compare the action in the gut of LOP and LOP+SIM in the gut in a model of acute diarrhoea achieved by ingestion of mannitol.

Methods

For this double-blind, placebo controlled, randomised, 3-way cross-over study, 18 healthy volunteers were imaged on a 1.5T Philips Achieva scanner with a SENSE 4-element abdominal body coil. Volunteers attended on three separate sessions: they were imaged in the fasted state as a baseline scan and then ingested capsules containing placebo (PLA) or 12 mg LOP or 12 mg LOP + 125 mg SIM. 100 minutes later they underwent a second baseline scan and 15 minutes after that they received a drink containing 5% mannitol in 350 ml of water, considered time 0. Volunteers underwent serial imaging at 45 minutes intervals for 4.5 hours after the drink. A range of MRI sequences were acquired: bTFE to image the stomach contents (TR=2.4 ms, TE=1.19 ms, rec. res = 1.56 x 1.56 mm^2, 25 slices 10 mm thick); high resolution bTFE to image the contents of the ascending colon (AC) (TR= 3.2 ms, TE=1.58 ms, rec. res = 0.86 x 0.86 mm^2, 8 slices 5 mm thick, 1 mm gap); RARE to measure SBWC and AC water content (ACWC) (TR=8000 ms, TE=320 ms, rec. res.= 0.78 x 0.78 mm^2, 24 slices 7 mm thick); T2-prep bTFE sequence (TR=3.0ms, TE values (ms): 20, 29, 43, 63, 93, 137, 201, 295, 434, 637) to measure the T2 values in the ascending colon [4]; bTFE (TR=3.0 ms, TE=1.50 ms, rec. res = 0.86 mm x 0.86 mm, 15 mm thick acquired every second for 3 minutes) used to identify AC walls motility. Net secretion was assessed by subtracting the ingested 350 ml from the sum of stomach contents, SBWC and ACWC.

Results

Gastric emptying (fig 1a): LOP and LOP+SIM significantly reduced the overall area under the curves (AUCs) of the gastric emptying curves, $p<0.03$. Dunnett's multiple comparison post tests showed a significant difference of LOP versus PLA, $p<0.05$. *Small bowel (fig 1b):* LOP and LOP+SIM markedly reduced the AUCs of the SBWC during the late phase (135 to 270 min), $p<0.009$ while no significant effect was found in the early phase (time 0 min to 135 min- data not shown). Dunn's multiple comparison post tests showed a significant difference of LOP versus PLA in the late phase, $p<0.05$. *Ascending colon:* The drugs delayed the arrival of fluid in the AC volume, fig. 2, and this was also observed in the high resolution bTFE images, fig. 3. During the early phase both LOP and LOP+SIM significantly reduce the ACWC ($p<0.01$ and $p<0.05$ respectively), fig. 1c. In the late phase there is an additional effect of SIM, $p<0.04$, fig. 1d. The T2 of the contents of the AC was higher for the PLA than for the drug cases ($p < 0.0001$ on the log 10 transformed data), fig. 4. In particular, at 90 min PLA versus LOP and PLA versus LOP+SIM is higher (both $p<0.001$); at 180 PLA versus LOP+SIM $p<0.01$. *Net secretion (fig. 5):* the net secretion is decreased for the drug cases, leading to a reduced AUC for the LOP and LOP+SIM in the early phase, $p<0.02$. Dunnett's multiple comparison post tests showed a significant difference of LOP+SIM versus PLA, $p<0.01$, whilst LOP versus PLA was not significantly different, $p>0.05$. *Motility:* the number of wall movements initially increased after the mannitol drink for all cases; more movements were found in the LOP and LOP+SIM cases in the later phase but this was not a statistically significant increase.

Discussion

The study was well tolerated by all subjects. The mannitol solution caused secretion in the small bowel as expected and thus was a reasonable model of an acute diarrhoea episode. Loperamide and Loperamide+simethicone accelerated gastric emptying, reduced the AUC of the SBWC and ACWC and the net secretion, delayed arrival in the AC and reduced the T2 of the AC contents. Simethicone caused an additional reduction in ACWC in the late phase. MRI can provide new insights into the mode of action of anti-diarrheal drugs.

Acknowledgments

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References

[1] Kaplan et al. Arch Fam Med 8 (1999); [2] Hoad et al. Phys Med Biol 52 (2007) [3] Marciani et al. Gastroenterology 138 (2010) [4] Hoad et al. Magn Reson Med 63 (2010).

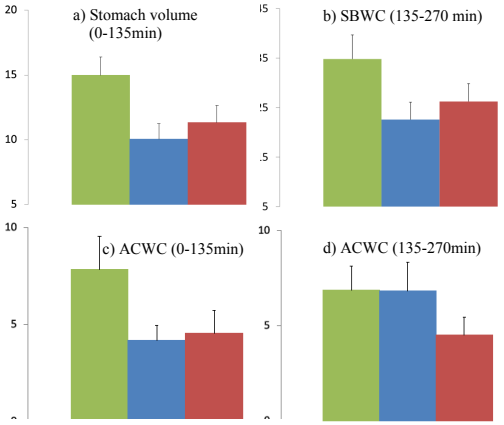

Fig. 1 AUC (ml*min*10^3)

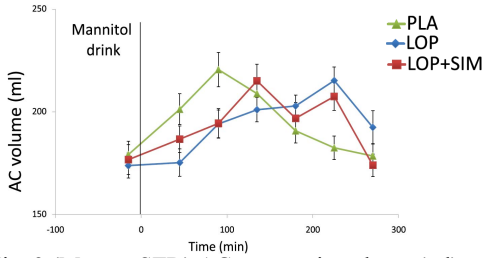

Fig. 2 (Mean ± STD) AC geometric volume (ml) versus time. The 2 baselines have been averaged

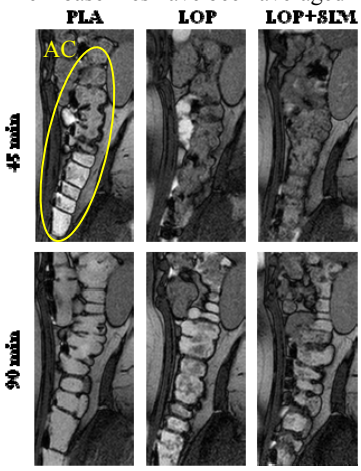

Fig. 3: High resolution bTFE sagittal images of the AC for the same volunteer

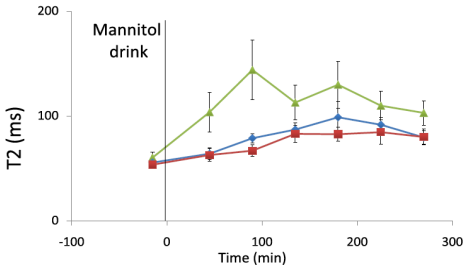

Fig. 4 (Mean ± STD) T2 in the AC (ms)

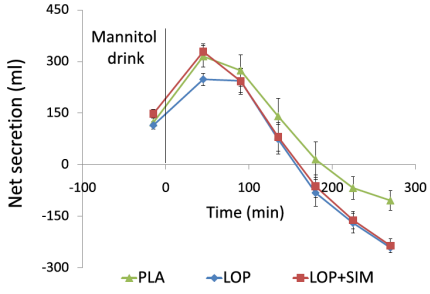

Fig. 5: (Mean ± STD) Net secretion over time (ml)