Can GTN Produce a Model of Migraine Induced Gastric Stasis?

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INTRODUCTION

Gastric stasis is an inhibition of gastric contractions, leading to delayed gastric emptying of stomach contents into the small intestine. It is a commonly reported symptom in migraine. The delayed emptying during a migraine attack will result in lower concentrations and a reduced therapeutic effect of orally administered analgesics taken to alleviate the symptoms [1]. It is therefore of value to develop a model of gastric stasis to investigate the efficacy of potential formulations for the reversal of this condition. We found previously that 400ml Clinutren® ISO, a nutrient drink, gives reproducible gastric emptying times (t_{50} and t_{90} values; 60±6, 120±13 minutes respectively) [2]. Glyceryl trinitrate (GTN), an exogenous donor of nitric oxide (NO) can slow down the gastric emptying rates of liquid meals [3-8]. It is postulated that by administering GTN sublingually the emptying of Clinutren® ISO will be delayed. Vitamin C, a powerful antioxidant, may enhance the action of GTN by scavenging anions capable of destroying NO. By administering a 3 day supplement of Vitamin C we investigated if the GTN model of gastric stasis could be further enhanced.

METHODS

Design

Single-centre, randomised, double blind three-way crossover study.

Subjects

8 healthy, non-smoking males aged 22 to 35 years (mean 25±4 yrs).

Study schedule

Three days prior to each study day subjects ingested, twice daily, either 100ml of a lemon flavoured placebo drink (LPD) or 100ml of a lemon drink containing 1000mg of vitamin C (LD-Vit C). Table 1 shows the protocol for each study arm. The saline placebo spray (SPS) and the GTN spray (0.8mg) were both given sublingually. At dosing the subject received 400ml of Clinutren® ISO which was labelled with 4MBq technetium diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) and consumed within one minute.

Table 1: Study Protocol

Time (mins)	Arm 1 (Control)	Arm 2 (GTN)	Arm 3 (GTN/VitC)
-45	100ml LPD	100ml LPD	100ml LD-VitC
-5	100ml water	100ml water	100ml water
0	400ml Radio-labelled Clinutren	400ml Radio-labelled Clinutren	400ml Radio-labelled Clinutren
+15	SPS	GTN spray	GTN spray

Imaging Schedule

Immediately after consuming Clinutren® ISO, subjects were asked to stand in front of the gamma camera. Anterior and posterior static acquisitions of 25 second duration were acquired every 5 minutes for 50 minutes and then every 10 minutes until 90% of the meal had left the stomach. Subjects were allowed to move around between images.

Scintigraphic Analysis

Images were analysed using the Weblink® image analysis program. Data was corrected for background activity and decay. Gastric emptying curves for Clinutren® ISO were plotted and the t_{50} and t_{90} (time taken for 50% and 90% of the Clinutren® ISO to leave the stomach) were calculated.

Statistical Analysis

t_{50} and t_{90} values of each treatment group were compared by ANOVA to detect any differences between treatments.

RESULTS AND DISCUSSION

Table 2: Mean t_{50} and t_{90} values. Mean (SD), n=8

	Arm 1 (Control)	Arm 2 (GTN)	Arm 3 (GTN/Vit C)
$t_{50\ (mins)}$	57 (8)	53 (12)	59 (12)
$t_{90\ (mins)}$	111 (14)	105 (18)	110 (17)

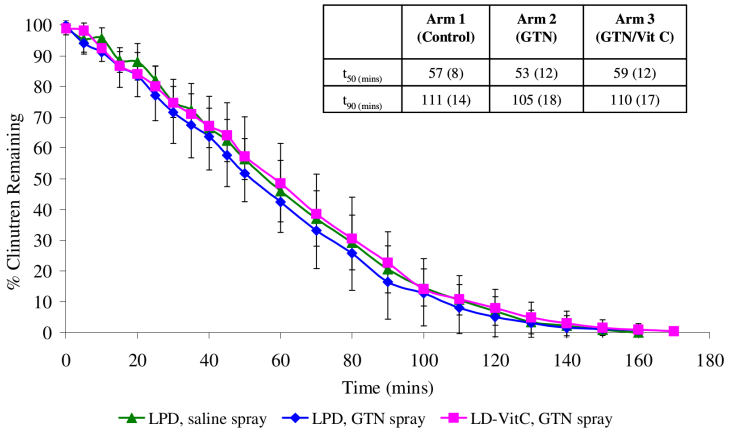

Figure 1: Mean gastric emptying curve. (Mean±SD, n=8)

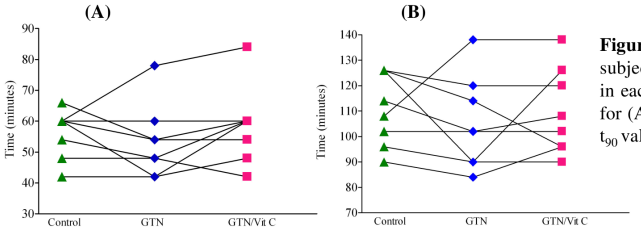

Figure 2: Intra-subject variation in each study arm for (A) t_{50} and (B) t_{90} values. (n=8)

Table 2 shows the t_{50} and t_{90} values for each study arm. These results indicate that the gastric emptying of Clinutren® ISO was not influenced by the sublingual administration of GTN alone or with pre-treatment of vitamin C. (p>0.05, ANOVA). The mean gastric emptying curves (Figure 1) also illustrate the lack of effect of each treatment on the emptying rates.

The data obtained for the emptying rates of Clinutren® ISO is in good agreement with the values previously reported [2] and the curves are typical of that of a nutrient liquid meal.

Figure 2 shows the intra-subject variation for each study arm. From this it can be seen that one subject has the hypothesised longer gastric emptying time after GTN and GTN/Vit C but this is not significant when taken as a whole data set.

Our findings are not in agreement with previous literature using the same 0.8mg dose of GTN, where a significant difference (p<0.01) in the emptying rates of a 500ml liquid meal was found [8]. The reason for this difference is unclear .

Figure 3 shows representative scintigraphic images for subject 3 for a range of time points in the control and the GTN/Vit C arms. The t_{90} value for both arms was 102 minutes which occurred between the last two images.

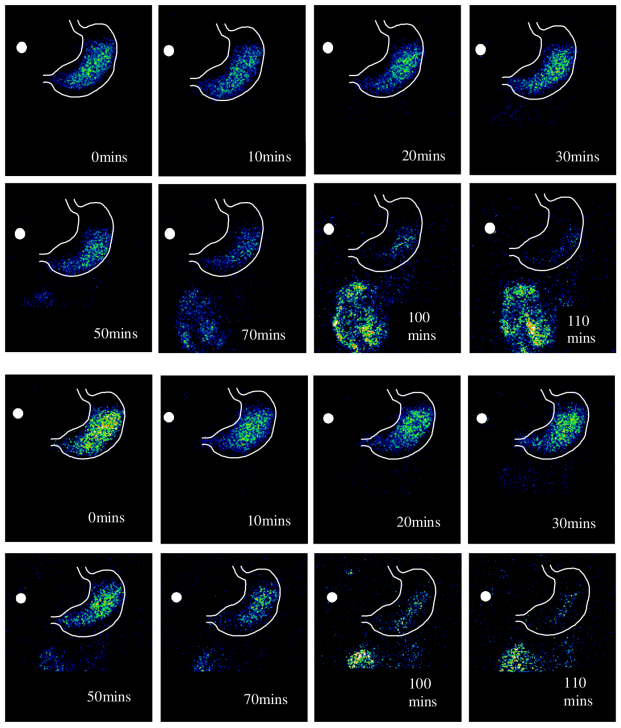

Figure 3: A series of scintigraphic images for subject 3 showing up to 90% gastric emptying. (A) shows images in the control arm of the study and (B) shows images from the GTN/Vit C arm.

CONCLUSION

The gastric emptying of Cinutren® ISO was unchanged by the sublingual administration of GTN alone or with vitamin C treatment. A reversible model of migraine induced gastric stasis was therefore not achieved.

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