THE EFFECT OF LONG CHAIN FATTY ACIDS ON THE GASTRIC EMPTYING OF A CO-ADMINISTERED TABLET IN FASTED HUMAN VOLUNTEERS

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INTRODUCTION

Many drugs are preferentially absorbed from the upper gastrointestinal (GI) tract. As a result, drug absorption can be highly dependent on GI transit transit rate. For such drugs, increased residence time in the stomach could lead to increased systemic absorption.

Nutrients in food trigger receptor-mediated responses in the small intestine, which serve to retard further gastric emptying. The fat receptors in the duodenum are the most potent inhibitors of gastric emptying[1]. Targeting of these receptors by a formulation could create an "after food effect" which retards GI transit and improves the absorption profile of certain drugs, particularly those given in controlled release formulations.

This scintigraphic study was conducted to assess the effect of two long chain fatty acids (myristic acid and palmitic acid) on the gastric emptying of a large non-disintegrating tablet.

METHODS

STUDY DESIGN

- Single centre, randomised, four-way cross-over
- Placebo-controlled
- Analyst-blind
- Twelve healthy male and female volunteers
- Age 36 to 48 years (mean 40.8 +/-3.6).

STUDY DAY PROCEDURE

	Formulations Administered	
Study Arm	Tablet (labelled with In^{111} DTPA)	Capsule (labelled with Tc^{99m} DTPA)
A	1 x non-disintegrating ethylcellulose tablet (dimensions 22 x 10 x 8mm) was administered in all study arms	200mg Lactose
B		100mg Myristic Acid
C		200mg Myristic Acid
D		200mg Palmitic Acid

Table 1. Dosing schedule

- Subjects fasted overnight
- Anterior and posterior static acquisitions of 30-second duration were acquired after dosing, then every 10 minutes to 1 hour, then every 15 minutes to 6 hours
- Volunteers remained fasted throughout the study period
- One week's washout between study arms was adhered to throughout the study

RESULTS

CAPSULE DISINTEGRATION TIMES

Disintegration times are quoted as the mid-points of the two images between which disintegration occurred. The results are shown in Table 2. There was no significant difference between disintegration times of the different capsule formulations.

	Lactose 100mg	Myristic Acid 100mg	Myristic Acid 200mg	Palmitic Acid 200mg
Mean	10.8	10.8	7.5	12.5
SD	5.1	7.9	4.5	7.5

Table 2. Capsule disintegration times (min).

TABLET GASTRIC EMPTYING TIMES

While gastric emptying times of the tablets were highly variable, there were no significant differences after dosing with the four capsule formulations. Mean gastric emptying times and standard deviations are shown in Table 3.

	Lactose 100mg	Myristic Acid 100mg	Myristic Acid 200mg	Palmitic Acid 200mg
Mean	51.3	48.3	55.0	46.5
SD	67.6	70.8	56.6	45.3

Table 3. Tablet gastric emptying times (min).

In order for the fatty acid to affect the gastric emptying of the tablet, it would be necessary for it to reach the duodenum while the tablet is still in the stomach. However, this did not occur in all cases. In eleven cases the tablet emptied from the stomach before the capsule had disintegrated, as shown in Figure 1. Large non-disintegrating tablets dosed in the fasted state are normally cleared from the stomach by Phase III of the migrating myoelectric complex (the *'housekeeper wave'*). Therefore, immediate emptying of the tablet would be expected to occur occasionally, if dosing was closely followed by a housekeeper wave. In one subject, however, immediate emptying of the tablet occurred on all four study days, which suggests that this subject may have an anatomical or physiological abnormality.

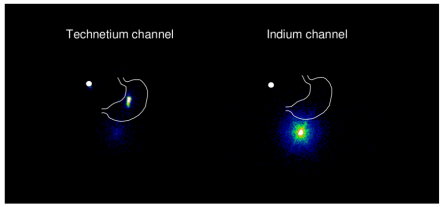

Figure 1. Scintigraphic images showing gastric emptying of the tablet before capsule disintegration

In a number of other cases it was unclear whether the capsule contents reached the duodenum before gastric emptying of the tablet, as the two events occurred at approximately the same time. Figure 2 shows disintegration of the capsule and gastric emptying of its' contents while the tablet remained in the stomach, which was the intended sequence of events.

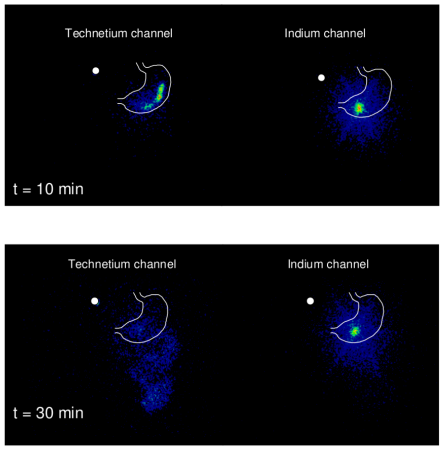

Figure 2. Scintigraphic images showing capsule disintegration and gastric emptying of its' contents while the tablet remains in the stomach

CONCLUSION

The fatty acids were not shown to affect gastric emptying of co-administered tablets at the doses employed. This might be due to a failure to deliver the fatty acids to their proposed site of action in the duodenum before the tablet had left the stomach, or to lack of dispersion in gastric fluid. Further work is necessary to elucidate the effects of the fatty acids *in-vivo*.

FUTURE WORK

Strategies to achieve more efficient and timely delivery of the fatty acid to the duodenum need to be investigated. For example, reformulation to improve dispersion in gastric fluid could lead to more rapid gastric emptying by eliminating floating of the fatty acid on the gastric contents. Other options may include altering the timing of fatty acid administration relative to that of the tablet.

REFERENCE

1. J. N. Hunt & M. T. Knox. *J. Physiol.* 194: 327-36 (1968)