A STUDY TO INVESTIGATE THE EFFECTS OF FOOD ADMINISTRATION POST GASTRIC EMPTYING ON A TIME-DELAYED FORMULATION IN HEALTHY VOLUNTEERS USING GAMMA SCINTIGRAPHY

Jason McConville[1], Bridget O'Mahony[2], Blythe Lindsay[2], Tamara Jones[2], Adrian Stanley[3], Bill Vennart[4], Tim Buchanan[4], Michael J. Humphrey[4], Clive G. Wilson[1,2], Howard N.E. Stevens[1,2]

[1]Department of Pharmaceutical Sciences, University of Strathclyde, Glasgow, G4 0NR, UK [2]Bio-Images Research Ltd, Glasgow, G4 0SF, UK, [3]Department of Gastroenterology, Glasgow Royal Infirmary, Glasgow, G4 0SF, UK, [4]Pfizer Ltd, Sandwich, CT13 9NJ, UK.

INTRODUCTION

An oral time delayed delivery formulation has previously been developed[1] and tested in healthy volunteers[2]. In vivo studies of time-delayed targeted systems can be problematic due to high inter- and intra-subject variability in gastrointestinal transit. Gastric emptying (GE) in fasted volunteers can vary from 0 to 3 hours, dependent on the random occurrence of the migrating myoelectric complex (MMC). In the study a minimal calorific value snack given 30 minutes prior to dosing gave a narrow range of gastric emptying times (mean 1.52 +/- 0.58 hours)[2]. This may be due to the production of a transient fed state resulting in triggering of the onset of MMC at similar time points. It was proposed that giving further calories post-gastric emptying of the formulation could reduce variability in small intestinal transit allowing enhanced control of site of release.

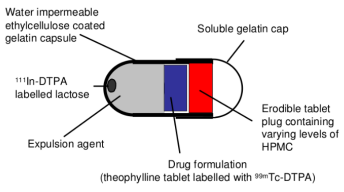

Fig. 1 Delivery device comprising insoluble capsule body sealed with erodible tablet plug. A swellable expulsion system is used to push the drug-containing tablet out of the capsule. The drug tablet contained the marker drug theophylline and was radiolabelled with ^{99m}Tc-DTPA to allow time and site of expulsion and complete disintegration to be determined. The capsule body was labelled with ^{111}In-DTPA to allow transit of the device to be assessed separately.

The formulation chosen for further study had an *in vivo* release time of 4 hours (Figure 1).

EXPERIMENTAL METHODS

Design
Single-centre, randomised, single dose study.

Subjects
12 healthy, non-smoking males age 19 to 43 years (mean 26.9 +/-8.3).

Dosing
Subjects received one 4h time delayed release formulation with 240ml water.

Meal Schedule
Fasted subjects received a light snack 30 minutes prior to dosing. Subjects were randomly assigned to one of two groups - six subjects received an 800kJ breakfast and 6 subjects received an 1800kJ breakfast post gastric emptying

All subjects received lunch (1300 kJ) 4 hours post-dose, an afternoon snack (600 kJ) 7 hours post-dose and an evening meal (2400 kJ) 10 hours post dose.

Imaging Schedule
Subjects were imaged in a standing position with the gamma camera. Anterior and posterior static acquisitions of 30-second duration were collected every 15 minutes until burst was observed, then hourly to 12 hours post dose.

Scintigraphic analysis
Images were analysed using the WebLink® image analysis program. Gastric emptying time, time and site of release and gastrointestinal transit were determined by two independent trained operators.

RESULTS

Subject No	GE time (h)	Tc release time (h)	Site of release	SI transit time (h)
001	0.50	3.00	SI	5.50
004	1.00	5.00	ICJ	5.00
006	2.25	3.50	SI	2.75
007	2.00	NR		10.00*
008	0.75	NR		11.25*
010	2.25	NR		4.00
Mean	**1.46**	**3.83**		**6.42**
SD	**0.80**	**1.04**		**3.42**
n	**6**	**3**		**6**

Table 1 Gastric emptying, release times, site of release and small intestinal transit times for subjects who received 800kJ breakfast post gastric emptying
SI small intestine, ICJ ileocaecal junction, NR No release, * indicates transit incomplete

Subject No	GE time (h)	Tc release time (h)	Site of release	SI transit time (h)
002	2.50	NR		2.00
003	2.50	3.75	SI	5.50
005	1.50	NR		5.00
009	0.75	5.00	SI	11.25*
011	1.00	NR		3.00
012	3.50	9.00	TC	2.00
Mean	**1.96**	**5.92**		**4.79**
SD	**1.05**	**2.74**		**3.49**
n	**6**	**3**		**6**

Table 2 Gastric emptying, release times, site of release and small intestinal transit times for subjects who received 1800kJ breakfast post gastric emptying
SI small intestine, TC transverse colon, NR No release, * indicates transit incomplete

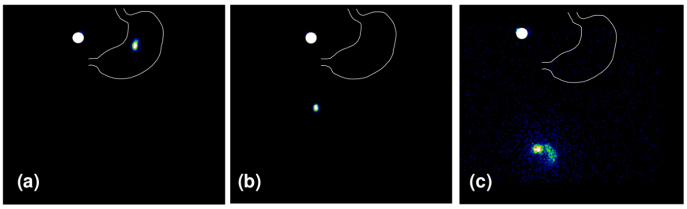

Figure 2: Representative scintigraphic images showing (a) formulation in stomach immediately post dose, (b) post gastric emptying, (c) dispersion of Tc label

The mean gastric emptying times for the two subject groups are 1.46+/-0.80 hours and 1.96+/-1.05 hours for the 800kJ and 1800kJ breakfast subject groups respectively (both n=6). This difference was not significant.

Mean SI transit times for the two subject groups were 6.42 +/- 3.42 hours and 4.79 +/- 3.49 hours for the 800kJ and 1800kJ breakfast groups respectively (both n=6). This difference was not significant.

However subjects 007, 008 and 009 have unusually long SI transit times (greater than 10, 11.25 and 11.25) which may account for the lack of any significant difference between subject groups.

A total of 6 out of 12 formulations failed to release scintigraphically. 5 of the 6 formulations were observed to release within the small intestine. One formulation (subject 012) released in the transverse colon.

CONCLUSION

In this study no evidence is seen of any effect of food on SI transit times. The lack of any obvious effect may be due to the high variability in SI transit times observed in this study. A further study using a crossover design would be necessary to elucidate whether food has any effect on SI transit.

REFERENCES

1. AC Ross *et al*, Chronopharmaceutical drug delivery from a pulsatile capsule device based on programmable erosion. *Journal of Pharmacy and Pharmacology* 52 903-909 (2000)
2. J McConville *et al*, Gamma Scintigraphic Investigation of drug release from a time delayed capsule. Proceed. Intern. Symp. Control. Rel. Bioact. Mater., (2001).

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