

Studies of Gastric Motility in Health and Diabetes

A thesis submitted by
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Table of Contents

Abstract	i
Declaration of originality	iv
Dedication	v
Acknowledgements	vi
Publications arising from this thesis	ix

Chapter 1 NORMAL GASTRIC MOTOR FUNCTION

1.1	Introduction	1
1.2	Anatomical and functional motor regions of the stomach	2
	1.2.1 <i>Proximal stomach</i>	3
	1.2.2 <i>Distal stomach</i>	4
	1.2.3 <i>Pylorus</i>	6
1.3	Patterns of gastric emptying	6
	1.3.1 <i>Solids</i>	7
	1.3.2 <i>Liquids</i>	9
	1.3.3 <i>Fats</i>	10
1.4	Determinants of gastric emptying	11
	1.4.1 <i>Small intestinal feedback inhibition</i>	11

1.4.2	<i>Posture</i>	12
1.4.3	<i>Meal temperature</i>	12
1.4.4	<i>Meal volume</i>	12
1.4.5	<i>Gastrointestinal peptides</i>	13
1.4.5.1	<i>GLP-1 and GLP-2</i>	13
1.4.5.2	<i>GIP</i>	15
1.4.5.3	<i>CCK</i>	15
1.4.5.4	<i>PYY</i>	16
1.4.5.5	<i>Ghrelin</i>	16
1.5	<i>Conclusions</i>	17

Chapter 2 MEASUREMENT OF GASTRIC MOTOR FUNCTION

2.1	<i>Introduction</i>	18
2.2	<i>Measurement of gastric emptying</i>	19
2.2.1	<i>Scintigraphy</i>	21
2.2.2	<i>Ultrasonography</i>	27
2.2.3	<i>Stable isotope breath tests</i>	30
2.2.4	<i>Magnetic resonance imaging</i>	31
2.2.5	<i>Single photon emission computed tomography</i>	32
2.2.6	<i>Radiopaque marker techniques</i>	32
2.2.7	<i>Applied potential tomography / Impedance epigastrography</i>	33
2.2.8	<i>Absorption kinetics of orally administered drugs</i>	34
2.2.8.1	<i>Paracetamol (acetaminophen) absorption</i>	34
2.2.8.2	<i>Oral glucose absorption</i>	35
2.3	<i>Measurement of intragastric pressure and contractions</i>	36
2.3.1	<i>Manometry</i>	37
2.3.2	<i>Barostat</i>	38
2.3.3	<i>Ultrasonography</i>	39
2.3.4	<i>Strain rate imaging</i>	40

4.3.4	<i>Cisapride</i>	69
4.3.5	<i>Antiemetic agents</i>	70
4.3.6	<i>Novel therapies</i>	71
4.4	Other medical therapies	74
4.4.1	<i>Intrapyloric botulinum toxin</i>	74
4.4.2	<i>Gastric electrical stimulation</i>	75
4.4.3	<i>Surgery</i>	76
4.5	Conclusions	78

Chapter 5 **EFFECT OF EXENDIN(9-39), A GLUCAGON-LIKE PEPTIDE-1 (GLP-1) ANTAGONIST, ON GASTRIC EMPTYING IN HEALTHY HUMANS**

5.1	Summary	79
5.2	Introduction	80
5.3	Materials and Methods	83
5.3.1	<i>Subjects</i>	83
5.3.2	<i>Experimental protocol</i>	84
5.3.3	<i>Measurement of gastric emptying</i>	84
5.3.4	<i>Measurements of blood glucose, plasma GLP-1, GIP, insulin and glucagon</i>	85
5.3.5	<i>Statistical analysis</i>	86
5.4	Results	87
5.4.1	<i>Gastric emptying and intragastric distribution</i>	87
5.4.2	<i>Blood glucose concentration</i>	88
5.4.3	<i>Relationships between blood glucose and gastric emptying</i>	89
5.5	Discussion	90

7.3.3	<i>Measurement of gastric emptying</i>	118
7.3.4	<i>Assessment of upper gastrointestinal and hypoglycaemic symptoms</i>	119
7.3.5	<i>Measurement of blood pressure and heart rate</i>	119
7.3.6	<i>Assessment of autonomic nerve function</i>	119
7.3.7	<i>Statistical analysis</i>	120
7.4	Results	120
7.4.1	<i>Gastric emptying</i>	121
7.4.2	<i>Upper gastrointestinal and hypoglycaemic symptoms</i>	125
7.4.3	<i>Blood pressure and heart rate</i>	126
7.5	Discussion	127

Chapter 8 **EFFECTS OF INTRAVENOUS FRUCTOSE ON GASTRIC EMPTYING AND ANTRYPYLORODUODENAL MOTILITY IN HEALTHY SUBJECTS**

8.1	Summary	132
8.2	Introduction	133
8.3	Materials and Methods	136
8.3.1	<i>Subjects</i>	136
8.3.2	<i>Experimental protocol</i>	136
8.3.3	<i>Measurement of blood glucose concentrations</i>	138
8.3.4	<i>Measurement of gastric emptying</i>	138
8.3.5	<i>Measurement of antropyloroduodenal motility</i>	139
8.3.6	<i>Statistical analysis</i>	139
8.4	Results	140
8.4.1	<i>Blood glucose</i>	140
8.4.2	<i>Gastric emptying and intragastric distribution</i>	141
8.4.3	<i>Antropyloroduodenal motility</i>	144
8.4.3.1	<i>Antral pressure waves</i>	144

8.4.3.2	<i>Isolated pyloric pressure waves</i>	145
8.4.3.3	<i>Duodenal pressure waves</i>	146
8.5	Discussion	148

**Chapter 9 EFFECT OF ITOPRIDE ON GASTRIC
EMPTYING IN LONGSTANDING DIABETES
MELLITUS**

9.1	Summary	151
9.2	Introduction	152
9.3	Materials and Methods	154
9.3.1	<i>Subjects</i>	154
9.3.2	<i>Experimental protocol</i>	155
9.3.3	<i>Measurement of gastric emptying</i>	156
9.3.4	<i>Measurement of glycaemic control</i>	157
9.3.5	<i>Assessment of upper gastrointestinal symptoms</i>	157
9.3.6	<i>Assessment of autonomic nerve function</i>	158
9.3.7	<i>Statistical analysis</i>	158
9.4	Results	159
9.4.1	<i>Gastric emptying</i>	159
9.4.2	<i>Blood glucose concentration</i>	161
9.4.3	<i>Upper gastrointestinal symptoms</i>	163
9.5	Discussion	163

**Chapter 10 ACUTE EFFECTS OF C-PEPTIDE ON
GASTRIC EMPTYING IN LONGSTANDING
TYPE 1 DIABETES**

10.1	Summary	168
10.2	Introduction	169
10.3	Materials and Methods	171
10.3.1	<i>Subjects</i>	171

10.3.2	<i>Experimental protocol</i>	171
10.3.3	<i>Measurement of gastric emptying</i>	172
10.3.4	<i>Assessment of autonomic nerve function</i>	173
10.3.5	<i>Assessment of upper gastrointestinal symptoms</i>	173
10.3.6	<i>Measurement of blood glucose and serum C-peptide concentrations</i>	174
10.3.7	<i>Statistical analysis</i>	174
10.4	Results	174
10.4.1	<i>Gastric emptying</i>	175
10.5	Discussion	176
Chapter 11	CONCLUSIONS	179
Chapter 12	REFERENCES	185

List of Figures

Figure 1.1: Representation of the distinct anatomical and functional motor regions of the stomach with an outline of motor events during normal gastric emptying. Adapted from Rayner and Horowitz (2005).

Figure 1.2: Scintigraphic gastric emptying curves for solid (100 g minced beef), semisolid / high-nutrient liquid (porridge / dextrose 25 %w/v) and low-nutrient liquid (beef soup). Solid, semisolid and high-nutrient liquid gastric emptying curves are characterised by a lag phase followed by a linear emptying phase, while low/non-nutrient liquids empty in a monoexponential fashion with minimal lag phase.

Figure 2.1: Scintigram of stomach (posterior view), divided into total, proximal and distal regions, following ingestion of 100 g minced beef labelled with 20 MBq ^{99m}Tc -sulphur colloid.

Figure 2.2: Parasagittal 2D ultrasonographic image of the antrum (indicated by arrow).

Figure 2.3: Ultrasonographic image of the stomach demonstrating region-of-interest (a) and 3D reconstructed volumetric image of the total stomach (b).

Figure 2.4: Schematic representation of manometric catheter with 16 sideholes (channels) spaced at 1.5 cm intervals, comprising six antral sideholes, two TMPD sideholes on either side of the pyloric sleeve sensor, seven duodenal sideholes and one infusion port.

Figure 3.1: Gastric emptying of solid (100 g minced beef) and liquid (10 % dextrose) in 87 patients with longstanding diabetes (67 type 1, 20 type 2) and 25 healthy subjects. Shaded areas represent normal ranges;

horizontal lines reflect median values. Reproduced from Horowitz *et al.* (1991).

Figure 3.2: Relationship between solid gastric emptying and cardiovascular autonomic nerve function in diabetes mellitus. The shaded area represents the normal range. Reproduced from Horowitz *et al.* (1991).

Figure 3.3: The effect of hypoglycaemia (~ 1.9 mmol/L) on solid and liquid gastric emptying in 8 uncomplicated type 1 diabetic patients. Reproduced from Schvarcz *et al.* (1993).

Figure 3.4: The relationship between upper gastrointestinal symptoms and gastric emptying of a solid meal in 87 type 1 and type 2 diabetic patients. The shaded area represents the normal range. Reproduced from Horowitz *et al.* (1991).

Figure 5.1: Retention of a mashed potato meal in the (a) total, (b) proximal and (c) distal, stomach during intravenous infusion of exendin(9-39) (300 pmol/kg/min) and placebo (0.9 %w/v saline at 1 mL/min). Data are mean values \pm SEM; n = 10.

Figure 5.2: Blood glucose concentrations during intravenous infusion of exendin(9-39) (300 pmol/kg/min) and placebo (0.9 %w/v saline at 1mL/min). Data are mean values \pm SEM; n = 10.

Figure 5.3: Relationship between the magnitude of the rise in blood glucose at 60 min and the T50 during intravenous infusion of exendin(9-39) (300 pmol/kg/min) and placebo (0.9 %w/v saline at 1 mL/min). Data are from both treatment visits; n = 20.

Figure 6.1: Retention of dextrose (75 g / 300 ml) in (a) total, (b) proximal and (c) distal stomach, quantified by scintigraphy and 3D ultrasonography. Data are mean values \pm SEM; *** P < 0.0001, ** P < 0.01, * P < 0.05.

Figure 6.2: Relationship between scintigraphic (SCT50) and 3D ultrasonographic (UST50) 50 % emptying times for the drink (75 g dextrose in 300 mL water).

Figure 6.3: Limits of agreement for scintigraphic (SCT50) and 3D ultrasonographic (UST50) 50 % emptying times (T50s) for the drink (75 g dextrose in 300 mL water).

Figure 6.4: Relationship between proximal stomach sagittal area (quantified by 2D ultrasonography) and proximal volume (quantified by 3D ultrasonography) in all patients across all time points.

Figure 6.5: Blood glucose concentrations following ingestion of the drink (75 g dextrose in 300 mL water). Data are mean values \pm SEM.

Figure 7.1: Blood glucose concentrations in studies conducted during hypoglycaemia and euglycaemia. Gastric emptying was measured between $t = 0$ and 120 min. Data are mean values \pm SEM; * $P < 0.05$ and # $P < 0.001$ compared with euglycaemia.

Figure 7.2: Gastric emptying and intragastric distribution of solid and liquid meal components during hypoglycaemia and euglycaemia. Data are mean mean values \pm SEM; * $P < 0.05$ and # $P < 0.01$ compared with euglycaemia.

Figure 7.3: The relationship between the magnitude of the change in gastric emptying for the solid retention at 100 min (T100) and liquid 50 % emptying time (T50) between hypoglycaemia and euglycaemia and the rate of gastric emptying during euglycaemia. Individual data for the 20 subjects are shown.

Figure 7.4: Symptoms of hypoglycaemia during hypoglycaemia and euglycaemia. Data are mean values \pm SEM. # $P < 0.01$ compared with euglycaemia.

Figure 8.1: Effects of intravenous fructose, glucose and saline on the blood glucose concentration following ingestion of 100 g minced beef. Data are mean values \pm SEM.

Figure 8.2: Effects of intravenous fructose, glucose and saline on (a) total, (b) proximal, and (c) distal, gastric emptying of 100 g minced beef. Data are mean values \pm SEM.

Figure 8.3: Effects of intravenous fructose, glucose and saline on number of (a) isolated pyloric pressure waves, (b) antral pressure waves (recorded by the last three antral channels), and (c) duodenal pressure waves (recorded by the first three duodenal channels), following ingestion of 100 g minced beef. Data are mean values \pm SEM (a) and mean values with upper and lower 95%CI (b, c).

Figure 9.1: Gastric emptying of (a) solid and (b) liquid meal components following treatment with itopride (200 mg po *tid*) and placebo (n = 25, data are mean values \pm SEM).

Figure 9.2: Relationship between the magnitude of the change in gastric emptying (placebo - itopride) for (a) solid (retention at 100 min) and (b) liquid (50 % emptying time) with gastric emptying on placebo (n = 25, data are mean values \pm SEM).

Figure 9.3: Gastric emptying of (a) solid and (b) liquid meal components following treatment with itopride (200 mg po *tid*) and placebo in patients with delayed gastric emptying of solids and/or liquids on placebo (n = 12, data are mean values \pm SEM).

Figure 9.4: Blood glucose concentrations during gastric emptying measurements following treatment with itopride (200 mg po *tid*) and placebo (n = 25, data are mean values \pm SEM).

Figure 10.1: Gastric emptying of (a) solid (100 g minced beef) and (b) liquid (150 mL 10 % dextrose) meal components in 8 patients with type 1 diabetes mellitus. Data are mean values \pm SEM.

List of Tables

Table 2.1: Methods in the assessment of gastric motor function.

Table 3.1: Common aetiologies of delayed gastric emptying

Table 4.1: Commonly used prokinetic agents

Table 4.2: Novel prokinetic agents

Abstract

The human stomach is a complex organ with sophisticated function. – The control of delivery of nutrients to the small intestine is tightly regulated, and the patterns and determinants of the associated processes are numerous, complex and interrelated. The presence of nutrients in the small intestine stimulates the release of a number of gastrointestinal hormones, including glucagon-like peptide-1 (GLP-1). Exogenous GLP-1 reduces fasting and postprandial glucose concentrations, and this is thought to be via a slowing of gastric emptying (GE). The effects of endogenous GLP-1 on GE and glycaemia were evaluated using exendin(9-39), a GLP-1 antagonist, in healthy subjects, in a randomised, placebo-controlled study, in Chapter 5. Exendin(9-39) increased postprandial glycaemia through an acceleration of GE; these findings support the putative role of GLP-1 as an enterogastrone. The capacity to measure GE has greatly increased the understanding of normal and disordered gastric physiology. 30 – 50 % of patients with longstanding diabetes have delayed GE. Scintigraphy remains the ‘gold standard’ in the measurement of GE, however, it is associated with a radiation burden. Recently, three-dimensional (3D) ultrasonography was validated against scintigraphy in healthy subjects. In Chapter 6, GE was measured concurrently

by 3D ultrasonography and scintigraphy in patients with diabetic gastroparesis, and good correlation and agreement was found between both techniques. Glycaemic control represents one of the main pathogenetic factors of diabetic gastroparesis. Hyperglycaemia slows, while hypoglycaemia accelerates, GE in healthy subjects and patients with uncomplicated type 1 diabetes. Chapter 7 reports a study investigating the effects of insulin-induced hypoglycaemia vs. euglycaemia on GE in longstanding type 1 diabetes. Hypoglycaemia accelerated GE of a mixed solid/liquid meal; the magnitude of this acceleration was greater when GE during euglycaemia was slower. In contrast to glucose, the effects of intravenous (*iv*) fructose (used widely in the diabetic diet) on GE are less well understood. The comparative effects of *iv* fructose, glucose and saline on GE and antropyloroduodenal motility in healthy males are reported in Chapter 8. Compared with saline, fructose infusion was associated with a slowing of GE and suppression of antral waves, the magnitude of which was comparable to glucose. Treatment for the management of gastroparesis is currently suboptimal and there is a need for novel prokinetic agents. Itopride has demonstrated prokinetic activity in dogs. The effects of itopride on GE, glycaemia and upper gastrointestinal symptoms were studied in patients with longstanding diabetes in a randomised, placebo-controlled trial (Chapter 9). There was a trend for itopride to accelerate both solid and liquid GE. 48 % of patients had delayed solid and/or liquid GE on placebo, and in this group, itopride accelerated liquid, but not solid, GE. Autonomic neuropathy represents another pathogenetic factor of diabetic gastroparesis, and delayed GE is more prevalent in patients with autonomic dysfunction. There is evidence that C-peptide improves autonomic nerve function (ANF) in type 1 diabetes. The effects of C-peptide on GE and ANF were studied in patients with longstanding type 1 diabetes in randomised, placebo-controlled design, in Chapter 10. C-peptide had no effect on solid or liquid GE, or ANF. Gastroparesis,

particularly in patients with diabetes, represents an important clinical problem. The studies presented in this thesis have provided fundamental insights into the measurement and determinants of gastric motor function and postprandial glycaemia, and treatment of gastroparesis, however, further studies which assess the complex pathogenesis and pathophysiology of gastroparesis, and which include a larger cohort of patients, are warranted.

Declaration of Originality

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Julie Eva Stevens and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Signed _____

Julie Eva Stevens

May 2009

Dedication

*To my parents,
for your unconditional love and sacrifice,
for the opportunities you have provided me,
for your unrelenting support and encouragement,
and for believing in me,
I am eternally thankful.*

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Publications arising from this thesis

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Stevens JE, Gilja OH, Gentilcore D, Hausken T, Horowitz M, Jones KL. Measurement of gastric emptying of a high-nutrient liquid by 3D ultrasonography in diabetic gastroparesis. 2009 (submitted).

Effects of intravenous fructose on gastric emptying and antropyloroduodenal motility in healthy subjects. 2009 (submitted).

Stevens JE, Russo A, Maddox AF, Rayner CK, Phillips L, Talley N, Horowitz M, Jones KL. Effect of itopride hydrochloride on gastric emptying in longstanding diabetes mellitus. *Neurogastroenterol. Motil.* 2008;20:456-463.

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Russo A, Stevens JE, Chen R, Gentilcore D, Burnet R, Horowitz M, Jones KL. Insulin-induced hypoglycemia accelerates gastric emptying of solids and liquids in long-standing type 1 diabetes. *J Clin Endocrinol Metab.* 2005;90:4489-4495.

OTHER PUBLICATIONS

Effects of exendin(9-39), a glucagon-like peptide-1 (GLP-1) antagonist, on gastric emptying and glycaemia in healthy humans.