Studies of Gastric Motility in Health and Diabetes

A thesis submitted by

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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
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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

PUBLISHED

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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OTHER PUBLICATIONS

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