GASTROINTESTINAL MOTOR AND SENSORY FUNCTION IN COMPLICATED AND UNCOMPLICATED PEPTIC ULCER DISEASE

A thesis submitted by

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THESIS SUMMARY

Peptic ulcer disease is common. The exact pathophysiology of peptic ulcer disease is still unclear. However, major causes of peptic ulcer disease are Helicobacter *pylori* infection and Non-steroidal anti-inflammatory drugs (NSAIDs) used. Peptic ulcer disease usually manifests as either dyspepsia or, less commonly, with life threatening complications such as bleeding and perforation (Linder and Wilcox 2001). Over the past two decades the incidence of uncomplicated peptic ulcer disease has dropped substantially, whilst the incidence of peptic ulcer bleeding seems to have remained unchanged (Lassen, Hallas et al. 2006; Post, Kuipers et al. 2006). Approximately 30% to 50% of patients with bleeding peptic ulcer are asymptomatic until bleeding occurs (Croker 1991) even though the endoscopic assessment may reveal multiple ulcer scars suggestive of previous ulceration. Moreover, the majority of patients dying from peptic ulceration have no symptoms of ulcer disease until the presentation of their final, fatal illness (Pounder 1989).

The mechanism of ulcer pain is still unclear. However, several factors have been associated with silent peptic ulceration. Older age and NSAIDs have been shown to be associated with asymptomatic peptic ulcer (Clinch, Banerjee et al. 1984; Mellem, Stave et al. 1985; Dew 1987), although this notion has been challenged

(Wilcox and Clark 1997; Lu, Chang et al. 2004). While, no study has reported in relate to visceral sensory function in patients with peptic ulcer disease. Altered gastric motor function has been proposed to be associated with the pathogenesis of peptic ulcer disease, though this idea is not well acknowledged. Gastric motor function and visceral sensory function may be the key responsible for the difference between clinical manifestations of complicated and uncomplicated peptic ulcer.

The incidence and proportion of patients between symptomatic and asymptomatic peptic ulcer is unknown. Few studies have shown the factors that could be associated with asymptomatic peptic ulcer such as age, NSAIDs and ulcer size.

This research aims of this thesis were, therefore, to examine: (i) the effect of age on gastric sensory function using the nutrient challenge test; (ii) assess symptom profiles and compare visceral sensory thresholds in patients with bleeding peptic ulcer, uncomplicated peptic ulcer disease and healthy controls; (iii) assess gastric emptying in patients with bleeding peptic ulcer, uncomplicated peptic ulcer and healthy controls, and the relationship between symptoms and gastric emptying; (iv) study the link between immune activation and clinical manifestation of patients with peptic ulcer disease and explore the link between anxiety or depression and the release of inflammatory cytokine; (v) determine the incidence and risk factors of uncomplicated peptic ulcer disease, bleeding peptic ulcer and asymptomatic peptic ulcer, and changes of epidemiology of peptic ulcer disease

over a 10-year period, between 1997 to 2007, at the Royal Adelaide Hospital; (vi) compare the symptoms reported in patients with uncomplicated peptic ulcer compared with bleeding peptic ulcer after 1 year of ulcer healing; (vi) assess the distribution of GNB3 C825T polymorphisms and the association between GNB 3 825 polymorphisms and symptoms during a nutrient challenge in healthy subjects.

The current study indicates that elderly people have decreased gastric visceral sensation compared with younger people. This study also shows that patients with uncomplicated peptic ulcer have an augmented symptom response and significantly delayed gastric emptying whilst patients with bleeding peptic ulcer have a symptom response to a test meal and gastric emptying time that is not different from that in healthy control, suggesting fundamental difference in visceral sensitivity and abnormal gastric motor function suggesting a between patients with bleeding or asymptomatic ulcers and those with symptomatic or uncomplicated ulcers. Our findings also showed that there were increased levels of systemic proinflammatory cytokines in patients with uncomplicated peptic ulcer, despite the ulcer had healed, compared with patients with bleeding peptic ulcer and healthy control. The findings further support the notion that patients with uncomplicated peptic ulcer share similarities with patients with functional dyspepsia.

The study in this thesis also demonstrates the epidemiology of symptomatic and asymptomatic peptic ulcer disease over the past 10 years at the Royal Adelaide

Hospital, including the risk of being asymptomatic peptic ulcer. The study shows that over the last 10 years, the incidence of uncomplicated peptic ulcer has decreased whereas bleeding peptic ulcer has remained stable.

The work described in Chapter 15 demonstrates that most patients with dyspeptic symptoms prior to the diagnosis of peptic ulcer disease continue to have dyspeptic symptoms 12 months after ulcer healing and Helicobacter *pylori* eradication. Patients with persistent dyspeptic symptoms have higher level of anxiety and depression score than patients without symptoms. The data suggest that most patients with symptomatic peptic ulcer disease have concomitant functional dyspepsia, which may have led to the diagnostic endoscopy being performed that probably prevented the development of a life threatening ulcer bleed.

Based upon our data it might be speculated that mechanisms that are involved into the manifestation of symptoms in patients with functional dyspepsia may actually prevent the manifestation of ulcer complications since ulcers manifest with symptoms that trigger health care seeking and treatment before complications occur.

Chapter 16 of this thesis might potentially explain one of the mechanisms of abdominal pain. The work described in this study shows that GNB3 825T-CC plays a role in the processing of visceral sensory information or the gastrointestinal motor responses to a nutrient challenge.

By doing so, the research studies which were conducted as part of this thesis have significantly improved and added new knowledge in the fields of gastric motor and sensory function in peptic ulcer disease.

In conclusion, the thesis has highlighted the differences in gastric motor function, gastrointestinal sensory function and immune activation between patients with uncomplicated peptic ulcer disease and bleeding peptic ulcer. This thesis also showed the epidemiologic data of patients with symptomatic and asymptomatic peptic ulcer disease, including the risk factors of being asymptomatic peptic ulcer. The results have important therapeutic implications, and suggest aggressive management of patients with peptic ulcer disease. In addition, the research study also suggests further studies in the areas of the mechanism and pathogenesis of peptic ulcer pain, and abdominal pain, which are likely to result in better strategies to manage and prevent this important clinical condition.

Declaration

For a thesis that does not contain work already in the public domain

I certify that 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 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. In addition, I certify that no part of this work will, in the future, be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Montri Gururatsakul

September 2013

DEDICATION

I dedicate this thesis to my dearest parents, Pramote and Harmitpal Kaur Gururatsakul.

To my dearest wife, Navarat Sachayansrisakul, without whom this would not have been undertaken. I am forever grateful for your unconditional love and support.

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PUBLICATIONS ARISING FROM THE THESIS

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