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ORIGINAL PAPER

Gastric Emptying is Altered with the Presence of Gastritis

Erin L. Symonds Æ Cuong D. Tran Æ
Ross N. Butler Æ Taher I. Omari

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Abstract *Helicobacter pylori* infection and gastritis can cause symptoms suggestive of altered gastrointestinal function; however, it is unclear if *H. pylori* inßuences gastric motility. This study assessed gastric emptying rates in mouse models of gastritis. Gastritis was induced in C57BL/6 mice via ethanol treatment or via challenge with *H. pylori* or *H. felis*. Gastric emptying rates of nutrient and non-nutrient liquids were assessed with the non-invasive ^{13}C-breath test, and the results were compared to healthy mice. Gastric emptying of the non-nutrient liquid was unaltered with the presence of gastritis; however, gastric emptying of the nutrient liquid was accelerated after a 4-week infection with *H. pylori*. *H. felis* infection and ethanol treatment caused a more severe gastritis and disruptions to the normal gastric emptying. Changes to gastric emptying in mouse models of gastritis are associated with the presence of nutrients. Altered gastric emptying may contribute to symptoms commonly reported in humans with gastritis.

Keywords Gastritis · Gastric emptying · *Helicobacter pylori* · ^{13}C octanoic acid breath test

E. L. Symonds (✉) · C. D. Tran · R. N. Butler · T. I. Omari
Gastroenterology Unit, Children, Youth and WomenÕs Health Service, 72 King William Road, North Adelaide 5006, South Australia
e-mail: erinsymonds@yahoo.com

R. N. Butler · T. I. Omari
Department of Paediatrics, The University of Adelaide, Adelaide, South Australia

Introduction

Helicobacter pylori (*H. pylori*) infection is one of the most common bacterial infections worldwide, and it is associated with a variety of gastrointestinal problems, including gastritis, peptic and duodenal ulcer, gastric cancer, altered hormone and acid secretion, reduced gastric accommodation [1], and antral hypomotility [2]. As well as being caused by *H. pylori* infection, gastritis can be induced by drugs, such as non-steroidal anti-inßammatory agents and alcohol. Inßammatory reactions can cause various clinical manifestations frequently associated with abnormalities of the gastrointestinal tract, such as nausea, vomiting, or diarrhoea. Many of these gastrointestinal disturbances and symptoms of stomach pain, nausea and bloating, which are common with *H. pylori* infection and gastritis, suggest that there may also be an association with altered gastric emptying. Gastric emptying rates in patients with *H. pylori* induced gastritis has been previously investigated [3Ð9], but the Þndings were contradictory. Thus, there are no deÞnite conclusions as to whether *H. pylori* is able to inßuence the motility of the upper gastrointestinal tract. Delayed gastric emptying may contribute to the commonly reported symptoms of nausea, early satiety and bloating, whereas an accelerated gastric emptying may be a contributing factor to the formation of duodenal ulcers due to exposure of the duodenum to gastric acid. It is, therefore, important to identify any gastric emptying abnormalities. The aim of this study was to determine if the gastritis due to *H. pylori* infection, *H. felis* infection or alcohol affects gastric emptying rates in the mouse.

Methods

The gastric emptying rates of nutrient and non-nutrient liquid meals were assessed in mouse models of gastritis that were induced by: [1] *H. pylori* infection, [2] *H. felis* infection, and [3] treatment with ethanol. All mice were female C57BL/6 aged >6 week. All experiments were approved by the Animal Ethics Committee of the Children, Youth and Women's Health Service (North Adelaide, South Australia).

Breath tests were used to assess gastric emptying rates, which we have previously shown in mice to be reproducible and sensitive [10, 11]. After a 15 h overnight fast (required to empty the stomach prior to the test) mice are placed into the breath testing chamber and the breath test does not proceed until the mice are settled (within 5 min). Following this a baseline breath sample was taken, followed by the administration of the test meal. The meals were the following: (a) a non-nutrient liquid meal consisting of 100 μl of water containing 2% hydroxypropyl methyl cellulose (15000cp, Aldrich, Milwaukee, WI, USA) and 1 μl/ml ^{13}C-acetic acid (99% enrichment, Cambridge Isotope Laboratories, Andover, MA, USA), and (b) a nutrient liquid meal consisting of 100 μl of 20% Intralipid (Kabi Pharmacia AB, Stockholm, Sweden) and 1 μl/ml ^{13}C-octanoic acid (99% enrichment, Cambridge Isotope Laboratories, Andover, MA, USA). After the liquid meal was gavaged to the mice, breath samples were collected at 2.5 min intervals up to 10 min, followed by collection at 5 min intervals until 30 min, and then collection at 15 min intervals until 120 min. To collect breath samples, mice were placed in individual breath collection chambers with a continual flow of air as described previously [10]. In order to obtain a breath sample the airflow through the chamber was stopped for 120 s to allow CO_2 levels to accumulate to >1%. At the end of the breath accumulation period, 10 ml of breath was syringed out of the chamber and the airflow was restored. Breath samples were injected into evacuated 10 ml Exetainer tubes (Labco Limited, High Wycombe, England) for later analysis. Each mouse was maintained in the chamber for the total sampling period. Body weight was assessed at the completion of the breath test.

H. pylori induced gastritis

Mice were inoculated with *H. pylori* (Sydney strain 1) via a single orogastric gavage of 100 μl of a *H. pylori* suspension of $1 \cdot 10^9$ cfu/ml (using McFarland turbidity standards). Gastric emptying rates of the non-nutrient liquid and the nutrient liquid were assessed in mice at 4 week ($n = 10$) and at 7 week ($n = 10$) post-infection. The tests were performed on separate days. The gastric emptying rates from the infected mice were compared to age-matched non-infected mice ($n = 10$). After the breath test, mice were sacrificed by CO_2 asphyxiation and followed by cervical dislocation and the stomachs were excised for histology.

H. felis induced gastritis

Mice ($n = 20$) were inoculated with *H. felis* via a single orogastric gavage of 100 μl of a *H. felis* suspension of $1 \cdot 10^9$ cfu/ml (using McFarland turbidity standards). Following 8 week of infection, gastric emptying rates of both the non-nutrient and nutrient liquids were determined in infected mice and age-matched non-infected mice as described above. After the breath test, mice were sacrificed by CO_2 asphyxiation and followed by cervical dislocation and the stomachs were excised for histology.

Ethanol induced gastritis

Healthy mice ($n = 7$) were gavaged with 100% ethanol (100 μl) to induce gastritis. Gastric emptying rate of the nutrient liquid was determined before and 24 h after gastritis was induced so that there were three days between the breath tests being performed. Only the emptying of the nutrient liquid was assessed due to the results obtained with the *H. felis* infected mice. After the final breath test, the mice were sacrificed by CO_2 asphyxiation and followed by cervical dislocation and the stomachs and duodenums were removed for histology.

Histology

The stomachs were cut along the greater curvature and then washed in saline. Half of the stomach was retained for histology. The duodenum was removed from the small intestine at the ligament of Treitz. The tissues were fixed in 10% formalin for 24 h and embedded in paraffin wax. Gastritis was assessed by using a modified Sydney grading system for gastritis [12]. Briefly, paraffin-embedded tissues were cut at a thickness of 4 μm and stained with haematoxylin and eosin. Severity of damage was assessed blindly by an impartial observer in the body, transitional zone and antrum regions of the stomach, and in the duodenum. Gastritis was assessed in the lamina propria (superficial and basal layer), submucosa, muscularis propria and serosa of each region of the stomach for both acute and chronic inflammatory cells. The inflammatory cells were graded as 0 for none, 1 for occasional, 2 for multi-focal, 3 for discontinuous band and 4 for continuous band. The duodenal

segments were scored from 0 to 3 for histological features such that the maximum severity score indicated the most damage [13]. Features examined of the duodenal mucosa included villus fusion and stunting, enterocyte disruption, reduction in goblet cell numbers, reduction in mitotic figures, crypt and crypt cell disruption, crypt abscess formation, lymphocyte and neutrophil infiltration, and capillary and lymphatic dilatation, whereas the submucosa and muscularis were examined for thickening.

Data analysis

Breath $^{13}CO_2$ content was determined by isotope ratio mass spectrometry (Europa Scientific, Crewe, England) and the measured $^{13}CO_2$ recovery was expressed as percentage excretion per hour of the given ^{13}C dose. The CO_2 production rate of the mice was assumed to be 40 ml/kg/min based upon normal values for resting metabolic parameters measured in C57BL/6 mice [14]. The $^{13}CO_2$ excretion data were analysed by non-linear regression analysis for curve fitting and for calculation of the gastric emptying parameters of gastric half excretion time ($t_{1/2}$) [15].

Gastric emptying data are expressed as mean ± SE as they displayed a normal distribution (Kolmogorov–Smirnov test). Unpaired Student's t-tests were used to compare data between control and *H. felis* mice, a paired Student's t-test was used to analyse gastric emptying rates before and after ethanol treatment, and one-way ANOVA with a Tukey post hoc test was used to compare gastric emptying rates at different infection duration. Mann–Whitney rank sum tests were used to compare gastritis scores between the groups as these data were non-parametrically distributed. $P < 0.05$ was considered significant.

Results

H. pylori induced gastritis

The presence of *H. pylori* infection at 4 week and 7 week post-infection resulted in a mild gastritis which did not significantly change over time (data not shown, $P > 0.05$), whereas non-infected control mice had no gastritis. There were also no apparent morphological changes to the duodenum of the infected mice. Gastric emptying of the non-nutrient liquid was not significantly different to control mice at 4 week or 7 week post-infection ($P > 0.05$, Table 1). The gastric emptying following the nutrient solution was significantly accelerated after 4 week of infection ($P < 0.05$), but there were no differences at 7 week post-infection compared to controls (Table 1)

Table 1 Gastric half excretion time in *H. pylori* infected mice

	$t_{1/2}$ 4 week infection (min)	$t_{1/2}$ 7 week infection (min)
Non-nutrient		
Control (n = 10)	19.60 ± 1.11	19.85 ± 1.83
H. pylori (n = 10)	23.06 ± 2.01	20.37 ± 1.70
Nutrient		
Control (n = 10)	29.91 ± 1.51	36.24 ± 3.85
H. pylori (n = 10)	22.44 ± 1.65*	33.97 ± 2.62

Gastric half excretion time ($t_{1/2}$) of the non-nutrient liquid and the nutrient liquid after 4 week and 7 week *H. pylori* infection compared to non-infected control mice. Data are mean ± SE. * $P < 0.05$ compared to control

H. felis induced gastritis

Infection with *H. felis* resulted in a moderate gastritis (data not shown) with no damage to the duodenum. There were no significant differences between the gastric emptying of the non-nutrient liquid of the control mice and the *H. felis* infected mice (Table 2). Following the nutrient liquid, the gastric emptying curves obtained from the infected mice were divided into two obvious groups: one group that consisted of a 'typical' gastric emptying curve shape (n = 12), and the other group consisting of curves with double peaks (n = 8, Fig. 1). Gastric emptying curves usually consist of one peak and can be fitted by a curve which has a correlation of $r > 0.95$ with the measured values. The presence of a double peak was characterised by: (1) a correlation of $r < 0.95$ between the fitted curve and the measured values, and (2) a time interval of at least 20 min between the two peaks [16]. In *H. felis* infected mice 40% of the gastric emptying curves were found to consist of two distinct peaks. The first peak occurred at 4.06 ± 0.46 min and the second peak occurred at

Table 2 Gastric half excretion time in *H. felis* infected mice

	$t_{1/2}$ (min)
Non-nutrient	
Control (n = 10)	19.85 ± 1.83
H. felis infected (n = 20)	19.36 ± 1.51
Nutrient	
Control (n = 10)	36.24 ± 3.85
H. felis infected (n = 12)	26.91 ± 3.01

Gastric half excretion time ($t_{1/2}$) of the non-nutrient liquid and the nutrient liquid after 8 week *H. felis* infection compared to non-infected control mice. Data are mean ± SE.

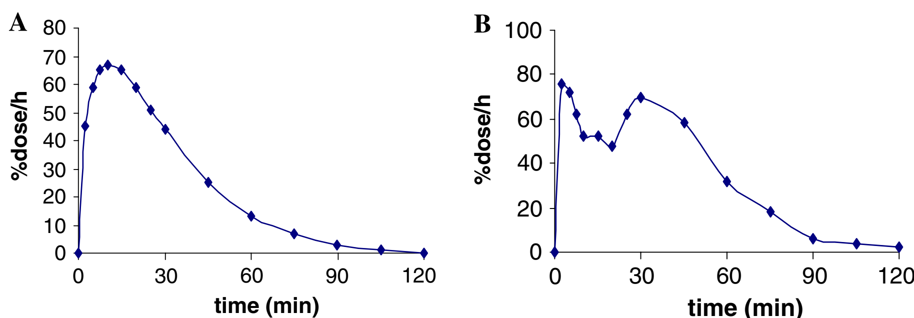

Fig. 1 Examples of the typical gastric emptying curve containing only one peak (A) and the double peaked gastric emptying curve (B) that was observed in 40% of *H. felis* infected mice and 43% of ethanol treated mice after ingestion of the nutrient liquid

44.38 ± 5.21 min. These peaks occurred at significantly earlier and later times, respectively, compared to the time at which the control gastric emptying curve peaked (10.45 ± 1.29 min, $P < 0.001$). There were no significant differences between the gastric emptying of the single-peaked curves compared to control mice following ingestion of the nutrient test meal (Table 2). There were also no significant differences between the median gastritis scores of the *H. felis* infected mice with abnormal gastric emptying curves compared to those with normal gastric emptying ($P > 0.05$).

Ethanol induced gastritis

Ethanol treatment resulted in a mild gastritis with no significant damage to the duodenum. Following the nutrient solution, 43% of the gastric emptying curves for the ethanol treated mice consisted of double-peaks, whereas all of the gastric emptying curves prior to ethanol treatment consisted of only one peak. The gastric emptying parameters of the single peaked curves were not significantly different compared to before ethanol treatment (Table 3). Dividing the ethanol treated mice into groups of normal gastric emptying (single peaked curves) and abnormal gastric emptying (double peaked curves) and comparing the median gastritis scores of the different regions showed no significant differences ($P > 0.05$).

Discussion

This study has shown that gastric emptying of a nutrient solution is altered with the presence of gastritis. *H. pylori* infection was found to accelerate the gastric emptying of the nutrient liquid compared to non-infected mice, but this was only observed in the initial weeks of infection. Infection with *H. felis* and treatment with ethanol resulted in approximately 40% of the mice displaying double peaked $^{13}CO_2$ excretion curves that may be indicative of an abnormality to gastric emptying. The altered $^{13}CO_2$ excretion curves only occurred following the nutrient containing liquid.

Many of the gastrointestinal disturbances which are common with *H. pylori* infection include stomach pain, nausea and bloating, which suggests that there may be altered gastric emptying resulting in these symptoms; however, it is not known if *H. pylori* is able to influence gastrointestinal motility. Previous investigations have reported delayed [7, 8], unaltered [3, 5, 9], and accelerated [4, 6] gastric emptying in *H. pylori* positive patients when compared to non-infected controls. These varying results may be due to different meal composition, unsuitable control subjects and small groups of subjects. Physiological studies of infected patients are difficult due to the large interindividual variation, which may lead to problems with interpretation of results since the symptoms between patients will differ as will the duration of infection (time of acquisition of *H. pylori* is usually unknown). Varying gastric emptying results may also be due to different measuring techniques used. Breath tests using stable isotopes have been recently developed to assess gastrointestinal function and motility. The ^{13}C breath tests that are now used to assess gastric emptying rates can replace the arduous or invasive nature of other measuring techniques. An additional advantage of assessment of gastric emptying with the breath test is that the results show the dynamics of flow since they are expressed as a rate curve. The ‘‘gold standard’’ gastric emptying measuring technique of radioscintigraphy and many other techniques express the results only as the percentage of the initial amount of test meal still remaining in the stomach and therefore represents cumulative data and not the dynamics of flow. This therefore does not allow any conclusions regarding the rate or pattern of gastric emptying. Gastric emptying rates that we have measured have been showing

Table 3 Gastric half excretion time following ethanol treatment

	$t_{1/2}$ (min)
Control ($n = 7$)	28.01 ± 2.84
Ethanol treated ($n = 4$)	35.74 ± 2.53

Gastric half excretion time ($t_{1/2}$) of the nutrient solution before and after treatment with ethanol. Data are mean ± SE

altered patterns of gastric emptying that with any other technique would not have been detected.

H. pylori infection in the mouse model accelerated gastric emptying of the nutrient liquid but only in the initial stage of infection. Since the majority of studies have been performed in humans that have an unknown duration of *H. pylori* infection, these studies are unable to investigate what physiological changes occur in the early stages of infection. One study, however, suggested that during the initial stages of gastritis there is a temporary suppression of gastric acid secretion which appears to facilitate colonisation of *H. pylori* organisms in the stomach [17]. It has also been shown that in the early stages of infection in animals, the number of bacteria will decrease by the eleventh week [18], which suggests that other inßammatory changes may also be occurring in the initial stages of infection. Gastrointestinal hormone levels, such as CCK, somatostatin and gastrin, are altered with the presence of gastritis [3, 4, 6, 19, 20]. CCK is a hormone which is released by fat in the intestine that causes inhibition of gastric secretion and emptying [21]. A previous study found that liquid gastric emptying was accelerated, prompting the authors to speculate that it was due to impaired action of CCK [6]. It has also been shown that the type A CCK-receptor antagonist accelerates the gastric emptying of Intralipid and eliminates its inhibitory effect [22]. This may explain why gastric emptying was accelerated only for the nutrient-containing liquid in the current study. The impaired action of CCK may only occur during the initial stages of *H. pylori* infection. This should be investigated in future studies by measuring circulating CCK levels, or its expression in the tissue, at different stages of *Helicobacter* infection.

H. felis is a close relative of *H. pylori* and will colonise the stomach of mice, which provides a convenient small animal model. Long-term infection of mice with *H. felis* results in the development of low-grade B-cell gastric lymphomas indistinguishable to those found in *H. pylori* infected humans [23]. Infection with *H. felis* in mice results in a gastritis that is possibly the best animal model in which to study human gastritis, but gastric emptying rates have not been previously assessed in this mouse model. After 8 week of *H. felis* infection, the mice had a moderate severity of gastritis and abnormal $^{13}CO_2$ excretion curves following ingestion of the nutrient liquid in 40% of the mice. The difference of these results to the *H. pylori* results may be due to the strains of bacteria having different characteristics or causing varied topographic distribution and severity of gastritis.

Ethanol treatment also caused abnormal nutrient gastric emptying curves, which did not occur prior to treatment. The mechanism for these results observed for both the *H. felis* and ethanol treated mice would, therefore, be related to inßammatory changes, rather than a substance secreted from the bacteria or an action of the bacteria such as metabolism of the ^{13}C-octanoic acid in the stomach. The abnormal gastric emptying curves may be due to alterations in gastric acid secretion, receptive relaxation, or pyloric function. A previous study found similar results such that the emptying of liquids was not quantitatively different from controls but it was faster within the Þrst 30 min [24]. The mechanism for this was thought to be disturbed sensitivity of duodenal receptors, but this may not be the mechanism for the results of the current study, since no apparent morphological changes to the duodenum were found.

The initially rapid gastric emptying that caused the Þrst peak of the $^{13}CO_2$ excretion curve may be due to a pyloric dysfunction, allowing the liquid to empty faster than normal, or an altered function of the proximal stomach. Gastritis patients have reduced receptive relaxation and accommodation [1], which may increase intragastric pressure following a meal and accelerate emptying [25]. Once the meal is in the duodenum, the duodenal receptors will be activated, creating the negative feedback to slow the emptying of the rest of the meal, causing the second section of the $^{13}CO_2$ excretion curve.

The reason that abnormal gastric emptying did not occur in all of the *H. felis* and ethanol treated mice is unknown, but may be due to pathologic differences between the mice. It is unlikely that it is related to gastritis severity, because comparison of gastritis scores between the mice with and without abnormal gastric emptying showed no differences. It is also unlikely that the abnormal gastric emptying is due to morphological changes to the small intestine because it has been previously reported that the bacteria does not reside here [26], and no apparent histological changes in the small intestine were found.

In conclusion, these studies have shown that the changes to gastric emptying in gastritis mouse models are associated with the presence of nutrients, whether it is the initial infection with *H. pylori* causing an acceleration to gastric emptying, or the double-peaked gastric emptying curves observed with *H. felis* infection or ethanol treatment. The current study only assessed gastric emptying of liquid meals, but it will be important to measure emptying of solid meals in future studies. If accelerated gastric emptying is found to occur in humans with gastritis, this may be important in the pathogenesis of duodenal ulcers through exposure of the duodenum to gastric acid. *H. pylori* infection is associated with over 90% of duodenal ulcer but the mechanism responsible for ulcer formation is unclear [6]. Altered gastric emptying may also contribute to the other gastrointestinal symptoms commonly reported in humans with gastritis. Abnormalities to gastric emptying should be taken into account when designing trials and may lead to more effective therapeutic strategies.

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