Lithium fluxes across the gastric mucosa after truncal vagotomy and drainage – an objective assessment of mucosal injury

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SUMMARY Gastric mucosal permeability to lithium has been measured in 20 patients with an untreated duodenal ulcer, eight patients who were asymptomatic for more than one year after truncal vagotomy and drainage, 14 patients with an endoscopically proven recurrent ulcer, and 21 patients with an unsatisfactory result from truncal vagotomy and drainage for other reasons. Lithium fluxes were lowest in the asymptomatic postoperative patients (0.149 ± 0.028 mmol Li^+ /15 min), but were not significantly different to the measured fluxes in patients with a duodenal ulcer before treatment (0.160 ± 0.020 mmol Li^+ /15 min) or a recurrent ulcer after truncal vagotomy and drainage (0.169 ± 0.022 mmol Li^+ /15 min) (SEM). By comparison the mean lithium flux in patients who were dissatisfied with the results of their previous surgery for reasons other than a recurrent ulcer (0.234 ± 0.019 mmol Li^+ /15 min) was significantly higher than that observed in patients with a duodenal ulcer ($p < 0.05$), patients with a recurrent ulcer ($p < 0.05$) or patients who were asymptomatic after definitive ulcer surgery ($p < 0.02$). Furthermore, when the lithium fluxes observed in 11 patients whose major postoperative complaint was bile vomiting (0.243 ± 0.027 mmol Li^+ /15 min) were compared with results from the remaining 52 patients included in the study (0.173 ± 0.012 mmol Li^+ /15 min) fluxes were significantly higher in the 'bile vomiters' ($p < 0.05$).

Significant bile vomiting occurs in 3–11% of patients who have undergone truncal vagotomy and a drainage procedure^{1,2} and is one of the major symptoms of postoperative reflux gastritis. No correlation exists between the presence, severity and type of histological changes in the gastric mucosa and postoperative symptoms,^{3,4} however, and thus the selection of patients for revisional gastric surgery cannot be made on the basis of such changes.

Many workers have shown that the presence of bile acids, together with acid will disrupt the gastric mucosal barrier to the back diffusion of hydrogen ions.^{5–8} Thus it might be postulated that such a technique would provide a quantitative assessment of gastric mucosal injury by bile acids in patients after ulcer surgery. Unfortunately, after any opera-

tion in which the pylorus has been removed, bypassed, or rendered incompetent, enterogastric reflux of unknown quantities of duodenal or jejunal juice that is rich in bicarbonate ions occurs and makes accurate measurement of H^+ back diffusion impossible. In this study the problem of enterogastric reflux has been overcome by using lithium as a probe of gastric mucosal permeability which Chung *et al*⁹ have shown to accurately reflect hydrogen ion fluxes across gastric mucosa. Furthermore, the calculation of lithium fluxes are not influenced by gastric secretion.

Lithium fluxes have been measured in patients with a duodenal ulcer before treatment and in patients who were asymptomatic, patients with a recurrent ulcer and patients with an unsatisfactory result from truncal vagotomy and drainage for other reasons, in an attempt to assess alterations in gastric mucosal permeability after ulcer surgery and to relate such changes to the clinical result of operation. Furthermore, in order to try and elucidate the

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pathophysiology of alterations in gastric mucosal permeability basal bile acid reflux, gastric acid secretion and gastric emptying of a liquid test meal have also been assessed.

Methods

PATIENTS

Sixty three patients were included in the study. Of these, 20 patients had an endoscopically proven duodenal ulcer and were investigated before either medical or surgical therapy. Eight asymptomatic patients were investigated 13–123 months (mean 77.1 months) after truncal vagotomy and drainage and a further 14 patients with an endoscopically proven recurrent ulcer were investigated 12–168 months (mean 72.7 months) after surgery. The main study group comprised 21 patients with an unsatisfactory result from truncal vagotomy and a drainage procedure for reasons other than recurrent ulceration. The major symptoms in this latter group of patients are shown in Table 1. The age and sex distribution, together with the nature of previous gastric surgery in the three postoperative groups of patients is shown in Table 2.

Patients with a benign gastric ulcer were excluded from the study because such patients are said to have enhanced gastric mucosal permeability.^{10 11}

ACID SECRETORY STUDIES

Basal (BAO) and maximal (MAO) acid outputs in response to pentagastrin were measured in all patients. Pentagastrin was administered by intramuscular injection at a dose of 6 µg/kg body weight in patients investigated before vagotomy and at a dose of 10 µg/kg body weight in patients assessed after surgery. An insulin test was also carried out in postvagotomy patients (0.15 U soluble insulin/kg body weight, iv).

BILE ACID REFLUX

Enterogastric bile reflux was assessed by measuring the bile acid content of a one hour basal collection of

Table 1 Symptoms of 21 patients with an unsatisfactory result from truncal vagotomy and drainage for reasons other than a recurrent ulcer

	n	%
Bile vomiting	11	52
Abdominal pain	17	81
Early dumping	6	29
Vomiting	3	14
Diarrhoea	5	24
Gastro-oesophageal reflux	3	14

Table 2 Age, sex and previous surgery of duodenal ulcer patients

No	Age	M:F	TV & P	TV & PGJ
DU 20	39.2 (19–73)	17:3	—	—
Asym 8	44.4 (28–65)	7:1	4	4
RU 14	50.5 (27–77)	12:2	10	4
NRU 21	48.3 (23–74)	17:4	7	14

gastric juice. Assays were done using a steroid dehydrogenase technique.¹²

GASTRIC EMPTYING

Gastric emptying of a 500 ml test meal of 5% glucose was measured by the double sampling dye dilution technique. Three parameters of gastric emptying were calculated, namely the starting index, half-life ($T_{1/2}$) and total emptying time of the meal.¹³

BACK DIFFUSION OF LITHIUM

Lithium fluxes across the gastric mucosa were measured by the method described by Chung.⁹ The test solution contained LiCl 5 mmol, NaCl 150 mmol and 0.1% PEG 4000 as a non-absorbable marker. Lithium fluxes were estimated over two 15 minute periods and the mean flux for each patient calculated.

STATISTICAL METHODS

The Wilcoxon's rank sum test for unpaired data was used for all statistical analyses.

Results

ACID SECRETORY STUDIES

The results of the acid studies are summarised in Table 3. Both basal acid output and maximal acid output were significantly higher in patients with an untreated duodenal ulcer than in any of the post-operative groups of patients ($p < 0.01$). Of the patients investigated after truncal vagotomy and drainage, acid output was greatest in patients with a recurrent ulcer whilst acid secretion in asymptomatic postoperative patients was similar to that in patients with an unsatisfactory result from ulcer surgery for reasons other than a recurrent ulcer.

BILE ACID REFLUX

Mean basal bile acid reflux in untreated duodenal ulcer patients was 6 ± 3 µmol/h (SEM). This was

Table 3 Gastric acid secretion in four groups of duodenal ulcer patients before and after vagotomy (mmol/h $\pm$ SEM)

No	BAO	MAO	PAO _i
Duodenal ulcer pre-op 20	6.5 $\pm$ 0.9	34.9 $\pm$ 1.9	—
Asymptomatic post-op 8	1.7 $\pm$ 0.8	14.1 $\pm$ 2.9	4.0 $\pm$ 1.5
Recurrent ulcer post-op 14	6.0 $\pm$ 1.4	24.3 $\pm$ 2.6	16.5 $\pm$ 3.9
Unsatisfactory post-op, no ulcer 21	2.3 $\pm$ 0.7	10.8 $\pm$ 2.0	3.4 $\pm$ 1.3

significantly less than that measured in patients who were asymptomatic after surgery (254 $\pm$ 99 μ mol/h; $p<0.02$, patients with a recurrent ulcer (186 $\pm$ 127 μ mol/h; $p<0.05$) and patients with an unsatisfactory result from previous surgery (327 $\pm$ 108 μ mol/h; $p<0.01$). The differences in bile acid reflux between the three groups of patients investigated after surgery were not significant. Similarly there was no significant difference in basal bile reflux between patients whose major complaint was bile vomiting (492 $\pm$ 178 μ mol/h) and all other patients investigated after truncal vagotomy and a drainage procedure (190 $\pm$ 62 μ mol/h).

GASTRIC EMPTYING

The results of the gastric emptying studies are summarised in Table 4. There were no significant differences in any of the parameters of gastric emptying between any of the postoperative groups of patients. Not surprisingly all three groups of patients investigated after surgery emptied the test meal more rapidly than patients with an untreated duodenal ulcer.

BACK DIFFUSION OF LITHIUM

The mean lithium flux in patients with an unsatisfactory result from truncal vagotomy and drainage for

Table 4 Gastric emptying times of a 5% glucose test meal in four groups of DU patients, before or after surgery (min $\pm$ SEM)

	Starting index	Half-life	Emptying time
Duodenal ulcer pre-op 18	4.7 $\pm$ 4.3	22.2 $\pm$ 2.9	106.4 $\pm$ 9.4
Asymptomatic post-op 6	-9.0 $\pm$ 9.8	5.8 $\pm$ 8.0	75.0 $\pm$ 12.4
Recurrent ulcer post-op 10	-16.0 $\pm$ 9.3	2.6 $\pm$ 8.6	88.5 $\pm$ 18.3
Unsatisfactory post-op, no ulcer 18	-13.0 $\pm$ 5.5	1.3 $\pm$ 4.2	55.3 $\pm$ 10.2

reasons other than a recurrent ulcer was 0.234 $\pm$ 0.019 mmol/15 min (SEM). This loss was significantly greater than that in patients with an untreated duodenal ulcer (Li⁺ flux 0.160 $\pm$ 0.020 mmol/15 min; $p<0.05$), patients with a recurrent ulcer (Li⁺ flux 0.169 $\pm$ 0.022 mmol/15 min; $p<0.05$) and patients who were asymptomatic after definitive ulcer surgery (Li⁺ flux 0.149 $\pm$ 0.028 mmol/15 min; $p<0.02$). Furthermore, when the results of the lithium back diffusion studies in patients whose major complaint was bile vomiting (Li⁺ flux 0.243 $\pm$ 0.027 mmol/15 min) were compared with the results obtained from all other patients investigated after truncal vagotomy and a drainage procedure (Li⁺ flux 0.173 $\pm$ 0.012 mmol/15 min), lithium fluxes were significantly higher in the 'bile vomiters' ($p<0.05$). These results are summarised in the Figure.

Because lithium fluxes appeared to be greatest in patients with a clinical diagnosis of reflux gastritis, attempts were made to correlate these measurements with the results of the bile acid reflux studies.

Calculation of the correlation coefficient from the linear regression of lithium flux and basal bile acid reflux, however, failed to produce a significant result. In contrast, a significant negative correlation was shown between the total emptying time of the

Figure Lithium fluxes in duodenal ulcer patients before and after surgery.

glucose test meal and lithium fluxes in 48 patients in whom gastric emptying was assessed ($n=48$, $r=-0.36$, $p<0.05$).

Discussion

The quantitative assessment of gastric mucosal injury after operations in which the pylorus has been destroyed or bypassed has long been the focus of surgical interest. Microscopic changes in the gastric mucosa can be detected in almost all patients who have undergone such surgery although these bear no relationship to the development of postoperative symptoms.^{3,4} Similarly the measurement of intra-gastric bilirubin¹⁴ and sodium concentrations,⁶ or bromosulphthalein¹⁵ and indocyanine green¹⁶ in gastric juice after excretion in the bile have proved unreliable indicators of enterogastric reflux.

More recently interest has focused on the measurement of bile acids and lysolecithin in fasting gastric aspirates.^{17,18} Hoare *et al*¹⁷ suggested that patients with a basal bile acid aspirate of $>120 \mu\text{mol/h}$ should be offered revisional gastric surgery as these levels of reflux were not found in patients who were asymptomatic after gastric surgery. It is therefore interesting to note that such levels of bile acid reflux occurred in five of eight asymptomatic patients in this study.

The technique of biliary excretion scintigraphy using technetium-labelled HIDA has recently been described as a method for assessing enterogastric reflux without nasogastric intubation.¹⁹ The validity of this technique in patients after truncal vagotomy and drainage, however, has not been assessed.

All these techniques can only provide an indirect assessment of gastric mucosal injury in patients with reflux gastritis after ulcer surgery and thus lithium has been used as a probe of gastric mucosal permeability to provide a direct measurement of mucosal damage in such patients.

Experimental studies have indicated that bile salts and lysolecithin exert a powerful and disruptive effect upon the gastric mucosal barrier^{5,9,20} resulting in so-called 'back diffusion' of hydrogen ions from the gastric lumen together with a concomitant influx of sodium ions. Similar changes in gastric mucosal permeability have also been shown in the intact human stomach after exposure to bile salts.^{6,21}

The measurement of hydrogen back diffusion across human gastric mucosa requires a number of elaborate calculations, based on certain assumptions as regards the composition of gastric juice in order to correct the measured hydrogen ion flux for gastric acid and bicarbonate secretion and gastric emptying. Furthermore, enterogastric reflux of un-

known quantities of pancreatic juice, which is rich in bicarbonate ions, introduces errors for which no allowance can be made in patients investigated after ulcer surgery. In view of these difficulties the measurement of lithium fluxes across the gastric mucosa has been undertaken. This technique has been described by Chung *et al*⁹ and Smith *et al*²² who reported a constant relationship between hydrogen ion fluxes and lithium back diffusion. Like hydrogen, lithium is a monovalent cation from the same group of the periodic table that can easily and accurately be measured at low concentrations. Furthermore, lithium is present in the tissues only in trace amounts and cannot be detected in normal gastric juice. Finally, gastric secretion and entero-gastric reflux of bicarbonate ions do not influence the measurement of lithium fluxes.

Despite these advantages of the lithium test some doubts have been raised about its validity as a marker for hydrogen ion back diffusion. Ivey *et al*²³ failed to confirm a significant loss of lithium ions from the gastric lumen of five healthy, human volunteers after exposure of the gastric lumen to sodium taurocholate at a concentration of 10 mmol/l , although such a finding could represent concomitant absorption of the non-absorbable marker ($^{51}\text{CrCl}_2$, mol wt 157.5) thus masking simultaneous back diffusion of lithium. Chadwick *et al*²⁴ have produced some evidence to support such a hypothesis showing significant absorption of molecules with a molecular weight of 550 after exposure of canine fundic pouches to sodium taurocholate.

Saik and Brown²⁵ also failed to confirm a significant loss of lithium from the canine gastric lumen after exposure to sodium taurocholate despite showing an increased flux of hydrogen ions. Rather surprisingly they failed to show the expected concomitant influx of sodium ions^{21,23} and it would seem quite possible that their failure to record a significant loss of lithium from the gastric lumen represented a failure to inflict sufficient injury to the gastric mucosa.

The results of this study have indicated that lithium fluxes were significantly higher in patients with an unsatisfactory result from surgery, but without a recurrent ulcer than fluxes in other groups of postoperative patients and that these changes in gastric mucosal permeability were greatest in patients with symptoms of bile vomiting.

On the basis of these results it might be expected that a correlation would exist between lithium fluxes and a quantitative assessment of bile reflux. Attempts to correlate basal bile acid reflux with lithium fluxes in any of the study groups, however, failed to show such a correlation. This presumably reflects the fact that changes in gastric mucosal

permeability after exposure to bile acids are also dependent upon the pH in the gastric lumen.^{8 26}

Experimental work has indicated that gastric emptying is quickest in animals with increased fasting or postprandial duodenogastric reflux after gastric surgery^{27 28} although a correlation between fasting bile reflux and total emptying times of the glucose meal in this study just failed to reach statistical significance ($n=30$, $r=0.34$, $p<0.1$, >0.05). It would seem, however, that there is a trend to suggest that fasting bile reflux is probably greatest in those patients with more rapid gastric emptying. Furthermore, there was a significant negative correlation between lithium fluxes and the total emptying times of the test meal in patients included in this study ($n=48$, $r=-0.36$, $p<0.05$) indicating that the more rapid the rate of gastric emptying, the greater the gastric mucosal permeability to lithium. These results presumably reflect the loss of a functioning sphincter between the stomach and duodenum or proximal jejunum in patients investigated after truncal vagotomy and drainage.

There are other reasons why the severity of fasting bile reflux may not reflect postoperative changes in gastric mucosal permeability. The importance of pancreatic and intestinal secretions, as well as gastric acid secretion, in the production of the histological changes of gastritis after surgery have already been stressed. Furthermore, the finding by some workers that the histological changes of gastritis may persist after revisional gastric surgery suggests that enterogastric reflux of duodenal or jejunal contents may not be the only factor in the production of these changes.^{17 29} It must be admitted, however, that this last point is somewhat contentious as Drapanas and Bethea³⁰ and Lygidakis³¹ have claimed that histology of the gastric mucosa returns to normal after Roux-en-Y conversion. It could also be postulated that lithium fluxes after surgery might correlate with acid secretion because reflux gastritis results in a diminution of the parietal cell mass and a reduction in gastric acid output.^{32 33} Thus, after ulcer surgery BAO and MAO should be lowest in those patients with the highest lithium fluxes. The time required for these changes to develop is variable, however, and thus it was not possible to show such a correlation.

In conclusion, this study has shown that gastric mucosal permeability to lithium is significantly increased in patients with an unsatisfactory result from truncal vagotomy and drainage for reasons other than a recurrent ulcer and that these changes are greatest in patients with bile vomiting and symptoms of reflux gastritis. Conversely lithium fluxes were lowest in patients with either a recurrent

ulcer or in those patients who were asymptomatic following their previous surgery.

The results of this study undoubtedly reflect the complex nature of the pathogenesis of increased gastric mucosal permeability after ulcer surgery. The loss of a functioning sphincter between the stomach and duodenum or jejunum is clearly an important factor both in terms of alterations in the pattern of gastric emptying and enterogastric reflux of bile and pancreatic secretion.

Although this study has provided important evidence as to the pathogenesis of changes in gastric mucosal permeability in patients after ulcer surgery it seems unlikely that these measurements will prove of discriminatory value in selecting patients for revisional gastric surgery.

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