Acute toxic gastric mucosal damage induced by Lugol’s iodine spray during chroemoendoscopy

Lugol’s solution, named after the French Physician JGA Lugol (1786–1851), has a high affinity for glycogen in non-keratinised squamous epithelium. Since the 1960s when Lugol’s iodine was first used to investigate oesophageal diseases, advances in the field of diagnostic endoscopy have resulted in its increasing use to detect early mucosal abnormalities and to target biopsies from unstained areas. We have been performing chroemoendoscopy using Lugol’s solution for the last 10 years, carrying out 10–15 procedures every year. Here we report the first case of gastric mucosal damage induced by Lugol’s solution spray during diagnostic endoscopy.

Chromoendoscopy using Lugol’s solution is not without hazards. Local irritation of the oesophageal mucosa may cause retrosternal discomfort. General allergic reactions include laryngospasm, bronchospasm, and even cardiac arrest. The concentration of the solution used in studies ranges from 0.5% to 5%, and higher concentrations (3–5%) may be associated with a higher risk of complications. A Japanese study reported that washing the mucosa with sodium thiosulphate may neutralise the iodine solution and reduce retrosternal discomfort. Only two cases of gastric mucosal erosions have been reported after the application of iodine.

In this case, the histological features of localised oedema and loss of superficial gastric epithelium in the absence of significant inflammatory cell infiltrate supported an acute toxic injury to the gastric mucosa. The toxic reaction was confined to the columnar epithelium in the greater curve of the stomach that was in direct contact with the pooled 5% Lugol’s iodine while the squamous oesophageal mucosa remained unremarkable both endoscopically and histologically. Gastric columnar epithelium may be more susceptible to the toxic effect of Lugol’s iodine and mucosal injury may go unrecognized unless the stomach is re-examined after application of the dye. To reduce the risks, we now use 10–20 ml of 1.5% Lugol’s solution and routinely aspirate the gastric pool before assessing the oesophageal mucosa.

Previous studies have shown that Lugol’s staining is useful in screening for early oesophageal cancer in high risk populations such as patients with previous or current non-oesophageal malignancy and those with a high alcohol intake. However, none of these studies commented on the adverse reactions to Lugol’s staining during endoscopy. We suggest that the adverse reactions and safety profile of iodine staining need to be addressed, in particular before recommending its routine use for screening purposes. Also, where it has to be used, a lower concentration of 1.5% may be less toxic to the gastric mucosa and is thus recommended.

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References
It is well accepted that the pathophysiology of GORD is related to failure of antireflux mechanisms but several phenomena are not fully explained on the basis of this sequence. It is not known why the same amount of refluxate determines GORD in one patient and not in another. It is also unclear whether there is a relation between these unexplained questions and the possible influence of proliferative responses of epithelial proliferating cells to damage. Hence we evaluated cell proliferation of the oesophageal epithelium using Ki67 immunostaining in normal subjects and in patients with GORD, with or without erosions.

Patients gave written informed consent to participate in the study which was approved by the ethics committee. The design was blinded for epithelial cell kinetic evaluation. Thirty five subjects were enrolled: nine were healthy voluntary controls with normal pH testing and normal endoscopic, histological, and ultrastructural patterns. Twenty six patients were affected by GORD, defined as frequent heartburn for at least a year, and abnormal 24 hour pH, histological, and ultrastructural parameters. Of these 26 patients, 13 had a normal appearing oesophageal mucosa at endoscopy (NERD) while 13 had ERD (table 1).

All subjects underwent gastroscopy; six biopsies were obtained within the lower oesophageal mucosa (NERD) or one of its complications. It has been hypothesised to be one of the causes of the existence of an individual predisposition to stronger or weaker cell proliferative efficacy of epithelial mucosa to chronic insults. This concept supports the idea that in genetically susceptible individuals, chronic acid and pepsin exposure may trigger or accelerate the development of ERD while in others more efficient cell proliferation can repair the damage due to acid and pepsin insults. We believe that the second hypothesis is worth considering in future studies, also because cell replication of basal layers has been hypothesised to be one of the causes implicated in the resistance of the mucosa and in structural epithelial defence. To date, this concept has not been taken into account.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>NERD</th>
<th>ERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of subjects</td>
<td>9</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>4/5</td>
<td>4/9</td>
<td>7/6</td>
</tr>
<tr>
<td>Age [mean (SD)]</td>
<td>38.67 (17.36)</td>
<td>41.62 (11.77)</td>
<td>42.54 (13.33)</td>
</tr>
<tr>
<td>% Time oesophageal pH &lt;4</td>
<td>5.42 (1.1)</td>
<td>9.1 (2.3)</td>
<td>10.4 (1.9)</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>Normal</td>
<td>A</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>0</td>
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<td></td>
<td>C</td>
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<tr>
<td></td>
<td>D</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Histology</td>
<td>Normal</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>0</td>
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</tr>
<tr>
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<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>TEM value [mean (SD)]</td>
<td>0.54 (0.08)</td>
<td>2.24 (0.53)</td>
<td>2.39 (0.44)</td>
</tr>
</tbody>
</table>

TEM, transmission electron microscopy.

References


Role of IL-10 promoter haplotypes in Helicobacter pylori associated gastric inflammation

We read with great interest the article by Rad et al (Gut 2004;53:1082–9) on the influence of cytokine gene polymorphisms on mucosal cytokine expression, gastric inflammation, and host specific colonisation in Helicobacter pylori infection. The authors reported an association of the proinflammatory interleukin 10 (IL-10) promoter haplotype (GCC) with higher mucosal mRNA levels and colonisation with more virulent cagA+, vacA S1+, and babA2+ strains in 207 patients with H pylori induced chronic gastritis. Rad et al identified pathogenicity genes of H pylori isolates by polymerase chain reaction based techniques from gastric biopsies. However, the human stomach is colonised by more than one strain of H pylori, which obscures the investigation of germline mutations and host specific colonisation. Moreover, within an apparently homogenous population, remarkable genetic differences exist among single colony isolates. The capacity of H pylori to lose and possibly acquire exogenous DNA is consistent with a model of continuous microevolution within its cognate host. Thus identification of bacterial virulence factors is directly dependent on localisation of the biopsies. This means that if cagA+, vacA S1+, and babA2+ were not detected in biopsy specimens, cocolonisation with strains harbouring these genes at another location cannot be excluded. Interestingly, the degree of inflammation and frequency of gastric atrophy and intestinal metaplasia was not different in patients carrying pro- or contrainflammatory haplotypes. The significance of genetic association studies is highly dependent on a well defined phenotypic contrast with the degree of granulocytic and lymphocytic infiltration in chronic gastritis, which may again vary regionally, the development of gastric ulcer is an unambiguous hallmark for the severity of H pylori induced mucosal damage.

We recruited 614 consecutive Caucasian patients from Northern Germany who underwent gastroscopy with confirmed H pylori infection by rapid urease test or histology. Endoscopic findings and results of histopathological examination of biopsies, classified according to the Sydney classification, were recorded. In total, 316 patients presented with chronic gastritis and served as controls and 124 patients suffered from gastric ulcer. DNA was extracted by standard techniques from 5 ml of EDTA blood. All patients were genotyped for IL-10 −1082, −819, and −592 by TaqMan technology. Samples were recoded and genotypes assigned without knowledge of clinical status. Single marker and haplotype analysis was conducted to assess associations with development of gastric ulcer.

There were no associations between any of the single nucleotide polymorphisms tested and H pylori related pathological findings (data not shown). The proinflammatory low secreting haplotype ATA did not confer a risk factor for the development of an ulcer and the contrainflammatory haplotype GCC did not protect patients from gastric ulcer (table 1). Our results are in agreement with the study of Hida et al who reported higher IL-10 mRNA expression in cagA+ H pylori gastritis, with no relation to endoscopic diagnosis. Therefore, we conclude that genetic variations in the IL-10 promoter may influence mucosal cytokine expression but pro- and contrainflammatory haplotypes do not influence the clinical course of gastric inflammation, at least in Northern Germany. Furthermore, we suggest that association studies of germline polymorphisms with the outcome of chronic H pylori infection should focus on clearly defined phenotypes such as ulcer disease, gastric carcinoma, or primary gastric B cell lymphoma.

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Table 1 Haplotype analysis of the interleukin 10 (IL-10) promoter in 440 patients with chronic gastritis and gastric ulcer disease

<table>
<thead>
<tr>
<th>IL-10 promoter</th>
<th>Chronic gastritis (n = 316)</th>
<th>Gastric ulcer (n = 124)</th>
<th>OR</th>
<th>p Value (χ²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>−1082 −819 −592</td>
<td>G C C</td>
<td>48.0%</td>
<td>48.3%</td>
<td>1.01</td>
</tr>
<tr>
<td></td>
<td>A T A</td>
<td>23.6%</td>
<td>24.2%</td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td>A C C</td>
<td>28.2%</td>
<td>27.5%</td>
<td>0.97</td>
</tr>
</tbody>
</table>

OR, odds ratio.

Gastric ulceration due to chronic mesenteric ischaemia treated by stenting of the inferior mesenteric artery

We report a case of gastric ulceration due to visceral ischaemia treated successfully by stenting of the inferior mesenteric artery (IMA) alone. Gastric ulceration has very rarely been described as a complication of visceral ischaemia.[1–3] Four of the five cases described in these reports were treated surgically and one by angioplasty to the superior mesenteric artery (SMA). All were reported to have successful resolution of gastric ulcers. To our knowledge, there is no other case of successful stenting of the IMA alone, with resolution of gastric ischaemia described in the medical literature.

Our patient was a 50 year old woman presenting with abdominal pain, loss of appetite, vomiting, and weight loss. Pain was maximal in the epigastrium and precipitated by meals. Apart from being a smoker there was no other significant medical history. She was empirically started on omeprazole. Oesophagastroduodenoscopy (OGD) revealed multiple serpiginous ulcers affecting the body of the stomach with extension to the cardia (fig 1D). Histology from the ulcers demonstrated ulceration with regenerative hyperplasia with no evidence of Helicobacter pylori infection. An abdominal computed tomography scan showed non-specific thickening of the pylorus and first part of the duodenum but was otherwise normal. A small bowel follow through revealed no abnormality. Fasting gut hormone levels, including gastrin level, after stopping omeprazole were normal and a vanillylmandelic acid (VMA) was negative.

Her abdominal pain was controlled by morphine 120 mg/day. A repeat OGD 10 weeks after treatment with omeprazole 40 mg once daily showed continuing ulceration with no improvement since the previous examination. Further histology showed similar findings as before.

Abdominal angiography demonstrated complete occlusion of the SMA origin (fig 1B), and tight ostial stenoses of the IMA (fig 1A) and coeliac axis. The SMA branches filled sluggishly and were reconstructed almost exclusively via the left colic branch of the IMA.

Attempts to bypass the coeliac axis stenosis and proximal SMA occlusion were
The mesenteric axis, even the IMA alone, can provide enough blood flow to treat the complications of chronic mesenteric vascular disease.

The awareness of hospital doctors about radiation exposure and associated cancer risk is poor. From personal experience, many gastroenterologists involved in diagnostic and therapeutic procedures using ionising radiation do not routinely wear full protective clothing (omental apron, lead gloves, lead trousers, and amitriptyline).

Her symptoms resolved completely and amitriptyline and warfarin were discontinued three months later. A repeat OGD showed complete healing of the ulcers. She was weaned off the omeprazole and aspirin was discharged on omeprazole, aspirin, warfarin, and amitriptyline.

The interest in this case lies in the fact that only the IMA needed to be stented to achieve an appropriate vascular supply to the stomach, despite severe occlusions and reduced flow in the coeliac and mesenteric axes. This has not been described before, and demonstrates that minimally invasive radiological stenting of only one territory of the mesenteric axis, even the IMA alone, can provide enough blood flow to treat the complications of chronic mesenteric vascular disease.

In the UK, diagnostic x-rays related cumulative risk of cancer to age 75 years was recently estimated at 0.6%, which is equivalent to approximately 700 cases of cancer per year. Adherence to these guidelines may well be an explanation for the comparatively low frequency of diagnostic x rays in UK practice.

Clinicians should use these recommendations when considering radiological investigations. Protection of operators and nursing staff using recommended protective clothing should also be followed. Change in clinical practice may not be easy to achieve as, for example, endoscopic capacity to reduce the number of alternative radiological investigations, such as barium enemas, is limited. In contrast, barium enemas are often used to reduce the demand on endoscopic services. New technologies and methods may well reduce radiation exposure. Examples in gastroenterology include magnetic resonance cholangiopancreatography or endoscopic ultrasound instead of ERCP and magnetic resonance enteroclysis instead of small bowel enema.

Technological advances, in particular low-dose helical CT scanners, may reduce radiation exposure by 40–70%. However, availability of these technologies is limited or only slowly increasing and it is therefore unlikely that their use will influence radiation exposure in the near future.

What remains is the judicious use of radiological investigations and close liaison with radiologists in order to keep the radiation exposure of patients and staff as low as possible.

References

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Adalimumab use in pregnancy

Infliximab, a chimeric antibody to tumour necrosis factor alpha (TNF-α), has demonstrated efficacy for the induction and maintenance of remission in patients with Crohn’s disease. Antibodies to the chimeric component of infliximab can lead to infusion reactions and possible loss of response. A human recombinant monoclonal antibody to TNF-α, adalimumab, has recently demonstrated safety and efficacy for induction of remission in Crohn’s disease. It has also been effective in patients who have lost response to infliximab. Currently, this drug is FDA approved for the treatment of rheumatoid arthritis but it is being administered off label for the treatment of Crohn’s disease and rheumatoid arthritis. Am J Gastroenterol 2004;99: 2385–92.


Can gastro-oesophageal reflux be predicted while advancing the endoscope through the laryngeal area?

We read with great interest the article by Mullhaupt et al regarding examination of the laryngopharyngeal area during upper gastrointestinal endoscopy, after being trained for examination of these anatomical structures (Gut 2004; 53: 1232–4). Twenty six laryngeal pathologies were discovered in 1311 cases, the most important of which was demonstration of an early supraglottic cancer.

Upper gastrointestinal endoscopy has been performed in children for various indications. In paediatric gastroenterology practice, endoscopy is an important procedure beginning from the mouth. After inserting the endoscope through the oral cavity, the uvula, epiglottis, and cricoarytenoid cartilages with the vocal cords above are seen. While passing through the epiglottic area, the concomitant laryngitis, oedema, hyperaemia or ulceration of the arytenoids, and laryngeal granulomas can be visualised. Examination of the laryngopharyngeal area is not a routine part of the endoscopic procedure in children.

Although supraglottic cancer is extremely rare among children, a more common problem of the laryngeal area during childhood is gastro-oesophageal reflux (GOR), which affects almost 10% of children. Recurrent upper or lower respiratory tract infections, and weight loss are frequent clinical findings with GOR. Extraoesophageal manifestations of GOR have been identified and recognised more recently in the past decade. The phrase “extraoesophageal reflux” refers to the effects of refluxed gastric material far from the oesophagus. It has been shown that the contents of the gastric juice, including hydrochloric acid and pepsin, are damaging not only to the oesophagus but also to pharyngeal and laryngeal tissues. Resistance of the laryngeal mucosa to refluxed gastric contents is due to the presence of the larynx, oedema, hyperaemia, or ulceration of the arytenoids, and laryngeal granulomas can be visualised. Examination of the laryngopharyngeal area is not a routine part of the endoscopic procedure in children.
CD40 antisense based strategy for inflammatory bowel disease: shutting down multiple cellular communication systems

We read with great interest the paper by Gao et al, where the authors elegantly proved the efficacy of a CD40 antisense oligonucleotide for the treatment of trinitrobenzene sulfonic acid (TNBS) induced colitis in rats (Gut 2005;54:70–7). Their results are in keeping with previous reports in which immune-blockade of CD40 ligand (L) was also able to ameliorate experimental colitis. The authors conclude that interruption of interactions between CD40 bearing monocytes and endothelial cells and CD40L positive T cells is crucial for the beneficial effect exerted by CD40 antisense oligonucleotide in TNBS induced experimental colitis.

In the past few years we have been investigating the role of the CD40/CD40L pathway in the pathogenesis of inflammatory bowel disease (IBD).1 We and others have recently shown that, apart from endothelial cells and monocytes, human intestinal fibroblasts (HIF) also express this immunological surface.1,2 HIF significantly upregulate CD40 expression, both at the mucosal and submucosal levels, in patients with active IBD. Moreover, we and others have shown that colchicine of CD40 expression inhibiting CD40L positive T cells induces fibroblast activation, leading to chemokine and cytokine production, cell adhesion molecule upregulation, and activation of the intracellular signalling machinery, by triggering MAP kinases and nuclear factor xB activation. All of these events are biologically relevant for the inflammatory process as fibroblast derived chemokines mediate T cell recruitment.3 Another intriguing observation was the demonstration that CD40L positive T cells modulate collagen synthesis by HIF, thus suggesting the potential involvement of the CD40/CD40L pathway in stenosis formation in Crohn’s disease (CD).4 Therefore, blockade of HIF CD40 is another potential mechanism of the therapeutic efficacy of CD40 antisense.

We have also shown that platelets express high levels of biologically active surface CD40 in a constitutive manner.5 This molecule provides a novel pathway for platelet activation, as shown by the observation of RANTES release after platelet stimulation.6 These events are particularly relevant at sites of intense immune activation where local inflamed endothelial cells retain RANTES on their surface and mediate T cell adhesion, thus locally amplifying the inflammatory response.7 Moreover, recent studies showed that the CD40/CD40L system also plays a critical role in mediating platelet adhesion to and activation of intestinal microvasculature or leukocytes.8

As far as the delivery of CD40L positive T cells could stimulate CD40 endothelium, and that CD40L antisense could prevent such cell interactions. Recently, we

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References
have described that apart from T cells, activated platelet also express CD40L. Platelets display enhanced levels of membrane bound CD40L in CD and ulcerative colitis patients, and secrete higher amounts of soluble CD40L, compared with healthy controls. Therefore, abrogation of endothelial or platelet CD40 expression would not only block T cell-endothelial interactions but also interrupt platelet-endothelial and platelet-leucocyte cell cross-talk in the gut microvasculature.

Taken together, these observations suggest that the CD40 antisense oligonucleotide used by Gao et al excerts its beneficial effect not only by disrupting the interaction between CD40 bearing monocytes and endothelial cells and CD40L positive T cells, but also by acting on a much wider array of cell types able to express either CD40 or CD40L. We conclude that the use of CD40 antisense oligonucleotides appears to be a very promising therapeutic approach to turn off intestinal inflammation, by disconnecting a crucial and almost ubiquitous communication system used by multiple cell types during inflammation.

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Conflict of interest: None declared.

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