Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse drug reaction reports to the Committee on Safety of Medicines

We were interested to read the report by Ransford and Langman of their analysis of yellow card reports of suspected adverse drug reactions for sulphasalazine and mesalazine (Gut 2002;51:536–9). These reports, submitted to the Committee on Safety of Medicines, may provide useful flags to signal unrecognised hazards of drugs. However, as adverse reactions are not always recognised or reported to the regulatory authorities by physicians, these reports usually underestimate the frequency of any adverse drug reaction. Of greater importance, underreporting is usually not random but selective, which may introduce serious bias when comparing different drugs. Various examples have been described previously of drugs that showed substantive differences in reporting rates, which were not substantiated after further research. For this reason, it is recommended that, once there is a signal for a suspected adverse drug reaction, other sources of data are investigated.

We recently initiated a study to quantify the risk of renal toxicity in patients taking aminosalicylate (5-ASA) drugs in the UK. The General Practice Research Database (GPRD) was used for this study, with data collected as part of routine medical practice. The GPRD has previously been demonstrated to be a representative sample of the general population of England and Wales, and the completeness and validity of the GPRD recording of medically significant events is well established. Its data have been used frequently to quantify the risk of adverse drug reactions. Our study population included almost 40 000 patients. We found that the overall incidence of renal damage (which included interstitial nephritis) was rare in patients taking 5-ASA drugs, but was increased relative to control patients (table 1). The risk of renal toxicity in patients taking mesalazine and sulphasalazine was comparable. Interestingly, we found that the risk of renal disease was related to indicators of severity of inflammatory bowel disease and to concomitant disease and drug treatment. A recent report also suggested that the kidney can be an extraintestinal target in Crohn’s disease. We presented the results of this study at the recent British Society of Gastroenterology meeting.

Our findings also highlight the substantive underreporting of the data used by Ransford et al (table 1). Given the selected and incomplete nature of the reports of suspected adverse drug reactions, one needs to establish whether physicians reported cases of interstitial nephritis equally for users of different 5-ASA drugs. The authors did not provide any data for the comparability of the users of the various 5-ASA drugs in the UK.

In conclusion, while we agree that renal function should be evaluated and monitored in patients taking 5-ASAs, the results of our large epidemiological study show no difference in renal toxicity between mesalazine and sulphasalazine and that confounding factors can also significantly affect the overall risk. A statistical analysis of suspected adverse drug reaction reports may generate signals but does not provide conclusive evidence of differences in safety between drugs.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Rates of renal events in the General Practice Research Database (GPRD) study and in the study of Ransford et al</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate per 1000 person years</td>
</tr>
<tr>
<td>GPRD</td>
<td></td>
</tr>
<tr>
<td>Renal toxicity</td>
<td></td>
</tr>
<tr>
<td>During 5-ASA use</td>
<td>1.2</td>
</tr>
<tr>
<td>Mesalazine</td>
<td>1.2</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>1.7</td>
</tr>
<tr>
<td>Control cohort</td>
<td>0.6</td>
</tr>
<tr>
<td>Ransford et al</td>
<td></td>
</tr>
<tr>
<td>During 5-ASA use</td>
<td></td>
</tr>
<tr>
<td>Mesalazine</td>
<td>0.1</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Author’s reply

We do of course recognise that making deductions from examination of spontaneous adverse reaction reports poses problems from the incomplete nature of the data, and the limited knowledge of biases. Thus we say ‘spontaneous reporting…cannot be used to determine true rates of reaction’. We also speculate that reporting rates of interstitial nephritis with mesalazine may be high ‘because a specific warning of possible renal toxicity had been issued’.

The comparatively equal values quoted by Logan and van Staa for 1.2 (mesalazine) and 1.7 (sulphasalazine) cases of interstitial nephritis per 1000 patient years are very different from the 29 cases reported spontaneously on yellow cards for mesalazine with none for sulphasalazine in the time period assessed (there are a total of 47 for mesalazine and two for sulphasalazine, a fairly large difference).

Being aware of the problems of judging true rates of reaction from spontaneous reports, and knowing that there was (as for interstitial nephritis) a relative paucity of reports for pancreatitis with sulphasalazine, we have recently analysed data from the General Practice Research Database (GPRD) on prior drug exposure in cases of acute pancreatitis. This clearly shows raised odds ratios for mesalazine, but not for sulphasalazine, and with the odds ratio for mesalazine being particularly high in those with first exposure in the prior three months. The finding is consonant with the spontaneous adverse drug reaction data presented by us.

Rates from GPRD for interstitial nephritis, as presented by Logan and van Staa per 1000 patient years, are difficult to relate to individual patient exposures. It would be valuable to have such information. Given that sulphasalazine is the older drug, one would expect longer exposure in each such taker (particularly if it was for inflammatory bowel disease). It would also be valuable to know if the cases of renal toxicity in sulphasalazine takers identified by Logan and van Staa were in patients with inflam-
matory bowel disease rather than in those with rheumatoid disease, where confounding by use of other agents, notably penicillamine and gold, and by complicating renal amyloidosis, would need to be borne in mind. Differences between our findings may be resolved in due course by current surveillance studies being conducted by the British Society of Gastroenterology.

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Reference

Worsening of steatosis and fibrosis progression in hepatitis C

We thank Ratziu et al for their interest in our work.1 To grade steatosis, we used the Metavir scoring system, shown by their group to be accurate and reproducible.2 Worsening was characterised by an increase in the amount of lipids in hepatocytes, as defined in this grading system. As emphasised in our paper, our main finding was that worsening of steatosis was the only independent factor associated with fibrosis progression in multivariate analysis. This study was observational and not aimed at establishing causal links, a goal that requires a combination of prospective clinical studies and careful in vitro experiments. Ratziu’s discussion of our data is interesting but remains purely speculative.3 The issues raised by our results and their discussion in both our paper and Ratziu’s letter are currently being addressed through appropriate studies in our centre.

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References

Complete regression of advanced HCC with long acting octreotide

Various therapeutic approaches for unresectable hepatocellular carcinoma (HCC) have been suggested in recent years. However, major advances concerning tumour regression or patient survival were not achieved. A few trials have assessed the effect of the somatostatin analogue octreotide in advanced HCC with divergent results.1,2 The latter might be due to expression of somatostatin receptor type 2 (sSTR2) in some but not all patients with HCC.3 Here, we describe a patient with advanced HCC who was treated with long acting octreotide, which resulted in complete and prolonged regression of the tumour.

The patient was diagnosed with HCC after a suspect nodule was detected in the abdominal ultrasound. Laboratory testing revealed a highly increased alpha fetoprotein (AFP) level and positive hepatitis C virus antibodies. Computed tomography (CT) of the liver displayed multiple tumours (maximum diameter 5 cm) in segment seven and two smaller nodules in segments six and one. Histology of an ultrasound guided biopsy revealed HCC. Due to the advanced stage of the tumour, surgical resection was not feasible. As the patient refused local ablative therapies, treatment with octreotide was initiated (initially 250 µg twice daily followed by long acting octreotide (Sandostatin LAR) 10 mg monthly). Four months later a 50–70% reduction in the size of the multifocal tumours was demonstrated by CT. Furthermore, complete regression of the formerly described tumours was noted 10 months after initiation of octreotide therapy. This was paralleled by normalisation of the formerly elevated AFP levels (33.1 ng/ml to 7615.3 ng/ml). Octreotide receptor scintigraphy performed after 12 months and 19 months of therapy did not reveal any suspicious enhancement. However, after 13 and 19 months a gradual increase in AFP levels from 37 to 223 ng/ml and a new suspicious liver nodule by CT scan was observed. To date, the patient has not experienced any tumour associated symptoms or drug related side effects and has been in excellent condition during the 22 months of treatment.

The survival improving treatment effects of octreotide described by Koumouralis and colleagues were not confirmed in a subsequent randomised placebo controlled trial.4 Of the octreotide receptors expressed in the liver, octreotide has the highest affinity for SSTR2 compared with the four other isoforms (33.1 ng/ml to 7615.3 ng/ml). Octreotide receptor scintigraphy performed after 12 months and 19 months of therapy did not reveal any suspicious enhancement. However, after 13 and 19 months a gradual increase in AFP levels from 37 to 223 ng/ml and a new suspicious liver nodule by CT scan was observed. To date, the patient has not experienced any tumour associated symptoms or drug related side effects and has been in excellent condition during the 22 months of treatment.

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Based on our observation and the divergent results of recent studies, evaluating the effect of octreotide in advanced HCC might additionally stratify patients according to the respective somatostatin receptor expression profile of tumour cells.

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References

Diagnosing small bowel Crohn’s disease with wireless capsule endoscopy

We read the article by Fireman et al (Gut 2003;52:390–2) with great interest. We agree that full visualisation and imaging of the entire length of the small bowel is unsatisfactory at present and that capsule endoscopy (CE) is a novel technique and can be considered as a promising new approach for the diagnosis of obscure disease located in the small bowel.

The authors diagnosed Crohn’s disease (CD) in 12 of 17 patients with clinically suspected CD according to the findings of CE. The authors state that the majority of diagnostic lesions were located in the distal ileum. At least one coloscopy had been performed prior to CE in 11 of these patients. Unfortunately, the investigators do not report whether or not they were able to explore the terminal ileum in all of these patients. Hence the important question arises of which endoscopic and histologic findings in the terminal ileum should be considered as the most likely clinical symptom and histological finding. Furthermore, the authors did not compare their non-diagnostic x ray findings with the CE results.

To date, we have performed a total of 130 capsule endoscopy procedures. In 50 patients with obscure gastrointestinal bleeding, we were able to disclose CD as the most probable underlying cause of bleeding in four patients.

In addition, one patient suffering from Peutz-Jeghers’ syndrome was diagnosed as also having CD of the small bowel. We have performed CE in eight patients in whom the diagnosis of CD had been established prior to CE to “stage” the small bowel for additional lesions that could influence treatment decisions. In the majority of our patients we found that the main pathological lesions were located in the terminal ileum. We were however able to confirm most CD lesions histologically by applying a second ileocolonoscopy with special emphasis on the small bowel biopsies in most of these patients, which allows for a greater diagnosis validity.
as small bowel ulcerations obtained with CE may also be caused by non-steroidal anti-inflammatory drug abuse, ulcerative ileitis, or coeliac disease. Hence from our experience we strongly recommend that patients with suspected CD should initially undergo careful ileocolonoscopy with close inspection of as much as the ileum as possible, and acquisition of multiple ileal biopsies to histologically establish CD prior to therapy. We believe that at present CE is only clinically indicated in patients with signs and symptoms suggestive of small bowel CD in whom:

- a stenosis/stricture has clearly been excluded,
- the terminal ileum looks unremarkable on endoscopy, or
- the ileum cannot be intubated for technical reasons.

The present study does not elucidate whether CE is really superior to conventional endoscopy plus histological assessment, which must still be considered the gold standard for the diagnosis of CD. As there is a substantial risk of capsule retention in the gastrointestinal tract in patients with stenosed CD, it should be determined if the benefits of CE findings outweigh the risks of this otherwise remarkable novel technique in individual patients.

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Authors’ reply

We thank Drs Schulmann, Hollerbach, and Schmigel for their interest in our paper on the subject of diagnosing small bowel Crohn’s disease with wireless capsule endoscopy.1 Regarding colonoscopy,2 please note that in the materials and methods section, under study population, it is clearly stated that all underwent colonoscopies elsewhere, at most six months prior to entering the study, and this statement is repeated in the first paragraph of the results section. As these patients came to us from other medical centres with the results of their previous colonoscopies, we sent the results of capsule endoscopy (CE) to their own physicians (Re: exploration of the terminal ileum). In the results section, we state that six patients underwent ileoscopy which was normal.

We appreciate the experience of your group and agree with your indications and contra-indications regarding the CE study.

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Reference


Cost effectiveness of pegylated interferon alpha 2b and ribavirin combination in chronic hepatitis C

I read with great interest the excellent cost effectiveness presented by Drs T Poynard and colleagues for pegylated interferon alpha 2b and ribavirin combination in patients with chronic hepatitis C (Gut 2003;52:425–32). I was surprised by the relatively low cost of treatment initiation in Germany (table 3). The cost estimate of pre-therapeutic diagnostics, at 473, included a pregnancy test, quantitative hepatitis C virus-RNA, thyroid stimulating hormone, thyroxine, liver biopsy, and partial inpatient cost for initiation of treatment. Do you exclude the genotype assessment in these baseline tests? In a previous US cost effectiveness study1 and in our hospital, the same pre-therapeutic diagnostics seems more expensive (>1000). How do you estimate the cost of a liver biopsy? Even without taking into account the complications of liver biopsy (three severe complications out of 1000 and three deaths out of 10 000), the cost of the baseline diagnostics could be decreased by using non-invasive biochemical markers of liver features, such as the Fibrotest-Actitest, which costs only 90 euros.2

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Conflict of interest: T Poynard has participated in clinical trials for viral hepatitis and as an advisor with the following companies: BMS, Boehringer, Gilead Science, GlaxoSmithKline, Idexen, Reche, and Schering Plough. He is a consultant and has financial ties to the following companies: Gilead Sciences, GlaxoSmithKline, Idenix, Roche, and Schering-Plough. He is a consultant and has financial ties to the following companies: Gilead Sciences, GlaxoSmithKline, Idenix, Roche, and Schering Plough. He is a consultant and has financial ties to the following companies: Gilead Sciences, GlaxoSmithKline, Idenix, Roche, and Schering-Plough. He is a consultant and has financial ties to the following companies: Gilead Sciences, GlaxoSmithKline, Idenix, Roche, and Schering Plough. He is a consultant and has financial ties to the following companies: Gilead Sciences, GlaxoSmithKline, Idenix, Roche, and Schering-Plough. He is a consultant and has financial ties to the following companies: Gilead Sciences, GlaxoSmithKline, Idenix, Roche, and Schering Plough.

References


Risk of fracture in coeliac disease

We agree that the risk of fracture in coeliac disease needs to be estimated more precisely and that judicious use of DEXA scanning is appropriate in this group, as it is in the general population. However, as Walters and colleagues (Gut 2003;52:1229–30) and others have clearly shown, bone mineral density does improve following treatment with a gluten free diet, so recommendations to screen all patients with coeliac disease at diagnosis do not seem judicious.1 Larger studies are needed and one such is in progress. Nevertheless, the small increases in risk which were found are similar to those found in the only other population based study of fracture risk in patients with coeliac disease.2 In the absence of robust data showing a marked increase in the risk of fracture in patients with coeliac disease, perhaps the onus should be on those making such recommendations3 to provide evidence supporting their efficacy and cost effectiveness.

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References


NOTICES

Sir Francis Avery Jones British Society of Gastroenterology Research Award 2004

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2004 Award. Applications (TWENTY COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years old or less on 31 December 2004 but need not be a member of the Society. The recipient will be required to deliver a 30 minute lecture at the Annual meeting of the Society in Glasgow in March 2004. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2003.

British Society of Gastroenterology Hopkins Endoscopy Prize 2004

Applications are invited by the Endoscopy Committee of the British Society of Gastroenterology who will recommend to the Council the recipient of the 2004 Award. Applications (TEN COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

An applicant need not be a member of the Society. The recipient will be required to deliver a 20 minute lecture at the Annual meeting of the Society in Glasgow in March 2004. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2003.
Complete regression of advanced HCC with long acting octreotide

J T Siveke, C Folwaczny and C Herberhold

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doi: 10.1136/gut.52.10.1531-a

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High magnification chromoscopic colonoscopy as a screening tool in acromegaly

We read with great interest the paper by Jenkins et al (Gut 2002;51:V13–14) regarding screening guidelines for colorectal cancer (CRC) and polyps in patients with acromegaly. We report an experience in 38 patients with acromegaly reviewed in detail by Renihan in the subsequent discussion on screening for colorectal cancer in acromegaly. We have recently reported on our experience with colorectal neoplasms in acromegaly. Twenty two (58%) of the 38 patients had adenomatous polyposis syndrome. Twenty four (63%) of the 38 patients had colorectal carcinoma, 16 (42%) of whom had invasive carcinomas. The neoplastic risk for this group is technically demanding and often complicated by inadequate bowel preparation. The neoplastic risk for this group however requires clarification. Colonoscopy in this patient group is therefore carried out with great clinical care.

A flat lesion was defined as a lesion with a flat or slightly convex surface combined with a height of less than half the diameter of the lesion. High magnification views of all suspected lesions were then obtained and reported according to the modified Kudo criteria. Tissue sampling was performed with cold biopsy or endoscopic mucosal resection following exclusion of a Kudo type V/n/III invasive crypt pattern which suggests deep submucosal invasion. Mean intubation and extubation times were recorded. Neoplastic change was classified according to the Vienna criteria. Caecal intubation was achieved in 37/38 (97%) patients with 36/38 (94%) receiving confirmatory terminal ileal biopsies. Males represented 14/37 (37% of the cohort, mean age 64 years (range 40–75)). The mean duration of intubation to the caecum was 16.5 minutes (range 3–31) and extubation (excluding interventional procedures) was 35 minutes (range 20–55). There were no complications.

A total of 28 lesions were identified in 15 patients. Twenty two hyperplastic lesions were identified (79%) of which 17 (77%) were flat (JRSC II). Twenty (91%) were located in the right colon and rectum. Of the five adenomas identified, four (80%) were present in the right colon with 4/5 (80%) being of JRSC II morphology. A single adenoma with high grade dysplasia was present in the right colon and was flat with a small area of central depression. No invasive carcinomas were diagnosed. Results are summarised in table 1.

Although the numbers entering this study are small, our results show a clear prevalence for JRSC II lesions in this select patient group. Although only one adenoma with high grade dysplasia was detected, it was small (5 mm) and was not identified prior to chromoscopic and magnification enhancement, and therefore carries major clinical connotations.

We suggest that further large prospective studies are required to establish the true prevalence of flat and depressed colorectal lesions in acromegaly so that the optimal screening modality and frequency can finally be established. Furthermore, colonoscopists require training in chromoscopic techniques if a higher endoscopically “treatable” lesion frequency is to be detected at a screening level, so as to avoid the high apparent incidence of interval neoplasms.

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References
1 Renihan AG, O’Dwyer ST, Shalet SM. Colorectal neoplasia in acromegaly: the reported increased prevalence is overestimated. Gut 2000;46:440.

Table 1 Lesion demographics

<table>
<thead>
<tr>
<th>Histology</th>
<th>n</th>
<th>Morphology (JRSC)</th>
<th>Anatomical location</th>
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<tr>
<td></td>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Hyperplastic</td>
<td>22</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Adenoma LGD</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Adenoma HGD</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Invasive neoplasia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(T2 or beyond)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LGD, low grade dysplasia; HGD, high grade dysplasia.
place all of these mucosae in the oesophagus, proximal to the gastro-oesophageal junction. “Primitive oesophageal mucosa” is a ciliated epithelium that continues for about 24 weeks. “Proximal stomach mucosa” is a layer of flat columnar cells containing depressions that correspond to early gland pits distally. “Cardiac mucosa” is composed of foveolar and surface epithelium overlying glandular structures containing no parietal cells. The description of “cardiac mucosa” and figs 2 and 4 show a very thin columnar epithelium composed of uniform mucous cells with foveolar pits and rudimentary sac-like structures devoid of any inflammation. Dedroy et al’s “cardiac mucosa” and Park et al’s “transition zone” are identical in appearance. I have never seen this fetal epithelium in any adult patient. The fact that these authors call it “cardiac mucosa” does not make it identical to the more conventional cardiac mucosa seen in adults. The only similarity is that it is a glandular mucosa composed of mucous cells only. It is much thinner than adult cardiac mucosa, it has no inflammation, and its glands are much less developed if present at all.

I would like to propose an alternate explanation for the changes seen in all three papers that perhaps provides a better explanation of the data in the papers. The early fetal oesophagus is lined by primitive undifferentiated ciliated columnar epithelium. It begins differentiating into squamous epithelium proximally and gastric mucosa distally. Gastric differentiation is marked by the appearance of true glands containing parietal cells. In the second trimester, the oesophageal squamous epithelium is separated from the continuing gastric mucosa by a columnar epithelium composed of foregut columnar stem cells forming a flat surface and a foveolar pit. This is uncommitted fetal columnar epithelium. This continues to develop into either squamous epithelium proximally or parietal cell containing gastric mucosa distally. Overall length decreases as fetal age increases (as shown in De Hortegh et al and Dedroy et al’s studies). With progression of the development of the lower oesophageal sphincter in early infant life, the physiological gastro-oesophageal junction is defined and the uncommitted columnar epithelium continues its differentiation. Squamous in the oesophagus and gastric mucosa with parietal cells distal to the lower oesophageal sphincter. The uncommitted foregut columnar epithelium disappears. The only normal mucosa seen after development is complete are squamous and gastric with parietal cells. This is proven by illustrations that show children with a direct transition of squamous epithelium to gastric mucosa with parietal cells (Chandrasoma and colleagues2 and fig 2A of Park and colleagues). The absence of cardiac mucosa in these illustrations is proof that cardiac mucosa is not universally present in children. Adult-type cardiac mucosa is also absent universally in fetuses. The only reason why De Hortegh et al reach the conclusion that it is universally present in fetal life is that they erroneously apply the term “cardiac mucosa” to the uncommitted fetal columnar epithelium that is universally present in fetal life.

Fetal “cardiac mucosa” is not adult cardiac mucosa

De Hortegh et al’s autopsy study of the fetal gastro-oesophageal region provides valuable insight into the development of foregut epithelium in the 13–24 week gestational period (Gut 2003;52:791–6). Coincidentally, two other studies appeared on the same subject in April 2003. These studies were stimulated by our hypothesis that cardiac mucosa does not exist as a normal structure in man.

Three columnar epithelial types are reported between squamous epithelium and parietal cell containing gastric mucosa in De Hortegh’s study (Gut 2003;52:791–6). These are: “primitive oesophageal mucosa”, “primitive stomach mucosa”, and “cardiac mucosa”. Careful anatomical correlation

References


Author’s reply

We would like to thank Dr Chandrasoma for his constructive initiatives and kind comments on our work published in Gut. We have also provided the readers with an admirable synthesis of the most recent research on the development of the different mucosal types in the gastro-oesophageal junction region. By means of this letter, we want to reflect on some of his comments.

The quintessence of Dr Chandrasoma’s vision on cardiac mucosa (CM) is that it is not a normal structure but rather a remnant of the oesophago-gastric meta-plasia in the context of gastro-oesophageal reflux disease. The presence of a small length of CM in many “normal” adults could be the result of asymptomatic low level reflux. According to his main hypothesis, “non-committed non-glandular late fetal foregut epithelium” (which we call CM in our study) will develop into either oesophageal squamous epithelium or gastric mucosa with parietal cell containing glands. The necessary corollary of his theory is that there can be no such thing as a normal CM. He also puts forward the notion that the presence of CM in some infants might be due to deviant differentiation of the uncommitted epithelium in the context of reflux or other trauma such as nasogastric intubation. Even if this hypothesis is correct, we think that other possibilities should be considered. One possible situation could be the persistence of the uncommitted epithelium with development of a sort of heterotopic CM (analogous to the heterotopic fundic-type mucosa described in the upper third of the oesophagus). Clearly, much more research is needed for future research. As Dr Chandrasoma himself says, the most important reason for the divergent conclusions of his work and ours are the terminology and interpretation of the data. What we call CM, is, in Dr Chandrasoma’s opinion, an uncommitted epithelium devoid of glands. He specifically warns against applying the designation “gland” to the tangentially cut tortuous ends of the foveolar pits (our fig 2 and fig 4). We believe glands are present in these illustrations. We formed this conclusion both on a purely morphological basis (the gland cells are cuboidal to triangular and contain a centrally located round nucleus, as opposed to the tall columnar foveolar and pit cells with basically located nuclei) and after histochemical evaluation (the foveolar and pit cells contain a large amount of mostly neutral mucins, whereas the gland cells after a long time contain only a small amount of mostly acidic mucins). We used the term CM

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www.gutjnl.com
Helicobacter pylori infection in Africa and Europe: enigma of host genetics

Helicobacter pylori infection is one of the most common bacterial infections. The prevalence varies from 25–50% in developed countries to 70–90% in the third world. Despite improved treatment modalities, H. pylori related gastrointestinal pathology, in common with gastritis, peptic ulcers and consecutive bleeding events, gastric MALT lymphoma, or carcinoma, remains a major burden on Western health systems. In the USA, approximately four million people have active peptic ulcers and about 350,000 new cases are diagnosed each year. Four times as many duodenal ulcers as gastric ulcers are diagnosed. Epidemiological evidence suggests that both infection with H. pylori and the consecutive development of clinically relevant pathology are influenced by genetic predisposition as only a fraction of exposed individuals develop infection and likewise a fraction of infected individuals develop ulcers or even gastric cancer.

Thye et al used H. pylori reactive serum immunoglobulin G as a marker of H. pylori infection in Senegalese siblings and provided further evidence for the first time concrete statistical evidence for a hereditary predisposition to H. pylori infection. The authors reported an association between IFNGR1 polymorphisms and high antibody concentrations. Inclusion of the three variants (H1318P, L450P, G56 T/C) in the linkage analysis increased the LOD score to 4.2. The two African amino acid exchange variants, H1318P and L450P, were not found in 100 unselected Caucasian individuals.

Immediately, the question arises of whether variation in the interferon-γ receptor 1 (IFNGR1) locus is related to H. pylori infection or pathology in Caucasian populations. We genotyped two polymorphisms at the IFNGR1 locus (rs608914, rs11914) in 344 H. pylori infected individuals undergoing upper gastrointestinal endoscopy from northern Germany and 311 healthy blood donors. H. pylori infection was tested by rapid urease test from a gastric biopsy or histology. Patients were grouped according to the severity of the mucosal inflammation, ranging from mild inflammation such as gastritis or duodenitis, to erosions and ulcer disease. Polymorphisms were selected from the Applied Biosystems “Assay-on-Demand” service (https://store.appliedbiosystems.com) and genotyped by Taqman using standard protocols. Because both polymorphisms were non-functional single nucleotide polymorphisms (rs11914: synonymous T/G exchange in exon 1, frequency in blood donors 13.5%; rs608914: C/T exchange at about 6.5 kb downstream from the transcriptional start site, frequency in blood donors 31.3%) a haplotype case control analysis was performed using Hapmap to assess the association of the locus with the respective phenotypes. The markers exhibited a low degree of linkage disequilibrium (LD) (D’ ≤ 0.14) yielding a highly informative haplotype analysis of the locus (frequencies in normal controls: TC 0.386; TT 0.100; GC 0.279; GT 0.335). No significant association with infection status or severity of H. pylori associated inflammation was found (table 1).

We conclude that IFNGR1 is unlikely to be involved in the aetiology of H. pylori infection or the development of clinical sequelae in German Caucasians. This may be due to aetiological difference between African and Caucasian individuals, as suggested pathophysiologically by Mitchell et al., who demonstrated major differences in the IgG subclass response to H. pylori in the first and third world.

In relation to clinical disease manifestations, the IFNGR1 locus may affect antibody concentrations but not the clinical course of H. pylori infection in Caucasians. Alternatively, other immunoregulatory genes, in the vicinity of the IFNGR1 locus such as the interleukin 20 receptor α (200 kb distance) or MAP kinases 5 (600 kb distance) could harbour the causative variants. High density LD mapping of the locus is required to unravel the causative genetic variants in both African and Caucasian populations. Our data support the hypothesis that the genetic diversity of the host immune system may contribute to the differences in H. pylori clinical outcome and prevalence in African and Caucasian populations.

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References


Platelet activation in patients with irritable bowel syndrome may reflect a subclinical inflammatory response

We read the recent article by Houghton et al and found the results very interesting (Gut 2003;52:663–70). Their observations included higher platelet concentrations of 5-hydroxytryptamine among patients with irritable bowel syndrome (IBS) compared with controls. It is interesting that a small but significant subgroup of IBS patients report onset of their symptoms after an episode of acute gastroenteritis and a role of subclinical inflammatory aetiology has been suggested for the condition. The role of platelets in various inflammatory conditions has previously been demonstrated but their importance in IBS remains largely unknown. We recently looked at the possibility of platelet activation in IBS patients by determining surface expression of the activation markers at baseline and after stimulation. Stimulation involved the use of thrombin receptor activating peptide (TRAP), activation markers P-selectin (CD62) and glycoprotein 53 (CD63), and glycoprotein (GP) receptors GPIb-IX and GPIIb/IIIa, using whole blood flow cytometric analysis (Becton Dickenson Flow Cytometer).

Twenty consecutive IBS patients (18 females), mean age 29 years (20–62), fulfilling the Rome II criteria (90% d-IBS) and 15 healthy controls (11 females), mean age 28 years (22–49), were included. Raised inflammatory markers, previous bowel dis-

Table 1 Haplotype analysis of infection status and clinical manifestation of Helicobacter pylori infection

<table>
<thead>
<tr>
<th>Comparison groups</th>
<th>n (groups)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection status (normal controls versus all H. pylori positive patients)</td>
<td>311 vs 344</td>
<td>0.39</td>
</tr>
<tr>
<td>Moderate versus mild pathology in H pylori infected patients</td>
<td>66 vs 166</td>
<td>0.32</td>
</tr>
<tr>
<td>Severe versus mild pathology in H pylori infected patients</td>
<td>112 vs 166</td>
<td>0.61</td>
</tr>
</tbody>
</table>

The table shows the comparative frequencies of the IFNGR1 haplotype described above. Susceptibility to H. pylori infection was tested by comparison of all H. pylori positive patients (n: all subgroups: 66+112+166 = 344) against normal controls (top row). Genetic predisposition for complications of H. pylori infection was tested by comparison of patients with severe pathology (gastric or duodenal erosions, n = 66) and severe pathology (gastric or duodenal ulcers n = 112) against patients with mild or no pathology grouped together (no pathology, gastritis, or duodenitis, n = 166).

Significance was assessed by a z2 test of the global likelihood ratio of the case control haplotype estimations.
ease or surgery, diverticulosis, and current or recent (past four weeks) use of non-steroidal anti-inflammatory drugs were exclusion criteria.

Standard venupuncture precautions were observed for sample collection and final analysis. A fluorescein isothiocyanate (FITC) conjugated GPIb specific antibody was used to gate around the platelet population and list mode data on 10 000 platelets acquired. Mean fluorescence intensity (MFI) was used to quantify FITC labelled GPIIb/IIIa and GPIb-IX specific antibody binding. Binding of P-selectin and GP53 to a phycocerythin labelled monoclonal antibody was expressed as the percentage of platelets positive for that antibody (% fluorescence). We tested varying concentrations of 223 mM (concentration used for reactivity of circulating platelets at a concentration of 253 mM (concentration used for activation studies). Differences between groups (p) were assessed using the Mann-Whitney U test for unpaired data. All analyses were performed using the Minitab statistical software and SPSS for windows (10.0.5).

Baseline expression of P-selectin was significantly increased in the IBS group (median 5.9 (interquartile range (IQR) 4.4–8.9)) compared with healthy controls (median 4.1 (IQR 3.2–5.9)) (p = 0.03), all values representing per cent expression. Baseline expression of GP53 was higher in the IBS group (median 3.0 (IQR 1.9–4.0)) compared with normal controls (median 2.3 (IQR 1.9–2.8)) but failed to reach clinical significance. TRAP stimulation resulted in increased expression of P-selectin and GP53 in both groups. Glycoprotein reactivity post stimulation was significantly lower in the IBS group compared with normal controls (p<0.05).

The numbers of GPIIIa/IIIa and GPIb-IX receptor sites on the platelet surface for each group were calculated using a calibration curve where MFI and the corresponding number of antibody sites of multiple bead conjugated GP1b specific antibody was used to gate around the platelet population and list mode data on 10 000 platelets acquired. Mean fluorescence intensity (MFI) was used to quantify FITC labelled GPIIIa/IIIa and GPIb-IX specific antibody binding.

Two errors have been noted in the paper by C Hawke et al in the June issue (Incidence of gastroduodenal ulcers in patients with rheumatoid arthritis after 12 weeks of roflxoxib, naproxen, or placebo: a multicentre, randomised, double blind study. Gut 2003;52:820–6). On page 822, the lower 95% CI for the difference between roflxoxib and placebo (4.05), is given as 93.37 rather than 93.31. On page 823, the correct order for the listing of authors et al was ordered incorrectly (Incidence of gastroduodenal ulcers in patients with rheumatoid arthritis after 12 weeks of roflxoxib, naproxen, or placebo: a multicentre, randomised, double blind study. Gut 2003;52:1531) the author list was ordered incorrectly (Incidence of gastroduodenal ulcers in patients with rheumatoid arthritis after 12 weeks of roflxoxib, naproxen, or placebo: a multicentre, randomised, double blind study. Gut 2003;52:1531) the author list was ordered incorrectly.