TPMT in the treatment of inflammatory bowel disease with azathioprine

We read with interest the recent article by Lennard on the role of thiopurine methyltransferase (TPMT) enzyme in predicting azathioprine related toxicity in patients with inflammatory bowel disease (IBD) (Gut 2002; 51:143–6). He concludes that measurement of TPMT activity has no specific role in identifying the risk of significant bone marrow toxicity in long term users of azathioprine. This conclusion is in agreement with other published work and emphasises the importance of ongoing haematological monitoring in IBD patients receiving this drug. Providing it isn’t libellous or obscene, it will be posted within seven days. You can retrieve it by clicking on “read letters” on our homepage.

The editors will decide as before whether to also publish it in a future paper issue.

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ulcerative colitis</th>
<th>Crohn’s disease</th>
<th>Indeterminate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>17</td>
<td>25</td>
<td>3</td>
<td>45</td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>48</td>
<td>2</td>
<td>65</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Abnormal LFTs</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Infections</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Liver function test</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

No of SE

Figure 1

Table 1: Characteristic and side effects encountered during the initial period of therapy (three months) with azathioprine in patients with inflammatory bowel disease.

Author’s reply

Measurement of thiopurine methyltransferase (TPMT) status, prior to the start of azathioprine therapy, has a role in identifying the TPMT deficient patient at risk of severe myelosuppression and TPMT heterozygous individuals who are prone to early myelosuppression. The risk of azathioprine toxicity is well recognised but, as the authors state, the duration of early monitoring is a matter of controversy. The matter for debate is the time of onset of potentially life threatening myelosuppression.

A Qasim, J Seery, M Buckley, O Morain

Gastroenterology Department, AMNCH, Tallaght, Dublin 24, Ireland

Correspondence to: A Qasim; qasim@cdl.ie

References

Quasi et al state that this information is not available for patients with inflammatory bowel disease (IBD). However, data can be derived from publications in other patient groups which may serve as useful guidelines for this time interval.

Reports of azathioprine induced severe myelosuppression in the TPMT deficient patient indicate that bone marrow toxicity is recorded after 3–10 weeks (median 4) of azathioprine therapy. In these reports the drug dosage varied from 1 to 2.9 mg/kg (median 1.7). One patient taking azathioprine at a dosage of 1 mg/kg developed myelosuppression (white blood cell count WBC 1.6×10^9/l, platelets 25×10^9/l) at 10 weeks while another dosed at 1 mg/kg developed myelosuppression (WBC 5.8×10^9/l, platelets 15×10^9/l) after 9 weeks.

The guidelines then continue, “this frequency of monitoring suggests that patients with previously recorded post-therapy myelosuppression after weeks or years of azathioprine therapy should be monitored for a minimum period of three months”. The additional observation that the frequency of monitoring myelosuppression after weeks or years of azathioprine therapy is “to ensure that the patient is not at risk of myelosuppression after years of therapy”. The guidelines state that patients should be monitored more frequently during the first three months of therapy. Specifically for the patient with Crohn’s disease, Colombel and colleagues have reported that TPMT deficient individuals experience myelosuppression within 1 months of azathioprine therapy (100–150 mg/day) and that TPMT heterozygotes developed toxicity after 1–18 months (median 4) of therapy. Similar observations have been made by Schwab and colleagues who reported myelosuppression in a TPMT deficient Crohn’s patient after 1.7 months of azathioprine at 1.5 mg/kg and in two TPMT heterozygous patients after 2.5 and 3 months of therapy at dosages of 1.0 and 1.5 mg/kg, respectively. Additional observation that those individuals with wild-type alleles (“normal” TPMT activity) can experience myelosuppression after weeks or years of azathioprine therapy illustrates the multifactorial nature of myelosuppression in this patient group and supports the need for continued vigilance with respect to blood count monitoring.

The drug manufacturer’s guidelines, as stated in the “Association of the British Pharmaceutical Industry (ABPI) medicines compendium”, advise that a minimum committee should be monitored weekly during the first eight weeks of therapy. The guidelines then continue, “this frequency may be reduced during later therapy to monthly intervals, or at least at intervals no longer than three months”. The data presented in the reports above indicate, particularly for the patient on low dosage of TPMT deficient patients, who is an inflamed appendix was not associated with a decreased risk of ulcerative colitis, suggesting that appendicitis rather than appendectomy protects against ulcerative colitis. Cosnes et al state that these results may not be correct as they included all patients with previous appendicectomy and still found a less severe course. We believe they are incorrectly assuming this, as another possible explanation is that the effect of appendicitis is actually higher than the effect of appendicectomy reported in the present study, which could have been due to the inclusion of patients without appendicitis.

In conclusion, we believe that at present healthy persons at risk of developing ulcerative colitis should not be considered candidates for appendicectomy outside clinical trials as evidence showing that appendicectomy will protect these persons is lacking.

Appendicectomy and ulcerative colitis

Cosnes et al demonstrated that previous appendicectomy is not only associated with a lower incidence of ulcerative colitis, but also with a less severe course of the disease. Although we may fully agree with this result, we disagree with the recommendation that appendectomy should be considered for appendicectomy patients genetically at high risk of developing ulcerative colitis. The association may as well have been caused by an unknown confounding factor, both leading to an increased risk of appendicitis and a decreased risk of developing (severe) ulcerative colitis. To illustrate this point is the following theoretical example: an epidemiological study on cardiovascular morbidity finds that the risk of cardiovascular events is inversely related to the risk of developing upper gastrointestinal haemorrhage. This could be due to the factor “treatment with aspirin” that could well explain the increased bleeding risk and the lower incidence of cardiovascular events. The confounding factor is the use of aspirin. It would be wrong to conclude that in patients with a history of bleeding, aspirin should be undertaken to reduce upper gastrointestinal bleeding in order to prevent cardiovascular morbidity.

Another argument against performing this surgical procedure in healthy persons is the finding that appendicectomy in the absence of an inflamed appendix was not associated with toxicity: Relationship to thiopurine methyltransferase genetic polymorphism. Clin Pharmacol Ther 1999; 66:69–74.


Appendectomy and ulcerative colitis

Many French surgeons in 1900 did recommend removing preventively all appendices of young people (see Marcel Proust, “A l’ombre des jeunes filles en fleur”). That was not our purpose. Indeed, the sentence pointed out by Ter Borg and van Buuren in our paper did not give a recommendation but only made a suggestion to consider for appendicectomy patients genetically at high risk of developing ulcerative colitis. Ter Borg and van Buuren speculate that appendicectomy and a benign course of ulcerative colitis may be linked through a confounding factor but they do not document their hypothesis. In fact, there is a large body of evidence supporting a causal relationship between appendicectomy and no (or benign) ulcerative colitis, and the strongest demonstration of this relationship is the protective effect of early appendicectomy in the T cell receptor α (TCR-α) knockout mouse model. Note also that the Swedish study which found that only appendicectomy for inflammatory conditions protects against ulcerative colitis did not take into account cases of mild ulcerative colitis, a subgroup in which appendicectomised patients may be over represented.

Finally, we do not believe that the effect of appendicectomy on the course of ulcerative colitis is so high that it would remain after excluding all patients without appendicitis, thus probably two thirds of our patients. A key point however, like in the TCR-α knockout mouse model, is the date of appendicectomy. Appendicectomy protects against severe ulcerative colitis only when performed at a young age, and therefore disease onset. This latter observation argues against any therapeutic effect of appendicectomy after onset of ulcerative colitis. The problem is different when considering patients at risk for the disease.

We do believe that in a few years it will be possible to screen out young patients with a
predisposing genotype for ulcerative colitis, and a clinical trial assessing the benefits of prophylactic appendectomy will be warranted.

J Cosnes, F Carbonnel, L Beaugerie, J-P Gendre
Service de Gastroenterologie et Nutrition, Hopital Saint-Antoine, Paris, France

Correspondence to: Professor J Cosnes, Service de Gastroenterologie et Nutrition, Hopital Saint-Antoine, 184 rue du Faubourg Saint-Antoine, 75751 Paris cedex 12, France; jacques.cosnes@bat-ap-hop-paris.fr

References

Screening and surveillance for asymptomatic colorectal cancer in IBD

We would like to voice our concerns about some of the recommendations in the guidelines recently published by the British Society of Gastroenterology and Association of Coloproctology for screening and surveillance for asymptomatic colorectal cancer in patients with inflammatory bowel disease (Gut 2002;51(suppl V):10–12).

(1) In the present medicolegal environment, failure to comply with guidelines which carry the imprimatur of respected national bodies will require vigorous defence should mishap occur. We do not believe the evidence is strong enough to justify the recommendation that every patient with extensive colitis of duration greater than 8–10 years should undergo regular colonoscopy. Firstly, it must be determined at each hospital whether it is possible and considered sufficiently cost effective to offer such a service within the constraint of local resources available. Secondly, if regular colonoscopy can be offered, then each patient should decide whether or not to accept regular colonoscopy after full discussion of its possible advantages and limitations.

(2) The success of colonoscopic surveillance programmes is disputed. Although some centres (including our own) have been protagonists for this approach, others have argued that it is not only labour intensive but also ineffective. Before imposing global national guidelines we should have firm evidence of a scheme’s efficacy or, failing this, we should have multicentre consensus. The guidelines, as published appear to be the soundly held opinions of a single consultant team based on their own research and assessment of the literature, followed by approval of a committee, but no indication is given of widespread consultation.

(3) The recommendations for patients with extensive colitis of duration every third year during the second decade of disease, every second year during the third decade, and annual colonoscopies thereafter are complex. The evidence for an increasing risk of cancer in the second, third, and succeeding decades of disease duration is controversial, and is not borne out by the unstratified figures for patients with extensive colitis based on 26 reported studies in the meta-analysis reported by the authors of the guidelines, although an increase was observed in stratified data. The strategy suggested therefore is not based on firm data, and in particular published data after the third decade are few due to the small numbers involved.

(4) We have concerns about the benefits during routine colonoscopic examinations of taking two to four random biopsy specimens every 10 cm. This approach is time consuming for both the colonoscopist and the pathology department, and adds a considerable financial burden to the programme (which is not included in Eaden and Mayberry’s cost analysis). In theory, the risk of a false negative examination is reduced as more biopsies are taken but in practice the additional yield is very low indeed. During a recent study at St Mark’s Hospital, almost 3000 random surveillance biopsies from such patients yielded no dysplasia (unpublished data).

(5) Considering the disputed efficacy of current colonoscopic surveillance programmes for patients with extensive ulcerative colitis, it is inappropriate at present to extend this to default to patients with left sided colitis or (by implication) those with Crohn’s disease.

A Forbes, S Gabe, J E Lennard-Jones, K Wilkinson
St Mark’s Hospital and Academic Institute, Watford Road, Harrow HA1 3UJ, UK
Correspondence to: Dr A Forbes; alastair.forbes@ic.ac.uk

Reference

Authors’ reply

We would like to thank Dr Forbes et al for their response to the guidelines published by the British Society of Gastroenterology (BSG) and the Association of Coloproctology of Great Britain and Ireland on screening and surveillance for asymptomatic colorectal cancer in patients with inflammatory bowel disease (Gut 2002;51(suppl V):10–12). They raise a number of points which will be answered in turn.

(1) There are medicolegal implications of failing to comply with recommendations from a respected body but a guideline is precisely that—a guideline. They are not etched in stone and may need to be amended at future dates to continue to reflect best practice. The case of Wilsher v Essex Area Health Authority demonstrated that guidelines have now not to practice to the highest standards. However, the courts (Early v Newham Health Authority) will consider local guidelines. This will be of particular relevance to units that are unable to deliver standards that have been identified nationally, provided the local practice has been formulated into a local guideline.

There is a wealth of data supporting the increased cancer risk in patients with ulcerative colitis and although evidence of the effectiveness of surveillance as practiced in some centres is uncertain, such an approach is widespread. The purpose of guidelines is to identify good practice and to achieve a uniform approach throughout the country. The alternatives are to abandon surveillance or to offer haphazard and unstructured (and ineffective) service. The alternative of surveillance for both colitis and Crohn’s patients is estimated to be £9600 per annum. Hopefully, even at this cost but we realise funds may not be available initially which is one of the reasons for suggesting the guidelines are audited in five years. It is clearly stated in the guidelines that a discussion should take place between the doctor and patient informing them of their individual risk so that the patient can make an informed decision before embarking on a surveillance programme. Gone are the days of a paternalistic attitude, at patients should now accept some responsibility for their illness.

(2) Forbes et al raise the point that before any guidelines are imposed there needs to be firm evidence of a scheme’s efficacy. There are no randomised studies comparing different surveillance protocols or for that matter even uncontrolled trials. However, authorities such as the NICE are well aware, it will never be possible to provide grade A recommendations on this issue and the best we can do is to assess surveillance programmes retrospectively. Data are accumulating that surveillance participants have reduced morbidity and mortality, as outlined in the guidelines, and one of the signatories to your letter has stated that surveillance improves survival. Another notable review of surveillance programmes from the Leeds group did not show any benefit from surveillance but the group had very stringent criteria. They felt inclusion of dysplasia alone as a measure of success was of debatable value. Therefore, they limited their audit to those eventually found to have cancer. They also decided to exclude patients in whom cancer was found at an initial colonoscopy undertaken at least 12 years after the onset of symptoms. We feel that finding dysplasia is the very aim of surveillance programme because it is found on the first colonoscopy in a surveillance programme it should not be deemed a failure of surveillance.

As the theoretical and practical possibility was obtained before the guidelines were published. A national audit of the surveillance practices of gastroenterologists was conducted which revealed that although 94% of gastroenterologists performed surveillance, there was wide variation in practice. This alone suggests there would be little chance of a consensus opinion across the UK. Once the guidelines had been formulated, the Clinical Services and Standards Committee comprising 40 individuals reviewed them. They then went through the usual guidelines process after being seen by the Clinical Services Committee and were examined by the IBD section of the BSG. After this they were posted on the BSG website for six weeks to attract comments from other members of the society. The guidelines then went back to the Clinical Services Committee after amendments were made on the basis of comments from the wide range of consultees. Finally, the guidelines were sent to the Executive Committee of the BSG for a further review and signing off. Thus the guidelines evolved and were accepted and published. They are not simply the opinions of two consultant gastroenterologists.
(3) We appreciate that increasing the colonoscopy frequency with increasing duration of disease is more complicated than 1–2 yearly surveillance. However, we are sure that it is not too difficult to calculate and it actually reduces the number of colonoscopies being performed initially, so this must be regarded as an improvement on the present routine practice of some gastroenterologists.

The meta-analysis shows an increasing cancer risk in the second and third decades of life, by 20 years, and 18.4% (95% CI 13.1–23.5%) by 30 years. The decade incidence stratified by decade and duration of patient follow up (19 studies). The decade incidence where only duration of patient follow up was reported—that is, the incidence rates were not broken down for each decade. Even when these unstratified data were examined the cancer incidence still increased by decade of disease! The unstratified cumulative probabilities give a risk of 4.4% (95% CI 2.0–6.8%) at 10 years, 8.6% (95% CI 4.0–13.3%) at 20 years, and 12.7% (95% CI 6.0–19.3%) at 30 years.

Therefore, the strategy suggested is based on firm data. Of course the numbers of patients by the third decade are few but this is the nature of the beast. The use of a meta-analysis of cancer risk in ulcerative colitis overcomes the inadequacies of any reliance on smaller studies from single specialist centres.

(4) We accept that the cost of biopsies was not included in the cost analysis. There are numerous articles debating the number of biopsies which should be taken during a surveillance colonoscopy. Yes it is time consuming, but do we really want to stand any chance of detecting dysplasia, the more biopsies taken the better. What is the point in surveillance at all if it is not conducted to the best standards and this indicates to the published data no longer relevant?

(5) As patients with Crohn's colitis have been shown to have the same cancer risk as patients with extensive ulcerative colitis, it would be doing them a disservice to exclude them from a surveillance programme.4 Left sided colitis also carries an intermediate risk for colorectal cancer and as such our guidelines reflect this. Indeed, one of the signatories to the Forbes et al letter has himself advocated a similar approach after discussion with patients.4

The guidelines were formulated on the best evidence available at present. Surveillance was being conducted in an extremely disorganised fashion in the UK, which is not acceptable in the current climate of clinical governance. The BSG has properly encouraged a national approach to cancer surveillance in a rare disease. The principles, which underlie such an approach, are that of best practice throughout the country. The law no longer relies on the Bolam principle; rather we are now expected to practice to the best standards.1 If we are to offer long term care to patients with inflammatory bowel disease we must discuss with them the nature of surveillance and its inadequacies. If patients then choose to have surveillance we are obligated to provide a service which reaches the highest standards—standards similar to those in other screening services.

J A Eaden, J F Mayberry
Department of Gastroenterology, Walsgrave Hospital, Clifford Bridge Road, Coventry CV2 2DX, UK

Correspondence to: J F Mayberry; jmaybrick@ct.scail.co.uk

References

1 Wilcher v Essex Area Health Authority. [1986] 3 All ER 803
2 Early v Newham Health Authority. [1984] 5 Med LR 214

Crohn's disease: ethnic variation in CARD15 genotypes

Crohn's disease shows significant variability in incidence between different world populations. For example, little is known about the ethnic variations in population frequency of the CARD15 gene in various ethnic groups. This work was supported in part by U01 GM63340.

Acknowledgements

This work was supported in part by U01 GM63340.

References

3 Ogura Y, Inohara N, Benito A, et al. NOD2, a Nod1 / Apol-1 family member that is required to produce monocytes and activates NF-kB. J Biol Chem 2001;276:6482–18.

Doctor or technician

In 1984, Sir Christopher Booth (President British Society of Gastroenterology (BSG) 1979) gave a lecture in Berlin on the effect of technology on clinical practice. He lauded the rapidly expanding benefits of diagnostic and interventional gastrointestinal endoscopy but was led to ask “Will the gastroenterologist simply become a technician who carries out a plethora of tests but personally satisfying techniques?”

Most gastroenterologists remain general physicians but in talking with specialist...
registrar I have been surprised by their over-welming interest in honing endoscopic skills. If this leads to a simplistic approach to the investigation of possible gastrointestinal pathology, it has its dangers. Analysis of two cases in the past month reminded me of this.

Case No 1

An elderly man was admitted to hospital with severe anemia. The houseman obtained: a history of aspirin ingestion and, over the preceeding few weeks, recurrent melena. He described feeling a hard liver edge. A blood count showed haemoglobin (Hb) 4.3, mean corpuscular volume (Mcv) 55.7, white blood cell count (Wcc) 6.6, and platelets 63. The patient was transfused and without further investigation the physician/gastroenterologist arranged for osophago-gastro-duodenooscopy (OGD) and colonoscopy.

At OGD the stomach was described as showing a moderate erythematous/exudative gastritis. At colonoscopy no abnormality was seen apart from a little fresh bleeding, the cause of which was not apparent. The patient was told to return to the house only to be admitted 36 hours later with faecal peritonitis. The colon had been perforated at the rectosigmoid junction. The patient recovered well after repairative surgery but died six weeks later of multiorgan failure. At necropsy he was found to have cirrhosis of the liver. In retrospect, photographs of the gastric mucosa were consistent with portal gastropathy.

Case No 2

An elderly man taking diclofenac for osteoarthritis of the hip began drinking heavily after resection of a short length of colon had been perforated at the rectosigmoid junction. The patient was referred promptly for surgery. There was little response to hospital. His blood count showed Hb 9.7, melaena. After the weekend he was admitted feeling faint, vomiting black fluid, and passing haematochezia. His blood count showed haemoglobin (Hb) 4.3, mean corpuscular volume (MCV) 55.7, white blood cell count (Wcc) 6.6, and platelets 63. The patient was transfused and without further investigation the physician/gastroenterologist arranged for osophago-gastro-duodenooscopy (OGD) and colonoscopy.

Which 5-ASA?

I read Dr Travis’ therapy update (Gut 2002;51:548-9) with interest; the topic is timely in a field about to be challenged by new generic mesalazine brands. I note the choice of time dependent mesalazine (Penta-ta) but, if mesalazine is to be relied upon exclusively, some clinicians suggest Penta-ta may not be the best choice. The recent study by Kruijs and colleagues1 in the maintenance of remission in ulcerative colitis (UC) found that with Pentasa 1.5 g, the six month remission rate was 56.8% compared with 77.5% with balsalazide 3 g twice daily (p=0.045).

The assertion that the advantages of the azo bond delivery to the distal colan can be matched by simply increasing the dose of pH dependent (Asacol) or time dependent release (Pentasa) has not been borne out by laboratory or clinical studies. Tissue level studies have indicated that double dose mesalazine is delivered to the kidney; not the colon. A large clinical trial of Pentasa in mild to moderate active UC found remission rates of 29% for both 2 g/day and 4 g/day.7 This latter study highlights the lack of efficacy of mesalazine released by a drug taking delivery system in active UC. In contrast, three studies comparing balsalazide with mesalazine (pH dependent release), containing a total of 1026 patients, have shown superiority in active UC, with rapid resolution of symptoms (median 10 days in one study2) and superior sigmoidoscopic scores (in all three studies). Plasma concentrations of 5-aminosalicylic acid (5-ASA) were 4.5-fold lower in patients treated with balsalazide than mesalazine (p=0.018). Patients with most to benefit are new patients with distal disease.8 The use of 5-ASA in the initial treatment of UC does not require mega doses, as Dr Travis suggests, indeed mega doses of mesalazine delivered by Asacol or Pentasa are ineffective, but it does require a reliable delivery system, such as the azo bond, and an inert carrier, as with balsalazide. The clinical implication of this efficacy in mild to moderate active UC is that the threshold for the use of steroids can be raised. Of interest in the North American trials of balsalazide versus mesalazine, 60 patients failing mesalazine therapy were treated after the trial with balsalazide open label, with 60% response (data on file, Shire Pharmaceuticals Ltd).

Advocates of the new mesalazine (SASP) and those wishing to use the least expensive treatment crite trials of SASP versus newer agents9 and conclude that SASP is the most cost effective; these trials are in patients with known UC and specifically exclude patients who are SASP intolerant. In two recently published randomised controlled trials, patients who were diagnosed or previously untreated UC were randomised to SASP or balsalazide; 34% were intolerant of SASP at the modest dose of 3 g daily compared with 5% of patients taking 6.75 g daily. The number needed to treat to avoid SASP intolerance at this rate is only 3, and in new patients it seems particularly important as use well tolerated effective treatment first line and avoid the loss of confidence that drug intolerance produces.

It seems a sad reflection on the pharmaceutical industry sponsored research that the most recent trial on UC treatment with 5-ASA quoted in the therapy update was from 1998. Large clinical trials of one 5-ASA brand against another are expensive and the advent of generic mesalazine preparations is unlikely to improve this situation. My interpretation of recent published trials continues to support the mesalazine release mechanism is important for the efficacy, reliability of delivery, and safety of the oral preparations and that balsalazide is now the gold standard for other agents to be judged against.

J C Mansfield
Royal Victoria Infirmary, Newcastle NE1 4LP, UK; john.mansfield@nuthn.nhs.uk

References
1 Kruijts W, Schreiber S, Theurer D, et al. Low dose balsalazide (1.5 g twice daily) and mesalazine (0.5 g three times daily) maintained remission of ulcerative colitis but high dose balsalazide (3 g twice daily) was superior in preventing relapses. Gut 2001; 49:783-9.
TIPS for gastric varices

We recently read with interest the study by Tripathi and colleagues investigating the outcome of TIPS in patients with gastric (GV) compared to oesophageal varices (OV). This study confirmed the previous finding of lower mean portosystemic pressure gradient (PPG) in patients with GV bleeding relative to those with a history of OV bleeding. Indeed in this study 35% (14/40) of GV patients compared to only 8% (20/2320) of OV patients had a PPG <12 mm Hg. The group of patients who bled at PPG <12 mm Hg (group 1) is particularly intriguing. As mentioned by the authors, low PPG in GV patients has been linked to the presence and size of a spontaneous gastrorenal shunt (GRS) which is present in up to 85% of GV patients but present in only about 20% of OV patients. Previously, Sanyal et al. found that 50% (6/12) of patients who underwent TIPS for prevention of GV re-bleeding failed to decompress the varices as documented by endoscopy, 4/6 of these patients had a large GRS and a PPG <12 mm Hg. Thus based on probability, the group 1 patients in the current study (both GV and OV) are likely to have had a spontaneous GRS already decompressing the portal system. It would be valuable to know if the authors have any data on the presence of GRS in their patient population, perhaps documented by portogram taken at the time of TIPS? Also, did they document decompression of varices post-TIPS as an indicator of the clinical efficacy of the procedure? For example, it would be interesting to know if patients in group 1 failed to decompress varices post-TIPS more often than patients in group 2. Alternatively, we have experience of a number of patients with large GV who had a baseline PPG <12 mm Hg and a large GRS. Following TIPS in these patients, there was a minimal or no reduction in PPG and filling of the GV was not shown to be reduced on post-TIPS portogram.

Finally, the authors noted in group 2 (baseline PPG >12 mm Hg) that lower post-TIPS PPG was associated with a lower risk of re-bleeding. Thus based on probability, the group 1, in the current study (both GV and OV) are likely to have had a spontaneous GRS already decompressing the portal system. It would be valuable to know if the authors have any data on the presence of GRS in their patient population, perhaps documented by portogram taken at the time of TIPS? Also, did they document decompression of varices post-TIPS as an indicator of the clinical efficacy of the procedure? For example, it would be interesting to know if patients in group 1 failed to decompress varices post-TIPS more often than patients in group 2. Alternatively, we have experience of a number of patients with large GV who had a baseline PPG <12 mm Hg and a large GRS. Following TIPS in these patients, there was a minimal or no reduction in PPG and filling of the GV was not shown to be reduced on post-TIPS portogram.

We agree that the presence of gastrorenal shunts (GRS) is likely to explain the low portal pressure gradient (PPG) post-transjugular intrahepatic portosystemic stent shunt (TIPS). Portography at the time of index TIPS insertion was primarily performed to identify varices and not specifically to look for the presence of GRS, although the splenic vein was visualised if not always in its entirety. Given these limitations, we have looked at the portograms of over 400 patients who have had TIPS for any cause, and identified shunts in 18.3%. A wider portographic review and a prospective magnetic resonance angiography on postoperative collaterals in cirrhotic patients.

References

Authors’ reply

We recently read with interest the study by Tripathi and colleagues investigating the outcome of TIPS in patients with gastric (GV) compared to oesophageal varices (OV). This study confirmed the previous finding of lower mean portosystemic pressure gradient (PPG) in patients with GV bleeding relative to those with a history of OV bleeding. Indeed in this study 35% (14/40) of GV patients compared to only 8% (20/2320) of OV patients had a PPG <12 mm Hg. The group of patients who bled at PPG <12 mm Hg (group 1) is particularly intriguing. As mentioned by the authors, low PPG in GV patients has been linked to the presence and size of a spontaneous gastrorenal shunt (GRS) which is present in up to 85% of GV patients but present in only about 20% of OV patients. Previously, Sanyal et al. found that 50% (6/12) of patients who underwent TIPS for prevention of GV re-bleeding failed to decompress the varices as documented by endoscopy, 4/6 of these patients had a large GRS and a PPG <12 mm Hg. Thus based on probability, the group 1 patients in the current study (both GV and OV) are likely to have had a spontaneous GRS already decompressing the portal system. It would be valuable to know if the authors have any data on the presence of GRS in their patient population, perhaps documented by portogram taken at the time of TIPS? Also, did they document decompression of varices post-TIPS as an indicator of the clinical efficacy of the procedure? For example, it would be interesting to know if patients in group 1 failed to decompress varices post-TIPS more often than patients in group 2. Alternatively, we have experience of a number of patients with large GV who had a baseline PPG <12 mm Hg and a large GRS. Following TIPS in these patients, there was a minimal or no reduction in PPG and filling of the GV was not shown to be reduced on post-TIPS portogram. Finally, the authors noted in group 2 (baseline PPG >12 mm Hg) that lower post-TIPS PPG was associated with a lower risk of re-bleeding. Thus based on probability, the group 1, in the current study (both GV and OV) are likely to have had a spontaneous GRS already decompressing the portal system. It would be valuable to know if the authors have any data on the presence of GRS in their patient population, perhaps documented by portogram taken at the time of TIPS? Also, did they document decompression of varices post-TIPS as an indicator of the clinical efficacy of the procedure? For example, it would be interesting to know if patients in group 1 failed to decompress varices post-TIPS more often than patients in group 2. Alternatively, we have experience of a number of patients with large GV who had a baseline PPG <12 mm Hg and a large GRS. Following TIPS in these patients, there was a minimal or no reduction in PPG and filling of the GV was not shown to be reduced on post-TIPS portogram.

Finally, the authors noted in group 2 (baseline PPG >12 mm Hg) that lower post-TIPS PPG was associated with a lower risk of re-bleeding. Thus based on probability, the group 1, in the current study (both GV and OV) are likely to have had a spontaneous GRS already decompressing the portal system. It would be valuable to know if the authors have any data on the presence of GRS in their patient population, perhaps documented by portogram taken at the time of TIPS? Also, did they document decompression of varices post-TIPS as an indicator of the clinical efficacy of the procedure? For example, it would be interesting to know if patients in group 1 failed to decompress varices post-TIPS more often than patients in group 2. Alternatively, we have experience of a number of patients with large GV who had a baseline PPG <12 mm Hg and a large GRS. Following TIPS in these patients, there was a minimal or no reduction in PPG and filling of the GV was not shown to be reduced on post-TIPS portogram. Finally, the authors noted in group 2 (baseline PPG >12 mm Hg) that lower post-TIPS PPG was associated with a lower risk of re-bleeding. Thus based on probability, the group 1, in the current study (both GV and OV) are likely to have had a spontaneous GRS already decompressing the portal system. It would be valuable to know if the authors have any data on the presence of GRS in their patient population, perhaps documented by portogram taken at the time of TIPS? Also, did they document decompression of varices post-TIPS as an indicator of the clinical efficacy of the procedure? For example, it would be interesting to know if patients in group 1 failed to decompress varices post-TIPS more often than patients in group 2. Alternatively, we have experience of a number of patients with large GV who had a baseline PPG <12 mm Hg and a large GRS. Following TIPS in these patients, there was a minimal or no reduction in PPG and filling of the GV was not shown to be reduced on post-TIPS portogram.

We agree that the presence of gastrorenal shunts (GRS) is likely to explain the low portal pressure gradient (PPG) post-transjugular intrahepatic portosystemic stent shunt (TIPS). Portography at the time of index TIPS insertion was primarily performed to identify varices and not specifically to look for the presence of GRS, although the splenic vein was visualised if not always in its entirety. Given these limitations, we have looked at the portograms of over 400 patients who have had TIPS for any cause, and identified shunts in 18.3%. A wider portographic review and a prospective magnetic resonance angiography study will be required to answer the questions raised. For the present study, we used a post-TIPS PPG <12 mm Hg as an indicator of the efficacy of the TIPS procedure for patients with both gastric and esophageal varical bleeding. In light of our findings we have revised our target PPG post-TIPS to <7 mm Hg.

Our finding of a lack of a statistical difference in the post-TIPS PPG of those patients who did or did not rebleed may be due to the small numbers in group 1. It may be that factors other than portal pressure such as variceal size and varical wall tension play an important part in the risk of varical bleeding in patients with a PPG of <12 mm Hg. It is also true that portal pressure directly affects the varical wall tension, and attempts to reduce the portal pressure by a TIPS will be beneficial. We strongly believe that TIPS has a significant role in patients who have refractory gastric varical bleeding, as mirrored by studies from others. At the present time it is the most effective non-surgical method of treating gastric varical haemorrhage and preventing rebleed. Other therapeutic op-
Therapeutic Roles of Selective COX-2 Inhibitors


The review editor sent me a book to review for Gut with holidays looming. He left a week before the deadline and is currently observing whales off the east coast of the USA where I hope he will encounter the albino whale. I, on the other hand, am in a more peaceful location surrounded by the truly magnificent lochs, standing stones, stone circles, chambered cairns, duns, and crannogs on the Outer Hebridean island of North Uist.

The book "Therapeutic Roles of Selective COX-2 Inhibitors" is the latest in a series of similar books edited by Vane and Bolting, and I have found it in many ways as interesting and extraordinary as my surroundings. It exceeds all expectations, bringing together some of the people that have driven the COX-2 story through from birth of a concept to a marketable drug.

Vane and Bolting set the pace with an authoritative introduction, elegantly outlining the history, biochemistry, and physiology of COX and prostaglandins and their clinical potential. In this book they gracefully allow etodolac and nimesulide into the privileged COX-2 selective club or, as they call it, the "COX-1 sparing drug" club. Then follow high quality chapters on the discovery and studies on rofecoxib and celecoxib along with discussions on the various test systems to assess selectivity. The excerpt from my recent review and its clinical potential is set firmly in context.

At last (Ballou et al) a detailed and intelligent account of the lessons that we should have learned from the study of COX-1 and -2 deficient animals. Indeed, the knee jerk response, if not silence, to "unexpected" data obtained from these animals, such as the lack of gastrointestinal damage in COX-1 knockouts, simply allows prevailing simplistic theories on the role of the two enzymes to be maintained a bit longer. The following chapters on enzymes in nocioception, Alzheimer's disease, and rheumatoid arthritis, and bone are a treat, and reflect the scope of the book. Whittle, Hawkey, and Rodriguez could have combined their three chapters on the gastro-intestinal toxicity of NSAIDs as their knowledge is complementary. They invade each others "intellectual" territory which gives the impression of conflict and confusion where none exists. The chapter by Dulois on COX-2 in colorectal cancer is only disappointing because of its brevity; the man has so much more knowledge to share! However, this is partially compensated by an excellent review of the role of COX-2 in other cancers. The book ends with rather biased accounts on the virtues of each of the COX-2 selective agents.

This book is currently the best available reference source on a subject that is growing in importance and complexity. The only irritations are some unnecessary self-congratulatory comments and unashamed pleas for financial support that will raise the eyebrows of the purchaser of this book in Hay-on-Wye bookshops at the end of this century. I can thoroughly recommend it for all established prostaglandin and COX research- ers, and PhD students. Clinical gastroenterologists will find something new of interest. Those with time, concentration, and a biochemical background will surely enjoy this book as much as I did.

Aah! Catherine my lifelong comrade has just brought me a wee dram (Talisker single malt whisky with 10% v/v local water). Life just does not get much better than this. My euphoria is however marred by the knowledge that the COX-2 selective drugs are not available to the citizens of Cuba as a result of the USA's embargo.

P Hungin

Drug-Induced Liver Disease


On the face of it, this hardback does not sound like a very good bedtime read and splashing out £195 might seem a little extravagant for what might appear to be some dry tome that would readily gather dust on a shelf. It was therefore with some trepidation that I received this ostensibly unwieldy 773 page bound and green covered book, and turning the pages quickly, the casual reader might still be deceived into casting it into the nether regions of a desk drawer or the inner corners of an office. However, I am pleased to say that these were all poorly grounded misapprehensions, because this is an expertly written and very readable account of an excellent galaxy of experts, covering the mechanisms of drug induced liver injury in an easily readable format (who cannot stand up and say that paracetamol/acetaminophen poisoning is a mystery to most mere mortals, despite the fact we all know the antidote?). The book also contains 412 pages of clinical cases, ranging from a packed volume of chapters on the hepatotoxicity of specific drugs for quick and easy reference, which is set firmly in clinical context, and for the generalist, a very useful clinical section on diagnosis and management of drug induced liver disease.

Another reason not to look at such a book might be that many of those emanating from the USA have an American perspective only, but this is a real exception as at least one third of the chapters are written by authors from countries as far apart as Switzerland and India and the book as a whole develops a truly international theme. It is well referenced in a very authoritative and up to date way, and sheds light on a whole host of topics that are bothersome to most gastroenterologists, such as the usage of methotrexate in psoriasis and rheumatoid arthritis (with helpful guidelines on when to offer baseline and follow up liver biopsy and to whom), antithrombotic agents (and when to worry!), and in this day and age, sections on psychotropic agents, drugs of abuse, and importantly, when many patients actually do see the gastroenterologist for complaints of nausea or vomiting. The history, biochemistry, and physiology of many of the drugs covered is also covered in an excellent manner. DuBois on COX-2 in colorectal cancer is only mentioned in passing, but it is a bit of a mystery to me how he can maintain a bit longer. The following chapters on the role of COX-2 in other cancers, increasing incidence of certain liver tumours, are keen to seek out the veritable pharmacopoeia that can be found in the average health food shop or in Chinatown, an authoritative compendium on alternative medicines, vitamins, and natural hepatotoxins. With the increasing incidence of certain liver tumours, I found sections on the adverse effects of hormones (covering everything from adrenals, focal nodular hyperplasia, and frank malignancies to vascular abnormalities in the liver) and on environmental toxins very interesting and informative.

In closing, I would say that at the price, most people would not want to rush out and buy a copy immediately, I would wholeheartedly recommend that every hospital library invests in a copy for use by gastroenterology trainees, trainees from other disciplines, and even the odd consultant gastroenterologist! The book would be very useful for hospital pharmacists, nurse practitioners, and also for medical students who need to reference the subject in more depth. However, on considered reflection, I think that most gastroenterology units should think carefully about buying a copy—with increasing drug usage by patients, illicit or otherwise, it is an exploding problem. The book provides an aide memoire for those that need it and it won’t gather dust for long!

S D Taylor-Robinson

New In Vivo Imaging Modalities for Molecular Biology, Cell Biology and Physiology

This Jacques Monod conference will be held on 31 May–4 June 2003 in Roscoff, France. Further information: Bertrand Tavitian, INSERM M10103, Service Hospitalier Frédéric Joliot, CEA Direction des Sciences du Vivant, Direction de la Recherche Médicale, 4 place du Général Leclerc, 91401 Orsay Cedex, France. Tel: +33 169 867 779; fax: +33 169 867 739; email: tavitian@shfj.cea.fr

www.gutjnl.com

Downloaded from http://gut.bmj.com/ on April 22, 2022 by guest. Protected by copyright.
Prague Hepatology Meeting
To be held on 5–7 June 2003 in Prague, Czech Republic. Leading speakers from Europe and the USA will present new ideas and suggestions on pathophysiology, diagnostics, and therapy of liver diseases in ten programmes blocks. Further details: Ms Veronica Revicka. Tel: +420 241 445 759; fax: +420 241 445 806; email: veronika@congressprague.cz

Falk Symposium—New Findings on Pathogenesis and Progress in Management of IBD
Two symposia and a workshop will be held on 10–14 June 2003 in Berlin, Germany. Further details: Falk Foundation e.V., Congress Division, PO Box 6529, Leinenweberstr. 5, 79041 Freiburg/Bt, Germany. Tel: +49 761 15 140; fax: +49 761 15 14 359; email: sympo@falkfoundation.de; website: www.falkfoundation.de

Gastroenterology and Endotherapy: XXIst European Workshop
This will be held on 16–18 June 2003 in Brussels, Belgium. Further details: Nancy Beaufrez, Administrative Secretariat of the Workshop, Gastroenterology Department, Erasme Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 (0)2 555 49 00; fax: +32 (0)2 555 49 01; email: beaufrez@ulb.ac.be

The Association of Coloproctology of Great Britain & Ireland
This annual meeting will be held on 7–10 July 2003 in Edinburgh, UK. Further details: Conference Secretariat, The ACGBI at the Royal College of Surgeons of England, 39–43 Lincoln’s Inn Fields, London WC2A 3PE. Tel: +44 (0)20 7973 0307; fax: +44 (0)20 7430 9235; email: acpgbri@aasgbi.org.uk; website: www.acpgbi.org.uk

European Helicobacter Study Group (EHSG)
This meeting, on Helicobacter infections and gastroduodenal pathology, will be held on 3–6 September 2003 in Stockholm, Sweden. Further details: Professor Torkel Wadstrom, President- EHSG, Lund University, Department of Infectious Diseases & Medical Microbiology, Division of Bacteriology, Solvegatan 23, SE-223 62 Lund, Sweden. Tel: +46 46 173 241; fax: +46 46 152 564; email: torkel.wadstrom@mmb.lu.se; website: www.helicobacter.org

Falk Symposium 135—Immunological Diseases of Liver and Gut
This symposium will be held on 12–13 September 2003 in Prague, Czech Republic. Further details - see Falk Symposia above

The European Society of Parenteral and Enteral Nutrition (ESPEN)
ESPEN will celebrate its silver anniversary at the time of the annual congress, which is to be held on 20–23 September 2003 in Cannes, France. Further details: www.espen.org

XII Falk Liver Week
The XII Falk Liver Week, in honour of Hans Popper's 100th birthday, will be held on 15–22 October 2003 in Freiburg, Germany. Further details - see Falk Symposia above.

European Course on Laparoscopic Endoscopy
This course will be held on 18–21 November 2003 in Brussels, Belgium. Further details: Secretary to Professor Cadière, Service de Chirurgie Digestive, Rue Haute 32, Brussels 1000, Belgium. Tel: +32 (0)2 648 07 60; fax: +32 (0)2 647 86 94; email: straeb.asmb@proximedia.be; website: www.straeb-asmb.com

Hong Kong-Shanghai International Liver Congress 2004
This conference will be held on 14–17 February 2004 in Hong Kong. The topic of the conference is “Liver Diseases in the Post-Genomic Era”. Further details: Ms Kristie Leung, Room 102–105 School of General Nursing, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong. Tel: +852 2818 4300/8101 2442; fax: +852 2818 4030; email: kristieleung@hepa2004.org; website: www.hepa2004.org