**LETTERS**

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**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 after initiation of azathioprine treatment. These data are not available for patients with IBD.

In a retrospective study, we analysed the time of onset of all drug related toxicity in IBD patients post initiation of azathioprine therapy. A total of 110 consecutive IBD patients with a history of azathioprine use were identified (table 1). Patients were identified from the hospital inpatient enquiry system, IBD clinic, and pharmacy records. Mean azathioprine dose was 2 mg/kg/day (range 1–3). Mean age of the patients on azathioprine was 38.11 years (18–76). Seventeen (15%) patients (13%) suffered from azathioprine related early toxicity (table 1). Mean azathioprine dose in those showing drug toxicity was 100 mg/day (50–150). Most (77%) drug related toxic events manifested within the first 12 weeks of therapy (fig 1). However, the mean time of onset of drug related toxicity depended on the side effect observed. For example, most drug related nausea was observed within two weeks of commencing treatment while all cases of deranged liver function tests were detected within eight weeks of treatment onset. Significantly, this was not true for bone marrow suppression. The mean duration of treatment in the two patients who experienced this side effect was 11 weeks (range 10–12). Both cases occurred outside the “stringent” eight week monitoring period recommended by the drug’s manufacturer. Hence identification of bone marrow suppression would have been delayed using the current British and manufacturer’s guidelines. Three further episodes of neutropenia were identified during long term (>3 months) treatment in three patients who continued on maintenance azathioprine (mean duration 101 weeks/patient, range 2 weeks to 5 years). In our practice, we feel that significant toxicity during the early (<3 months) period of therapy could have been missed by strictly following existing guidelines.

Early detection of abnormalities in asymptomatic patients helped in dose adjustment with resolution of side effects. In addition, early detection of azathioprine related bone marrow suppression is likely to save lives. We recommend that gastroenterologists employ an extended (three month) period of intensive haematological monitoring after initiation of azathioprine therapy in IBD. Although neutropenia is occasionally observed beyond this point, intensive monitoring for the duration of treatment, which may continue for years, is clearly not practical from a patient or service perspective. However, this serves to emphasise the importance of continuous patient education concerning “alarm symptoms” throughout the duration of azathioprine therapy.

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**Table 1** Patient characteristics and side effects encountered during the initial period of therapy (three months) with azathioprine in patients with inflammatory bowel disease

<table>
<thead>
<tr>
<th>Ulcereative 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>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>48</td>
<td>2</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal LFTs</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td>Hepatitis rash (1)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous associated symptoms</td>
<td>Tiredness (1)</td>
<td>Headache (1), allergic skin rash (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

LFT, liver function test.

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**References**


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**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.1 2 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.
Quasim et al. state that this information is not available for patients with inflammatory bowel disease (IBD). However, data can be derived from observations 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 3.8×10^9/L; platelets 11×10^9/L) at 7 months of treatment. Because severe bone marrow toxicity can be precipitated by the addition of aminosalicylate derivatives, marrow toxicity can be precipitated by the addition of aminosalicylate derivatives.

Weekly full blood counts during the first three months of treatment are recommended. Because severe bone marrow toxicity can be precipitated by the addition of aminosalicylate derivatives, marrow toxicity can be precipitated by the addition of aminosalicylate derivatives. Additionally, the additional observation that patients genetically at high risk of developing ulcerative colitis may be considered as candidates for appendectomy for the objectives of preventing the development of ulcerative colitis and also decreasing its severity.

Appendectomy and ulcerative colitis

Cosses et al. demonstrated that previous appendectomy is not only associated with a lower incidence of ulcerative colitis, but also with a less severe course of the disease. Although we can fully agree with this result, we disagree with the recommendation that previous appendectomy and still found a less severe course of the disease. We believe they are incorrectly arguing 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 influenced by 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 appendectomy outside clinical trials as evidence showing that appendicectomy will protect these persons is lacking.

P C J ter Borg, H R van Buuren
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Reference


Authors’ reply

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. 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 before disease onset. This latter observation argues against any therapeutic effect of appendicectomy after onset of ulcerative colitis. The problem is different excluding all patients without appendicitis, 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 before disease onset. This latter observation argues against any therapeutic effect of appendicectomy after onset of ulcerative colitis. The problem is different

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 a decreased risk of ulcerative colitis, suggesting that appendicectomy rather than appendicectomy protects against ulcerative colitis. Cosse 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 arguing 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 influenced by 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.

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References


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predisposing genotype for ulcerative colitis, and a clinical trial assessing the benefits of prophylactic appendectomy will be warranted.

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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 2001;48:suppl V):v10–12).

(1) In the present medicolegal environment, failure to comply with guidelines which carry the imprimatur of respected national bodies will require vigorous defence should a mishap occur. We do not believe the evidence is strong enough to justify the recommendation that every patient with extensive colitis and annual colonoscopy thereafter are the best we can do 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.1 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 alone is the very aim of surveillance and just because it is found on the first colonoscopy in a surveillance programme it should not be deemed a failure of surveillance.

(2) 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 2001;48:suppl V):v10–12). 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 Wiseher v Essex Area Health Authority3 demonstrates that we now need to practice to the highest standards. However, the courts (Early v Newham Health Authority)4 will consider local guidelines. This will be of particular importance in 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 by centres is uncertain, such an approach is widespread. The purpose of guidelines is to identify good practice and to provide a uniform approach throughout the country. The alternatives are to abandon surveillance or to offer haphazard and unstructured (and ineffective) service. The necessity of surveillance for both colitis and Crohn’s patients is estimated to be £9600 per annum. Hopefully, all centres will be able to meet 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, as patients should now accept some responsibility for their illness.5

(2) Forbes et al raise the point that before any guidelines are imposed there should be firm evidence of a scheme’s efficacy. There are no randomised studies comparing different surveillance protocols or for that matter even a consensus opinion across the UK. Once the guidelines were published they were fully evaluated before they were accepted and published. They are not simply the opinions of two consultant gastroenterologists.

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 2001;48:suppl V):v10–12). They raise a number of points which will be answered in turn.

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References
2 Forbes, S Gabe, J E Lennard-Jones, K Wilkinson
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Reference
(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 a potential improvement on the present routine practice of some gastroenterologists.

The meta-analysis does show an increasing cancer risk in the second and third decades of life and is not controversial in the least. The whole point of stratified data was to see if the cancer incidence did increase by decade of disease. It is only stratified data that can be used in this way. Such data will give the most accurate estimate as it is only these data that included studies which reported cancer incidence stratified by decade and duration of patient follow up (19 studies). The decade specific incidence rates correspond to a cumulative risk of 1.6% (95% confidence interval (CI) 1.2–2%) by 10 years, 8.3% (95% CI 4.8–11.7%) by 20 years, and 18.4% (95% CI 1.2–2%) by 10 years, 8.3% (95% CI 4.8–11.7%) by 20 years, and 18.4% (95% CI 1.2–2%) by 10 years, 8.3% (95% CI 4.8–11.7%) by 20 years, and 18.4% (95% CI 1.2–2%) by 30 years.

The 26 studies Forbes et al refer to also included studies which reported cancer incidence where only duration of patient follow up was reported—that is, the incidence rates were not broken down for each decade. Even with 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 and we all know that 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 standard? It is concerning to us that the unstratified data from the unpublished St Mark’s data show a disease in different world populations. Atten reviews the annual incidence of Crohn’s disease in ulcerative colitis: An analysis of performance. Gastrointestinal Endosc 2000;52:153–6.


Crohn’s disease: ethnic variation in CARD15 genotypes

Crohn’s disease shows significant variability in incidence between different world populations. For example, Kurata and colleagues studied the annual incidence of Crohn’s disease in Caucasian, African, Asian, and Hispanic individuals, with an observed range from 43.6 per 100,000 population for Caucasians, 29.8 for African, 5.6 for Asian, and 4.1 for Hispanics. Recently, a genetic basis for Crohn’s disease has been described. The CARD15 gene (NOD2, MIM 601996) acts as a sensor for bacterial products. When functioning correctly, this would lead to activation of nuclear factor κB1. Sixty seven variations in the CARD15 gene in Crohn’s disease have been reported.* Of these 67, three variations (2104 C>T [R702W]; 2722 G>C [G908R]; 3020ins [007fs]) have been consistently correlated with increased susceptibility to Crohn’s disease.***

Currently, these three variants have only been extensively assessed in patients of European, French Canadian, or American Caucasian descent. Using Pyrosequencing, we analysed all three variants in genomic DNA from 95 European (American Caucasian), 93 African (Ghanaians), and 53 Asian (Chinese) unrelated healthy volunteers. Frequencies for the R702W variant allele were 2% and 0% in European and African samples, respectively, 3% and 1% for G908R, and 3% and 0% for 1007fs (p<0.05 in all cases). None of the variants was observed in the Asian population, consistent with a recent study of Japanese patients with Crohn’s disease.* The ethnic variation seen here could, in part, contribute to the variations in the frequency of Crohn’s disease in different world populations. Attention should be paid to the discovery of novel geographically selective variants before evaluating association with Crohn’s disease in non-European populations.

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References


Acknowledgements

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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 developing benefits of diagnostic and interventional gastrointestinal endoscopy but was led to ask “Will the gastroenterologist simply become a technician who carries out a series of complex but personally satisfying procedures?”

Most gastroenterologists remain general physicians but in talking with specialist

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Case No 1

An elderly man was admitted to hospital with severe anemia. The houseman obtained a history of aspirin ingestion and, over the preceding few weeks, recurrent melena. He felt faint, vomited black fluid, and passed melena. After the weekend he was admitted to hospital. His blood count showed Hb 9.7, MCV 105, WCC 10.3, and platelets 240. As in case No 1, he was listed for OGD and colonoscopy. At OGD he was found to have a marked antral gastritis and multiple duodenal erosions. The patient recovered well from the investigation of possible gastrointestinal pathology, but the patient died of a myocardial infarction a few days later. As the death was unexpected and, at post mortem, showed no evidence of gastrointestinal disease, the patient died of myocardial infarction.

Case No 2

An elderly man was admitted to hospital with a history of weight loss and melena on a diet of coffee and tobacco. He was listed for OGD and colonoscopy. At OGD the stomach was described as showing a moderate erythematous/exudative gastritis and multiple duodenal erosions. The patient was transfused and without further investigation the physician/gastroenterologist arranged for oesophago-gastro-duodenoscopy (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 then transferred to the home to be admitted to the gold service 36 hours later with faecal peritonitis. The colon had been perforated at the rectosigmoid junction. The patient recovered well from reparative surgery but died six weeks later from 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.

References

1 Booth CC. What has technology done to gastroenterology? Gut 1983;26:1088–94.
4 Which 5-ASA?

I read Dr Travis’ therapy update (Gut 2002;51:548–9) with interest; the topic is timely in a medical world so recently challenged by new generic mesalazine brands. I note the choice of time dependent mesalazine (Pentasa) but, if mesalazine is to be relied upon exclusively, some brand names suggest Pentasa may not be the best choice. The recent study by Kruis and colleagues1 in the maintenance of remission in ulcerative colitis (UC) found that with Pentasa 1.5 g/day, 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 colon 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.2 This latter study highlights the lack of efficacy of mesalazine released by a time dependent delivery system in active UC. In contrast, three studies comparing balsalazide with mesalazine (pH dependent release),3,4 containing a total of 426 patients, have shown balsalazide to be superior in active UC, with rapid resolution of symptoms (median 10 days in one study)3 and superior sigmoidoscopic scores (in all three studies).5 Concentrations of 5-aminosalicylic acid (5-ASA) were 4.5-fold lower in patients treated with balsalazide than mesalazine (p=0.018)4. Patients with most to benefit are new patients with distal disease.6 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). AdvaZ (Advacse of newly licensed SASP) and those wishing to use the least expensive treatment cite trials of SASP versus newer agents7 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 studies, patients diagnosed or previously untreated UC were randomised to SASP or balsalazide; 34% were intolerant of SASP at the modest dose of 3 g compared with 5% daily for balsalazide 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 to 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 trials shows that mesalazine release mechanism is important for the efficacy, reliability of delivery, and safety of the oral preparations and that balsalazide is not the usual standard for other agents to be judged against.

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Conflict of interest: The author has accepted hospitality from the manufacturers of all of the current 5-ASA preparations, and sat on an advisory panel for Shire.

References

1 Kruis W, Schreiber S, Theuer D, et al. Low does 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% (20/232) 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 have a higher chance of rebleeding compared 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, Syntay 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 in the current study the authors found that 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. Additionally, 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 PPG post-TIPS was associated with a lower risk of bleeding. This was 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. Additionally, 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.

For the group 1, there was no difference in post-TIPS PPG between patients who did and did not re-bleed, suggesting that PPG may not be a critical determinant of variceal bleeding in patients who have a low PPG to start with. The role of PPG in dictating the natural history of GV is not known. Conceptually, insertion of an artificial portosystemic shunt into a patient who already has a large spontaneous shunt effectively offloading the portal pressure would not seem to confer much benefit. Do these GV (and possibly OV) patients with low PPG pre-TIPS and with a possible CRS really benefit from TIPS?

MR angiography can accurately assess for presence of a spontaneous GRS. There is a compelling argument that this should be an essential part of the assessment algorithm of patients with GV if a large spontaneous shunt is present, and PPG (as measured by hepatic vein wedge pressure gradient (HVPG)) is <12 mm Hg, then perhaps other therapeutic options such as B-RTO (balloon occluded retrograde transvenous obliteration) should be considered. Hopefully more prospective data, examining the role of PPG, TIPS, and B-RTO in the management and outcome of GV will help clarify these issues.

References

Authors’ reply
We agree that the presence of gastrointestinal 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 a TIPS for any indication. Identified shunts were in 18.3%. A wider portographic review and a prospective magnetic resonance angiography study will be required to answer the questions raised. For the group 2 patients, 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 oesophageal 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 variceal wall tension play an important part in the risk of variceal bleeding in patients with a PPG of <12 mm Hg. It is also true that portal pressure directly affects the variceal 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 variceal bleeding, as mirrored by studies from others. At the present time it is the most effective non-surgical method of treating gastric variceal haemorrhage and preventing rebleeding. Other therapeutic options are promising, and we have previously reported on the effective use of human thrombin in the treatment of acute gastric variceal haemorrhage. However, controlled studies are required before universal recommendation of endoscopic therapies for gastric variceal haemorrhage.
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 Christmas and is currently observing whales off the east cost of the USA where I hope he will encounter the albino whale, T. 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 exceeded all expectations, bringing together some of the people who 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-1 and COX-2 in the context of enzymes in nocioception, Alzheimer’s disease, kidney, apoptosis, labour, cardiovascular system, 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 other’s “intellectual” territory which gives the impression of conflict and confusion where none exists. The chapter by DuBois 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 researchers, and PhD students; traditional 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 companion 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.

I Bjarnason

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 marketeagnost 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 773 page beige 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 bottom 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 authoritative introduction to vascular abnormalities in the liver) and on environmental toxins very interesting and informative.

The book is currently the best available reference source on the subject in much 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

PostScript

available evidence about different management approaches.

The book also has a feel of having been constructed from an upstream viewpoint. Apart from a hepatologist, the other five contributors are all surgeons—it might have been useful to have had the perspectives of a general physician and a general practitioner even if only to raise the pragmatic queries that arise at the earlier stage of management of hepatobiliary problems. An example is the potential prophylactic management of patients with varices. As it stands, variceal management in this publication commences essentially after the bleed with only a few lines on prophylactic management, and even those largely dismissive of possible measures apart from the global use of beta blockers. So what should a primary care practitioner dealing with a patient who might have varices actually do, and at what stage of abnormal liver tests or clinical findings is referral likely to be rewarding?

Increasingly, on a worldwide basis, a primary care clinician or a general practitioner with generic interests provides initial health care. Many of them will rely on such publications as a ready source of information. Ease of access to the information is important—this is assisted in this ABC by the use of summary points and clear illustrations. The aim of the publishers and the desire to provide an overview and to enable the clinician to keep abreast of advances in the common and the rarer conditions. It succeeds in this.

P Hungin

This Jacques Monod conference will be held on 31 May–4 June 2003 in Rozel, France. Further information: Bertrand Tavitian, IN- SERM 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@shlj.cea.fr

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

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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 Symposia—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/B, Germany. Tel: +49 761 15 14 359; email: symposia@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 Beausprez, 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: beausprez@ulb.ac.be

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 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, 33–43 Lincoln’s Inn Fields, London WC2A 3PE. Tel: +44 (0)20 7973 0307; fax: +44 (0)20 7430 9235; email: acgbi@asgbi.org.uk; website: www.acgbi.org.uk

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 Cadère, Service de Chirurgie Digestive, Rue Haute 322, 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
TPMT in the treatment of inflammatory bowel disease with azathioprine

A Qasim, J Seery, M Buckley and C O Morain

*Gut* 2003 52: 767
doi: 10.1136/gut.52.5.767

Updated information and services can be found at:
http://gut.bmj.com/content/52/5/767

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**Notes**