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) activity 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 monitoring in IBD patients receiving this drug.

The importance of ongoing haematological monitoring in IBD patients receiving this drug.

The importance of ongoing haematological monitoring in IBD patients receiving this drug. This conclusion is in agreement with other published work and emphasises the role of thiopurine methyltransferase (TPMT) activity in inflammatory bowel disease (IBD) (Gut 2001;49:278–81). Thiopurine related toxicity in patients with a history of azathioprine use has been 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 of 110 patients (15%) suffered from azathioprine related early toxicity (table 1). Mean age of the patients on azathioprine was 38.11 years (18–76). Seventeen of 110 patients (15%) 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 toxicity during 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.

A Qasim, J Seery, M Buckley, C O Morain
Gastroenterology Department, AMNCH, Tallaght, Dublin 24, Ireland

Correspondence to: A Qasim, qasim@tcd.ie

References


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 role of early monitoring is a matter of controversy. The matter for debate is the time of onset of potentially life threatening myelosuppression.

Table 1

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>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>45</td>
</tr>
<tr>
<td>female</td>
<td>15</td>
<td>48</td>
<td>65</td>
</tr>
<tr>
<td>nausea/vomiting</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Abnormal LFTs</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
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<td>Infections</td>
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<td>1</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous associated symptoms</td>
<td>Tiredness (1)</td>
<td>Headache (1), allergic skin rash (1)</td>
<td>3</td>
</tr>
</tbody>
</table>
Quasi 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.1 14 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 0.9×10^11/L) within one month of starting azathioprine (2–3 mg/kg) as second line therapy for Crohn’s disease.

Specifically for the patient with Crohn’s disease, Colombel and colleagues5 have reported that TPMT deficient individuals experience leucopenia or thrombocytopenia within 15 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 colleagues6 who reported myelosuppression in a TPMT deficient Crohn’s patient after 1.75 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.

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.

P C J ter Borg, H R van Buuren
Erasmus MC, Rotterdam, the Netherlands
Correspondence to: Dr P C J ter Borg, Dr Molewaterplein 40, Rotterdam, the Netherlands; pterborg@zonnelt.nl

Reference

Authors’ reply
Many French surgeons in 1900 did recommend removing preventively all appendixes of young people (see Marcel Proust, “À 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.15 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 overrepresented.

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’1 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.15 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 warrant-
ized.

J Cosnes, F Carbonnel, L Beaugerie, 
Service de Gastroentérologie et Nutrition, Hôpital St-Antoine, Paris, France

Correspondence to: Professor J Cosnes, Service de Gastroenterologie et Nutrition, Hôpital St-Antoine, 184 rue du Fauquier St-Antoine, 75571 Paris cedex 12, France; jacques.cosnes@bat-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 2001;48:112–18).

(1) In the present medicolegal environ-


ment, 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 with 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 protagon-


ists 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, are to be the sincerely 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 con-


sideration. (3) The recommendations for patients with extensive colitis of colonoscopy 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 ulcerative 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 pub-


lished data after the third decade are few due to the small numbers involved.

(4) We have concerns about the benefits of 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 reduction is examination is reduced as more biopsies are taken in practice the additional yield is very low indeed. During a recent study at St Mark’s Hospital, almost 3000 random surveil-


lace 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 by 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, Walford Road, Harrow HA1 3JU, 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 surveil-


ance for asymptomatic colorectal cancer in asymptomatic patients with inflammatory bowel disease (Gut 2001;48:112–18). 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 Wishart v Essex Area Health Authority demonstrates that even guidelines now need to practice to the highest standards. However, the courts (Early v Newham Health Authority) will consider local guidelines. This will be of particular importance to units that are unable to deliver standards that have been identified nationally, provided the local prac-


tice has been formulated into a local guide-


line. There is a wealth of data supporting the increased cancer risk in patients with ulcerative colitis and evidence of the effect of surveillance as practice in some centres is uncertain, such an approach is widespread. The purpose of guidelines is to identify good practice and to develop a uniform approach throughout the country. The alternatives are to abandon surveillance or to offer haphazard and unstructured (and therefore ineffective) service. The appropriate level of surveillance for both colitics and Crohn’s patients is estimated to be £960 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 accept some responsibility for their illness.

(2) Forbes et al raise the point that before any guidelines are implemented, there must be firm evidence of a scheme’s efficacy. There are no randomised studies comparing different surveillance protocols or for that matter even baseline screening versus surveillance. Although Forbes et al are well aware, it will never be possible to provide grade A recommendations on this issue and that the best we can do is to assess sur-


veillance programmes retrospectively. Data are accumulating that surveillance partici-


pant patients 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 One 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 alone is the very aim of surveillance and because it is found on the first colonoscopy in a surveillance programme it should not be deemed a failure of surveillance.

As such, consultation as was possible was obtained before the guidelines were pub-


lished. 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 exam-


ined by the IBD section of the BSG. After this they were posted on the BSG website for six weeks to attract comments from other mem-


bers of the society. The guidelines then went back to the Clinical Services Committee after amendments were made on the basis of com-


ments from the wide range of consultants. Finally, the guidelines were reviewed by the Executive Committee of the BSG for a further review and signing off. Thus the guidelines were evaluated, accepted and published. They are not simply the opinions of two consultant gastroentero-


ologists.
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 Caucasian, 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. The CARD15 gene has been studied extensively in patients with Crohn's disease. In 1999, the CARD15 gene was found to be associated with susceptibility to Crohn's disease. Over 67, three variations (2104G→A, 2282A→G, and 3020insC) 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 analyzed all three variants in genomic DNA from 95 European (American Caucasian), 93 African (Ghanaians), and 58 Asian (Chinese) unrelated healthy volunteers. Frequencies for the 8702W 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.

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 series of complex but personally satisfying techniques?”

Most gastroenterologists remain general physicians but in talking with specialist

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References


Acknowledgements

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Correspondence to: J M Mayberry, Department of Gastroenterology, Walsgrave Hospital, Clifford Bridge Road, Coventry CV2 2DX, UK

J A Eaden, J F Mayberry

Department of Gastroenterology, Walsgrave Hospital, Clifford Bridge Road, Coventry CV2 2DX, UK

Correspondence to: J F Mayberry; jmaybe@tiscali.co.uk

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Case No 1
An elderly man was admitted to hospital with severe anaemia. The houseman obtained a history of aspirin ingestion and, over the preceding few weeks, recurrent melena. He described feeling a hard liver edge. A blood count showed Hb 9.7, 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 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 discharged only to be admitted 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.

Case No 2
An elderly man taking diclofenac for osteoarthritis of the hip began drinking heavily preceding few weeks, recurrent melaena. He was allowed to go home only to be admitted 36 hours later with faecal peritonitis. The junction. The patient recovered well from hospital. His blood count showed Hb 9.7, 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 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 discharged only to be admitted 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.

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Which 5-ASA?
I read Dr Travis’ therapy update (Gut 2002; 51:548–9) with interest; the topic is timely in a setting about to be 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 recent studies suggest Pentasa may not be the best choice. The recent study by Kruijs and colleagues 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. 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), containing a total of 426 patients, showed that balsalazide is superior in active UC, with rapid resolution of symptoms (median 10 days in one study) and superior sigmoidoscopic scores (in all three studies). 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 benefit are new patients with distal disease. 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 newly developed balsalazide (SASP) and those wishing to use the least expensive treatment cite trials of SASP versus newer agents 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 multinational studies patients diagnosed or previously untreated UC were randomised to SASP or balsalazide; 34% were intolerant of SASP at the modest dose of 5 g daily compared with 5% daily for balsalazide, 3 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 and then lose the advantage of drug intolerance that 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 is that mesalazine release mechanism is important for the efficacy, reliability of delivery, and safety of the oral preparations and that balsalazide is presently the standard for other agents to be judged against.

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

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
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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 is hard to correlate with 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 rebleeding failed to decompensate the varices as documented by endoscopy. 4/6 of these patients had a large GRS and a PPG <12 mm Hg. Thus based on the large GRS, the PPG and the patient’s history it is likely that TIPS may not have altered the patient course. The group of patients who bled at PPG <12 mm Hg and a large GRS. Follow-up TIPS if the portogram taken at the time of TIPS? Also, did they document decompensation of varices post-TIPS? Is an indicator of the clinical efficacy of the procedure? For example, it would be interesting to know if patients in group 1 failed to decompensate 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 GRS 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 bleeding as would be hoped. However, in group 1, there was no difference in post-TIPS PPG between patients who did and did not rebleed, 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 GRS 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.

B M Ryan, R W Stockbruger
University Hospital Maastricht, Maastricht, The Netherlands

J M Ryan
Division of Interventional Radiology, Duke University Medical Centre, Durham, North Carolina

Correspondence to Dr Ryan, Department of Gastroenterology, University Hospital Maastricht, Postbus 5800, 6202 AZ Maastricht, The Netherlands; bryan@planet.nl

References

Authors’ reply

We agree that the presence of gastrorenal shunts (GRS) is likely to explain the low portal pressure gradient (PPG) post-transjugular intrapathetic 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 indication of identified shunts in 18.3%. A wider portographic review and a prospective review would be required to answer the questions raised. For the group that rebleeds, 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 <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.

D Tripathi, G Theraponodos, P C Hayes
Centre for Liver and Digestive Disorders and Department of Medicine, the Royal Infirmary, Edinburgh, UK

D N Redhead
Department of Radiology, the Royal Infirmary, Edinburgh, UK

Correspondence to: D Tripathi, Department of Medicine, Royal Infirmary of Edinburgh, Forrest Place, Edinburgh EH3 9YW, UK; d.tripathi@ed.ac.uk

References
available evidence about different management approaches.

The book also has a feeling of having been constructed from an upstream viewpoint. This is a true master at work! It is an easy book to read, even if only to raise the pragmatic queries that are at the earlier stage of management of hepatobiliary problems. An example is the potential prophylactic management of patients with varices. As it stands, valeric 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 present chapter on enzymes in nociception, Alzheimer’s disease, antiinflammatory drugs, 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 gastrointestinal 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 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. 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.

Aahl! Catherine my lifelong companion has just brought me a wee dram (Talisker single malt whisky with 10% vv 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. This is a profound injustice and a tragedy. COX-2 selective agents 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 adrenomas, focal nodular hyperplasia and frank malignancies to vascular abnormalities in the liver) and on environmental toxins very interesting and informative.

It is true to 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!...
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 Symposiums—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 14 359; fax: +49 761 15 14 359; email: syposia@falkfoundation.de; website: www.falkfoundation.de

Gastroenterology and Endotherapy: XXlst 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

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 46 147 241; fax: +46 46 152 556; 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, 35–45 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 Cadière, 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

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