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. The importance of haematological monitoring in the early detection and prevention of azathioprine related toxicity is well recognised. However, the duration of early monitoring is a matter of controversy. The current British National Formulary guidelines recommend that patients undergo blood tests at least weekly for the initial four weeks of therapy. The drug’s manufacturers recommend a more stringent monitoring policy and in their view, initial monitoring should continue for the first eight weeks of treatment. The American College of Gastroenterology guidelines recommend a slightly different approach, with fortnightly blood counts for the initial three months of therapy. The key issue in determining the value of these different approaches to monitoring is the time of onset of potentially life threatening bone marrow suppression following 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 38.1 years (18–76). Seventeen of 110 patients (15%) suffered from azathioprine related early toxicity (Table 1). Patients were identified by 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 38.1 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 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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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. 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.1–4 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) 1.6×10⁹/l, platelets 25×10⁹/l) at 10 weeks while another dosed at 1 mg/kg developed myelosuppression (WBC 3.8×10⁹/l, platelets 33×10⁹/l) after 12 weeks. Similar observations have been made by Schwab and colleagues1 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 this population.

The drug manufacturer’s guidelines, as stated in the Association of the British Pharmaceutical Industry (ABPI) medicines compendium,5 advise that at a minimum, complete blood counts 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 dose azathioprine in whom TPMT status is unknown, close adherence to the ABPI guidelines and continuation of, at a minimum, weekly full blood counts during the first three months of treatment. Because severe bone marrow toxicity can be precipitated by the addition of aminosalicylate derivatives6 to the azathioprine regime, the drug manufacturer’s more stringent blood count monitoring scheme should be considered following such adjustments in the combination therapy of refractory IBD.

Appendectomy and ulcerative colitis

Cosnes 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 patients genetically at high risk of developing ulcerative colitis may be considered as candidates for appendicectomy for the objectives of preventing the development of ulcerative colitis and also decreasing its severity.7–9

All previous studies, as well as the present study, have demonstrated an association between previous appendicectomy and a benign course of ulcerative colitis. It has not been shown that performing appendicectomy in healthy persons at increased risk of developing ulcerative colitis is beneficial. 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 disease 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 without a history of bleeding, attempts should be undertaken to induce 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 a decreased risk of ulcerative colitis, suggesting that appendicitis rather than appendicectomy 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 appendicectomy is actually higher than the effect of appendicectomy reported in the present study, which could have been caused 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.

References
1 Lennard L
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.10 Note also that the Swedish study1 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.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.11 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 decreased risk of ulcerative colitis, suggesting that appendicitis rather than appendicectomy protects against ulcerative colitis.1 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 appendicectomy is actually higher than the effect of appendicectomy reported in the present study, which could have been caused 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.
predisposing genotype for ulcerative colitis, and a clinical trial assessing the benefits of prophylactic appendicectomy 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;48:326–35).

(1) In the present medicoenviron-
mental 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 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 consultation.

(3) The recommendations for patients with extensive colitis of dysplasia every third year during the second decade of disease, every second year during the third decade, and annual colonoscopy 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 both 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.

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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 2001;48:326–35). We 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 Wisher vs Essex Area Health Authority clearly demonstrates this, and now need to apply 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.

Line. There is a wealth of data supporting the increased cancer risk in patients with ulcerative colitis and although evidence of the effect of surveillance as practiced by some centres is uncertain, such an approach is widespread. The purpose of guidelines is to identify good practice and to offer a uniform approach throughout the country. The alternatives are to abandon surveillance or to offer haphazard and unstructured (and ineffective) service. The absence of surveillance for both colitis and Crohn's patients is estimated to be £9600 per annum. Hopefully, at some stage we 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.

(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 surveillance with no surveillance (as Forbes et al 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.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.2 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 and because it is found on the first colonoscopy in a surveillance programme it should not be deemed a failure of surveillance.

As is possible, all guidelines were 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.3 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 approximately 40 individuals reviewed them. They then went through the usual guidelines process after being seen by the Clinical Services Committee before being submitted to 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 consultants. Finally, the guidelines were reviewed by the Executive Committee of the BSG for a further review and signing off. Thus the guidelines evolved and are accepted and published. They are not simply the opinions of two consultant gastroenterologists.
(3) We appreciate that increasing the colonoscopy frequency with increasing dura-
tion 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 positive improvement on the previous routine practice of some gastroenterologists.

The meta-analysis also shows an increasing cancer risk in the second and third decades of
disease and is not controversial in the least.

Specific incidence rates correspond to a cumulative
risk of 1.6% (95% confidence interval
CI 1.3–2.8%) by 10 years, 8.5% (95% CI
4.8–11.7%) by 20 years, and 18.4% (95% CI
15.3–21.5%) by 30 years.

The 26 studies Forbes et al refer to also included studies which reported cancer inci-
dence 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 prob-
ability gives 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 sur-
veillance colonoscopy. Yes it is time consuming but we all know that to stand any chance of detecting dysplasia, the more biopsies taken the better. What is the point in surveil-
ance at all if it is not conducted to the best standards—standards similar to those in other screening services.

References
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Crohn’s disease: ethnic variation in CARD15 genotypes

Crohn’s disease shows significant variability in incidence between different world popula-
tions. For example, the CARD15/NOD2 mutational analysis and phenotype correlation in 612
family members that is
consistent with a recent study of Japanese
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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 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 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 allowed to go home 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 of a pulmonary embolus.

Case No 2

An elderly man taking diclofenac for osteoarthritis and aspirin for angina was seen apart from a little fresh bleeding, the cause of which was not apparent. The patient was allowed to go home 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 of a pulmonary embolus.

Which 5-ASA?

I read Dr Travis’ therapy update (Gut 2002;51:548–9) with interest; the topic is timely in a world 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 evidence suggests Pentasa 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/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 advantage 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 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 pH 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, indicated that balsalazide to be superior in active UC, with rapid resolution of symptoms (median 10 days in one study3) 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).5 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 balsalazide (SASP) and those wishing to use the least expensive treatment cite trials of SASP versus newer agents6 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 published7,8 studies, patients newly 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% 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 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 literature is that balsalazide may be the standard for other agents to be judged against.

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PostScript

registars I have been surprised by their overwhelming 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 taking diclofenac for osteoarthritis of the hip began drinking heavily after the death of his wife. One Saturday 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 in a deformed duodenal cap. At colonoscopy, multiple diverticulae were found in the sigmoid one of which was associated with minimal perforation occurred. The patient was referred promptly for surgery. There was little faecal contamination and the patient recovered well after resection of a short length of colon.

In both of these cases the physician-gastroenterologists appeared to be working to the dictum: bleeding from the gut requires reparative surgery but died six weeks later of a pulmonary embolus.

References

1 Kruijs W, Schreiber S, Theuer 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% (20/232) of OV patients had a PPG <12 mm Hg. 

The group of patients who bleed at PPG <12 mm Hg (group 1) is particularly intriguing. As mentioned by the authors, low PPG in GV patients has been associated 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, Sanjay 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, if 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 bleeding. But based on probability, group 1 in the current study did not have a 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 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.

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References


Authors’ reply

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 study period, 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 varical 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 varical haemorrhage. However, controlled studies are required before universal recommendation of endoscopic therapies for gastric variceal haemorrhage.

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References


available evidence about different manage-
ments as a ready source of information. Ease of
access to the information is important—this
largely dismissive of possible measures apart
even if only to raise the pragmatic queries that
potential prophylactic management of pa-
tients with varices. As it stands, variceal man-
agement in this publication commences es-
entially after the bleed with only a few lines
on prophylactic management, and even those
merely dispensable 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 pri-
mary care clinician or a general practitioner
with generic interests provides initial health-
care. Many of them will rely on such publica-
tions as a ready source of information. Ease of
access to the information is important—this
was assisted in this A BC by the use of summary
points and clear illustrations. The aim of the
primary care physician or the general doctor,
for the desire to provide a succinct overview
and to enable the clinician to keep abreast of advances in the common and
rare conditions. It succeeds in this.

P Hungin

Therapeutic Roles of Selective
COX-2 Inhibitors

Edited by J R Vane, R M Batting. William Har-

The review editor sent me a book to review for Gut with holidays looming. He left a week before the end of the term 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 cairs, duns, and crannogs on the Outer Hebr-
idian 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 ex-
ceeded 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 outlin-
ing the history, biochemistry, and physiology
of COX-1 and -2 and its clinical potential. In
this book they gracefully allow etodolac and
toradol aponeurotic myths to be thrown on
the floor. The overtures are played by the COX-2
inhibitors, with inroads into the familial COX-2
selective drug. 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 ref-
ERENCE source on a subject that is growing in
importance and complexity. The only
irritations are some unnecessary self con-
gratulatory 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. Medical gastroenter-
ologists will find something new of interest.

Those with time, concentration, and a bio-
chemical background will surely enjoy this
book as much as I did.

Aah! Catherine my lifelong companion has
found 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

Edited by N Kaplowitz, L D Deleve. New York:

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
uninviting 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 dimmer corners of an office.

However, I am pleased to say that these
were all poorly grounded misapprehensions,
because this is an expertly written and
terribly oriented whole galaxy of experts, covering the mechanisms of drug
induced liver injury in an easily readable for-
mat (who cannot stand up and say that
paracetamol/acetaminophen poisoning is a
mystery to most mere mortals, despite
the fact we all know the antitode?). The book also
contains a comprehensive set 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 man-
ger 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. The book as a whole develops a true
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), antituberculous agents
(and when to worry!), and in this day and age,
sections on psychotropic agents, drugs of
abuse, and importantly, when many patients
have learned from the study of COX-1 and -2
how important the concept of drug
resistance is. 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 knock-
outs, simply allows prevailing simplistic
theories on the role of the two enzymes to be
maintained a bit longer. The following chap-
ters on enzymes in nocioception, Alzheimer’s
disease, kidney, apoptosis, labour, cardiovas-
tural system, arthritis, and bone are a treat,
and reflect the scope of the book. Whittle,
Hawkey, and Rodriguez could have com-
bined 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 confu-
sion 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! How-
ever, 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 ref-
ERENCE source on a subject that is growing in
importance and complexity. The only
irritations are some unnecessary self con-
gratulatory 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. Medical gastroenter-
ologists will find something new of interest.

Those with time, concentration, and a bio-
chemical background will surely enjoy this
book as much as I did.

Aah! Catherine my lifelong companion has
found 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

NOTICES

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, 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@shl.jcf.cea.fr

www.gutjnl.com

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May 10, 2002 by guest. Protected by copyright.
http://gut.bmj.com/
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

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 1PE. Tel: +44 (0)20 7973 0307; fax: +44 (0)20 7430 9235; email: acgibi@asgbi.org.uk; website: www.acgibi.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

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.

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