Risks and benefits of azathioprine therapy

D P B McGovern, D P Jewell

Inflammatory bowel disease

The risk of lymphoma may be increased by about fourfold in patients with inflammatory bowel disease treated with thiopurines. The increased risk could be a result of the medications, the severity of the underlying disease, or a combination of the two.

The benefits of the thiopurines, azathioprine (AZA), and 6-mercaptopurine (6-MP) in maintaining remission and corticosteroid sparing in inflammatory bowel disease (IBD) are beyond doubt. However, adverse events as well as benefits should always be considered when the effectiveness of any treatment is being evaluated. The “short term” side effects of thiopurines have been well documented and there have been a number of studies examining the role of thiopurine methyltransferase activity in predicting the risk of these side effects.

In this issue of Gut, Kandiel and colleagues address the difficult issue of the long term risk of lymphoma associated with thiopurine therapy (see page 1121). Using the technique of meta-analysis of cohort studies, the authors concluded that there was about a fourfold increase in lymphoma in IBD patients treated with thiopurines. The headline from this study will cause alarm among patients and clinicians alike but, as in all studies, closer examination of the limitations (as acknowledged by the authors) of the study is necessary before firm conclusions can be drawn. Meta-analyses have their own particular methodological problems and are only as good as the constituent studies. The authors demonstrated heterogeneity between the studies suggesting that the studies were “different” with respect to study population or methodology. The consistent risk of lymphoma, even after sensitivity analyses (to ensure that rogue studies had not radically influenced the risk), is somewhat reassuring but the negative correlation between size of cohort and risk of lymphoma is of concern.

Association does not prove causation and it is possible that the demonstrated risk is with IBD itself and not with thiopurines. The authors cite evidence that there is no association between IBD and lymphoma but other data suggest that there may be a significant but small association. The authors address this by demonstrating an increased lymphoma risk in patients treated with thiopurines when compared with IBD patients who had not received thiopurines. Thiopurine use however may simply be a marker for more severe disease which may itself increase the risk of lymphoma. This effect of disease severity may be small and already underpowered studies may have missed such a relationship.

The studies included in this analysis were mainly from tertiary referral centres and the largest population based study found no thiopurine-lymphoma association, further raising the possibility of a disease severity bias. Smoking has a deleterious effect on lymphoma. This effect of disease severity is with IBD itself and not with thiopurines. The increased risk could be a result of the medications, the severity of the underlying disease, or a combination of the two.

The Wellcome Trust Centre for Human Genetics, Headington, Oxford, UK

D P Jewell, Gastroenterology Unit, University of Oxford, Oxford, UK

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REFERENCES

5-HT₃ receptor antagonists ameliorate fatigue: so much potential, so little knowledge!

N M Barnes

There is growing evidence that 5-HT₃ receptor blockade will benefit patients with fatigue. Further research is needed to determine the mechanism underlying this widespread clinically important symptom and therapies may be derived from targeting the 5-HT system

Despite a high prevalence with massive socioeconomic implications, fatigue per se, or as a symptom of a diagnosed condition, remains poorly understood. Much of the evidence available arises from measurement of biochemicals or proteins; alterations in which may be primary or secondary to the symptom, or indeed associated with another aspect of an underlying disease. However, an increasing body of evidence implicates an altered central 5-HT (5-hydroxytryptamine; serotonin) system. Although apparent inconsistencies are evident (for example, see Hartz and colleagues), elevated 5-HT neurotransmission appears most likely. 2

Numerous distinct receptors have evolved to transduce 5-HT signalling. The majority of these receptors (at least 13) are G protein coupled receptors (GPCRs) but, unusual for monoamine neurotransmitters, an additional receptor, the 5-HT₃ receptor, is a member of the cyst-cys loop ligand gated ion channel superfamily; other members being the nicotinic acetylcholine receptor, the GABAA receptor, and the glycine receptor. 3 The 5-HT₃ receptor is predominantly expressed by central neurones and peripheral nerves and is known to mediate fast synaptic neurotransmission in the brain.

The clinical availability of 5-HT₃ receptor antagonists offers an opportunity to probe further for roles for this receptor. In this issue of Gut, Piche and colleagues provide further support for the use of 5-HT₃ receptor antagonists to alleviate fatigue, in this case arising from hepatitis C infection. They built on previous observations where these compounds have reduced fatigue in uncontrolled studies with small numbers of patients. 4, 5 The double blind placebo controlled trial with originally 36 patients demonstrated that chronic administration of the selective 5-HT₃ receptor antagonist ondansetron (Zofran; a relatively low oral dose of 4 mg twice daily for 30 days) improved the level of fatigue in patients relative to placebo (although a significant positive placebo response was also evident at one of the time points). As acknowledged by the authors, they selected patients with relatively high levels of fatigue, which may have allowed a greater scope for the detection of drug induced effects in this symptom that is notoriously difficult to quantify. Interestingly, depressive symptoms in patients also improved. Given the strong association of fatigue as a symptom of depressed patients, it would be pertinent to investigate whether the ondansetron induced reduction in the two symptoms are interrelated. Of further note, both the reduction in fatigue and depression were also evident 30 days after discontinuation of the drug treatment, suggesting that plastic changes may have occurred, as has been postulated for more traditional antidepressant therapies. It may be relevant, however, that another symptom often associated with hepatic disease, pruritus, also likely to be centrally mediated, appears responsive to 5-HT₃ receptor antagonists. 6, 7

From their early development in the mid- to late 1980s, the selective 5-HT₃ receptor antagonists have been hailed for their potential clinical utility. Much of the initial impetus for their synthesis and development came from the antiemetic efficacy of metoclopramide. At high dosage, metoclopramide afforded additional protection from the nausea and vomiting associated with aggressive anticancer treatment that appeared to correlate with the relatively low affinity to antagonise 5-HT₃ receptors (for review see Barnes and colleagues). 8 The strategy was vindicated with the substantial antiemetic efficacy of selective 5-HT₃ receptor antagonists such as ondansetron (Zofran), granisetron (Kytril), and tropisetron (Navoban).

Soon after the availability of selective 5-HT₃ receptor antagonists, pioneering work by Costall and Naylor, as well as others, demonstrated that these compounds displayed therapeutic potential in numerous animal models predictive of, for instance, anxiolytic, antipsychotic, and cognitive enhancing actions. The subsequent clinical trials however were largely disappointing and curtailed the development of these compounds for these indications (for reviews see Barnes and Sharp and Costall and Naylor). Clear reasons for these failures remain to be elucidated. Perhaps the animal models simply did not accurately mimic the human diseases? An often quoted explanation is that the unusual bell shaped dose-response curve often evident with 5-HT₃ receptor antagonists (that is, efficacy is lost at higher dosages) necessitates a wide dose range to prove the negative (that is, to prove that there really is no effect). This phenomenon still awaits a mechanistic rationalisation.

However, perhaps the failure simply reflects the different pattern of forebrain expression in humans compared with laboratory animals. For instance, the human cerebral cortex displays relatively low levels of 5-HT₃ receptor binding sites, unlike rodents. 9, 10 In contrast, human extrapyramidal regions such as the caudate nucleus and putamen display relatively high levels of 5-HT₃ receptor binding sites, whereas little corresponding expression is evident in rodents. 11, 12 The area is further complicated by the apparent species specific expression of individual 5-HT₃ receptor subunits. Thus central expression of the biophysical 5-HT₃ subunit is apparent in human but not rodent brain. 13, 14 The presence of at least three further purported 5-HT₃ receptor subunits (5-HT₃C, 5-HT₃D, and 5-HT₃E subunits) within the human genome, with no corresponding genes identified in rodents, further highlights interspecies differences in the potential expression of different 5-HT₃ receptor isoforms. This area has received little investigation to date, yet in terms of pharmacology, at least the homomeric 5-HT₃A receptor and the heteromeric 5-HT₃A/3B receptor appear nearly identical, 15 although major functional differences are apparent—for instance, the differing ionic selectivity of the ion channel integral with the receptor, with homomeric 5-HT₃A receptors displaying high permeability to Ca²⁺ relative to the heteromeric 5-HT₃A/3B receptor complex. A further difference is the single channel conductance, which is an order of
Alcoholic hepatitis

Predicting mortality by the Glasgow alcoholic hepatitis score: the long awaited progress?

H Tilg, A Kaser

The new Glasgow alcoholic hepatitis score may represent a substantial improvement in clinical phenotyping and could catalyse the development of new treatments in severe alcoholic hepatitis

Severe alcoholic hepatitis is associated with a high mortality and the presence of liver failure, manifested by jaundice, coagulopathy, and often encephalopathy. Whereas insights into the pathophysiology of this devastating disease have improved over the past years, clinical progress in the last two decades has been minor. For more than two decades, steroids have remained the only moderately effective treatment option. One key confounder to most therapy studies has been the use of the discriminant function to identify patients at highest risk of mortality in the absence of better scoring systems more accurately predicting the outcome of severe alcoholic steatohepatitis. The now reported Glasgow alcoholic hepatitis score might represent a substantial improvement in clinical phenotyping and could catalyse the development of new treatments in this disease.

The appearance of steatohepatitis is an important rate limiting step in the development of progressive alcoholic liver disease. One month mortality rates of 40–50% have been reported in patients hospitalised with acutely decompensated liver disease due to alcohol induced steatohepatitis.1 Patients with severe alcoholic steatohepatitis typically present with fever, hepatomegaly, jaundice, and anorexia. The presence of liver failure manifested by...
survival of 96%. The MELD score above this cut off value of 32 has been used to apply to alcoholic hepatitis. In a study recently, the MELD score has been demonstrated that patients with a score >32 had a survival of 46% and 52% at days 28 and 84, respectively, whereas patients with a GAHS >9 had a survival of 46% and 40% at days 24 and 84, respectively. The GAHS at days 1 and 7 was significantly more accurate in predicting day 24 and 84 outcome than the mDF and had an impressive better overall accuracy. Furthermore, the GAHS was also significantly more accurate than the MELD score in predicting short and long term survival.

(Diii) Future developments and aspects which might be considered in further new scores

Whereas the new GAHS for the first time includes an inflammatory parameter (white blood cell count) which is important for such a highly inflammatory disease, other inflammatory and immune parameters may also be helpful for future scoring systems. C reactive protein levels and plasma levels of tumour necrosis factor soluble receptors p55 and p75 have been demonstrated to correlate with short and long term survival. On the other hand, extra-cellular matrix markers such as laminin might be accurate markers predicting survival in these patients. Apart from immune markers, early changes in bilirubin levels and major changes in portal flow are prognostic factors in alcoholic hepatitis.

DO WE NEED BETTER SCORING SYSTEMS IN ALCOHOLIC HEPATITIS?

(i) We need a simple test which can be calculated at the bedside

Calculation of mDF relies on the absolute value of the prothrombin time and there exists significant variation in the absolute values of prothrombin time obtained using different assays in different countries (for example, UK, USA). This may thereby affect the validity of the mDF score in countries such as the UK where a greater severity score will be generated based on the prothrombin time. This creates a definite inaccuracy in the mDF value and limits its translation between different facilities. Furthermore, the presence of encephalopathy has often been included when making a treatment decision, in addition to just calculating the mDF. This is problematic, as encephalopathy is very subjective in its milder forms. Kulkarni and colleagues have also shown that addition of encephalopathy displayed a slight increase in sensitivity but a dramatic decrease in specificity compared with the MDF.

(ii) We need a score which identifies as many patients as possible with a high mortality risk

Apart from the positive reports on the relevance of an mDF cut off value of 32, its accuracy in predicting survival has been repeatedly questioned. Kulkarni et al recently reported that patients with a low mDF (<32) also had significant mortality, approaching 17%. In this study, the mDF was only moderately sensitive (66.7%) and specific (61.7%). Considering the considerable mortality in patients with a DF ≤32, it would be reasonable to consider treatment options for these patients also. In addition, even more importantly, re-evaluation of current criteria for assessing disease severity is needed to more accurately identify patients at risk for short and long term mortality.

Given the relatively poor ability of the mDF to predict short term mortality, a new indicator of mortality and severity was eagerly awaited. Forrest and colleagues report in this issue of Gut the derivation of a score termed the Glasgow alcoholic hepatitis score (GAHS) based on a large patient population and its validation using a new and independent set of patients (see page 1174). Importantly, overall survival was studied in a large patient population (n = 241) until day 84, allowing more accurate judgement about the clinical course and not only short term survival (day 28). In their analysis, mDF was highly sensitive in the prediction of death from alcoholic hepatitis but lacked specificity. This was dramatic as it incorrectly predicted the outcome at 28 days after admission in 51% of cases. By multiple stepwise logistic regression they developed the key factors for later deriving and developing their GAHS. All of these factors (age, white blood cell count, blood urea, prothrombin time ratio, and bilirubin) are well known from other studies to affect mortality but have never been used in combination to calculate survival. In their analysis, patients with an admission mDF ≥32 had a survival of 64% and 52% at days 28 and 84, respectively, whereas patients with a GAHS ≥9 had a survival of 46% and 40% at days 24 and 84, respectively. The GAHS at days 1 and 7 and 7 was significantly more accurate in predicting day 24 and 84 outcome than the mDF and had an impressive better overall accuracy. Furthermore, the GAHS was also significantly more accurate than the MELD score in predicting short and long term survival.

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patients with severe alcoholic steatohepatitis treated with corticosteroids.

Treatment of severe alcoholic hepatitis has hardly progressed in recent years. Lack of a scoring system with appropriate overall accuracy may have contributed to this poor situation by confounding clinical studies. Current clinical strategy favours a “watch and wait” strategy awaiting disease progression in those patients incorrectly identified as low risk by a low DF (<32). Such a strategy may be counterproductive in a severe disease with high mortality and is an uncommon strategy in modern medicine. In addition, patients with a DF >32 often have contraindications for steroid treatment and cannot receive this treatment. Therefore, the new score presented here raises hopes of a more accurate clinical tool to predict survival and therefore advance the field, initiating new studies with innovative treatment modalities reflecting current pathophysiology. In conclusion, the new Glasgow alcoholic hepatitis score might indeed be the long awaited progress in this field.

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Authors’ affiliations

H Tilg, A Kaser, Department of Medicine, Division of Gastroenterology and Hepatology, University Hospital Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria; Herbert.Tilg@uibk.ac.at

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REFERENCES

8 Sheth M, Riggs M, Patel T. Utility of the Mayo end-stage liver disease (MELD) score in assessing prognosis of patients with alcoholic hepatitis. BMC Gastroenterol 2002;2:2
9 Stewart SF, Day CP. The management of alcoholic liver disease. J Hepatol 2003;38(suppl 1):S2–13

2nd annual BSG-AGA research meeting “The pathogenesis and prevention of oesophageal and gastric adenocarcinoma”

This meeting will take place in the Medical Sciences Teaching Centre, South Parks Road, Oxford, on 1–2 September 2005. The closing date for applications is Wednesday 10 August 2005. The speakers are leading USA and UK clinicians and scientists in the field. There will also be abstract presentations. The meeting will have a strictly limited number of attendees to ensure a workshop atmosphere and vibrant discussion.

The cost for the meeting, including accommodation at Wadhams College for Wednesday 31 August – Thursday 1 September and a dinner at Wadhams College on 1 September, is only £140 or $250.

We encourage people to submit abstracts, although this is not in any way compulsory. Depending on the number submitted, we may be willing to consider late submissions. For full details, a programme, and an application form please visit the BSG website at www.bsg.org.uk. Alternatively please email: simon.travis@orh.nhs.uk or victoria.mcneile@ndm.ox.ac.uk or phone Simon Travis on +44 (0)1865 224829.