Helicobacter pylori, harmful to the brain?

Traditional views of the pathogenesis of hepatic encephalopathy (HE) have emphasised the role of neurotoxins arising from the gut. These compounds gain access to the systemic circulation as a result of the combined effects of hepatocellular failure and portal-systemic shunting. In the past years, a new mechanistic paradigm has been developed, emphasising changes in brain astrocyte function with subsequent alterations in glial-neuronal communications. Astrocyte dysfunction results from several factors. These include a decrease in plasma osmolarity, effects of circulating cytokines, and the changes brought on by accumulation of glutamine, the product of ammonia detoxification in glial cells. After many years of research, ammonia continues to play a central role in the pathogenesis of HE.

Under normal conditions, ammonia is generated in both the small bowel (from the effects of glutaminase on glutamine) and large intestine (from the urease activity of the colonic flora). The relative contribution of each site is difficult to quantitate but hyperammonaemic coma can still occur in hepatectomised germ free rats where the main source of ammonia is presumably the small bowel. Neomycin, an antibiotic active against urease containing bacteria in the colon, also inhibits small bowel glutaminase in the rat. Regardless of the origination site, portal vein ammonia levels are markedly elevated, fuelling the subsequent synthesis of urea and glutamine in the liver. An efficient hepatic extraction of ammonia, more than 0.8 in humans, contributes to the narrow range of ammonia levels seen in the periphery.

Several factors shape the anatomical and functional derangement of this pathway in cirrhosis with portal hypertension. Variables include alterations in the intestinal flora as a result of altered small bowel transit, extra- and intrahepatic portal-systemic shunts, as well as alterations in perportal (site of urea synthesis) and perivenous (glutamine synthesis) hepatocyte function. In the past decade, several studies have implicated gastric infection with Helicobacter pylori as an additional pathogenic factor in hyperammonaemia. The basis for this tenet is seemingly logical: the urease activity of this organism would generate enough gastric ammonia to increase portal levels and subsequent peripheral ammonia values with worsening of the course of HE. Critical to this line of reasoning is whether the density of the urease containing bacterial population in the colon, being several log-fold higher than the gastric counterpart in cases of H pylori infection, makes the contribution of the latter to ammoniagenesis quantitatively less important. However, qualitative differences in the urease activity of H pylori may be present, such as a marked increase in activity at a lower pH.

Investigators have employed two frameworks to prove or refute a pathogenic role for H pylori in HE: an epidemiological analysis and an assessment of the effects of eradication. In the first approach, subjects with alcoholic hepatitis and cirrhosis were examined according to serology or antral biopsy results: HE was more evident in patients with H pylori infection. Other cross sectional studies have failed to confirm this finding. In the second approach, several groups noted a beneficial effect on ammonia levels and in clinical symptomatology after eradication of H pylori. Concomitant changes in the colonic bacterial flora brought on by antibiotics cloud the interpretation of such positive results. In a careful study examining cirrhotic patients with minimal encephalopathy, no improvement in clinical or biochemical parameters of HE could be seen two months after eradication. However, the extent of portal-systemic shunting and hepatocellular failure may be less prominent in these compensated patients. A preliminary analysis of patients with cirrhosis after placement of TIPS, a procedure that results in maximal portal-systemic shunting, indicated no increase in encephalopathy in those subjects infected with H pylori.

In the current issue of Gut, a third approach is reported in an experimental animal: assessment of the effects of de novo infection with H pylori in a model of cirrhosis (see page 605). H pylori grows in the gastric mucosa of the Mongolian gerbil, resulting in inflammation and even gastric cancer. The authors noted a significant increase in portal and peripheral ammonia levels coupled with decreased survival in infected gerbils made cirrhotic with a choline deficient diet. In their view, data support their previous results on H pylori eradication in humans, while providing additional evidence for a pathogenic role of this infection in HE.

The study is not without flaws. While hepatocellular function was similar in cirrhotic gerbils with and without infection, the extent of portal-systemic shunting was not described, a variable that could independently influence the results. The two end points of the study were also confusing: the increased death rate reported in infected cirrhotic gerbils was not well analysed and suggests additional pathology beyond HE, as the degree of hyperammonaemia was not as severe to explain a neurological death. Furthermore, ammonia levels, reported in this study from a peripheral vein, display less accuracy than arterial values in view of muscle extraction. Even if arterial levels were used, nocturnal eating habits and retained gastric contents can affect ammonia results in rodents.

Despite these criticisms, the authors deserve recognition for tackling the question in a paradigm that provides a fresh perspective of the problem. Behavioural tools have been used in rodent models to quantitate HE and should be the end point in future studies rather than the use of single measurements of ammonia blood levels. In the meantime, the practising clinician faces the therapeutic dilemma of whether to search for and treat H pylori in patients with cirrhosis. The sum of clinical evidence does not support a recommendation for therapy at this time. Additional studies along the lines of the current report and careful eradication studies in patients with advanced cirrhosis and portal-systemic shunting (the group most likely to be influenced by an increased ammonia load) should offer definitive answers on this controversy.
Metabolism of 6-mercaptopurine (6-MP) and azathioprine (AZA) is complex. Azathioprine is a prodrug that is non-enzymatically converted to 6-MP. 6-MP is then either inactivated by thiopurine methyltransferase (TPMT) to 6-methylmercaptopurine or by xanthine oxidase to 6-thiouric acid, or it is activated via a multistep enzymatic pathway to the putative active metabolites, the 6 thioguanine nucleotides (6-TGNs) [1]. The enzyme activity of TPMT is genetically determined. There is a trimal distribution of TPMT activity in the general population: homozygous low activity occurs at a frequency of 0.3%; heterozygous or intermediate activity occurs at a frequency of 11%; and homozygous high or normal activity occurs at a frequency of 89%. [2] At least 10 variant alleles for TPMT have been associated with decreased enzyme activity (*2, *3A, *3B, *3C, *3D, *4, *5, *6, *7, *10). Patients with low or intermediate TPMT enzyme activity shunt 6-MP away from the metabolite and towards 6-TGN. Excess concentrations of 6-TGN have been associated with leucopenia. The practical application of these clinical pharmacology discoveries and the results of randomised controlled trials in patients with inflammatory bowel disease (IBD) who require treatment with AZA or 6-MP are reviewed below.

The first question that clinicians must ask is which drug to use? There is virtually no published information regarding the relative immunosuppressive properties of AZA or 6-MP. Clinical experience suggests that they are equivalent if the doses are adjusted for differences in the content of 6-MP. Approximately 88% of AZA is converted to 6-MP. Azathioprine is 55% 6-MP by molecular weight. Thus a conversion factor of 2.08 will convert a dose of 6-MP to AZA. Clinicians often over dose 6-MP or under dose AZA because they fail to take this conversion into account.

The second question clinicians must ask is what dose of AZA or 6-MP to use? Controlled trials have demonstrated that AZA doses of 2.0–3.0 mg/kg/day and 6-MP doses of 1.5 mg/kg/day (equivalent to an AZA dose of 3.0 mg/kg/day) are effective for the treatment of Crohn’s disease. [1] In clinical practice, many clinicians begin treatment with AZA 1 mg/kg/day or 6-MP 50 mg/day (less than 1 mg/kg/day) for fear of toxicity. This approach is not rational and leads to under dosing of patients with predictable suboptimal response rates. Two studies have suggested baseline measurement of TPMT activity (phenotype) or genotype could be used to “customise” the drug dose and reduce the frequency of leucopenia. One study prospectively determined TPMT genotypes in 67 consecutive patients with rheumatological diseases who were initiating AZA therapy at a dose of 2–3 mg/kg/day. [3] Six of 67 patients (9%) were heterozygous for TPMT activity of whom five (83%) continued therapy. (The sixth patient did not adhere to therapy). The median duration of therapy was two weeks (range 2–4 weeks) in the group with heterogeneous TPMT activity and 39 weeks (6–180 weeks) in the group with wild-type TPMT activity. In a second study, 41 patients with Crohn’s disease who had developed severe myelosuppression (white blood cell count <3000 or platelet count <100 000) during treatment with AZA or 6-MP were evaluated for TPMT genotype. [4] Four of 41 patients (10%) had low activity and seven of 41 (17%) had intermediate activity. Early leucopenia was noted in subjects with low or intermediate TPMT activity whereas normal TPMT activity was noted in patients with late leucopenia. The results of these studies have led to the recommendation that patients with normal TPMT activity receive standard doses of AZA or 6-MP and that patients with intermediate TPMT enzyme activity have their dose of AZA or 6-MP reduced. Patients with low TPMT activity in general should not be treated with AZA or 6-MP due to a high mortality from leucopenia and sepsis.

The third question clinicians must ask is how long do AZA and 6-MP take to work? Present and colleagues reported that the mean time to response in patients with Crohn’s disease treated with 6-MP was 3.1 months. [5] However, the frequency of clinical assessment was only every 12 weeks, suggesting that the time to response may be much sooner. 6-TGNs have a half-life of several days or more. Steady state concentrations of the 6-TGNs occur after 2–4 weeks of oral dosing with AZA 2.0 mg/kg/day. [6] A recent controlled trial of AZA in steroid treated Crohn’s disease suggested that the time to response was 4–8 weeks. [7]

The fourth question clinicians must ask is whether or not to perform therapeutic drug monitoring of 6-TGN concentrations in patients with IBD treated with AZA or 6-MP? Two studies have reported that patients with IBD treated with AZA or 6-MP who respond to therapy have higher median concentrations of 6-TGN than patients who fail to respond to therapy. [8,9] The most recent study in 93 patients with IBD reported that the median concentration of 6-TGN in erythrocytes in responding patients was 312 pmol/8×10^11 red blood cells (RBCs) compared with a median concentration of 170 pmol/8×10^11 in patients who fail to respond. [10] The breakpoint between the lower two quartiles and the higher two quartiles of 6-TGN concentrations was 235 pmol/8×10^11 RBCs. Sixty five per cent of responding patients had an erythrocyte 6-TGN concentration >235 pmol/8×10^11 RBCs.
New pouches for old?

It is now 25 years since the ileal pouch procedure was introduced for patients with ulcerative colitis and familial adenomatous polyposis, holding out the promise of life without a permanent ileostomy. As time has gone by the procedure has been modified, refined, and the indications widened until the present situation where most teams use a hand sewn anastomosis for enterocutaneous fistulae.

The far end is covered by a fascial flap and the pouch is divided into a narrow neck and a wider body, a shape up to the existing competition and are there any theoretical advantages or disadvantages?

The new pouches for old? operation is clearly a demanding procedure as a technical exercise this is clearly a demanding procedure. But problems remain. A tiny cuff of the muscle coat over the last 15 cm or so of the ileum, preserving a couple of strips of muscle wall to act as a skeleton (see fig 1 in Andriesse and colleague). The far end is hand sewn endoanally to the dentate line and the mucosa is painstakingly stripped off. The indication is not to treat patients with AZA or 6-MP. Patients should routinely be tested for TPMT activity (phenotype) or genotype prior to initiating AZA or 6-MP therapy. Patients with normal TPMT activity or the wild-type genotype should receive drug doses that have been proved to be efficacious in controlled trials (AZA 1–1.5 mg/kg/day or 6-MP 1.5 mg/kg/day). Patients with intermediate TPMT activity or the heterozygote genotypes should initially have an empiric reduction of 50% in drug dose (AZA 1–1.5 mg/kg/day or 6-MP 0.75 mg/kg/day). Patients with absent TPMT activity or the homozygous low activity genotypes should only be treated with great caution at very low doses (approximately 10% of the standard dose), and perhaps not at all. Clinicians should expect that the clinical effect of AZA or 6-MP will be reached over approximately 1–2 months. Routine therapeutic drug monitoring of 6-TGN in patients being treated with AZA or 6-MP is not necessary but can be considered in selected settings: patients suspected of non-compliance; patients receiving alosetron; patients with intermediate or low TPMT activity; and possibly patients who are failing to respond to standard doses of drug. Less experienced clinicians who are uncomfortable prescribing the full standard doses of AZA or 6-MP proven to be effective in clinical trials may be reassured by the laboratory finding of a “subtherapeutic” 6-thioguanine concentration and subsequently be convinced to increase the drug dose, similar to the experience reported by Cuffari et al.

Where do we go from here?

The new pouches for old? operation is clearly a demanding procedure. It is now 25 years since the ileal pouch procedure was introduced for patients with ulcerative colitis and familial adenomatous polyposis, holding out the promise of life without a permanent ileostomy. As time has gone by the procedure has been modified, refined, and the indications widened until the present situation where most teams use a hand sewn anastomosis for enterocutaneous fistulae.

The far end is covered by a fascial flap and the pouch is divided into a narrow neck and a wider body, a shape up to the existing competition and are there any theoretical advantages or disadvantages?

The new pouches for old? operation is clearly a demanding procedure as a technical exercise this is clearly a demanding procedure. But problems remain. A tiny cuff of the muscle coat over the last 15 cm or so of the ileum, preserving a couple of strips of muscle wall to act as a skeleton (see fig 1 in Andriesse and colleague). The far end is hand sewn endoanally to the dentate line and the mucosa is painstakingly stripped off. The indication is not to treat patients with AZA or 6-MP. Patients should routinely be tested for TPMT activity (phenotype) or genotype prior to initiating AZA or 6-MP therapy. Patients with normal TPMT activity or the wild-type genotype should receive drug doses that have been proved to be efficacious in controlled trials (AZA 1–1.5 mg/kg/day or 6-MP 1.5 mg/kg/day). Patients with intermediate TPMT activity or the heterozygote genotypes should initially have an empiric reduction of 50% in drug dose (AZA 1–1.5 mg/kg/day or 6-MP 0.75 mg/kg/day). Patients with absent TPMT activity or the homozygous low activity genotypes should only be treated with great caution at very low doses (approximately 10% of the standard dose), and perhaps not at all. Clinicians should expect that the clinical effect of AZA or 6-MP will be reached over approximately 1–2 months. Routine therapeutic drug monitoring of 6-TGN in patients being treated with AZA or 6-MP is not necessary but can be considered in selected settings: patients suspected of non-compliance; patients receiving alosetron; patients with intermediate or low TPMT activity; and possibly patients who are failing to respond to standard doses of drug. Less experienced clinicians who are uncomfortable prescribing the full standard doses of AZA or 6-MP proven to be effective in clinical trials may be reassured by the laboratory finding of a “subtherapeutic” 6-thioguanine concentration and subsequently be convinced to increase the drug dose, similar to the experience reported by Cuffari et al.

Where do we go from here?

The new pouches for old? operation is clearly a demanding procedure. It is now 25 years since the ileal pouch procedure was introduced for patients with ulcerative colitis and familial adenomatous polyposis, holding out the promise of life without a permanent ileostomy. As time has gone by the procedure has been modified, refined, and the indications widened until the present situation where most teams use a hand sewn anastomosis for enterocutaneous fistulae.

The far end is covered by a fascial flap and the pouch is divided into a narrow neck and a wider body, a shape up to the existing competition and are there any theoretical advantages or disadvantages?

The new pouches for old? operation is clearly a demanding procedure as a technical exercise this is clearly a demanding procedure. But problems remain. A tiny cuff of the muscle coat over the last 15 cm or so of the ileum, preserving a couple of strips of muscle wall to act as a skeleton (see fig 1 in Andriesse and colleague). The far end is hand sewn endoanally to the dentate line and the mucosa is painstakingly stripped off. The indication is not to treat patients with AZA or 6-MP. Patients should routinely be tested for TPMT activity (phenotype) or genotype prior to initiating AZA or 6-MP therapy. Patients with normal TPMT activity or the wild-type genotype should receive drug doses that have been proved to be efficacious in controlled trials (AZA 1–1.5 mg/kg/day or 6-MP 1.5 mg/kg/day). Patients with intermediate TPMT activity or the heterozygote genotypes should initially have an empiric reduction of 50% in drug dose (AZA 1–1.5 mg/kg/day or 6-MP 0.75 mg/kg/day). Patients with absent TPMT activity or the homozygous low activity genotypes should only be treated with great caution at very low doses (approximately 10% of the standard dose), and perhaps not at all. Clinicians should expect that the clinical effect of AZA or 6-MP will be reached over approximately 1–2 months. Routine therapeutic drug monitoring of 6-TGN in patients being treated with AZA or 6-MP is not necessary but can be considered in selected settings: patients suspected of non-compliance; patients receiving alosetron; patients with intermediate or low TPMT activity; and possibly patients who are failing to respond to standard doses of drug. Less experienced clinicians who are uncomfortable prescribing the full standard doses of AZA or 6-MP proven to be effective in clinical trials may be reassured by the laboratory finding of a “subtherapeutic” 6-thioguanine concentration and subsequently be convinced to increase the drug dose, similar to the experience reported by Cuffari et al.

Where do we go from here?

The new pouches for old? operation is clearly a demanding procedure. It is now 25 years since the ileal pouch procedure was introduced for patients with ulcerative colitis and familial adenomatous polyposis, holding out the promise of life without a permanent ileostomy. As time has gone by the procedure has been modified, refined, and the indications widened until the present situation where most teams use a hand sewn anastomosis for enterocutaneous fistulae.

The far end is covered by a fascial flap and the pouch is divided into a narrow neck and a wider body, a shape up to the existing competition and are there any theoretical advantages or disadvantages?

The new pouches for old? operation is clearly a demanding procedure as a technical exercise this is clearly a demanding procedure. But problems remain. A tiny cuff of the muscle coat over the last 15 cm or so of the ileum, preserving a couple of strips of muscle wall to act as a skeleton (see fig 1 in Andriesse and colleague). The far end is hand sewn endoanally to the dentate line and the mucosa is painstakingly stripped off. The indication is not to treat patients with AZA or 6-MP. Patients should routinely be tested for TPMT activity (phenotype) or genotype prior to initiating AZA or 6-MP therapy. Patients with normal TPMT activity or the wild-type genotype should receive drug doses that have been proved to be efficacious in controlled trials (AZA 1–1.5 mg/kg/day or 6-MP 1.5 mg/kg/day). Patients with intermediate TPMT activity or the heterozygote genotypes should initially have an empiric reduction of 50% in drug dose (AZA 1–1.5 mg/kg/day or 6-MP 0.75 mg/kg/day). Patients with absent TPMT activity or the homozygous low activity genotypes should only be treated with great caution at very low doses (approximately 10% of the standard dose), and perhaps not at all. Clinicians should expect that the clinical effect of AZA or 6-MP will be reached over approximately 1–2 months. Routine therapeutic drug monitoring of 6-TGN in patients being treated with AZA or 6-MP is not necessary but can be considered in selected settings: patients suspected of non-compliance; patients receiving alosetron; patients with intermediate or low TPMT activity; and possibly patients who are failing to respond to standard doses of drug. Less experienced clinicians who are uncomfortable prescribing the full standard doses of AZA or 6-MP proven to be effective in clinical trials may be reassured by the laboratory finding of a “subtherapeutic” 6-thioguanine concentration and subsequently be convinced to increase the drug dose, similar to the experience reported by Cuffari et al.

Where do we go from here?

The new pouches for old? operation is clearly a demanding procedure. It is now 25 years since the ileal pouch procedure was introduced for patients with ulcerative colitis and familial adenomatous polyposis, holding out the promise of life without a permanent ileostomy. As time has gone by the procedure has been modified, refined, and the indications widened until the present situation where most teams use a hand sewn anastomosis for enterocutaneous fistulae.
and the inevitable anal dilatation, which may impair continence. In expert hands this can be minimised but there is still a tendency to more nocturnal seepage. The creators of restorative proctocolectomy believed that a long rectal muscular cuff was essential for the sensation of pouch filling, but we now know that stretch receptors lie within the pelvic floor muscles. Pouch patients with an anastomosis to the top of the anal canal with hardly any rectal muscle cuff can feel and empty satisfactorily.

The long mucosectomy needed to strip a sizeable cuff can be difficult and incomplete. Tiny islands of remaining mucosa not amenable to surveillance increase the risk of cuff abscess and the inevitable poor function, and later malignant change. Of the published cases of cancer complicating pouches, the majority are in those who have had a mucosectomy.

While theoretically elegant, there is no evidence that preserving the rectal wall and putting on an ileal mucosal graft improves function. As day and night time stool frequency declined, sensation, pressures, and anal integrity were preserved and rectal compliance improved with time, but these are changes seen with a conventional pouch procedure. Overall stool frequency was higher than reported for J pouches and even after preserving the rectal wall, recto-anal inhibitory reflexes were not maintained.

One of the arguments against ileorectal anastomosis in ulcerative colitis is the long term effect of repeated inflammation on rectal compliance. A narrow stiff fibrotic rectum would probably remain so after mucosectomy and INRA. This would have implications for case selection favouring “mild” cases and ruling out those with dysplasia or established rectal cancer. Indeterminate colitis and Crohn’s disease would be worries too.

Three of the 11 cases developed what the authors have chosen to call neoproctitis. As the meshed mucosa grows over the denuded rectal wall there will be healing and degenerative changes but once complete the ileal mucosa would become analogous to pouch mucosa. It is not clear why the authors have chosen not to call this pouchitis and use the well established histopathological definitions and scoring systems. This would allow an easier comparison between the two techniques but it is obvious that INRA patients also develop pouchitis.

Although the INRA approach may have theoretical advantages over the established pouch operation, there is no evidence that any of these have been fulfilled. It is likely to be a more difficult procedure with higher morbidity and just now, it seems inappropriate for patients to be exposed to these added risks.

N MORTENSEN

Department of Colorectal Surgery,
Oxford Radcliffe Hospital, Oxford, UK
renath@hotmail.com

Rational dosing of azathioprine and 6-mercaptopurine

W J SANDBORN

*Gut* 2001 48: 591-592
doi: 10.1136/gut.48.5.591

Updated information and services can be found at:
http://gut.bmj.com/content/48/5/591

These include:

**References**
This article cites 13 articles, 2 of which you can access for free at:
http://gut.bmj.com/content/48/5/591#BIBL

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/