LETTERS

An alternative to prophylactic colectomy for colon cancer prevention in HNPCC syndrome

The French Ad-Hoc Committee on Hereditary Non-polyposis Colon Cancer (HNPCC) management meeting on behalf of the French Health Minister has recently released its statement. The report on prophylactic colorectal resections for HNPCC related adenocarcinomas (Gut 2003;52:1752–5) is in contrast with ours and we would like to discuss this point.

Use of decision analysis models is a smart approach in dealing with such complex situations. However, life expectancy related to the occurrence of metachronous colorectal carcinoma should be balanced against the negative impact on quality of life in the case of prophylactic extensive colorectal resections. Thus quality adjusted life expectancy, integrating the individual patient’s choice, might be a more accurate approach. Comprehensive, fair, and loyal information of what the patient can hope for is mandatory in such a shared decision. From the data reported by de Vos tot Nederveen Cappel et al (Gut 2003;52:1752–5) as well as from other data not mentioned in their paper, we derived some considerations. If not totally opposite conclusions, five year survival rates for colorectal cancer considered in their model seem at the least optimistic. Five year survival rates reported for Dukes’ B and C colorectal cancers in HNPCC patients by Bertario and colleagues’ were 70% and 41%, respectively. The overall five year survival rate of patients with colorectal cancer in HNPCC is approximately 55%. Multidimensional analyses has not shown HNPCC to be an independent parameter when comparing five year survival rates of HNPCC with sporadic colorectal cancer.

Although these data strongly demonstrate a need for surveillance in HNPCC patients, they underscore the fact that if the decision for an extended prophylactic resection is made before the exact pathological staging of the tumour is known, 45% of patients will sustain a substantial decrease in quality of life with no counterpart in quantity (that is, life expectancy). de Vos tot Nederveen Cappel et al (Gut 2003;52:1752–5) calculated life expectancy for a hypothetical 27 year old patient with colorectal cancer whereas in our experience only 6% of MMR gene carriers belong to that very early onset group. The median age of patients with colorectal cancer under surveillance programmes for HNPCC is 44 years and the compared mean estimation of increased life expectancy after extended resection for a 47 year old affected person is only one year. Different indications should be made in men and women because of their significantly different relative risks for metachronous cancer as well as for the competing risk of endometrial cancer (unless there is also a “recommendation” for “incidental” prophylactic hysterectomy). Last, but not least, the negative impact on life expectancy related to other tumours from the spectrum as well as to the prophylactic resections themselves are not taken into consideration. For young patients between the ages of 27 and 47 years with colorectal cancer, the choice between prophylactic surgery or segmental colectomy is a complex decision. One should ask honestly if these same patients who on one colorectal cancer to face the anxiety generating information that they have cancer are also ready or capable of making any reasonable decisions about a 2–3 year increase in life expectancy versus a potential decrease in their quality of life. Let us assume that the first expectation for these patients is to be alive with no recurrent disease 5–10 years later. An increased life expectancy is a somewhat theoretical conception which entails additional years at the end of one’s life while the negative impact on quality of life of extended operations will start from the first postoperative day.

The patient’s individual choice is pivotal in decisions for prophylactic extended resections and fully unbiased information may be more valuable than any doctor’s “recommendation”. The results of the study of de Vos tot Nederveen Cappel et al (Gut 2003;52:1752–5) should therefore be part of the information offered to patients. For these reasons, the conclusions of the French Ad-Hoc Committee are that not only are routine extended prophylactic resections not recommended but, on the contrary, given the efficacy of screening programmes, extended surgery is also not indicated. Controversial conclusions derived from the same scientific “evidence” in different cultural background have already been reported.

S Olschwang, P Laurent-Puig, F Eisinger, B Millat
INSERM U434, Marseille, France

Correspondence to: Dr S Olschwang, INSERM U434, 13009 Marseille, France; olschwang@marseille.inserm.fr

References


Serum pro-hepcidin: measuring active hepcidin or a non-functional precursor?

We read with great interest the paper “Pro-hepcidin: expression and cell specific localisation in the liver and its regulation in hereditary haemochromatosis, chronic renal insufficiency, and renal anaemia” (Gut 2004;53:733–43).

We have two observations. Firstly it was shown that pro-hepcidin and hepcidin were colocalised within the liver and in Hep-G2 cells. However, it was not possible, using serum ELISA, to identify the C terminus of hepcidin (the mature form of hepcidin 29). Is it possible that the functional N terminal antibody used for serum analyses represents non-functional precursor amino acids and not the active molecule? This might explain the lack of correlation between iron parameters and hepcidin seen from the patient data.

Furthermore, the authors comment on the paradoxically elevated levels of pro-hepcidin in patients with chronic renal insufficiency on erythropoietin (EPO). All of these patients were reported to have normal haemoglobin levels. Previous studies have shown that EPO inhibits hepatic hepcidin expression. The authors speculate that the elevated circulating levels of pro-hepcidin may reflect reduced renal clearance of the molecule in these patient. However, other studies have suggested chronic inflammatory diseases are associated with elevated serum hepcidin (in animal models) and urine hepcidin in humans. Another possibility, therefore, is that patients have elevated iron stores, in relation to chronic disease, and this may have a direct effect on hepcidin release. It would be interesting to know the iron metabolic parameters in these patients, as obviously haemoglobin in isolation is not an accurate measure of iron stores. It is unclear from the paper whether fig 8 represents data from patients with haemochromatosis patients, whom hepcidin expression is likely to be dysregulated due to direct effects of the HFE gene product.
Clearly future clinical studies in this field hold much promise.

M J Brookes, N K Sharma, C Tsleipis, T H Hapal
City Hospital, Birmingham, UK
Correspondence to: Dr M J Brookes, City Hospital, Dudley Rd, Birmingham B18 7QG, UK; mbro45339@oal.com

References

Use of oesophageal dilatation in clinical practice

Drs Riley and Attwood are to be commended for their recent publication (Gut 2004; 53: 1–6). We were surprised by one recommendation related to dilatation. Under 6.1, it is stated that during oesophageal dilatation the endoscopist should be supported by at least two endoscopy assistants. We agree that this is desirable when the complicated stricture is dilated or if one is dealing with an achalasia patient. However, for dilatation of Schatzki’s rings or simple peptic strictures, one endoscopy assistant generally is sufficient. At our institution, over the years numerous dilatations have been done with only one assistant and without any adverse consequences. As written, your guidelines seem to indicate that the standard of care would be to have two endoscopy assistants present and I think this is both unrealistic and unwarranted.

S J O Veldhuysen van Zanten
Correspondence to: Dr S J O Veldhuysen van Zanten, Division of Gastroenterology, Dalhousie University, Queen Elizabeth II Health Sciences Centre, Room 928, Centennial Building, 1278 Tower Rd, Halifax, Nova Scotia B3H 1Y9, Canada; zanten@dal.ca

Variant Creutzfeldt-Jakob disease: update

Two years ago we reported current thinking on the potential for gastrointestinal endoscopy to act as a vector for patient to patient transmission of variant Creutzfeldt-Jakob disease (vCJD) in that article we stressed that the advice would be updated if new evidence became available. Gastroenterologists may be aware of a recently published article in the Lancet that describes the tissue distribution of abnormal prion protein (PrPSc) in monkeys that have been inoculated with brain homogenate from first passage animals with bovine spongiform encephalopathy (BSE) via the oral route, which is the route by which the vast majority of patients developing vCJD will have become infected. As the prion protein responsible for vCJD is found in all lymphoid tissue, our advice was to reduce “random” biopsies to an absolute minimum and ensure that re-useable biopsy forceps were meticulously cleaned and decontaminated according to the strict British Society of Gastroenterology (BSG) guidelines. We also advised on the use of disposable biopsy forceps, particularly in the ileum, as it was felt that biopsies from this area posed the greatest risk to both endoscope and forceps becoming contaminated. Other inexpensive accessories such as cleaning brushes and the rubber cap covering the biopsy port were also to be disposed of if a biopsy had been taken.

The paper from Herzog and colleagues1 is the first to look specifically at the tissue distribution of PrPScP after oral and intravenous inoculation in a primate model utilising Cynomolgus macaques. The findings confirm that the highest concentration of PrPSc is in the tonsil and that it is also abundantly present in the terminal ileum and ileocecal fold where gut associated lymphoid tissue is present in large amounts. The whole of the gastrointestinal tract was positive for PrPScP from the duodenum to the rectum. Both gut associated lymphoid tissue and the autonomic nervous system were highly involved, including nerve fibres lying just below the mucosal boundary. The authors suggested that the possible role of transmitting vCJD via endoscopic procedures might be currently underestimated as the detection of PrPSc is the best marker for infectivity in prion diseases.

This new information will help to inform gastroenterologists that the risk of transmitting vCJD via an endoscopic procedure remains a distinct possibility and the advice of two years ago remains as relevant today as it was then. All patients undergoing gastrointestinal endoscopy should be considered potential carriers of vCJD in the context that the majority of the UK population is likely to have had dietary exposure to the BSE agent during the 1980s. Perhaps the most important aspect of this new information is the increasing realisation that any biopsy from anywhere in the gastrointestinal tract is “high risk” as a biopsy of the terminal ileum. It is not logical to reserve disposable biopsy forceps for this one area; it seems more appropriate for endoscopy units to move entirely into using disposable forceps for all procedures and phase out the use of re-useable equipment that might be difficult to trace or decontaminate. Biopsy should only be performed where this is likely to influence clinical management.

Although one recent case of vCJD has been associated with blood transfusion,2 no case of vCJD has so far been attributed to an endoscopic procedure. However, we would urge all staff involved in endoscope decontamination to remain vigilant and adhere strictly to guidelines already issued by the BSG in order to minimise this risk.

M G Bramble
James Cook University Hospital, Middlesbrough, UK

J Ironside
National CJD Surveillance Unit, Western General Hospital, Edinburgh, UK
Correspondence to: Professor M G Bramble, James Cook University Hospital, Marton Rd, Middlesbrough TS5 3BW, UK; mike.bramble@stees.nhs.uk

References

Is mesalazine really safe for use in breastfeeding mothers?

Mesalazine containing preparations are commonly used for the treatment and maintenance of remission of inflammatory bowel disease. The young age of many inflammatory bowel disease sufferers means that the issue of whether to continue therapy in nursing mothers often arises.

We report a small study that was instigated after a nursing mother with Crohn’s disease approached us concerned about the safety of continuing to breastfeed while taking mesalazine. She had a cracked bleeding nipple and was worried about the dose of the drug that her baby would be receiving. We agreed to analyse the drug levels in her breast milk and the limited evidence in this area we designed a study to measure levels of mesalazine (5-ASA) and its metabolite (N-acetyl-5-ASA) in breast milk from other mothers who were breastfeeding. The study was approved by the local Ethics Committee.

It is thought that maternal use of 5-ASA medication is safe for the breastfed infant although bloody diarrhoea in an infant being breast fed by a woman taking sulphasalazine has been reported,3 as has watery diarrhoea in the infant of a woman using 5-ASA suppositories.4 There has in fact been little research into excretion of 5-ASA and N-acetyl-5-ASA in breast milk.

We obtained breast milk samples from four breastfeeding mothers with inflammatory bowel disease who were taking a 5-ASA preparation. Ethics approval for the study was obtained from the local ethics committee. Breast milk analysis was performed using high performance liquid chromatography. Concentrations of 5-ASA in the breast milk of 5-ASA treated patients were 4–40 ng/ml while those of N-acetyl-5-ASA were 5.0–14.9 ng/ml (some 1000 times higher). These results are similar to levels found by other investigators.4,5

Based on an average intake of a breastfeeding infant of 150 ml of milk/kg of body weight/day, concentrations of 5-ASA found in breast milk samples equate to a dosage of 0.0006–0.006 mg/kg. This falls well below 10% of the standardised therapeutic dose, and therefore by this conventional criteria the risk of 5-ASA on the infant is considered clinically unimportant. However, our finding of high levels of metabolite (N-acetyl-5-ASA) in breast milk suggests that the metabolite is greatly enriched in breast milk. Differences in the physical properties of 5-ASA and N-acetyl-5-ASA may well account in part for some difference in their rate of transfer into breast milk. But it is more likely that the findings reflect the result of active metabolism of 5-ASA taking place within the glandular cells of the breast.

We have shown that the concentration of 5-ASA in the breast milk of patients receiving 5-ASA therapy is low. It is therefore interesting to speculate whether the low levels of 5-ASA may, in part, be due to metabolism of 5-ASA to N-acetyl-5-ASA by breast tissue as a
mechanism to prevent high levels of active 5-ASA from accumulating in milk. N-Ac-5-ASA is a relatively inactive metabolite and is therefore unlikely to have a toxic effect on the infant, although to our knowledge the effect of N-Ac-5-ASA on infants has not been studied. We therefore cautiously support the view that 5-ASA containing medication is safe for breastfeeding mothers with inflammatory bowel disease. In addition to our specific findings relating to 5-ASA, the discovery of active drug metabolism in the breast has potentially wider implications. Based on our findings we would recommend that future studies looking at breast milk drug levels explore the possible effects of metabolism by breast tissue and the potential toxic effects of any metabolites produced.

D A Silverman, J Ford, I Shaw, C S J Probert
University of Bristol Division of Medicine, Bristol Royal Infirmary, Bristol, UK
Correspondence to: Dr C S J Probert, University of Bristol Division of Medicine, Bristol Royal Infirmary, Bristol BS2 8BW, UK; c.s.j.probert@bristol.ac.uk

References

Duodenal adenoma and cancer in FAP
We congratulate the authors (Gut 2004; 53:381–6) on gathering this large cohort of patients in this important area in familial adenomatous polyposis (FAP) but would like to report our experience with regard to the study. Our first concern relates to the means of endoscopic assessment. Standard forward viewing endoscopy was used, whereas in clinical practice side viewing endoscopy is recommended as duodenal polyposis in FAP is more severe in the periampullary region and this is likely to be missed with standard endoscopy. This will therefore underestimate both adenoma staging and frequency. This matter is raised in their discussion where they describe side viewing endoscopy as unrealistic. We however feel this is unreasonable in an era where ERCP services are available in most hospitals, at least in the UK. Furthermore, the need for appropriate endoscopy technique and biopsy protocols has been highlighted in a recent study which reveals the side effects duodenal disease when comparing biopsy specimens and resected specimens, in addition to the finding of invasive cancer in a number of specimens resected for “severe duodenal adenomatosis” (that is, Spigelman stage 3 with high grade dysplasia or stage 4). The need to operate before biopsy proven carcinoma is demonstrated by the high mortality rates from metastatic disease in those with duodenal carcinoma. Accurate staging and assessment for endoscopic or surgical intervention is, in our opinion, not possible by standard forward viewing endoscopy.

Our other concern relates to the quoted cancer incidence, which we feel must be biased. The cohort was not followed up from a young age and the true range of the cohort at first endoscopy was 20–81 years. Both the authors’ own data and others have shown that there is an increased risk of stage 4 disease and cancer with increasing age. As such, those older patients in this group we would expect to be self selected and to have less severe disease. Those who were destined to develop severe duodenal disease or cancer may well have developed it prior to screening. Of note, the median age of those developing cancer was 52 years (range 26–58).

In addition, those 12 patients undergoing open duodenotomy and polypectomy are likely to be those with most advanced disease and a highest risk of malignant transformation, thus again biasing the likely natural incidence of duodenal carcinoma. There are also few details with regard to medical intervention which may affect duodenal staging and disease progression. In the discussion, the authors mention that a few patients may have been on periodic sulindac but feel that this would have a negligible impact on their analysis. In the present era of selective COX-2 inhibition, our current clinical practice is to consider celecoxib treatment in those with stage 3 or 4 disease as well as those who have undergone surgical intervention. If this practice were followed using sulindac in the centres involved in this trial, then up to 91 (24%) patients in this cohort could have been exposed to non-steroidal anti-inflammatory drugs.

A R Latchford, R K S Phillips
St Mark’s Hospital, London, UK;
andylatch@doctors.org.uk

Correspondence to: Dr A R Latchford, The Polyposis Registry, St Mark’s Hospital, Northwick Park, Watford Rd, Harrow, Middlesex HA1 3UJ, UK; andylatch@doctors.org.uk

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References

Treatment of recurrent gastrointestinal haemorrhage in a patient with von Willebrand’s disease with octreotide LAR and propranolol
Von Willebrand’s disease (vWD) is the most common inherited bleeding disorder, which is caused by quantitative deficiency or qualitative abnormalities of von Willebrand factor (vWF). Until recently, treatment of bleeding from the gastrointestinal tract in patients with vWD included administration of tranexamic acid or clotting factor products such as freeze-dried plasma, cryoprecipitated vWF concentrates, or preparations that contain vWF and factor VIII. Desmopressin, beta blocking drugs, and hormonal therapy with oestrogen with or without progesterone have also been used.

We report a patient with vWD who had suffered recurrent and life threatening bleeding from the gastrointestinal tract in whom, despite an extensive investigation, no apparent cause of haemorrhage was identified. He was successfully treated with combined administration of octreotide LAR (long active released) and propranolol. This is the first report on the use of octreotide LAR in a patient with vWD.

A 55 year old man presented to our department because of recurring episodes of melaena, which first appeared five years previously. He had a history of epistaxis during his childhood. During investigation of his bleeding diathesis, he was found to have type 1 vWD. His niece was also diagnosed with type 1 vWD whereas his father, brother, and grandmother suffered from a bleeding diathesis which an investigation had been undertaken. Laboratory investigation was compatible with the diagnosis of vWD, with prolonged bleeding time (15 minutes), moderate prolongation of activated partial thromboplastin time (41 seconds), mild deficiency of factor VIII (42%; normal range 50–150%), complete absence of ristocetin induced platelet aggregation, moderate decrease in vWF (29%; normal range 50–160%), and a moderate decrease in vWF antigen (33%; normal range 50–160%). Platelet count and prothrombin time were within normal limits and the extensive laboratory investigation excluded the presence of concomitant disorders.

Over a period of 17 months, the patient had been admitted 14 times for recurrent episodes of melaena with an overall hospitalisation time of 96 days and consequent sick leave from his job. On one occasion the haemoglobin concentration on admission was 6 g/dl. He required 40 red cell transfusions and 22 000 IU of purified vWF. During this period, upper endoscopy was performed five times, small bowel examination twice, and colonoscopy three times; computed tomography of the abdomen, radionuclide scanning with 99mTc pertechnate labelled autologous red blood cells, angiography of the superior mesenteric artery, and exploratory surgery with intraoperative enteroscopy were also performed, but the source of bleeding could not be localised. He had received intranasal desmopressin for three months with no effect on the frequency of bleeding. He was subsequently treated with octreotide LAR 20 mg (Sandostatin LAR; Novartis, Athens, Greece) intramuscularly once a month, along with propranolol 20 mg orally three times a day. With this therapeutic regimen the bleeding stopped completely, haemoglobin values stabilised at normal levels (13.2 g/dl), and no treatment related side effects were observed. During a follow up period of eight months, bleeding did not recur and the patient has returned to his work. Repeated evaluation of vWF revealed that vWF levels did not rise (28%), but ristocetin induced platelet aggregation remained absent, and activated partial thromboplastin time and bleeding time prolongations remained unchanged.
Antiviral treatment initiation costs in chronic hepatitis C

We thank Dr Poynard for his comments highlighting the role of pretreatment evaluation costs prior to antiviral treatment of patients with chronic hepatitis C (Gut 2003;52:1352). The rate of fibrosis progression varies in patients with chronic hepatitis C, so liver biopsy can identify those with advanced disease who are at greatest risk for progressing to decompensated cirrhosis when therapeutic options are limited. Other testing, such as genotyping and viral load, can help estimate the likelihood of antiviral response or determine the duration of therapy, and still others are obtained for baseline values to monitor for potential side effects from therapy.

In our cost effectiveness analyses of antiviral treatment strategies for chronic hepatitis C, treatment initiation costs included those related to procedures performed before the beginning of antiviral therapy: pregnancy test, quantitative hepatitis C virus (HCV)-RNA testing, HCV genotypeotyping, thyroid stimulating hormone, thyroxine, and liver biopsy, as well as partial inpatient costs for initiation of antiviral therapy. Previously published cost effectiveness studies have applied different biopsy costs depending on the country and health care system.1 2 The costs in our study are based on the German Hepatitis C Database and reflect the German health care system. However, there are different options for defining these costs. Liver biopsy can be performed as an inpatient or outpatient procedure. The German Uniform Assessment Standard (Einheitlicher Bewertungsmaßstab, EBM), which is the fee for service coding system in social health insurance for outpatient care in Germany, assigns a total of 1450–1630 score points to the performance of outpatient liver biopsy. This includes ultrasound guidance (530 points), biopsy (700 points), and histology (220–400 points), and translates to a cost between €49 and €55. The German Hepatitis C Model Clinical Expert Panel (in 2001) estimated that inpatient liver biopsy requires an average hospital stay of one day or less. Based on administrative per diem costs, a one day hospital stay in Germany costs €234.3 To bias our analysis against antiviral treatment, we applied a conservative estimate of the cost effectiveness of antiviral treatment, we applied a full hospital stay for all patients undergoing liver biopsy in our base case analysis.

When we performed sensitivity analyses on all cost parameters, we found little variation in the incremental cost effectiveness ratios of antiviral treatment compared with no antiviral treatment. When comparing combination therapy (pegylated interferon alfa-2b plus weight based ribavirin) with combination of standard interferon plus ribavirin, pretherapeutic costs do not alter the incremental cost effectiveness ratios of antiviral treatment strategies, they cancel each other out when we calculate the incremental cost of antiviral treatment (that is, the difference in treatment costs between antiviral treatment strategies)

References


Octreotide is mainly used in acromegaly and in gastrointestinal and pancreatic tumours. Nevertheless, it has also been proposed to be effective in controlling bleeding from the gastrointestinal tract due to angiodysplasia and variceal bleeding.4 5 It is postulated that it exerts its actions through a reduction in splanchic and portal blood flow.6 Octreotide, compared with conventional octreotide, has the advantages that it is administered once monthly, does not require hospitalisation, and has a similar efficacy and safety profile.

Only one report on the effectiveness of octreotide therapy in two patients with vWD was found in the literature.7 8 In one of these patients, vWF was increased after administration of octreotide LAR and propranolol was effective in preventing bleeding in our patient through a direct effect on the splanchnic circulation. In other patients, vWF was increased after administration of octreotide and propranolol appears to be an attractive alternative treatment in patients with vWD and recurrent bleeding from the gastrointestinal tract, particularly when other therapeutic modalities have failed.

U Siebert, J Wasem, S Rossol, G Sroczynski, P Aedelsburger, U Ravens-Sieberer, B Kuth, M P Mannis, J G McHutchison, J B Wong
Harvard School of Public Health, Boston, Massachusetts, USA

Correspondence to: Dr U Siebert, Harvard School of Public Health, 718 Huntington Ave, Boston, Massachusetts 02115, USA; usiebert@hsph.harvard.edu

References


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Adherence to BSG adenoma surveillance guidelines will reduce colonoscopic workload

There is an ever increasing demand for colonoscopy nationally which will increase further when colorectal cancer screening is rolled out nationally. To accommodate this, a marked improvement in the efficiency of endoscopy units is required. One simple way of reducing demand is to reduce the number of repeat procedures performed. We have found that by following the British Society of Gastroenterology (BSG) polyp follow up guidelines,1 our unit could prevent a significant number of unnecessary colonoscopies.

Our unit’s three month retrospective audit found that 79 of 528 patients undergoing colonoscopy had colonic polyps; 130 polyps in total were detected of which 65 were histologically confirmed adenomas (45 tubular, 18 tubulovillous, and two villous). Over two thirds were in the rectum/sigmoid. By classifying patients with polyps according to BSG guidelines:

- 32 were low risk, of which 16 had too short a follow up interval and 16 had correct follow up (of the 16 with too short a follow up, 10 had no follow up and six had a five year follow up);
- 13 were intermediate risk, with three having correct follow up, six too short a follow up interval, one too long a follow up, and three had no follow up;
- one patient was high risk and received too long a follow up interval;
- 11 had incomplete polyp removal of which four received appropriately rapid follow up, two had late follow up, and five received no follow up;
- of 22 patients with non-adenomatous polyps, only eight had an unnecessary repeat procedure arranged.

Strict adherence to the BSG guidelines would have added eight apparently overlooked procedures but could have saved up to 30 other surveillance procedures (if a policy of no follow up for low risk polyps was used), resulting in a net reduction of 22 procedures. This is equivalent to a 47% reduction in surveillance colonoscopies.

The simple measure of reviewing repeat requests for surveillance procedures to ensure they adhere to BSG guidelines should reduce the number of unnecessary procedures performed, creating additional capacity within our endoscopy unit and reducing the exposure of patients to unnecessary risk.

R C Thomas, C Selinger, M D Rutter
University Hospital of North Tees, Stockton, UK

Correspondence to: Dr R C Thomas, Department of Gastroenterology/GIM, University Hospital of North Tees, Hardwich, Stockton TS9 6ED, UK; r1cht72@aol.com

Conflict of interest: None declared.

Reference

NOTICE

6th International Symposium on Functional Gastrointestinal Disorders

This symposium will be held 7–10 April 2005, in Milwaukee, Wisconsin, USA, and is jointly sponsored by the University of Wisconsin Medical School and the International Foundation for Functional Gastrointestinal Disorders, in cooperation with the Functional Brain-Gut Research Group. An international audience of clinicians and investigators will gather to exchange information on the latest advancements in the areas of functional gastrointestinal disorders. The symposium will offer a format of plenary sessions, interactive workshops and mini symposia on both adult and paediatric functional gastrointestinal disorders. Further details: Terese Bailey, Office of Continuing Medical Education, 2701 International Lane, #208, Madison, WI 53704; tel: +1 (608) 240 2141; fax +1 (608) 240 2151; email: tmbailey@wisc.edu.

CORRECTION

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In the Editor’s quiz: GI snapshot entitled “An unusual treatment for a colonic polyp” (Gut 2004;53(7):1000, 1019) the last two authors were listed incorrectly. The correct order is M Crobu and then MG Porpora.
Is mesalazine really safe for use in breastfeeding mothers?

D A Silverman, J Ford, I Shaw and C S J Probert

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