References

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LETTERS

Terlipressin and arterial blood volume after paracentesis for tense ascites in cirrhosis

Moreau et al described the use of terlipressin, a vaspressin analogue, in ameliorating the reduction in effective arterial blood volume which can occur after paracentesis for tense ascites in cirrhosis (Gut 2002;50:90–4). The article states that the first 1 mg intravenous bolus dose of terlipressin was given at the onset of paracentesis. Previous work has shown that infusion of vasopressin in a haemodynamically stable circulation can lead to reduced cardiac performance and coronary blood flow. Moreover, a sustained pressor response can occur in cirrhotic patients, with reduction in heart rate, cardiac output, hepatic blood flow, and pressor effects also on the pulmonary circulation.

Although the authors state no episodes of arterial hypertension occurred in the terlipressin group and that there were no observed changes between pre- and post-treatment electrocardiograms (ECGs), it is not clear whether invasive continuous arterial pressure monitoring was employed in this study or whether continuous ECG readings were taken. Without this level of observation it is difficult to exclude the occurrence of transient asymptomatic episodes of cardiac ischaemia.

Exclusion of patients with a history of cardiac disease, cardiac failure, renal disease, and diabetes mellitus may render the conclusions of this pilot study, and those of any subsequent randomised controlled trials with the same exclusion criteria, difficult to interpret and apply. One may argue that it is these subgroups of patients with comorbid factors who are most likely to suffer the deleterious consequences of a reduction in effective arterial blood volume of any duration or magnitude.

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References


Cardiac response to exercise in cirrhosis

Reading the excellent article on the cardiac response to exercise in cirrhosis (Gut 2001;49:268–75), I was surprised that patients without ascites were labelled “preascitic”. The implication is that these patients have not as yet developed ascites, presumably because their disease is less advanced than in those patients with ascites. It is well known that many patients with cirrhosis will never develop ascites, regardless of the severity of other sequelae of portal hypertension that have developed or will ultimately develop. This is certainly borne out by my experience at a busy liver transplant centre. I would respectfully suggest that these patients be instead called simply “cirrhotic patients without ascites”.

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Authors’ reply

We thank Dr Wachsberg for his comments and apologise for not making ourselves clear. In contrast with cirrhotic patients without ascites, who may well have had ascites and used diuretics sometime in the past, preascites is a well characterised stage in the natural history of cirrhosis. It occurs early in the continuum of cirrhosis. Such patients have never had ascites nor required the use of diuretics, and yet they show evidence of abnormal renal handling of sodium. They maintain sodium balance while on a diet of 100 mmol/day sodium but retain sodium when given an acute sodium load such as 200 mmol/day sodium for one week or when challenged with an intravenous saline load. However, these patients can eventually come to sodium balance, after an intake of 200 mmol/day sodium but at the expense of an increase in total and central blood volume, together with suppression of renin-angiotensin-aldosterone and sympathetic activities in the supine position. The assumption of the erect posture leads to activation of these hormonal systems which are responsible for the subtle sodium retention in these patients. Preascites is further characterised by increased dopaminergic activity, a possible consequence of the expanded intravascular volume, and elevated plasma nitric oxide levels, which may partly contribute to the glomerular hyperfiltration observed in these patients. Finally, preascitic patients also have increased muscle sympathetic nervous activity although the significance of this is not clear at present. Thus the preascitic cirrhotic patient is not simply a cirrhotic patient without ascites but rather the syndrome of preascites is a syndrome with well defined characteristics. While many patients in Dr Wachsberg’s busy liver transplant unit may not have ascites, and they may well be receiving their liver transplant for reasons other than ascites, they certainly cannot be confused with preascitic cirrhotic patients.

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Aetiology of extrathepatic portal vein thrombosis

I read with interest the article by Janssen et al (Gut 2001;49:720–4) regarding the aetiology and determinants of survival of extrathepatic portal vein thrombosis (EPVT). Among others, this retrospective study investigated the systemic risk factors for EPVT. We would like to add hyperhomocysteinemia as a relatively new, not yet mentioned, risk factor. This is illustrated by a recent case in our clinic. A 54 year old woman was hospitalised because of worsening of upper abdominal pain which started two weeks before admission and was continuously present. Her personal and family history for thromboembolic processes was uneventful and she did not smoke. She did not use vitamin supplements. One day prior to admission she was...
using the progesterone norethinodrol (Primolut N) because of vaginal blood loss.

Combined portal-splenic vein thrombosis was diagnosed using colour Doppler ultrasound and computed tomography. There were already some venous collaterals in the hilum area of the liver; hence the thrombosis would have been present for at least several weeks.

After investigations for thrombophilia were carried out, intravenous heparin and oral anticoagulant therapy were started and the patient improved.

The patient was found to be heterozygous for the prothrombin gene G20210A mutation and for a methylenetetrahydrofolate reductase deficiency: mild hyperhomocysteinemia (fasting/six hour post methionine load values 18.91/11.4 µmol/l) was also detected. Plasma vitamin B12, B6, and folate levels were normal. The patient is currently on lifelong oral anti-coagulants and has not yet started to use vitamin supplements.

Mild hyperhomocysteinemia is a hypercoagulability risk factor for the development of portal vein thrombosis. At the time of the study of Janssen et al., had not been recognised as a prothrombotic factor. The association of hyperhomocysteinemia and prothrombin gene mutation in EPVT has been documented only recently in literature. It is still unclear if the association is additive or synergistic for the development of thrombosis. We would like to recommend determination of homocysteine levels in patients with idiopathic EPVT as vitamin B6, folate and cobalamin were normal.

References


Author’s reply

Spanier and Frederiks describe the role of diagnosing hyperhomocysteinemia in a patient with portal vein thrombosis. Their case not only illustrates the potential impact of hyperhomocysteinemia but also the confluence of multiple risk factors in portal vein thrombosis.”

2. "Two inherited thrombotic risk factors (methylene tetrahydrofolate and prothrombin gene G20210A mutation) predisposed the patient to a thrombotic event which became clinically manifest after the recent start of progesterone.

The hypothesis that hyperhomocysteinemia is an independent risk factor for cardiovascular diseases. Hyperhomocysteinemia can be diagnosed by genetic testing for the methylenetetrahydrofolate mutation and by measurement of increased plasma homocysteine levels, both fasting and after loading with methionine. The pathophysiological mechanism of homocysteine induced vascular disease is not well understood. It is even unclear whether homocysteine itself or a related metabolite or cofactor is primarily responsible for the thrombogenic effects of hyperhomocysteinemia. In our study on risk factors and determinants of survival for portal vein thrombosis, we did not investigate hyperhomocysteinemia. As mentioned by Spanier and Frederiks, this relates primarily to the fact that in most of our patients hyperhomocysteinemia was not recognised as an established thrombogenic risk factor at the time of diagnosis. Furthermore determination of homocysteine levels and its determinants or concurrent risk factors for portal vein thrombosis, which may lead to poor nutritional status and therefore interfere with plasma homocysteine measurement. These factors include the presence of liver cirrhosis, malignancy, and infections. Although testing for the point mutation (C677T) in the methylenetetrahydrofolate reductase gene avoids the problem of acquired hyperhomocysteinemia, this genetic defect by itself does not appear to be a significant independent risk factor for atherothrombotic disease. From a therapeutic viewpoint, testing for hyperhomocysteinemia is interesting, also for portal vein thrombosis, because vitamin supplementation (with folic acid, pyridoxine, and vitamin B12) is generally effective in reducing homocysteine concentrations. However, it is only recently known if this therapy confers a risk for either extensive splanchic thrombosis or other thrombotic manifestations which can develop in patients with portal vein thrombosis.

In my opinion, the lack of prospective controlled trials are investigating the potential beneficial effect of homocysteine lowering treatment on cardiovascular morbidity and mortality in subjects with hyperhomocysteinemia. However, it is undisputed that broad screening for hyperhomocysteinemia in patients with portal vein thrombosis, would be preferable to have a better understanding of the clinical efficacy of these therapeutic interventions.

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References


Rifampicin and treatment of cholestatic pruritus

Prince et al described three patients with primary biliary cirrhosis who developed hepatoxocity when given rifampicin to treat their cholestatic pruritus (Prince 2000;50:436–9). They describe the use of rifampicin as “secondline” treatment of cholestatic pruritus. Firstline therapy is generally considered to be cholestyramine, a bile acid sequestrant. Use of this agent is frequently unsuccessful because of gastrointestinal side effects, especially constipation. I am writing to summarise new evidence that retention of endogenous bile acids causes cholestatic pruritus, and to call attention to a recent abstract indicating that colesalame, a new bile acid sequestrant, appears to be more potent than cholestyramine and does not induce constipation.

The view that bile acid retention causes pruritus is a very old one. Varco in 1947 noted that biliary drainage reduced pruritus in patients with extrahepatic biliary obstruction and that when bile was fed to patients, their pruritus returned. Huet and colleagues reported that biliary drainage improved cholestatic pruritus in patients with intrahepatic cholestasis. Administration of cholestyramine, an anion exchange resin with high affinity for bile acids, improved pruritus as did passage of plasma over charcoal or anion exchange resins. More recently, extracorporal aminothiol dialysis, which removes bile acids, has been shown to diminish cholestatic pruritus. In all of these procedures, retained substances in addition to bile acids could have been removed at the same time so that cause and effect relationships were uncertain.

Partial biliary diversion is effective in treating cholestatic pruritus. A likely explanation for the efficacy of this surgical procedure is that it reduces the load of endogenous bile acids to the transport system and thence to the liver, resulting in less retention of bile acids. In an important study, Hollands et al reported that ideal cholestasis was effective in reducing cholestatic pruritus. The ideal transport system is considered to solely transport bile acids. Thus this report in the surgical literature provided unequivocal evidence for bile acids being related directly or indirectly to cholestatic pruritus.

If bile acids are causal agents, and if bile acid depletion improves cholestatic pruritus, then bile acid administration to cholestatic patients should induce pruritus. Recent authors have been sceptical of the role of bile acids in cholestatic pruritus. Despite these convincing lines of evidence, recent authors have been sceptical of the role of bile acids in cholestatic pruritus. This scepticism has arisen because of the lack of correlation between plasma bile acid levels and the magnitude of pruritus in some, but not all, studies. However, in my opinion, the lack of correlation between plasma bile acid levels and pruritus does not exclude a causal role for bile acids for three reasons. Firstly, plasma bile acids fluctuates diurnally and the composition of plasma bile acids in cholestasis is quite complex. Secondly, bile acids might act slowly on peripheral or central receptors (or cause the release of substances that act on these receptors) so there could be a long delay between elevated plasma levels and pruritus. Thirdly, endogenous molecules such as opiates could act synergistically with bile acids to induce cholestatic pruritus.

Cholestyramine binds bile acids but is frequently ineffective. The efficiency of cholestyramine binding is quite low because the Kd for the ileal transport system is in the micromolar range, and at this concentration
bile acid binding is relatively weak. Thus the ileal transport system for bile acids acts as a sink to strip the bound bile acids from the resin. A new bile acid binding polymer, colesevelam, was synthesised by GelTex Pharmaceuticals (now Genzyme General) with a much superior binding affinity for bile acids. Colesevelam is a hydrogel that was developed as therapy for hypercholesterolaemia. Berg, in a recent abstract, reported that in eight patients with cholestatic pruritus who had not responded to cholestyramine, colesevelam was effective in five.  Colesevelam has an additional advantage over cholestyramine in that colesevelam does not have gastrointestinal side effects.

In their thoughtful case report, Prince et al did not note that rifampicin has a striking effect on bile acid metabolism, inducing 6-hydroxylation. It could well be that 6-hydroxy bile acids either do not induce pruritus or are not conserved by the ileal transport system, as compared with endogenous bile acids, or both. Rifampicin is presumed to induce 6-hydroxylation of bile acids via cytochrome P450. A new bile acid binding polymer, sink to strip the bound bile acids from the bile acid binding is relatively weak. Thus the ileal side effects.

Oats and coeliac disease

We read the study by Janatuinen et al (Gut 2002;50:332–5) with great interest. However, we would like to highlight some concerns.

The initial study randomised patients who were doing well and not responding to cholestyramine, colesevelam, or rifampicin. Berg, in a recent abstract, reported that in eight patients with cholestatic pruritus who had not responded to cholestyramine, colesevelam was effective in five. Berg CI. Use of colesevelam hydrochloride (Welchol) as a rational therapeutic agent for the management of pruritus in chronic liver disease. Hepatology 2001;34:541.


supplements, would be an enormous effort. To date, our investigation is the largest controlled randomised study on oats in coeliac patients. Furthermore, it represents the first attempt in showing the long-term safety of oats in coeliac patients.

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Reference

NOTICES
Sir Francis Avery Jones BSG Research Award 2003
Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2003 Award. Applications (TWENTY COPIES) should include:
• A manuscript (2 A4 pages ONLY) describing the work conducted
• A bibliography of relevant personal publications
• An outline of the proposed content of the lecture, including title
• A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years or less on 31 December 2002 but need not be a member of the Society. The recipient will be required to deliver a 30 minute lecture at the Annual meeting of the Society in Birmingham in March 2003. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2002.

Broad Medical Research Program—Inflammatory Bowel Disease Grants
Funds for inflammatory bowel disease (IBD) research are available immediately from the Broad Medical Research Program of The Eli and Edythe L. Broad Foundation for innovative projects regarding etiology, therapy, or prevention. Grants totalling approximately US$100,000 per year are available for basic or clinical projects. Larger requests may be considered. Initial letter of interest (no substance, 6 headline lines, one page, application, rapid (60 day) peer review, and funding. Criteria for funding includes new ideas or directions, scientific excellence, and originality. Early exploratory projects, scientists not currently working in IBD, and/or interdisciplinary efforts are encouraged. Further information: Marciana Poland, Research Administrator, Broad Medical Research Program, 10900 Wilshire Blvd., 12th Floor, Los Angeles, CA 90024-6532, USA. Tel: +1 310 954 5091; email: info@broadmedical.org; website: www.broadmedical.org

3rd Nutrition and Health Conference
This will be held on 29–30 November 2002 in London, UK. This year’s topics include cancer prevention, cancer treatment, hot topics for coronary heart disease and diet, brain nutrition, gut nutrition, and a diet and lifestyle intervention session. Further information: Nutrition and Health Conference, 16 Brownlow Court, Lyttleton Road, London N2 0EA; tel: +44 (0)208 455 6570; fax: +44 (0)208 455 2126; email: admin@nutritionandhealth.co.uk; website: www.nutritionandhealth.co.uk

17th International Workshop on Therapeutic Endoscopy
This will be held on 3–5 December 2002 in Hong Kong. Further information: Professor SC Sydney Chung, Endoscopy Centre, Prince of Wales Hospital, Shatin, NT, Hong Kong. Tel: +852 2632 2233; fax: +852 2635 0075; email: info@hkse.org

Advances in the Inflammatory Bowel Diseases
This conference will take place on 6–7 December 2002 in New York, USA. Further information: Heather Drew, Imedex, 70 Technology Drive, Alpharetta, GA 30005-3969, USA. Tel: +1 770 751 7332; fax: +1 770 751 7343; email: h.drew@imedex.com; website: www.imedex.com

15th European Intensive Course (SMIER) Digestive Endoscopy
This course will take place on 16–17 December 2002 in Strasbourg, France. Further information: Michele Centenize Conseil, 6 bis Rue des Cendriers, 75020 Paris, France. Tel: +33 1 44 62 68 80; fax: +33 1 43 49 68 58.

The Future of Gastro-entero-hepato-pancreatology is bright
This Academic Farewell Symposium of Guido NJ Tytgat will be held on 12 December 2002 in Amsterdam, the Netherlands. Deadline for registration is 1 November 2002 (no registration fee) and registration should be done via email to: j.goedkop@amc.uva.nl

Cancer of Oesophagus and Gastric Cardia: from Gene to Cure
This conference will be held on 13–15 December 2002 in Amsterdam, The Netherlands. Further information: European Cancer Centre, PO Box 9236, NL 1006 AE Amsterdam, The Netherlands. Tel: +31 (0)20 346 2547; fax: +31 (0)20 346 2525; email: ecc@ikca.nl

The Sheila Sherlock Memorial Symposium
Dame Sheila Sherlock, who died earlier this year, was responsible for creating hepatology at the Royal Free Hospital, London. This memorial symposium will take place on 26–28 January 2003 at the Royal Free Hospital, London, UK. Further information: Terri Dolan, Royal Free and University College Medical School, Royal Free Campus, Centre for Hepatology, Upper 3rd Floor, Rowland Hill Street, London NW3 3PF, UK. Tel: +44 (0)207 433 2891; email: t.dolan@rfc.ucl.ac.uk

3rd Chester International Inflammatory Bowel Disease Meeting
This meeting will be held on 10–11 February 2003 in Chester, UK. An international programme includes speakers from the USA, France, Italy, and the UK, and will cover clinical problems, pathogenesis, medical and surgical treatment. Registration details and programme from: Professor Jonathan Rhodes, Department of Medicine, University of Liverpool, Daubly Street, Liverpool L69 3GA, UK. Tel: +44 (0)151 706 3558; fax: +44 (0)151 706 5832; email: rhodesjn@liverpool.ac.uk