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

Moreau R et al described the use of terlipressin, a vasopressin 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.1

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 may 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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References

Aetiology of extrahepatic 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 extrahepatic 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.1 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 norethisterone (Primolut N) because of vaginal blood loss. Combined portal-splenic vein thrombosis was diagnosed using colour Doppler ultrasonography and computed tomography. There were already some venous collaterals in the hilar area of the liver; hence the thrombosis would have been present for at least several weeks. After investigations for thrombophilias which carried our 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 the methylenetetrahydrofolate reductase defect; mutation. Mild hyperhomocysteinaemia (fasting/six hour post methionine load values 18.91 µmol/l) was also detected. Plasma vitamin B12, B6, and folate levels were normal. The patient is currently on lifelong oral anti-coagulant therapy and has not yet started to use vitamin supplements. Mild hyperhomocysteinaemia is a hypercoagulability risk factor for the development of portal vein thrombosis. When the time of the study of Janssen et al. had not been recognised as a prothrombotic factor. The association of hyperhomocysteinaemia and prothrombin gene mutation in EPVT has been documented only once in the literature. It is still unclear if the association is additive or synergistic for the development of thrombosis. 1 We would like to recommend determination of homocysteine levels in patients with idiopathic EPVT as vitamin B6 and folate supplementation is a cheap and safe therapy in preventing deleterious vascular complications.

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References

Author’s reply
Spanier and Frederiks describe the role of diagnosing hyperhomocysteinaemia in a patient with portal vein thrombosis. Their case not only illustrates the potential importance of hyperhomocysteinaemia but also the concurrence of multiple risk factors in portal vein thrombosis.1 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.

It is clear evidence that hyperhomocysteinaemia is an independent risk factor for cardiovascular diseases. Hyperhomocysteinaemia 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 hyperhomocysteinaemia.

In our study on risk factors and determinants of survival for portal vein thrombosis, we did not investigate hyperhomocysteinaemia as a concurrent risk factor. This relates primarily to the fact that in most of our patients hyperhomocysteinaemia was not recognised as an established thrombogenic risk factor at the time of diagnosis. Furthermore, we failed to measure folate or any other 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.3 Although testing for the point mutation (C677T) in the methylenetetrahydrofolate reductase gene avoids the problem of acquired hyperhomocysteinaemia, this genetic defect by itself does not appear to be a significant independent risk factor for atherothrombotic disease.4 From a therapeutic viewpoint, testing for hyperhomocysteinaemia 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 advisable to know that this therapy confers a risk for either extensive splanchnic thrombosis or other thrombotic manifestations which can develop in patients with portal vein thrombosis.5 Ongoing prospective controlled trials are investigating the potential beneficial effect of homocysteine lowering treatment on cardiovascular morbidity and mortality in subjects with hyperhomocysteinaemia. Before advocating widespread screening for hyperhomocysteinaemia in patients with portal vein thrombosis, it 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 hepato-
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, colesvalem, was synthesised by GelTex Pharmaceuticals (now Genzyme General) with a much superior binding affinity for bile acids. Colesvalem 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, colesvalem was effective in five. Colesvalem has an additional advantage over cholestyramine in that colesvalem 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 cyp3a, a microsomal enzyme, whose synthesis is induced by the interaction of rifampicin and the nuclear receptor PXR. PXR activation might also induce bile acid sulfa-

If the use of rifampicin is hazardous in cholestatic disease, as suggested by Prince et al, then management of cholestatic pruritus should involve a bile acid sequestran such as colesvalem and/or an opiate antagonist. It would seem desirable to initiate a prospective, placebo controlled, double blind study using state of the art methods for quantifying itching that would compare the efficacy, safety, and convenience of these two agents, alone or in combination, on cholestatic pruritus.

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Conflict of interest Professor Hofmann has served as a paid consultant of GelTex Pharmaceuticals and has received stock options for the purchase of shares in that company.

References
8 Berg CI. Use of colesvalem hydrochloride (Welchol) as a radiopacifying agent for the management of refluxatory pruritus in chronic liver disease. Hepatology 2001; 34: 541.

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 included patients randomised to two groups—oats and gluten free diet. 45 and 47 patients respectively—however, these numbers do not correspond to those in figure 1 of their paper. Patients were verbally consenting volunteers, thus introducing selection bias to compliance. The number of dropouts, especially in the control group, was surprisingly high (41 in total). Were there so many dropouts because of the long term safety of oats or concerns over their safety? If the latter, then surely this would be greater in the oats group.

It is not clear whether patients were followed up in the same time frame between 12 months and five years. It would be important to ascertain objectively whether the oats group were in fact including oats in their diet, as omission would not address their long term safety. Assessment of compliance and food diary are very subjective, introducing bias towards dietary compliance. How was this done? We were surprised to see that one third of the oats group did not in fact take oats at all, so only one in three patients were ingesting oats on a daily basis. The proportion adhering to a gluten free diet was paradoxically greater in the control group. If oats were allowed then this could be interpreted by patients as acceptance of other (gluten containing) foods also. The purity and amount of oats ingested in the first year was regulated but this was not monitored thereafter and contamination of oat products could lead to small bowel architectural changes.

Histological changes in coelic disease can be subjective but no mention was made as to whether blind reporting was carried out. Also, no explanation was given for the greater numbers of high values for ARA, AGA, and EMA in both groups at five years. This needs to be quantified and statistically analysed.

The safety of oats in coeliac disease is extremely important. This and other studies have shown that compliance with a strict gluten free diet is difficult, reflecting its uncompromising limitations as well its relative unpalatability. This paper suggests that oats are safe but the small numbers involved could mask subtle differences between the groups which may result in greater morbidity. In order to address this, further larger multicentre trials are required.

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Authors’ reply
Dor and Shanahan point out the inconsistency in the number of study patients in the dose chosen (in figure 1 of their paper) for ingestion by coeliac patients. Indeed, there is an error. The number of patients in the oats group in remission in the original study (Gut 2000; 45: 332–5) should have been 41 rather than 45. There were no figures given in the text are however correct.

Dor and Shanahan also emphasise the total number of dropouts (41) which covers both the original study of 6–12 months and the follow up period of five years. They ask whether this could be due to the possible unpalatability of oats. However, the number of dropouts was similar among controls (19) and those consuming oats (22). There was no evidence that the oats products were unpalatable. Probably the number of dropouts in many cases reflects the lack of motivation to participate, especially in the unpleasan
t part of the study—that is, gastroscopy to obtain small intestinal biopsies. As expressed in the text, many patients also felt uncertain about the long term safety of oats and no results show that such fear was not justified.

Patients had no strict follow up visits to the outpatient clinic of the University Hospital during the time period between 12 months and five years. However, they were advised to have regular follow up clinical and laboratory examinations in the local health care centres. Some also had regular visits to the outpatient clinic of Kuopio University Hospital.

As stated in the article, patients had free choice regarding the amount of oats they wished to consume and which they felt convenient. In this respect the study also helped to depend on the reality and usefulness of oat products. Information on the quantity of oats in the diet and the degree of compliance was based on an interview and a questionnaire carried out by a clinical nutritionist.

Dor and Shanahan raise the question of whether patients interpreted the use of oats as comparable with consuming gluten containing foods. They base this on the degree of compliance in our study. Compliance was 71.4% in the oats group and 78.6% among controls. In our opinion this does not justify such a conclusion. As stated in the article, the oats group also consumed a strict gluten free diet but part of their gluten free products were substituted by oats.

After 12 months, patients used oat products from major Finnish mills which had previously been found to be free of contamination. If oats by itself or oat products had any deteriorating effect on the duodenal mucosa or stimulated immune mechanisms, the results in the oats group would have differed from those of controls. This was not the case. The results indicate that oats were well tolerated.

As in our original study (Gut 2002; 50: 332–5), histological examination and use of oat products. Information on the quantity of oats in the diet and the degree of compliance was carried out blindly by an experienced pathologist. The values for the various antibody levels were statistically analysed comparing them at the end of the original study and at the five year time point. There were no statistically significant differences between time points or between the oats and control groups. The high values occurred only in a few patients in both the control and oats groups with no significant effect. As stated, those patients showed poor adherence to a gluten free diet.

We do agree with the final conclusion of Dor and Shanahan that larger multicentre trials could be worthwhile. However, to conduct a similar controlled study with larger numbers of patients and continuous frequent control of intake of oats, including multinational purity analyses of freely available oat
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

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 7334; email: h.drew@emedex.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 Centonze Conseil, 6 bis Rue des Cendriers, 75020 Paris, France. Tel: +33 1 44 62 68 88; fax: +33 1 43 49 68 58.

The Future of Gastro-entero-hepato-pancreatology is bright
This Academic Farewell Symposium of Guido NJ Tygat 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 2523; 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. This year, was responsible for creating hepatology, Upper 3rd Floor, Rowland Hill Street, London NW3 3PF, UK. Tel: +44 (0)207 433 2851; 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 UK, 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: rhodesj2@liverpool.ac.uk