The data presented here suggest that a bone biopsy should be performed when investigating dialysis encephalopathy, principally in cases where the etiology remains undefined after less invasive examination.

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Comparison of the urine acidification tests of torsemide vs furosemide in healthy volunteers

Sir,

The gold standard test to assess the ability to lower urine pH has traditionally been based on orally administered ammonium chloride (NH₄Cl) [1]. The use of ammonium chloride for this purpose is not well accepted because the drug has unpredictable GI absorption when given in tablet form and has an unpleasant taste when administered in a powder form. Furthermore, ammonium chloride causes many unpleasant side effects such as abdominal discomfort, nausea and vomiting. An alternative drug used to assess the ability to lower the urine pH with increasing popularity is a loop diuretic, furosemide, which blocks the sodium-potassium-chloride co-transporter (NKCC) in the thick ascending limb of Henlé. One drawback of the furosemide acidification test is a low specificity (82–89%) [2,3]. The likely reason for the low specificity is the carbonic anhydrase inhibitory effect, which is attributed to the presence within the molecule of a sulfonamide moiety [4,5]; this latter effect would partially negate the stimulatory effect on acid secretion by furosemide. In contrast, another loop diuretic, torsemide, contains a sulfonyleurea moiety, instead of a sulfonamide moiety, and therefore is devoid of the carbonic anhydrase inhibitory effect. For these reasons, it is hypothesized that torsemide would be more specific in detecting acidification defects than furosemide, and the following studies were carried out to test this hypothesis.

Studies were carried out in eight healthy male volunteers (aged 23–33 years) utilizing a single-blind randomized crossover format. Urine samples were collected immediately before oral administration of 40mg furosemide or 20mg torsemide, and then hourly for 4h after oral administration of the diuretic. Studies were repeated in the same subjects with the intravenous administration of the same medications in the same doses. pH measurements were made in all the urine samples, but only the baseline urine pH and the lowest urine pH following a loop diuretic were used for data analysis.

The baseline urine pH values were similar in all groups. The values with torsemide were 6.2 ± 0.2 (mean ± SE) with a range of 5.7–7.1 after oral administration and 6.2 ± 0.2 with a range of 5.6–7.2 after intravenous administration. The values after furosemide were 6.3 ± 0.3 with a range of 5.5–7.3 after oral administration, and 6.3 ± 0.2 with a range of 5.6–7.4 following intravenous administration. However, urine pH after the administration of torsemide was significantly lower than after that of furosemide (P < 0.05), regardless of the routes of administration. The values for torsemide were 4.9 ± 0.1 with a range of 4.5–5.2 after oral administration, and 4.9 ± 0.1, with a range of 4.5–5.6 after intravenous administration. The values for furosemide were 5.6 ± 0.2 with a range of 4.9–7.0 after oral administration, and 5.5 ± 0.2 with a range of 5.0–6.5 after intravenous administration. For furosemide, urine pH remained >5.5 in four of eight subjects after oral administration, and two of eight after intravenous administration. For torsemide none had urine pH >5.5 after oral administration, and only one of eight subjects after intravenous administration. If we define urine pH <5.5 following a loop diuretic in normal subjects as a true normal result [6], the specificity of furosemide test was 50% with oral administration and 75% after intravenous administration, whereas for torsemide they were 100% after oral administration and 88% after intravenous administration, respectively. No subjects developed any significant adverse effects with either loop diuretic regardless of the routes of administration.

In conclusion, torsemide appears to be as safe and simple as furosemide in testing the maximum ability to lower the urine pH, with greater specificity than the latter. However, the sensitivity of this test needs to be determined in subjects with impaired urine acidification.

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Beneficial haemodynamic and renal sodium handling effects of combined midodrine and octreotide treatment in a cirrhotic patient with large hepatic hydrothorax and mild ascites

Sir,
Hepatic hydrothorax complicates advanced liver cirrhosis resulting from the transfer of ascitic fluid into the pleural space in the absence of primary cardiopulmonary disease and, occasionally, of clinically evident ascites. When management with sodium restriction and diuretics fails and repeated thoracenteses are needed, potentially dangerous invasive procedures, such as pleurodesis, thoracoscopic repair of diaphragmatic defects with pleural sclerosis or transjugular intrahepatic portosystemic shunting should be considered [1]. Recently, octreotide-induced natriuresis and reduction of hepatic hydrothorax was described [2,3]. We report on a case of hepatic hydrothorax, which resolved after adding the α-adrenergic agonist midodrine to octreotide.

A large sterile right hepatic hydrothorax was diagnosed in a 66-year-old female with hepatitis C virus (HCV) cirrhosis (Child class C) with mild ascites and deteriorating dyspnoea. Increasing doses of spironolactone and furosemide induced marked hyponatraemia and encephalopathy without a reduction of the pleural effusion, and repeated paracenteses were required. Diuretics were discontinued and octreotide 600 mg/day was commenced on day 1; mean arterial pressure (MAP) was 80 mmHg, cardiac output (CO) 7.321/min, serum urea (Ure) 7.6 mmol/l, serum creatinine (Cre) 88.4 mmol/l, plasma sodium (Na) 124 mmol/l, urinary sodium (UNa) 16 mmol/day, urinary volume (UV) 1100 ml/day, glomerular filtration rate (GFR) with Tc99m-DTPA 112 ml/min, effective renal plasma flow (ERPF) with Tc99m-MAG3 615 ml/min, plasma active renin (PAR) 119 mU/ml, plasma aldosterone (PA) 82.5 ng/dl, plasma antidiuretic hormone (ADH) 11.4 pg/ml and plasma glucagon 298 pg/ml. On day 8, PAR, PA and plasma glucagon were 45.8 mU/ml, 39.4 ng/dl and 184 pg/ml, respectively, but ADH remained high (7.4 pg/ml). Octreotide did not improve the MAP (76 mmHg), CO (7.391/min) or renal function (Ure 7.3 mmol/l, Cre 97.2 μmol/l, Na 127 mmol/l, UNa 11 mmol/day, UV 850 ml/day, GFR 91 ml/min) despite an increase in ERPF (876 ml/min). The pleural effusion was not mobilized by octreotide whereas it decreased gradually after adding oral midodrine, up to 10 mg t.i.d., to octreotide. On day 17, the MAP was 98 mmHg, CO 6.021/min, Ure 5.2 mmol/l, Cre 79.5 μmol/l, Na 133 mmol/l, UNa 165 mmol/day, UV 2900 ml/day, GFR 138 ml/min, ERPF 866 ml/min, PAR 17.3 μU/ml, PA 17.6 ng/dl, ADH 3.5 pg/ml and plasma glucagon 192 pg/ml. Thereafter, she received octreotide 600 mg thrice weekly, midodrine 7.5 t.i.d., furosemide 40 mg/day and spironolactone 100 mg/day without recurrence of the hepatic hydrothorax until her death 4 months later.

Splanchnic arterial vasodilation with reflex activation of sodium- and water-retaining systems is involved in the pathogenesis of cirrhotic ascites and related pleural effusion [1]. Chronic octreotide administration seems to disrupt the circulatory homeostasis in decompensated cirrhotics by directly inhibiting the renin-angiotensin-aldosterone axis. As a result, it improves ERPF but not systemic haemodynamics, GFR and natriuresis [4]. However, octreotide ameliorates the splanchnic arterial hyporeactivity to vasoconstrictors by suppressing glucagon secretion [5]. Indeed, recent observations suggest that octreotide could potentiate the beneficial haemodynamic and renal effects of midodrine in decompensated cirrhotics [4]. The combination of midodrine and octreotide could therefore be considered in the treatment of hepatic hydrothorax.

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