Letters

Chronic tubulointerstitial nephritis and distal renal tubular acidosis in a patient with frusemide abuse

Sir,
Chronic tubulointerstitial nephritis (CTIN) is associated with a number of diseases of diverse aetiology. It is characterized by tubular atrophy, flattening of epithelial cells and tubular dilatation, interstitial fibrosis, and areas of monocellular cell infiltration within interstitial compartment and between tubules. A number of drugs have been found to be associated with CTIN, such as analgesics, lithium, cyclosporin, cisplatin, nitrosourea, Chinese herbs, and germanium lactate citrate [1]. To date, however, there are no reports regarding CTIN associated with frusemide. Distal renal tubular acidosis (dRTA) is one of the typical manifestation of CTIN [2]. The findings in classic dRTA include hypokalaemia, hyperchloreaemic acidosis, an abnormally low urinary ammonium excretion (positive urine net charge or low urinary osmolar gap), and an inappropriately high urine pH in the face of systemic metabolic acidosis.

We report on a young woman with a biopsy-proven CTIN and distal renal tubular acidosis (dRTA) associated with frusemide abuse. The pathogenesis of CTIN in this patient is unknown; however, the persistence or progression of repeated ATIN or hypokalaemia induced by frusemide might have played a role in CIN in this patient.

Case. In April 1999, a 25-year-old Korean woman was admitted because of generalized oedema and dyspnoea of 15 days duration. She had been suffering from cyclic oedema for 5 years, for which she was taking frusemide (1 or 2 tablets per day: 40–80 mg/day) without physician’s prescription. From that time, she gradually increased the dose of frusemide because of continuing weight gain and generalized oedema. Fifteen days before admission she developed weight gain (15 kg) and dyspnoea after suddenly stopping the diuretic. At that time, the total amount of frusemide ingested was almost 30 tablets a day (1.2 g/day). She denied taking any other medication.

On admission, physical examination was normal except for generalized oedema and mild dyspnoea. Her temperature was 36.5°C, pulse rate 74 beats/min, and blood pressure 130/90 mmHg. Laboratory tests showed a normal blood count. Serum levels of creatinine, urea, and uric acid were 0.8 mg/dl, 14 mg/dl, and 6.5 mg/dl respectively. Creatinine clearance was 65 ml/min, urinary creatinine 17 mg/kg body weight. Ten days after restriction of daily water (<1000 ml) and salt intake (<5 g), she had returned to her usual weight and no pitting oedema appeared.

After normalization of body weight, arterial blood gas analysis showed hyperchloreaemic metabolic acidosis with a normal anion gap (pH 7.32, pCO2 30.7 mmHg, pO2 93.7 mmHg, HCO3 17.9 mEq/l, serum sodium 140 mEq/l, serum potassium 3.2 mEq/l, serum chloride 111 mEq/l, serum calcium 9.2 mEq/l, and serum phosphorus 4.0 mEq/l). Despite systemic acidosis, the pH of the freshly voided urine was 6.7 with a specific gravity 1.010. Urine was negative for glucose and contained a trace of protein. The total serum protein was 6.1 g/dl, serum albumin 4.0 g/dl with normal immunoglobulin pattern. Proteinuria was 0.54 g/day. The urine anion gap was 11 and urine osmolar gap 35 mosm. Serum complement levels (C3, C4) were within normal limits. Serological survey including FANA, ANCA, HBsAg, HCV, HIV, CMV, and EBV was negative. A renal ultrasound showed both kidneys to be slightly decreased in size, with a diffuse increase in parenchymal echogenicity. A percutaneous
renal biopsy was performed. On light microscopy, there were 18 glomeruli of which four were entirely sclerotic. The rest were of normal appearance. The renal biopsy also showed tubular cell atrophy with flattened epithelial cells, interstitial fibrosis, and areas of mononuclear cell infiltration in the interstitium. Mesangial cells and matrixes had the usual appearance and capillary walls were normal with a patent lumen. There was no significant deposition of immunofluorescent material in the glomeruli and tubules.

After 14 hospital days in an oedema-free state, a NH4Cl loading test was carried out for three consecutive days. In the presence of systemic acidosis, urinary pH was 6.3. Therefore, a NaHCO3 loading test was also performed. The fractional excretion of HCO3 was 4% and the urine-blood pCO2 gradient (U-B pCO2) rose from 1.9 mmHg in the basal state to 43.1 mmHg after bicarbonate infusion. These results suggested normal distal proton pump function and the absence of a proximal acidification defect. A frusemide test was performed to evaluate a possible voltage-dependent defect (Table 1). The urine pH did not change significantly after frusemide stimulation (from 7.48 to 7.2), but fractional excretion of sodium and potassium increased from 1.7 to 23% and from 6.5 to 30% respectively. This suggested a collecting tubule permeability disorder with bicarbonate leak to the tubular lumen.

The patient was discharged with a prescription of oral sodium bicarbonate 3 g/day and enalapril 10 mg/day. Three months after discharge, the tests were repeated with the same result. At follow-up after 1 year there was no oedema or weight gain.

Comment. To our knowledge this is the first report of a biopsy-proven CTIN and dRTA associated with frusemide abuse in a young woman. CTIN accounts for approximately 15% of cases of end-stage renal disease in the United States [1]. The clinical manifestation of CTIN is dominated by tubular functional abnormalities. These abnormalities depend on a nephron site being mainly involved: for example, distal nephron dysfunction with salt wasting, metabolic acidosis, hyperkalaemia, and medullary injury with impaired concentration ability. Drug-related nephritis is one of the most common causes of tubulointerstitial nephritis (TIN) [1].

In our case, the two main points of interest are (i) whether frusemide can induce CTIN, and (ii) which mechanisms are involved.

As to the first point, acute TIN with fever, rash, and eosinophilia is an uncommon complication of frusemide. It may develop abruptly or some months after frusemide therapy has been started. Most patients recover fully after withdrawal [3]. Some forms of acute injury to the tubulo-interstitial compartment can result in an ongoing inflammatory process, leading to impaired renal function [4]. It is rare, however, for sustained hypokalaemia to cause CTIN [5]. There are both inherited and acquired forms of hypokalaemic nephropathy, if it is prolonged, irreversible damage will occur. Recently, an interesting case was reported of long-term hypokalaemia due to Bartter’s syndrome (frusemide-like inherited disorder) and chronic administration of frusemide led to CTIN and renal dysfunction [6].

The second point is whether dRTA in this patient is a result of a gradient defect with bicarbonate leak into the lumen. Our patient had hyperchloraemic acidosis with alkaline urine, hypokalaemia, high urinary sodium, and a low fractional excretion of bicarbonate, compatible with dRTA. The normal urinary pCO2 values and the differences in pCO2 between urine and blood after NaHCO3 indicate that tubular acidosis in our patient was caused by an H+ gradient defect in the distal part of the nephron, not by a defective proton pump. The inability to create a steep H+ gradient across the distal tubule may be due to a back-leak of secreted H+, or leaking of bicarbonate to the tubular lumen. The patient had never been exposed to amphotericin B, which causes dRTA due to back-leak of H+ [7]. In a patient exposed to amphotericin B, urinary pH remains above 5.5 during systemic acidosis, and after bicarbonate or neutral phosphate loading, urinary pCO2 reaches a normal value (above 70 mmHg) [7]. In our patient, the ability to increase urinary pCO2 after urine alkalinization was functioning normally, but frusemide administration failed to appropriately decrease urinary pH, accompanied by a marked increase in the urinary excretion of Na+ and K+. To date, there has been only one report of a patient with dRTA as a gradient defect of H+ with bicarbonate leak into the lumen. In our patient with CTIN, the collecting tubule permeability defect is probably a consequence of the defect of chronic tubular inflammation in the distal part of the nephron.

Frusemide is one of the therapeutic drugs used in dRTA, especially in patients with hyporeninaemic hypaldosteronism and hyperkalaemia accompanying hypertension or fluid retention [3]. Frusemide increases the distal delivery of Na+ and fluid and stimulates aldosterone secretion and PO4 reduction, and thereby enhances net H+ elimination. Thus, frusemide can increase renal acid excretion in patients with RTA. In contrast to these effects, our case suggests that larger doses of frusemide may, paradoxically, have a detrimental effect on the renal tubule.

In summary, this is the first reported case of CTIN accompanying dRTA associated with frusemide abuse. Although the exact mechanism of the adverse effect of frusemide in this patient is unclear, the persistence progression of repeated interstitial nephritis episodes and the chronic hypokalaemia induced by frusemide abuse might have played a role in the CIN of this patient. We conclude that frusemide abuse, like analgesic abuse, can be a cause of CTIN and dRTA.

Table 1. Effect of frusemide on urinary acidification and urinary Na+ and K+ excretion

<table>
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<th>Urine volume (ml/min)</th>
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<td>K (mEq/l)</td>
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<tr>
<td>pH</td>
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<td>139</td>
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<tr>
<td>K (mEq/l)</td>
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