Hypercalcaemia from non-prescription vitamin A

Sir,

Use of over-the-counter ‘natural’ supplements may have unnatural effects. We report this case as a cautionary example.

A 67-year-old white male patient was admitted to hospital in late January 2004, with malaise and hypercalcaemia. He had undergone kidney transplantation 6 years earlier for kidney failure of unknown cause. Chronic allograft nephropathy occurred and the plasma creatinine rose to 400 \( \mu \text{mol/l} \). He began to feel unwell in December 2003, and had a 5 kg weight loss. There was constipation, melena and haematochexia. His medications included prednisone, mycophenolate mofetil, atorvastatin, labetalol, bumetanide and potassium chloride. Blood tests showed a total plasma calcium of 4.2 mmol/l and he was admitted to hospital. On examination, there was a tremor and unsteadiness of gait. The plasma chloride was 1.7 mmol/l (normal 1.2–1.3). Intravenous normal saline was given. Chest X-ray was normal. Upper and lower gastrointestinal endoscopy showed antral gastritis and two benign colonic polyps. Serum and urine protein electrophoresis did not show a paraprotein. The parathormone (PTH) level was 17 pg/ml (normal 10–65) and that of PTH-related peptide was undetectable. The total plasma calcium reached 2.5 mmol/l by hospital day 4. On that day, further enquiry showed that he had been taking a dietary supplement containing vitamin A, on the advice of an eye doctor, for possible diagnosis of macular degeneration. The over-the-counter supplement contained 7000 U of \( \beta \)-carotene per tablet and he had been taking four tablets daily since the autumn of 2003. Because of the possibility of vitamin A-induced hypercalcaemia, this supplement was stopped immediately. A retinol plasma level was 2550 \( \mu \text{g/l} \) (expected values 350–1200). A month later, he was feeling his usual self, the total plasma calcium had fallen to 2.4 mmol/l, and the plasma creatinine had fallen to 400 \( \mu \text{mol/l} \).

The increasing use of dietary supplements and over-the-counter medicines, ‘natural’ or otherwise, may pose significant risks. In this case, the total daily dose of vitamin A that this patient was using was 28 000 U, whereas the recommended daily intake is only 5000 U. The association of vitamin A toxicity and hypercalcaemia is rare but well recognized. We found only eight case reports of this association in the past 30 years, the most recent being in 1988 [1].

The hypercalcaemia of vitamin A toxicity may occur because of activation of bone resorption by vitamin A [2]. This man’s reduced baseline kidney function may have predisposed him to vitamin A toxicity. Given the modern prevalence of use of alternative medicines and supplements, more such cases may occur, which emphasizes the ongoing importance of vigilance and a careful medication history.

Conflict of interest statement. None declared.

A fatal case of aluminium encephalopathy in a patient with severe chronic renal failure not on dialysis

Sir,

Aluminum (Al) toxicity in patients with end-stage renal disease is a well known adverse effect due to either dialysate Al contamination or oral intake of Al-containing phosphate binders [1]. At present, the clinical forms of Al toxicity have almost disappeared. Al-containing drugs are given mainly as antacid agents and are often used without special caution in patients with chronic renal failure (CRF) not yet on dialysis. Herein, we report a case of fatal Al-related encephalopathy in a patient with severe CRF, not on dialysis, due to the intake of large doses of antacids containing Al for at least 3 years.

Case. A 59-year-old white male patient with CRF due to diabetic nephropathy was followed as an out-patient in our chronic kidney disease clinic. When he was 47 years old, diabetes mellitus was diagnosed, and he was treated with oral antidiabetics for 2 years and thereafter with insulin. At 55, a severe polyneuropathy and distal occlusive arterial disease with foot gangrene occurred that required the amputation of the left foot. He suffered from gastric pain which he self-treated with Al hydroxide (Maalox® TC). A gastroduodenoscopy was performed that revealed antral gastritis positive for Helicobacter pylori. Despite the antibiotic treatment, the patient continued taking Al hydroxide. From the age of 57, he regularly attended our chronic kidney disease clinic. His serum creatinine was between 3 and 4 mg/dl.
The electroencephalogram showed wide theta and delta waves, often in a triphasic fashion, and diffuse slow spikes. Serum Al was checked and found to be 740 μg/l. After a dialysis session, the patient fell and fractured a femur. He was treated with 500 mg of desferroxamine/day intramuscularly (Novartis, Origgio, Italy) in 250 ml of physiological solution daily, for 1 month until death, but the neurological disturbances progressed steadily. Repeated general seizures occurred, and the patient died of a cardiogenic shock during a general convulsion.

At autopsy, the brain weighed 1280 g, it was slightly atrophic and no focal lesions were found. On light microscopy, the grey matter presented spongiosis, cortical gliosis and neuronal atrophy. Slight gliosis was present in the basal nuclei; neuronal thickening was observed in the pons. Silver staining of paraffin slides revealed argyrophilic deposits in epithelia of choroid plexus, the cytoplasm of glial cells and different neuronal populations of brainstem, cortex and subcortical grey matter. Al concentrations (μg/g fresh tissue) were 2.46 in the frontal lobe, 3.56 in the parietal lobe, 2.34 in the temporal lobe, 2.89 in the cerebellum, 15.5 in the kidney, 20.3 in bone and 6.5 in the heart.

Comment. This case showed all three syndromes related to Al toxicity, namely encephalopathy, bone disease and microcytic anaemia. The total amount of ingested aluminum was at least 3 kg in 3 years. He did not have end-stage renal disease when he started taking Al hydroxide, but moderate to severe renal failure with a serum creatinine between 3 and 4 mg/dl.

Most reported cases refer to patients on peritoneal dialysis or haemodialysis. Only a few have been described in patients not yet on dialysis: a patient who developed Al-related bone disease after the ingestion of 711 g in 1 year [2]; a child with microcytosis due to high Al doses given to treat hyperphosphataemia [3]; and two patients with dialysis encephalopathy syndrome due in one case to the use of Al-containing phosphate binders for 2 years, and in the other to the concomitant intake of citrate [4]. Four other CRF patients took Al hydroxide and citrate together and developed encephalopathy [5]. Finally, a case of osteomalacia due to prolonged antacid use was reported in a patient with normal renal function [6].

The peculiarity of the present case is the presence of the complete picture of Al toxicity and the exceedingly high levels of serum Al.

The kinetics of Al absorption in CRF were well described by Šáržegi et al. [7]. In patients with moderate CRF, serum Al concentration was twice as high as baseline, even 24 h after the administration of a compound containing 58.1 mg of Al. The most interesting finding was that CRF patients were unable to excrete Al as compared with healthy subjects, i.e. the problem was not absorption, but excretion. Moreover, Al kinetics were the same in patients with moderate and severe CRF.

Although sufficient evidence exists to show that some degree of Al overload occurs in Al-treated patients even in the presence of normal renal function, the problem arises with long-term treatments with Al-containing compounds. This was the case in our patient and in the other patients alluded to above [2–6]. The occurrence of Al intoxication is so rare at present that it no longer seems to be a problem. However, because we do not know the prevalence of the use of Al compounds in CRF patients, the symptoms of mild forms of intoxication may be easily missed. As a matter of fact, the cases described in the literature are very severe. Not much is known about the effects of low-dose long-term exposure, or whether it may contribute to patient morbidity and mortality in the long run.

It is well known that Al-containing compounds should be avoided in CRF patients, that care should be taken in limiting their use to the short-term reduction of high serum phosphate, and that all possible alternatives should be considered. However, sometimes, as in our case, the patient self-prescribes the drug. In this situation, only regular monitoring can detect patients at risk of Al intoxication.

Conflict of interest statement. None declared.

Sirolimus-induced pneumonitis, sinusitis and macular oedema

Sir,

Sirolimus is being used increasingly in calcineurin inhibitor-free regimens in solid organ transplant immunosuppression [1,2]. However, it has potential pulmonary toxicity due to a capillary leak syndrome [3,4]. We report for the first time one such case with involvement of the paranasal sinuses and retina in addition to sirolimus-induced pneumonitis, all probably related to the same underlying pathophysiology.

A 54-year-old male with presumed chronic tubulointerstitial nephritis and end-stage renal disease (ESRD) on intermittent haemodialysis treatment underwent cadaver renal transplantation in August 2003. He was given daclizumab induction, followed by mycophenolate mofetil (MMF) 1000 mg per day and sirolimus (6 mg loading followed by 2 mg once daily) and low dose prednisolone as immunosuppression. Cyclosporin was avoided due to delayed graft function. MMF was withdrawn and cyclosporin (3 mg/kg) was introduced after 2 weeks once adequate graft function was established. His baseline serum creatinine at this time was 1.8 mg/dl. One month post-transplant, he was found to have diabetes mellitus for which he was put on insulin therapy. Two months post-transplant, he presented with complaints of increasing breathlessness and headache. He was afebrile, normotensive and had no systemic oedema. Chest examination revealed bilateral crepitations. Fundoscopy showed bilateral macular oedema. Blood chemistry showed a haemoglobin of 11.2 g/dl, TLC 11 300/mm^3, serum urea 83 mg/dl and creatinine 1.8 mg/dl. One chest X-ray showed bilateral non-homogeneous opacities in the middle and lower zones, and X-ray of the paranasal sinuses revealed bilateral opaque maxillary sinuses and hazy frontal sinuses. Computed tomography (CT) scan showed mucosal oedema and thickening of all the sinuses (frontal, ethmoid, sphenoid and maxillary). Sputum cultures were sterile. Fluorescein fundus angiography showed pooling of contrast suggestive of central serous retinopathy.

Sirolimus was stopped and he was managed conservatively without antibiotics as there was no evidence of infection. A sirolimus trough level was not done as we did not have the facility at our centre. Bronchial alveolar lavage was not done due to rapid resolution of symptoms. His breathlessness and headache subsided during the next 48 h. At repeat X-rays of chest and paranasal sinuses, the initial findings were almost cleared up and at fundus examination a decreased macular oedema was found.

There have been several case reports of pneumopathy with the usage of sirolimus [3–5]. None of them have reported involvement of paranasal sinuses and the retina, probably because this was not looked for in view of the dominant pulmonary symptomatology. Case reports mention high drug levels, graft dysfunction and hypervolaemia to be possible risk factors [2,3].

This case reminds us of the importance of identification of potential toxicities of the immunosuppressive regimens, e.g. sirolimus. The acute toxic effects as a rule are reversible, and cessation of the drug usually leads to resolution of the side effects.

Conflict of interest statement. None declared.

Old-time features are back in renal transplanted patients

Sir,

Uraemic stomatitis is a very rare oral mucosal disorder possibly because nowadays patients are seldom left without dialysis at advanced and prolonged stages of renal failure. The present report details the features of uraemic stomatitis in a patient with longstanding chronic renal failure.

A 46-year-old male was referred by the nephrology department of Hospital das Clinicas to the oral medicine unit of UFPE, Recife, Brazil, complaining of a burning sensation of the oral mucosa and dysgeusia. The patient had developed chronic renal disease due to non-specific nephritis associated with severe hypertension in 1991, at which time he commenced haemodialysis. In the same year the patient underwent renal transplantation but the renal allograft was rejected 4 years later. The patient continued haemodialysis for 10 years until he underwent a further renal transplant in 2001. Perhaps surprisingly, at the time of referral his renal disease was considered stable, aside from elevation of plasma urea (288 mg/ml: normal range 18–21 mg/ml) and creatinine. Unfortunately, no details of calcium, phosphate or haemoglobin were available at that time. Intra-oral examination

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