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Cinacalcet in HIV haemodialysis patients

Sir,

Cinacalcet HCL (MIMPARA®), a positive allosteric modulator of the calcium-sensing receptor (CaR) on the surface of the parathyroid glands, reduces serum parathyroid hormone (PTH) levels in more than 80% of haemodialysis (HD) patients [1]. The efficacy and safety of cinacalcet has been demonstrated in several studies [1,2], but its use in HIV patients on chronic dialysis is not described. We report two HD patients with HIV infection treated simultaneously with anti-retroviral therapy and cinacalcet.

A 24-year-old black woman was admitted in July 2002 for end-stage renal disease (ESRD) of unknown origin that required chronic HD. Simultaneously, HIV-1 infection was diagnosed. A tritherapy with efavirenz 600 mg, lamivudine 25 mg and didanosine 100 mg per day was initiated in January 2004, resulting in sustained undetectable HIV plasma viral load and stable T4 levels ($>550/mm^3$). Cinacalcet was started in May 2007 at 30 mg/day and progressively increased to 90 mg without any efficacy (intact parathyroid hormone (iPTH) > 1000 pg/ml). In December 2007, cinacalcet was stopped and a parathyroidectomy was performed. Histological examination revealed a bilateral parathyroid adenoma. Efavirenz residual serum concentration after surgery and cinacalcet withdrawal was 1.5 μg/ml (normal range: 1.1–4 μg/ml).

A 45-year-old Caucasian man was treated by chronic HD for ESRD of unknown aetiology since July 2003. HIV-1 and hepatitis B virus (HBV) co-infection was discovered at the time of dialysis initiation. A combination of efavirenz 600 mg, lamivudine 50 mg, didanosine 125 mg per day and tenofovir 245 mg per week resulted in undetectable HBV and HIV plasma viral load with sustained stable T4 levels ($>600/mm^3$). Because of high serum iPTH (>1000 pg/ml), cinacalcet was initiated in May 2007 at 30 mg per day and further increased to 120 mg in November 2007 without efficacy. Efavirenz mean residual serum concentration on three consecutive measurements under cinacalcet therapy (120 mg) was 1.3 ± 0.5 (SD) μg/ml.

The two patients received concomitant treatment with sevelamer, calcium carbonate and vitamin D_3 during cinacalcet therapy. In both the cases, tolerance of cinacalcet and anti-retroviral treatment was good. Monthly monitoring of pancreatic and liver enzymes and serum calcium levels was not modified.

Analysis of the literature shows that more than 80% of HD patients on cinacalcet therapy achieve an ≥30% reduction in iPTH level from the baseline over 6 months [1]. In our cases, whereas cinacalcet was administered for more than 6 months, no effect on iPTH was observed despite increased cinacalcet dosage.

Little is known about the pathophysiology of resistance to cinacalcet. A role for non-compliance to the drug was excluded in both the cases. Defective sensitivity of the parathyroid cell to the calcimimetic drug has been proposed. Additionally, a relative resistance to cinacalcet was demonstrated in the case of severe decreased expression of CaR in parathyroid glands [3]. In our cases, resistance to cinacalcet was likely the result of drug interaction.

Cinacalcet is metabolized through cytochrome P450 (CYP) isoenzymes 3A4, 2D6 and 1A2. *In vitro* studies have demonstrated that cinacalcet is a potent inhibitor of CYP2D6. Additionally, data suggest that during concomitant treatment with cinacalcet, dose adjustment may be necessary for CYP3A4 and CYP1A2 inductors or inhibitors [4].

As the metabolism of lamivudine, didanosine and tenofovir do not involve CYP450, the culprit drug seems to be efavirenz. Efavirenz is metabolized via CYP450, particularly by 3A4 and 2B6 isoenzymes. Although efavirenz is an *in vitro* inhibitor for 2C9, 2C19, 3A4, 2D6 and 1A2 isoenzymes, it has been demonstrated in humans that efavirenz can be inductor for CYP450 enzymes and can also induce its own metabolism by this mechanism [5,6]. This enzymatic induction, especially for CYP3A4 isoenzyme, is probably responsible for most drug interactions with efavirenz. Despite the absence of a known pharmakokinetics interaction between cinacalcet and efavirenz, enzymatic induction of CYP3A4 metabolism by efavirenz is probably responsible for therapeutic failure of cinacalcet in the present cases. Unfortunately, this hypothesis could not be verified, as the measurement of the serum cinacalcet level is not currently available. However, a role for decreased numbers of CaR or defective sensitivity of parathyroid cells cannot be excluded.

In summary, cinacalcet in HD patients with chronic HIV infection treated by efavirenz seems inappropriate. Nephrologists need to be aware of this rare potential interaction. Surgical parathyroidectomy should be recommended.

Conflict of interest statement. None declared. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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Treatment of metformin-associated lactic acidosis with sustained low-efficiency daily dialysis

Sir,

Sustained low-efficiency daily dialysis (SLEDD) is an intermittent prolonged dialysis modality which is increasingly used for the treatment of acute renal failure [1,2], as it combines most of the advantages of both the classic intermittent treatments and the continuous modalities in terms of safety, efficacy, haemodynamic stability and costs. GENIUS® 90 Therapy System (GENIUS) (Fresenius Medical Care, Bad Homburg, Germany) gained interest for application in SLEDD for the treatment of acute renal failure [1,2] as well as of acute drug intoxication [3–6]. No published experience exists about the use of SLEDD in metformin-associated lactic acidosis (MALA). Here we report the case of a 64-year-old diabetic woman who on 12 November 2007 was admitted to the gynaecology unit of our hospital in order to undergo a surgical intervention for the correction of hysterocele, cystocele and enterocele. On 14 November 2007 she underwent colpohysterectomy, McCall culdoplasty, urethrocystopexy and colpoperineoplasty. Her past medical history included mild chronic renal failure (serum creatinine levels were between 1.3 and 1.5 mg/dl), arterial hypertension and type II diabetes mellitus. At the time of admission she was being treated with the following drugs (daily doses): metformin 3000 mg, allopurinol 300 mg, verapamil 120 mg, irbesartan 300 mg and furosemide 25 mg. On 17 November serum creatinine level was 1.4 mg/dl; on 18 November the patient

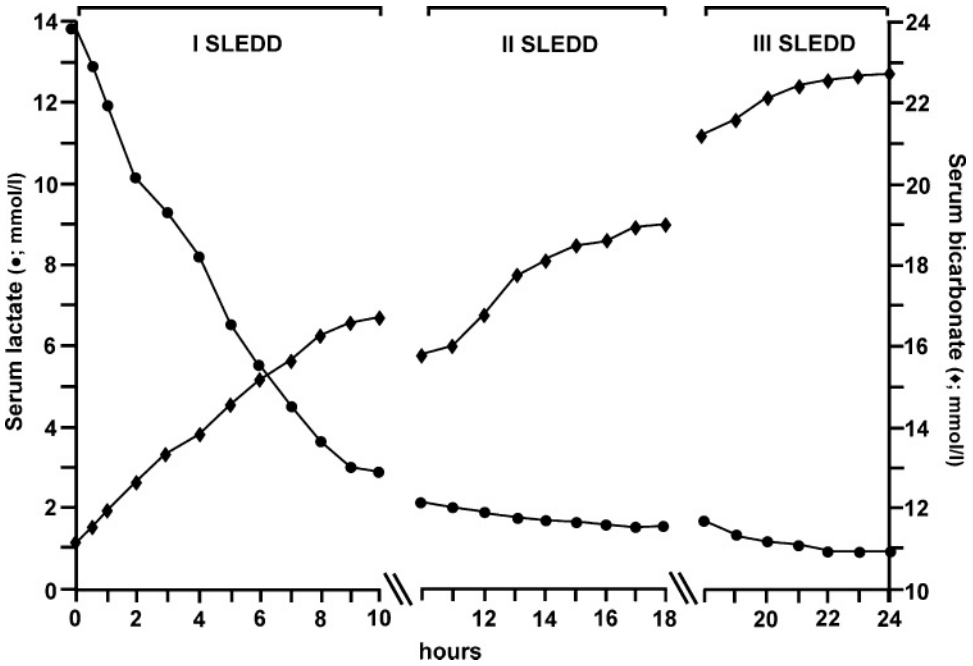

Fig. 1. Hourly measurements of serum lactate (•) and bicarbonate levels (♦) during the three sessions of SLEDD with GENIUS.