

LETTER TO THE EDITORS

Falsely decreased ionized calcium levels in kidney transplant recipients with polyomavirus-associated nephropathy treated with leflunomide

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Dear Sirs,

Polyomavirus-associated nephropathy (PVAN) is a serious complication after kidney transplantation, affecting up to 10% of kidney transplant recipients, and is one of the main causes of allograft dysfunction or graft loss. PVAN is mostly due to BK viremia due to re-activation of BK virus [1]. No clear preventive strategies for the development of PVAN are available as yet. In the treatment of PVAN, reducing immunosuppression is the first therapeutic step. In case of insufficient response, leflunomide, a synthetic isoxazole-derivative drug that possesses both immunosuppressive and antiviral properties, can be prescribed [2]. In a recent study comprising more than 200 young adolescent patients, successful treatment of BK viremia with leflunomide, in combination with ciprofloxacin, was reported without inducing serious side effects [3]. Furthermore, beneficial effects of leflunomide have been described in valganciclovir-resistant cytomegalovirus infection [4].

It is important to be aware that the use of leflunomide could result in falsely decreased ionized calcium (iCa) levels. This is caused by analytical interference of teriflunomide, which is the active metabolite of leflunomide, with measurements of iCa. This interference is dependent on the type of blood gas analyzer and is associated with the age of the electrode [5]. We observed this phenomenon in six kidney transplant recipients who were treated with leflunomide (Arava[®], Sanofi Aventis, Gouda, The Netherlands) because of PVAN.

The index patient was a 67-year-old woman who underwent kidney transplantation 9 months earlier. Because of PVAN, she was treated with leflunomide 5 months post-transplantation (40 mg/day). During routine electrolyte evaluation, an iCa level of 0.60 mmol/l (reference value 1.15-1.32 mmol/l) was measured. In our hospital, we use a Rapidlab-1265 blood gas analyzer (Siemens Healthcare Diagnostics, Breda, The Netherlands) to measure iCa levels. She was admitted, and active vitamin D and calcium supplementation were started. However, despite increased dosing, iCa level increased only slightly to 0.85 mmol/l. Because she had no neuromuscular or cardiovascular

symptoms and a suppressed parathormone (PTH) level, total Ca and albumin levels were measured in heparin plasma on a DxC 800 routine chemistry system (Beckman Coulter, Brea, California, USA). Serum albumin-adjusted Ca concentration was 3.15 mmol/l (reference value 2.20-2.60 mmol/l). Consequently, active vitamin D and calcium supplementation were stopped, after which serum albumin-adjusted Ca concentration normalized.

Patients 2, 3, and 4 used leflunomide in a dosage of 60 mg/day. All received a kidney transplant approximately 5 months earlier, but unfortunately developed PVAN.

Routine electrolyte evaluation revealed unexpected low iCa levels (0.74, 0.80, and 0.74 mmol/l, respectively). These low levels still persisted after treatment with active vitamin D and calcium supplementation. Remarkably, values for electrolytes and PTH were all within the normal range. However, serum albumin-adjusted Ca concentrations were all near the upper limit of normal (2.56, 2.29, and 2.57 mmol/l, respectively). After discontinuation of leflunomide, measured iCa values were nearly normal in a few weeks, as illustrated in Fig. 1. Nevertheless, reported iCa remained low, probably because of the long half-life time of teriflunomide. Eight months after stopping leflunomide, teriflunomide could still be measured in patient 2 (teriflunomide level 1.44 mg/l).

Patients 5 and 6 were transplanted 12 and 5 months before start of leflunomide. Both patients used 60 mg leflunomide per day. Routine electrolyte evaluation revealed iCa levels of 0.84 and 0.75 mmol/l. Serum albumin-adjusted Ca concentration was 2.62 and 2.59 mmol/l, respectively. After replacement of the ion-selective electrode of our blood gas analyzer, iCa levels increased to 1.09 and 0.98 mmol/l, respectively. In both patients, it was decided to continue leflunomide.

Our cases illustrate that iCa levels can be falsely decreased in kidney transplant recipients using leflunomide. This phenomenon is caused by interference of teriflunomide with the iCa electrode of certain blood gas analyzers. The precise mechanism is unclear, but is probably related to the absence of a protective cellophane mem-

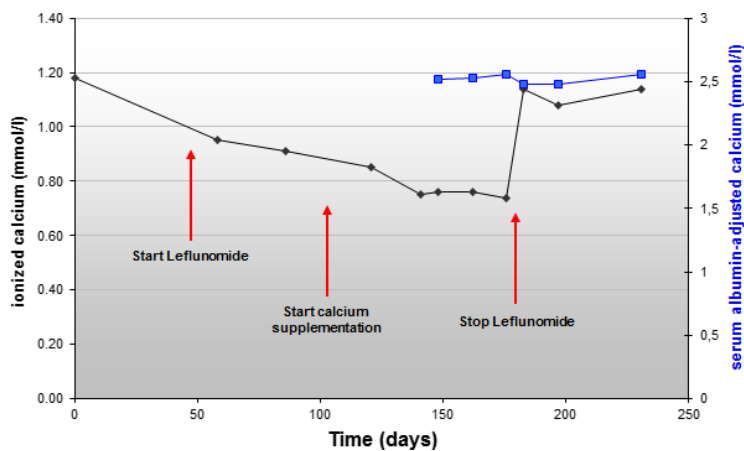


Figure 1 Ionized calcium and serum albumin-adjusted calcium levels in patient 4 (mmol/l).

brane in the Rapidlab-1265 blood gas analyzer, which makes direct contact between teriflunomide and the ion-selective electrode possible [5].

Therefore, we advocate to use serum albumin-adjusted Ca concentration in patients treated with leflunomide to avoid misinterpretation of calcium homeostasis and to avoid a possible inappropriate and potentially harmful treatment.

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Conflicts of interest

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