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Paricalcitol as an Antiproteinuric Agent Can Result in the Deterioration of Renal and Heart Function in a Patient with Fabry Disease

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 44
Final Diagnosis: Deterioration of renal and heart function
Symptoms: Hypercalcemia
Medication: —
Clinical Procedure: Laboratory
Specialty: Nephrology

Objective: Rare disease

Background: Fabry disease is a rare and progressive X-linked inherited disorder of glycosphingolipid metabolism that is due to deficient or absent lysosomal α-galactosidase A activity. Among its other associated signs and symptoms, patients present with renal failure and proteinuria, which are markers of disease progression. Renin-angiotensin-aldosterone system (RAAS) blockers can slow the progression of chronic renal failure and proteinuria. In fact, some studies have shown the beneficial effects of paricalcitol on proteinuria.

Case Report: We present a case of a female patient with the classic variant of Fabry disease. She was treated with a high dose of paricalcitol as an antiproteinuric agent due to unsatisfactory double-RAAS blockage, which resulted in transient worsening of cardiac and renal function.

Conclusions: Despite the positive effects of paricalcitol as an antiproteinuric agent, as previously shown by some authors, our case highlights the possible serious adverse effects associated with the use of high doses of this drug.

MeSH Keywords: 25-Hydroxyvitamin D 2 • Fabry Disease • Heart Failure, Diastolic • Proteinuria • Renal Insufficiency

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Background

Fabry disease (FD, OMIM ID #301500) is a rare and progressive X-linked inherited disorder of glycosphingolipid metabolism. As a result of deficient or absent lysosomal α-galactosidase A activity, globotriaosylceramide accumulates in the tissues and organs and leads to their functional impairment. Classically, FD affects hemizygous males (severe disease), while heterozygous females present with symptoms that range from very mild to severe disease. The disease presents with neurological pain, diffuse angiokeratoma, proteinuria, progressive kidney failure, cardiomyopathy, and arrhythmia, as well as hearing and cerebrovascular (transient ischemic attack, stroke) symptoms. Diagnosis in males is usually established based on low α-galactosidase A activity, whereas in females, it is confirmed with genetic testing [1,2].

Proteinuria is a marker of chronic kidney disease (CKD) progression and can predict cardiovascular disease development or death regardless of the cause of CKD [3]. Renin-angiotensin-aldosterone system (RAAS) blockers represent the basis of antiproteinuric and renoprotective treatment. Many patients have residual proteinuria despite RAAS blockage, even with double-RAAS blockade [4]. Moreover, vitamin D receptor activators have been used in the management of secondary hyperparathyroidism in CKD for several decades [5]. Short-term studies in humans suggest that treatment with vitamin D receptor activators (such as paricalcitol) can reduce proteinuria [4,6]. These agents are efficient not only as a monotherapy, but also as an adjuvant therapy to conventional RAAS blockers [5]. Several animal studies suggest that the renoprotective properties of vitamin D may be mediated by the suppression of RAAS. Although it primarily functions by suppressing renin production; it has also been suggested that it may also act by reducing renal inflammation and preserving the glomerular slit diaphragm [6,7].

Proteinuria is the hallmark of Fabry nephropathy and it presents as the predominant risk factor for CKD progression in FD. It is known that enzyme replacement therapy (ERT) alone does not decrease proteinuria; therefore, it is recommended that patients receiving ERT should also receive RAAS inhibitors [1]. The use of paricalcitol to treat proteinuria was recognized by experts [2,8] as a possible therapeutic approach when administered in combination with RAAS blockers.

In this report, we present a case of a female patient who presented with the classic variant of FD. She came to our clinic with multi-organ involvement and low α-galactosidase A activity. She was subsequently treated with a high dose of paricalcitol, which was used as an antiproteinuric agent, due to unsatisfactory double-RAAS blockade. The treatment course resulted in the transient and reversible worsening of her cardiac and renal function.

Case Report

A 55-year-old female, ex-smoker, with arterial hypertension, depression, chronic joint pain, and chronic obstructive pulmonary disease was diagnosed with the classic variant of FD featuring multi-organ involvement at the age of 44. Her genetic tests were positive for the disease, and she also exhibited low α-galactosidase A activity (4.6% of normal enzyme activity). At diagnosis, she was already in the advanced stages of the disease, as she predominantly presented with heart (left ventricular concentric hypertrophy with diastolic dysfunction), renal (a mildly reduced glomerular filtration rate [GFR] and non-nephrotic proteinuria), and nervous system (dizziness and depression) involvement. Signs of the disease in other organs were also present, as her eyes (cornea verticillata), skin (anhidrosis and angiokeratoma), and gastrointestinal tract (occasional diarrhea) were affected. A kidney biopsy revealed extensive typical inclusions of globotriaosylceramide in the podocytes and distal tubules with moderate vascular changes.

She began ERT with agalsidase alfa at the age of 45 years. She was already receiving an angiotensin-converting enzyme inhibitor as an antihypertensive treatment at the time of diagnosis. A year later, she started treatment with an angiotensin-receptor blocker for additional antiproteinuric effects.

At the age of 50 years, there was an increase in the proteinuria-to-nephrotic range despite dual RAAS blockage. As such, administration of an additional antiproteinuric agent (paricalcitol, 1 μg/day) was initiated. Two years later, the paricalcitol dose was increased to 2 μg/day in an attempt to lower her further increased levels of proteinuria. We recorded a slight decrease in her proteinuria, but it was still within the nephrotic range. At that point, a kidney biopsy was suggested to exclude other possible causes of her high-grade proteinuria, but she refused. In agreement with the patient, a high dose of paricalcitol was attempted, and the dose was further increased to 4 μg/day. Two weeks later, we noticed a slight increase in her total serum calcium, high-sensitive troponin T (hs-TnT), and N-terminal-pro-brain natriuretic peptide (NTproBNP) levels, whereas ionized calcium remained the same. We continued the treatment since the patient was asymptomatic. She was regularly monitored in clinic every two weeks and she developed no new symptoms. At her next regular laboratory testing, we also performed several functional tests. We noticed a slight decrease in her proteinuria (but it was still within the nephrotic range); however, there was also a further, more prominent increase in the patient's serum creatinine, cystatin C, calcium, hsTnT, and NTproBNP concentrations. In addition, the patient's serum intact parathormone (iPTH) levels and measured GFR had markedly decreased. Echocardiography revealed worsening of her diastolic dysfunction and an increase in the left ventricular filling pressure (Table 1). An electrocardiogram

Table 1. Echocardiographic parameters (obtained by the same echocardiographist). Treatment with paricalcitol was terminated after the November 2014 exam.

Date	Nov.2012	Nov. 2013	Nov. 2014	Nov. 2015
LA (ml/m^2)	23	24	30	23
E' (cm/s)	4.5	4	2.9	3.0
S' (cm/s)	6.4	5.5	5.1	5
E/E'	17	18	37	27
E (m/s)	0.8	0.7	1.1	0.8
A (m/s)	0.7	0.8	0.9	0.8
E/A	1.1	0.9	1.2	1

LA – left atrium; E' – early diastolic septal tissue Doppler velocity; S' – systolic septal tissue Doppler velocity; E – early diastolic transmitral velocity; A – late diastolic transmitral velocity.

showed no changes that were characteristic of hypercalcemia. Despite all of the serological and echocardiographic changes, the patient remained asymptomatic at all times. Furthermore, other potential causes of renal and cardiac function worsening were eliminated and paricalcitol therapy was discontinued.

The patient's calcium and iPTH levels normalized within 14 days after paricalcitol discontinuation (Figure 1). There was also a rapid and marked decrease in her serum creatinine levels (Figure 1), and the measured GFR recovered to baseline levels. The NTproBNP levels declined, while the left ventricular filling pressure decreased; however, the patient's diastolic dysfunction (according to tissue Doppler of the mitral annulus) remained unchanged.

After 1.5 years without paricalcitol, the patient is now on 1 µg of paricalcitol a day with close and regular monitoring of her serum calcium, phosphate, and iPTH levels. Due to the marked decrease in her renal function in the last three years, another kidney biopsy was suggested; however, the patient rejected it once more. She is now taking part in a program to prepare her for renal replacement therapy.

Discussion

Although not registered as a standard antiproteinuric treatment, Pisani et al. have shown that treatment with 1 µg of paricalcitol per day significantly reduced proteinuria in 15 patients with FD nephropathy. These patients were previously on a stable dose of RAAS inhibitors, which was titrated to the maximum tolerated dose [7]. The maximal registered dosage regimen of 2 µg of paricalcitol per day is used for the treatment of secondary hyperparathyroidism [9].

ERT with dual RAAS blockage did not prevent or decrease proteinuria in our patient. She also had an unsatisfactory response to a standard regimen of 1 µg/day of paricalcitol. There was a slow progressive increase in the patient's creatinine, calcium, and NTproBNP levels. We recorded a slight decrease in her proteinuria following the initiation of a higher paricalcitol dose (2 µg), which led to the initiation of a 4 µg paricalcitol treatment regimen in an attempt to further diminish her proteinuria. Soon after, we noticed that the patient developed hypercalcemia, and she also presented with laboratory signs of renal and cardiac function deterioration. Increased hsTnT values could suggest additional myocardial cell damage.

It has been reported that paricalcitol overdose as a consequence of aggressive treatment can result in increased blood urea and aminotransferases, as well as in hypertension and heart rhythm disorders, which are primarily related to acute hypercalcemia [9]. We did not notice any changes that were characteristic of hypercalcemia on electrocardiogram; furthermore, our patient developed no new symptoms, which suggests that her hypercalcemia was chronic in origin. It is not well established whether her hypercalcemia caused her worsening cardiac and renal function.

The current literature does not report any long-term associations between paricalcitol treatments and changes in left-ventricular structure, systolic or diastolic function, or NTproBNP levels [10,11]. In fact, Virtanen et al. showed that acute hypercalcemia can impair left-ventricular diastolic function, i.e., by decreasing the peak early diastolic velocity (E) and increasing peak late diastolic velocity (A) in CKD patients, whereas Ohara et al. were able to establish a relationship between changes in diastolic function and high levels of PTH, but not with hypercalcemia [12,13]. In addition, there was no negative impact of paricalcitol on renal function, whereas hypercalcemia can provoke acute renal failure [14–16].

The literature does not provide enough information on the effects of paricalcitol on renal and cardiac function at doses

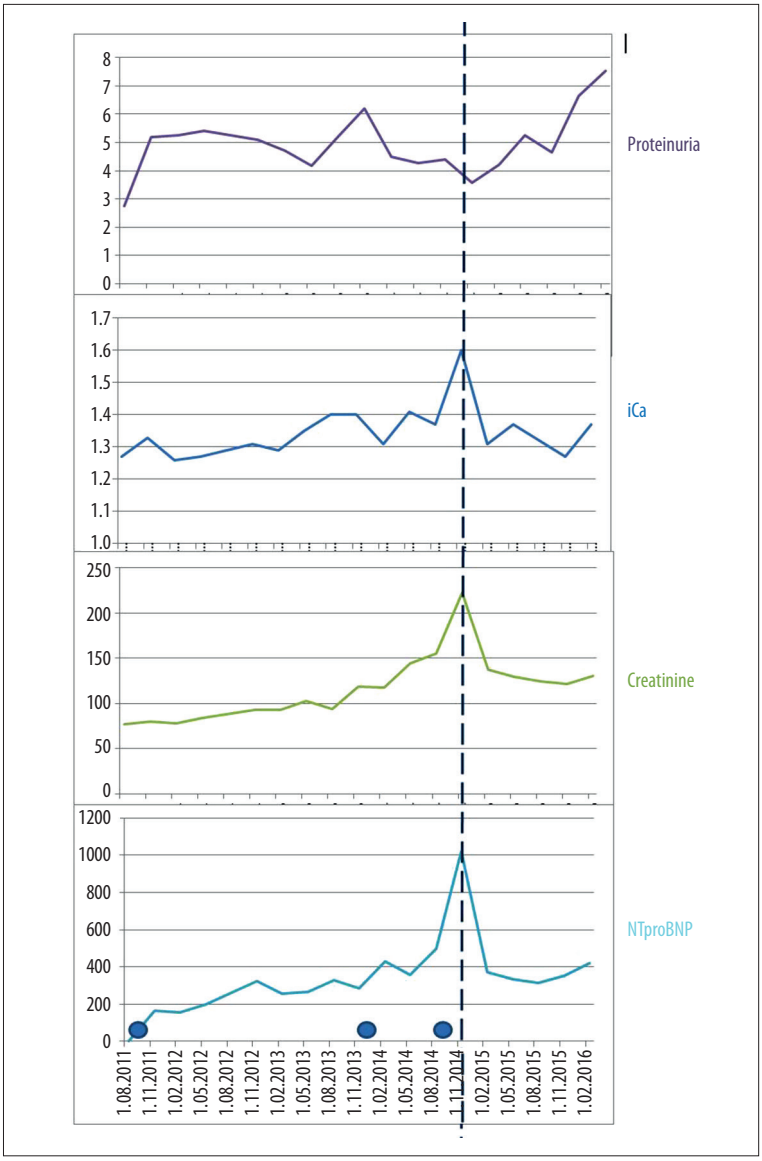

Figure 1. Proteinuria (from 24-hour urine samples), ionized calcium, creatinine, and NT-pro-BNP levels. The first blue dot represents the initiation of paricalcitol therapy, while the second and third dots mark the increases in the daily dose of paricalcitol. The dashed line represents termination of the paricalcitol treatment. Alcium and creatinine levels are reported in millimoles per liter, while NT-pro BNP is reported in picograms per milliliter.

higher than 1 µg, as used in our patient. The fact that the laboratory findings returned to baseline following paricalcitol discontinuation could suggest that there may be a causal relationship. However, there is also a clear connection between hypercalcemia and renal failure, which may have also resulted in renal impairment in our patient. Hypercalcemia can also lead to worsening cardiac diastolic function, but the precise nature of this relationship remains unclear due to contradictory literature findings.

Conclusions

Despite the positive effects of paricalcitol as an antiproteinuric agent, as previously shown by some authors, our case serves as an example of the possible serious adverse events that may occur when high doses of paricalcitol are used. In this case, only minor antiproteinuric effects were achieved.

Our experience suggests that when used as an antiproteinuric agent, only standard regimen doses of paricalcitol (1 µg/day) should be used. The mechanisms underlying the worsening of cardiac and renal function in our case were not completely understood; however, improvements in the patient's laboratory and functional findings following paricalcitol discontinuation demonstrated a causal relationship.

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Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.