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CASE REPORT

A rare case of hypocalcemia induced by nilotinib

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Abstract

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder characterized by increased proliferation of predominantly myeloid cells in the bone marrow and their accumulation in the peripheral blood. Nowadays, drugs known as tyrosine kinase inhibitors (TKIs) are the standard treatment for CML. Since TKIs specifically target BCR–ABL, the activated tyrosine kinase fusion protein, they are expected to cause less hematological and nonhematological side effects than medications used before. We report a case of a 61–year–old patient treated with the second–generation TKI, nilotinib, that presented with very common side effects (skin rash, myalgia, and paresthesia), and also with rare, but severe hypocalcemia and potentially dangerous and fatal QTc elongation.

Key words: Chronic myelogenous leukemia; tyrosine kinase inhibitors; nilotinib; side effects; hypocalcemia; QT interval

1. Introduction

Tyrosine kinase inhibitors (TKIs) can cause many hematological and nonhematological side effects. Our greatest interest in this case report is the influence of TKIs on serum calcium concentrations. Serum calcium concentrations are normally maintained within a very narrow range that is required for the optimal activity of many extracellular and intracellular processes. The major hormones that regulate calcium metabolism are parathyroid hormone (PTH) and vitamin D via effects on the bone, kidney, and gastrointestinal tract. Serum calcium concentrations can be altered in various pathological conditions.

2. Case Report

A 61-year-old man with a past medical history of an appendectomy was diagnosed with chronic myelogenous leukemia (CML) in 2010. The treatment of leukemia was started with imatinib (Gleevec™, Novartis), the first-generation TKI, achieving a good molecular response and remission. In June 2014, the initial drug was replaced by the generic drug (Neopax, Krka), which caused diverse side effects including a general feeling of discomfort or illness, stomach pain, chest pain, and swollen joints. This was the reason behind replacing imatinib with nilotinib, the second-generation TKI, used for the treatment of imatinib-intolerant and resistant patients. At first, there were no signs of nilotinib intolerance. In April 2016, the patient was hospitalized because of central retinal vein occlusion. The following month, he presented with weakness, shortness of breath, lightheadedness, blurred vision, dizziness, muscle cramps, paresthesia, dysphagia, swollen joints, xerosis, and pruritus. A diagnostic evaluation was performed to distinguish, whether the condition was caused by the current drug or was a consequence of a specific organ system dysfunction. On the first day of hospitalization, blood test results revealed an elevated serum creatine kinase (CK) and lactate dehydrogenase (LDH) level, marked hypocalcemia and hyperphosphatemia with a normal PTH value (Table 1). The patient also had electrocardiogram (ECG) changes, specifically, an elongated QTc interval of 508 ms (Table 1). These findings resulted in immediate drug cessation. Additional diagnostic tests were performed including a radiographic swallowing study (which showed irrelevant tertiary contractions of the distal part of the esophagus) and multi-slice computed tomography of the brain (which showed normal findings with the exception of a larger calcification along the frontal part of the cerebral falx). A neurologist also examined the patient, finding hypoesthesia of the polyneuritic type, along with bilaterally slightly reduced triceps surae reflexes, thus suggesting electromyoneurography, which showed initial sensorimotor neuropathy.

The patient's symptoms mentioned above were relieved seven days after nilotinib cessation and administration of 1000 mg calcium carbonate tablets twice daily and 0.5 mcg calcitriol capsule (Rocaltrol, Roche Pharma AG) twice daily during the hospitalization.

Table 1. Diagnostic laboratory tests performed in our patient during hospitalization

Parameter	Day of hospitalization								
	1	6	8	9	10	11	12	13	14
Total calcium (2.14-2.53 mmol/L)	0.94	1.09	1.16	1.30	1.40	1.41	1.41	1.49	1.69
Ionized calcium (1.15-1.32 mmol/L)			0.54	0.70				0.85	
Phosphates (0.79-1.42 mmol/L)	1.89	1.75				1.24	1.10		
PTH (1.6-6.9 pmol/L)			2.80						
LDH (103-241 U/L)	786	751	569		559		401	444	411
CK (50-177 U/L)	908	850	601		540				259
QTc interval (<400 ms)	508			507	483		479	463	464

Numbers in brackets represent reference range values of different parameters provided by our laboratory. PTH-Parathyroid hormone, LDH-Lactate dehydrogenase, CK-Creatine kinase

3. Discussion

There are different reports on the incidence of the most common side effects of nilotinib treatment. The majority of data confirm that adverse events are mostly grade 1 or 2 and manageable with appropriate dose adaptations. These include expected hematological toxicity in the form of anemia, thrombocytopenia, and neutropenia. Nonhematologic side effects include dermatologic, gastrointestinal, neurological, and metabolic disorders potentially caused by drug-mediated electrolyte imbalances [1].

The mechanism of hypocalcemia and hyperphosphatemia-induced by nilotinib is poorly understood. Theoretically, it could be attributed to drug-mediated changes in intestinal absorption, urinary resorption, and bone remodeling [2]. The first two mechanisms seem to play a smaller role in disturbing calcium-phosphate balance, while there is growing evidence that patients on nilotinib experience significant dysregulated bone remodeling. Patients taking nilotinib have low bone turnover manifested as inhibition of osteoclastogenesis and osteoblastic proliferation and differentiation induced by PTH stimulation [3]. In the case of low to normal PTH levels, as we presented in this case report, hypocalcemia can be the result of immune-mediated destruction of the parathyroid glands or drug interference with calcium sensing receptors (CaSRs). With CaSR interference, the set point of the CaSR is decreased so that PTH is not released at serum calcium concentrations that normally trigger PTH release [2].

On the contrary, cardiovascular toxicity associated with nilotinib remains largely unknown or underestimated. One of the most threatening complications is QT prolongation, with the risk of torsades de pointes and sudden death. A QT increase of >60 ms and QTc >500 ms associated with nilotinib was reported in 2.1% and <1% of patients, respectively [4]. In a study by le Coutre et al., a mean QTc increase of 5ms was detected, while 1% of patients had a QTc interval >500 ms on day 8 after initiating therapy [5]. Ederhy et al. reported five sudden deaths (0.6%) that were potentially related to nilotinib [6].

There are some indicators that besides its primarily cardiotoxic effect, nilotinib affects the QT interval by decreasing the concentration of circulating plasma calcium. Therefore, close monitoring and repletion of electrolytes should be performed before and during the treatment. All patients receiving nilotinib should have ECGs performed at baseline, 7 days after drug initiation, and periodically following dose adjustments to monitor the QT interval. A baseline QTc >470 ms in men and >480 ms in women should be considered abnormal and treatment initiation should be postponed. The procedure should be repeated periodically during therapy to detect asymptomatic QT prolongation. Treatment should be stopped if the QTc is >500 ms or in the case of QT prolongation exceeding 60 ms. In case of torsades de pointes, the offending drug should be stopped and the patient should be monitored in an intensive care unit [7].

Myalgias and muscle cramps are also common side effects among these patients. Gordonet et al. demonstrated that a high percentage of patients (almost 80%) developed CK elevations while taking imatinib [8]. However, no nilotinib-induced CK elevation or rhabdomyolysis case has been reported in the current literature, while Uz et al. described a case of rhabdomyolysis as an unexpected and devastating adverse event of dasatinib [9].

4. Conclusion

In patients with malignant disease, hypocalcemia is often found to be associated with extensive cell destruction, significant renal impairment, adverse drug reactions, cancer, or cancer treatment-related malabsorption syndromes, vitamin D deficiency, or osteoblastic metastases. Sometimes, hypocalcemia in cancer cannot be attributed to any of these causes and the effect of chemotherapeutic agent seems the most likely cause.

Clinicians must be aware of the rare and potentially life-threatening side effects caused by TKIs. That is why laboratory analysis of serum Calcium, CK, LDH, as well as ECGs should be obtained periodically. ECG monitoring helps us detect potential QT prolongation, the most dangerous and life-threatening complication of nilotinib-induced hypocalcemia.

Author Contributions

MR gave the idea for the article, participated in drafting the article and gave the final approval. MP, AM, and TM reviewed the previously published literature, participated in drafting the article and gave their final approval.

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