

Case Report

Electrolyte disturbances and acute kidney injury induced by imatinib therapy

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Abstract

Imatinib mesylate is an anticancer agent that selectively inhibits protein kinases involved in the pathophysiology of cancer. It is now the first-line therapy for patients with chronic myeloid leukaemia (CML) and is generally well tolerated. Here, we describe a case of a patient receiving imatinib for CML. The patient developed renal failure accompanied by severe hypophosphataemia, hypokalaemia and hypomagnesaemia. We discuss the pathophysiological characteristics of imatinib-induced renal injury, and we demonstrate that these electrolyte disturbances were caused by increased urinary excretion of phosphate and potassium. Early diagnosis and correction of imatinib-induced renal injury and electrolyte disorders can improve clinical outcomes.

Keywords: acute kidney injury; hypokalaemia; hypophosphataemia; imatinib

Introduction

Imatinib mesylate is an oral anticancer agent that selectively inhibits protein kinases involved in the pathophysiology of various human cancers. It is now the first-line therapy for patients with chronic myeloid leukaemia (CML) and has proven remarkably efficient in the treatment of patients with gastrointestinal stromal tumours and various myeloproliferative diseases, including idiopathic hypereosinophilic syndrome [1]. Here, we describe a case of a patient receiving imatinib for CML who developed severe hypophosphataemia accompanied by renal failure. We discuss the pathophysiological characteristics of imatinib-induced renal injury.

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Case Report

A 60-year-old man with a history of hypertension, type II diabetes and CML was admitted to the emergency room presenting diarrhoea, vomiting and malaise for 3 days. He was under regular treatment with enalapril, atenolol, aspirin, simvastatin, insulin and imatinib, the last having been initiated 4 years prior, upon diagnosis of the leukaemia. At that time, he was in haematologic, cytogenetic and molecular remission. On admission, his blood pressure was 130/70 mmHg, and his pulse was 80 bpm. He was confused and mildly dehydrated.

Although the laboratory tests revealed severe renal insufficiency and severe metabolic acidosis, the patient presented hypokalaemia and hypophosphataemia (Table 1). The enalapril and imatinib were discontinued, and the patient received saline infusion. Nevertheless, he required haemodialysis (a single session). During the renal recovery phase, daily supplementation of magnesium and potassium, as well as, principally, phosphate, was required (Table 1). On post-admission Day 10, there was complete recovery of renal function. However, the urinary fractional excretions of potassium and phosphate were elevated although that of sodium was normal. The transtubular potassium gradient was 14. Bone investigation showed a parathyroid hormone level of 107 pg/ml and normal serum bone alkaline phosphatase (Table 1). The patient was discharged from the hospital to outpatient follow-up care. A retrospective analysis of the outpatient records revealed evidence of episodes of hypophosphataemia and tubular renal dysfunction (Table 2).

Discussion

The options for treating patients with newly diagnosed CML have changed fundamentally since the introduction of imatinib, an orally administered inhibitor of the platelet-derived growth factor receptor (PDGFR) Bcr-Abl tyrosine kinase, the constitutive abnormal gene product of the Philadelphia chromosome in CML. Inhibition of this enzyme blocks proliferation and induces apoptosis in

Table 1. Recent laboratory test results

Examinations	02/25/08 (Admission)	02/26/08 (After saline infusion)	02/28/08 (1 day after the HD)	03/06/08 (Recovery)	03/10/08 (Discharge)	Normal range
Na (mEq/l)	141	141	142	141	136	135–145
K (mEq/l)	3.4	2.6	2.7	4.3	3.7	3.5–5
Creatinine (mg/dl)	8.48	8.22	2.10	1.60	1.38	0.6–1.4
Urea (mg/dl)	204	241	91	62	41	10–45
Mg (mg/dl)	2.48	1.86	1.68	1.2	1.58	1.58–2.55
Phosphate (mg/dl)		2.6	0.9	0.6	3.2	2.3–4.6
Ca (mg/dl)	5.5		5.1	5.0	4.9	4.6–5.3
Uric acid (mg/dl)		7.3		2.8	4.4	3.4–7
FENa (%)				0.74		>1
FEK (%)				22		
FEPO ₄ (%)				42		
FECa (%)				0.1		
TTKG				14		
Uosm				285		
PTH (pg/ml)				107		<87
25 hydroxyvitamin D (ng/ml)				5.9		9–37.4
Alkaline phosphatase (U/l)	94		69		92	40–129
pH		7.29	7.37	7.35		7.35–7.45
Bicarbonate		6.8	16.3	18.3		22–28

PTH, parathyroid hormone; FENa, fractional excretion of sodium; FEK, fractional excretion of potassium; FEPO₄, fractional excretion of phosphate; FECa, fractional excretion of calcium; TTKG, transtubular potassium concentration gradient; HD, haemodialysis.

To convert serum creatinine from mg/dl to mmol/l, multiply by 88.4; serum calcium from mg/dl to mmol/l, multiply by 0.2495; serum inorganic phosphorus from mg/dl to mmol/l, multiply by 0.3229; serum uric acid from mg/dl to mmol/l, multiply by 59.48; glucose from g to mmol, multiply by 0.05551 and urea from g to mmol, multiply by 357.

Table 2. Prior laboratory test results*

Test	May/04	Oct./04	July/05	Aug./06	Feb./07	Normal range
Na (mEq/l)	141	142	141	138	144	135/145
K (mEq/l)	4.9	3.2	5	4.1	4.4	3.5/5
Creatinine (mg/dl)	1.2	0.9	1.5	1.7	1.3	0.6/1.4
Urea (mg/dl)	48	36	45	47	42	10/45
Mg (mg/dl)	1.64	1.20	1.43	1.86	2.11	1.58/2.55
Phosphate (mg/dl)	3.9	2.5	2.0	1.8	2.6	2.3/4.6
Ca (mg/dl)	5.2	4.9	5.5	4.9	5.2	4.6/5.3
Uric acid (mg/dl)	7.3	4.5	4.4	8.5	3.9	3.4/7
Alkaline phosphatase (U/l)	87	109	121	71	74	40/129

*Aug./2004: Imatinib initiated.

Bcr-Abl-positive cell lines as well as in fresh leukaemic cells in Philadelphia chromosome-positive CML [1,2]. In addition to tyrosine kinase, imatinib inhibits the stem cell factor (SCF) c-kit and cellular events mediated by PDGF and SCF [2,3].

Here, we have described the case of a patient who developed acute kidney injury (AKI) while under treatment with imatinib. Renal impairment caused by imatinib seems to be a rare event. Druker *et al.* reported renal failure during imatinib treatment in <1% of patients with normal renal function at baseline [3]. Although such renal failure has not been thoroughly documented, several case reports have indicated that acute tubular necrosis (ATN) is the cause [2,4]. Tubular vacuolization was observed in proximal and distal tubules [2]. François *et al.* demonstrated a case in which apical vacuoles were observed in some tubular cells under electron microscopy, suggesting proximal tubular injury [2]. The molecular mechanisms by which imatinib induces ATN are not yet understood. It has been shown that ~81% of the dose of imatinib is eliminated within 7 days

in faeces (68% of dose) and urine (13% of dose). Of the total dose, 25% (5% urine, 20% faeces) was eliminated unchanged, the remainder being excreted as metabolites [5]. Imatinib targets the PDGFR and c-kit expressed in the kidney. Proximal tubule expression of the PDGFR has been reported [2]. In patients with ATN, proliferation and regeneration of proximal tubular cells depends on PDGFR activation [2]. Therefore, imatinib blockade of the PDGF pathway might promote ATN, especially in cases of preexisting renal failure [2].

Hypokalaemia is a known risk factor for the development of nephrotoxicity and ischaemic AKI [6]. In the present case, hypokalaemia might have represented an additional risk factor for the development of AKI. It is of note that, even in the presence of angiotensin-converting enzyme inhibitor treatment, diarrhea, metabolic acidosis and AKI, the patient presented hypokalaemia. The hypokalaemia was accompanied by an increased transtubular potassium concentration gradient, demonstrating that the cause of the hypokalaemia was renal wasting. There are only a few studies

in the literature demonstrating imatinib-induced hypokalaemia [7].

Cases of imatinib-induced hypophosphataemia have been reported. Joensuu and Reichardt reported that 80% of patients receiving imatinib presented hypophosphataemia on at least one occasion during the treatment [8]. François *et al.* described a case of Fanconi syndrome induced by imatinib [2]. Their patient presented hypophosphataemia and hypouricaemia, both caused by renal wasting. Laboratory test results showed that our patient had previously suffered from hypophosphataemia. Even during the acute phase, our patient presented hypophosphataemia, which was accompanied by a pronounced elevated urinary fractional excretion of phosphate. Berman *et al.* hypothesized that hypophosphataemia induced by imatinib was related to changes in bone and mineral metabolism [9]. In our case, the hypophosphataemia was attributed to tubular dysfunction, since the parathyroid hormone level was just slightly elevated, which cannot explain the markedly low serum levels of phosphorus. The slightly elevated serum level of parathyroid hormone and the low serum levels of 25-hydroxyvitamin D can be explained by the episode of AKI occurring a few days before and the limited exposure to sunlight in the preceding years, respectively.

During the acute phase, our patient did not present hypomagnesaemia although it occurred later during the recovery phase. Previous laboratory test results showed that our patient had suffered from hypomagnesaemia, which typically occurred during hypokalaemic episodes. Therefore, the hypomagnesaemia might be attributable to the hypokalaemia alone. Hypokalaemia decreases reabsorption of sodium, potassium and chloride in the thick ascending limb of Henle's loop, as well as decreasing the lumen-positive potential difference at this site, reducing reabsorption of magnesium via the paracellular pathway, which can explain the hypomagnesaemia [10]. However, we cannot rule out the possibility that imatinib has a direct effect within the distal nephron. Since imatinib is a potent inhibitor of tyrosine kinase and c-kit, which is also expressed in the distal tubule [2], we hypothesize that reduced expression of the encoding membrane renal transporter genes might form the molecular basis for the electrolyte disorder observed in imatinib-treated patients.

In the case described here, the patient developed various hypoelectrolyte disorders (hypokalaemia, hypophosphataemia and hypomagnesaemia). This occurred even in the presence of AKI. Early diagnosis and correction of imatinib-induced AKI and electrolyte disorders can improve clinical outcomes for the critically ill. Therefore, increased knowledge of these conditions is of immediate clinical significance.

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Conflict of interest statement. None declared.

References

- Schiffer AS. BCR-ABL tyrosine kinase inhibitors for chronic myelogenous leukemia. *N Engl J Med* 2007; 357: 258–265
- François H, Coppo P, Hayman JP *et al.* Partial Fanconi syndrome induced by imatinib therapy: a novel cause of urinary phosphate. *Am J Kidney Dis* 2008; 51: 298–301
- Druker BJ, Talpaz M, Resta DJ *et al.* Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001; 344: 1031–1037
- Kitiyakara C, Atichartakarn V. Renal failure associated with a specific inhibitor of BCR-ABL tyrosine kinase, STI 571. *Nephrol Dial Transplant* 2002; 17: 685–687
- Gschwind HP, Pfaar U, Waldmeier F *et al.* Metabolism and disposition of imatinib mesylate in healthy volunteers. *Drug Metab Dispos* 2005; 33: 1503–1512
- Seguro AC, Shimizu MH, Monteiro JL *et al.* Effect of potassium depletion on ischemic renal failure. *Nephron* 1989; 51: 350–354
- Cortes J, Jabbour E, Daley GQ *et al.* Phase 1 study of lonafarnib (SCH 66336) and imatinib mesylate in patients with chronic myeloid leukemia who have failed prior single-agent therapy with imatinib. *Cancer* 2007; 110: 1295–1302
- Joensuu H, Reichardt P. Imatinib and altered bone and mineral metabolism. *N Engl J Med* 2006; 355: 627–629
- Berman E, Nicolaides M, Maki RG *et al.* Altered bone and mineral metabolism in patients receiving imatinib mesylate. *N Engl J Med* 2006; 354: 2006–2013
- Elkjaer ML, Kwon TH, Wang W *et al.* Altered expression of renal NHE3, TSC, BSC-1, and ENaC subunits in potassium-depleted rats. *Am J Physiol Renal Physiol* 2002; 283: F1376–F1388

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