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BRIEF REPORT

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Acute renal failure following deferoxamine overdose

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Abstract A 17-year-old patient with sickle cell-beta thalassemia undergoing treatment with home iron chelation therapy inadvertently received ten times the recommended dose of intravenous deferoxamine. Acute renal failure (ARF) developed within hours. Immediate treatment with high-efficiency hemodialysis resulted in the prompt return of renal function after only one hemodialysis session. No long-term nephrotoxic effects of the deferoxamine overdose developed after more than 1 year of follow-up. Children with sickle cell disease who are on intravenous deferoxamine and their parents should be cautioned about the possibility of ARF with overdose due to malfunction of the pump and/or inadequate monitoring during treatment. ARF, should it occur in such children, appears to respond well to treatment with high-efficiency hemodialysis.

Keywords Chelation · Deferoxamine · Hemoglobinopathies · Acute renal failure · Hemodialysis

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Introduction

Iron chelation therapy with deferoxamine has become the mainstay of treatment of patients with thalassemia and other transfusion-dependent anemias. It has effectively prolonged survival and reduced morbidity from iron overload caused by the frequent transfusions required by these patients [1]. Deferoxamine therapy, however, is not without risks and complications. In this case, a teenage boy with sickle cell-beta thalassemia developed acute renal failure (ARF) following an accidental deferoxamine overdose. Prompt institution of hemodialysis led to a complete recovery of renal function.

Case report

The patient was a 17-year-old African-American boy with sickle cell-beta thalassemia who became severely iron overloaded as a consequence of chronic blood transfusions and noncompliance with either nightly subcutaneous or intravenous iron chelation with desferrioxamine (Deferoxamine, Desferal, Novartis Pharmaceuticals, East Hanover, N.J., USA). Among his many sickle cell-related complications, he had a prior history of hematuria and papillary necrosis of the kidneys at age 15 years and again at 16 years.

Because of concern over the degree of iron overload, the patient and his mother were offered a more convenient schedule of deferoxamine, 700 mg/kg per week administered as a continuous 96-h infusion. A home intravenous AIM pump (Abbott Medical Products, San Diego, Calif., USA) and instructions regarding its programming were provided. Over the next 9 months his serum ferritin slowly dropped from 8,000 to 2,000 μg/l.

On one occasion his mother accidentally programmed his pump to deliver the full 96-h dose of 45 g (700 mg/kg) over a period of 8 h. He presented the next day to the emergency room with a complaint of generalized itching, a burning sensation of the skin, shortness of breath, chest pain, crampy abdominal pain, and decreased urine output.

Physical examination revealed blood pressure of 147/82 mmHg, heart rate of 108 beats/min, temperature of 36.5°C, and pulse oximetry of 100% in room air. There were no signs of dehydration or fluid overload and the remainder of his examination was unremarkable. Laboratory data demonstrated significant metabolic acidosis and azotemia (Table 1). The urine was red-orange in color as is characteristic during iron chelation. Urinalysis revealed pH 5.0, specific gravity 1.020, protein 15 mg/dl, and trace blood. Micro-

Table 1 Laboratory values in our patient before and after deferoxamine overdose (*AST* aspartate aminotransferase, *ALT* alanine aminotransferase)

	Baseline[a]	Pre dialysis	Post dialysis	Follow-up[b]	Long-term follow-up[c]
Bicarbonate (mEq/l)	28	11	24	24	28
Urea nitrogen (mg/dl)	13	23	6	5	5
Creatinine (mg/dl)	0.4	2.2	0.6	0.6	0.7
Calcium (mg/dl)	9.6	8.5	9.0	9.2	9.1
Potassium (mEq/l)	4.0	4.3	3.8	4.3	3.9
Phosphorus (mg/dl)	4.6	6.6	5.5	3.5	–
AST (IU/l)	55	114	–	53	85
ALT (IU/l)	47	79	–	43	49
Ferritin (μg/l)	1596	2,009	–	–	–
Hemoglobin (g/dl)	9.4	8.1	7.8	9.0	6.4
Platelet ($\times 10^3/mm^3$)	142	–	127	178	360

[a] Baseline readings were most recent laboratory values prior to overdose
[b] Follow-up readings were laboratory values obtained at first post-dialysis outpatient clinic visit
[c] Follow-up readings at 1 year post acute renal failure

scopic examination revealed 25–50 hyaline casts per high-power field (hpf), 3–5 white blood cell casts/hpf, and no red blood cells. Liver enzymes were elevated (Table 1), but these results were not appreciably different from baseline measurements obtained over the preceding 6 months. Serum iron was 122 mg/dl and serum ferritin was 2,009 μg/l. Chest radiograph was normal.

Despite intravenous hydration and forced diuresis with mannitol, the patient remained oliguric, with urine output of just 200 ml over the next 8 h (0.5 ml/kg per hour) and onset of hypertension (blood pressure 140/93 mmHg). Because of the rapid onset of oliguria, the development of hypertension, progressive azotemia (Table 1), and the lack of response to more conservative measures, hemodialysis was recommended. A 12-Fr triple-lumen femoral hemodialysis catheter was placed, and high-efficiency hemodialysis performed utilizing a cellulose triacetate hollow-fiber dialyzer (CT-190, Baxter Healthcare, Deerfield, Ill., USA), standard dialysate flow rate, and blood flow rate of 400 ml/min (8.2 ml/kg per min). Dialysis (3 h) was performed without incident. The patient remained stable throughout. Serum was drawn prior to and following dialysis for possible determination of deferoxamine levels, but no laboratory able to perform this test could be identified, despite contacting the manufacturer. A gradual change in the color of the patient's urine from cloudy orange to clear amber was observed following completion of hemodialysis.

Following dialysis, the patient's urine output increased tenfold to 2,050 ml/8 h (5.2 ml/kg per hour), and his creatinine continued to fall (Table 1). Recovery of renal function was accompanied by the development of mild hypertension that was treated with oral isradipine for 12 days. At 1 month post hospitalization the patient was well, with normal blood pressure, normal urine output, a creatinine of 0.6 mg/dl, and no obvious residual renal sequelae. At last follow-up, 1 year after the episode of renal failure, his creatinine was 0.7 mg/dl, electrolytes were within normal limits, and he remained normotensive.

Discussion

Mortality and morbidity in thalassemia and similar hematological conditions are caused in part by iron overload leading to myocardial siderosis, hepatic fibrosis, and endocrine complications such as diabetes and hypothyroidism. Deferoxamine removes chelatable iron from parenchymal tissues and the reticuloendothelial system [2], and has been used successfully in iron overload states [1]. It is the only widely available treatment for prophylaxis against iron accumulation in vital organs, such as the liver, heart, and the endocrine system, in patients undergoing chronic blood transfusion therapy [3]. Recently, continuous infusions of deferoxamine, as performed in our patient, have been shown to be an effective alternative approach for patients with life-threatening iron overload and/or unable to tolerate subcutaneous infusions of deferoxamine [4].

Numerous side effects of deferoxamine chelation have been reported, including abnormal skeletal growth [5], retinal toxicity [6], ototoxicity [7], sensorimotor toxicity [8], pulmonary embolism [9], and nephrotoxicity [10, 11, 12]. Most of these toxicities can be avoided with close monitoring during deferoxamine therapy, decreasing the doses appropriately or discontinuing the drug at the appearance of signs of toxicity [7, 8].

Deferoxamine has been demonstrated to affect renal hemodynamics in animal studies, decreasing renal blood flow and glomerular filtration rate. Koren et al. [10] reported three patients who developed temporary, acute decreases in creatinine clearance after receiving high-dose deferoxamine that returned to baseline when the infusions were discontinued. The fact that deferoxamine inhibits vascular prostacyclin synthesis in vitro [13] suggests that it may also play a role in preventing the normal activation of the renin angiotensin system that usually occurs in hypovolemic states, thereby setting the stage for the development of azotemia. Finally, a proximal tubular defect may occur that can inhibit the reabsorption of sodium, potassium, and phosphates, resulting in a relative diuresis, and contributing further to development of a hypovolemic state. Moreover, although deferoxamine-associated nephrotoxicity is largely dose dependent, if a patient has underlying renal dysfunction, ARF can occur even with usual therapeutic doses [12].

There have been two previous reports of ARF in children treated with intravenous deferoxamine [12, 14]. In the first report, a teenager with thalassemia major with hepatic and cardiac failure due to iron overload developed ARF after 9 days of high-dose intravenous deferoxamine and subsequently died while receiving peritoneal dialysis. In the second case, ARF developed after a teenager accidentally received 700 mg/kg of deferoxamine over 18 h. Onset of ARF was rapid, and hemodialysis was initiated. The patient underwent 3 days of dialysis utilizing a polyacrylonitrite dialyzer, with restoration of normal urine output and return of normal renal function. Clearance of the deferoxamine by dialysis was in-

ferred by a fall in urinary iron excretion following dialysis. The long-term renal function of this patient was not reported.

Our patient received a similar dose of deferoxamine on milligram per kilogram basis as the second case mentioned above. The natural history of ARF following deferoxamine overdose is unknown. Early institution of high-efficiency hemodialysis may have prevented the development of severe renal insufficiency and/or long-term renal sequelae. We were unable to prove clearance of deferoxamine by dialysis due to the lack of a test for measurement of deferoxamine levels, but we are reasonably sure that dialysis was effective in clearing deferoxamine from our patient for two reasons. First, deferoxamine [molecular weight 656.79 kilodalton (package insert)] is small enough to be readily removed by the highly permeable cellulose triacetate dialyzer that was used. Second, it is thought that ferrioxamine, the iron-deferoxamine complex, is distributed almost entirely in the extracellular space, which should make it easily removable by hemodialysis. These pharmacokinetic assumptions are supported by the disappearance of the characteristic orange color produced by chelated iron from the patient's urine after hemodialysis.

Given the effectiveness of continuous outpatient infusions of deferoxamine, especially for otherwise noncompliant patients or those with life-threatening complications from iron overload, overdoses such as that seen in our patient may become more common. Home infusion therapy regimens and newer pumps have made deferoxamine infusion therapy simpler and more convenient for patients, but it is important that supervision of the dosage and the instructions for pump failure be addressed adequately with the family. When overdose occurs despite these measures, early institution of hemodialysis can result in prompt return of renal function without long-term nephrotoxic effects.

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