LETTERS TO THE EDITOR

Fatal congestive heart failure with deferiprone

Insuffisance cardiaque congestive fatale lors d’un traitement par déférixone

Introduction

Deferiprone (1,2 dimethylpyridin-3-hydroxy-4-one) is an orally active iron chelating agent licensed in Europe for the treatment of iron overload in patients with thalassemia major, when deferoxamine therapy is contraindicated or inadequate. The most frequently reported side effects of deferiprone include gastrointestinal symptoms, neutropenia with rare but severe instances of agranulocytosis, and joint symptoms. Retrospective studies have suggested that deferiprone might be more effective than deferoxamine in chelating cardiac iron to prevent the major cause of death in transfusional iron overload [1].

We report a case of cardiac failure preceded by severe arthralgias after six weeks of deferiprone and discuss possible mechanisms of drug toxicity.

Case report

A 40-year-old man had had idiopathic sideroblastic anemia since 1984. Red blood cell transfusions had been given regularly for four years (120 red blood cell units) until disease remission in 1988 with chloroquine treatment. At that time the patient presented with severe iron overload (serum ferritin = 6360 μg/L; N < 300; magnetic resonance liver iron concentration > 300 μmol/g; N < 36) and was treated by subcutaneous deferoxamine treatment until total removal of iron in 1995 (ferritin = 75 μg/L; magnetic resonance liver iron concentration = 40 μmol/g). The patient was infected by the hepatitis C genotype 1b virus. Liver biopsy showed minimal sinusoidal iron deposits, a histological picture of chronic hepatitis and Metavir F3 fibrosis. He was treated by a 12-month course of interferon monotherapy, which normalized transaminases, but HCV-RNA remained positive at the end of treatment.

Sideroblastic anemia relapsed in 2002. Transfusions were resumed (120 red blood cell units from 2002 to 2004) and hepatic iron reaccumulated (serum ferritin = 2000 μg/L; magnetic resonance liver iron concentration = 230 μmol/g). Deferoxamine treatment was begun again (3 g/day using nocturnal, 8 h long, subcutaneous infusions, 5 days/week). After 22 months of deferoxamine treatment, the patient developed serious vestibular toxicity, leading to discontinuation of deferoxamine. The patient was evaluated for bone marrow transplantation and underwent a complete physical examination and a cardiac ultrasound examination which was considered normal showing a 60% ventricular ejection fraction (February 2004). There was no sign of arterial pulmonary hypertension and no sign of right heart dysfunction. The serum ferritin level was 1950 μg/L.

Deferiprone treatment was begun to control iron load (25 mg/kg, three times a day = 75 mg/kg/day). After six weeks of treatment, the patient experienced sudden severe arthralgia of the knees with inflammatory swelling leading to drug discontinuation. In the next few days, he presented with severe dyspnea and two weeks later, he was hospitalized in intensive care unit for congestive cardiac failure. The ventricular ejection fraction was dramatically decreased to 30% with dilated and hypokinetic cardiomyopathy (May 2004). There were no other known etiological factors of cardiomyopathy. There were no signs of viral infection. He did not take other treatments and was abstinent from alcohol. The coronarography was normal. Despite the cardiac insufficiency, a bone marrow transplantation was performed, but the evolution was unfavorable and the patient died three months later.

Discussion

The absence of preexisting cardiac abnormalities, the time relationship between deferiprone treatment and cardiac failure, and the absence of other causes of cardiomyopathy suggest that deferiprone was responsible for congestive heart failure in this case.

The occurrence of acute cardiac failure secondary to deferiprone treatment is a rare event. Most studies, although retrospective, did not find this relationship and suggested that deferiprone was more effective than deferoxamine for removing cardiac iron, presumably because of its greater intracellular penetration [2]. However, whether cardiac failure, which is a frequent complication of severe iron overload and is still responsible for 70%
of deaths in patients with thalassemia major, might have been attributed to iron overload itself rather than any potential drug toxicity cannot be totally excluded. Four of 51 patients treated with deferiprone by Hoffbrand et al. [3] and nine out of 532 patients treated by Ceci et al. [4] had cardiac failure during deferiprone treatment, but most of them had left ventricular dysfunction prior to deferiprone treatment. In contrast, a recent cardiac investigation was normal in our patient. It is interesting to note that Agarwal et al. reported a similar case of a patient who died of congestive heart failure four weeks after discontinuation of deferiprone because of intolerable arthropathy [5]. The mechanism which makes deferiprone cardiotoxic remains unknown. It could have a direct toxic effect or an effect due to an increase in non-transferring bound iron. The heart selectively takes up this labile iron species. This iron form, and especially its component called labile plasma iron, is particularly prone to generate reactive oxygen species [6] and is thought to play a major role in iron-related heart failure. A similar mechanism has been reported for vitamin C heart toxicity in case of massive iron overload.

Deferiprone is bidentate and three molecules of deferiprone are needed to chelate one atom of iron. Therefore, the avidity of deferiprone for iron is much lower than that of other chelators, including deferoxamine, and might explain circulating deferiprone—iron complexes dissociation, with "redistribution" of this toxic compound which might potentiate or precipitate cardiac dysfunction. A similar mechanism could explain deferiprone-related arthropathy [7]. The short biological half-life of the molecule could also play a role. In this respect, the novel oral chelator deferasirox, which is a tridentate chelator with a longer biological half-life and is not responsible for arthropathy, might have a more favorable safety profile [8] but whether this compound will prove to be highly beneficial for the heart remains to be demonstrated.

In conclusion, this case report suggests the possible cardiac toxicity of deferiprone preceded by severe arthralgia. These symptoms should lead to careful cardiac monitoring to detect any early cardiac dysfunction and lead to treatment discontinuation.

References


Available online 12 June 2008


Sustained alanine aminotransferase increase during hepatitis A due to concomitant lymphogranuloma venereum infection in an HIV-1 positive patient

Cytolyse prolongée au cours d’une hépatite A associée à une infection vénérienne lymphogranulomateuse chez un malade infecté par le VIH-1

Hepatitis A is due to a virus and is generally acute and self-limiting. Clinical severity is age-dependent, and the infection is usually asymptomatic in children under five. In older patients, the systemic symptoms and jaundice resolve within three or four weeks. Hepatitis A rarely causes fulminant liver failure or recurrent, prolonged or cholestatic disease. The hepatitis A virus is mainly transmitted by the fecal—oral route or from person to person. Hepatitis A may also be sexually transmitted in homosexual men (MSM) [1]. We report a case of prolonged hepatic dysfunction in an HIV-seropositive man with hepatitis A due to concomitant lymphogranuloma venereum (LGV) infection.

This 44-year-old MSM was diagnosed with HIV infection in 1992. He had received highly active antiretroviral treatment (HAART) since 1997, and had been taking lamivudine, abacavir and atazanavir since March 2005. The CD4 cell count and the HIV RNA level were 884 cells/mm³ and less than 50 copies/mL (Versant® HIV-1 RNA 3.0 assay, Bayer; detection limit < 2.79 log copies/mL) respectively. The patient history was otherwise unremarkable. In June 2005, he presented with fatigue, anorexia, abdominal pain, fever and jaundice. The white blood cell count was 4900 mm⁻³ in serum, the C-reactive protein was 18 mg/L.