Case Report

Chelation of gadolinium with deferoxamine in a patient with nephrogenic systemic fibrosis

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Abstract

A 65-year-old female with biopsy-confirmed nephrogenic systemic fibrosis (NSF) received a kidney transplantation. Despite good kidney function, her symptoms continued to progress. Deferoxamine was administered intramuscularly at 500 mg/day and later 1000 mg/day after 1 week with no adverse effects. Urine excretion of gadolinium increased from 6.0 μg/day to 11.6 μg/day and subsequently to 13.0 μg/day with 500 mg/day and 1000 mg/day of deferoxamine, respectively. Serum levels, however, remain unchanged from 1.7 ng/ml to 1.4 ng/ml. Although chelation therapy may have a role in the treatment of NSF, deferoxamine is too weak and a stronger chelator is needed.

Keywords: chelation; deferoxamine; gadolinium

Introduction

Nephrogenic systemic fibrosis (NSF) is a debilitating disorder characterized by oedema, plaques, discolouration and severe thickening of the skin resulting in contractures and immobility. Currently, exposure to gadolinium-based contrast agents (GBCA) during low glomerular filtration rate (GFR) states appears to be the most consistent risk factor [1]. Since GBCA is excreted by the kidney, exposure is prolonged in patients with renal insufficiency [2]. The extended exposure permits transmetallation to occur which allows free gadolinium to come in contact with proteins and other cellular components. At the present time, the downstream effects leading to NSF are still not well understood [3]. No standard treatment currently exists for NSF.

In the past, dialysis patients were commonly plagued with iron or aluminium overload. Deferoxamine was used to chelate the excess metals in their trivalent state [4]. The chelated metals were excreted in the urine or removed with dialysis. Since gadolinium exists in a trivalent state, we hypothesize that deferoxamine may chelate gadolinium. We report our experience with a patient who underwent deferoxamine treatment for her NSF.

Case report

A 65-year-old female kidney transplant recipient presented with worsening symptoms of NSF. The patient had chronic glomerulonephritis for many years and was started on dialysis in February 2003. In October 2005, she developed a fungal peritonitis secondary to microperforation from colonoscopy. A MR angiogram was performed with 20 cc of a GBCA (estimated 0.13 mmol/kg). Details of the specific agent were unavailable from her outside records. Within a month, the patient began to notice hardening of her legs and hips making walking extremely difficult. The symptoms later spread to her waist and hands. NSF was confirmed by a skin biopsy. The patient underwent UVA-1 phototherapy that seemed to slow the progression of her disease but did not improve it. In August 2007, she received a living-related donor kidney transplantation from her sister. Despite excellent renal allograft function (Scr = 0.9 mg/dl and GFR = 65 ml/min/1.73 m²), her skin symptoms continued to progress. The patient was experiencing more pain and was having increasing difficulty walking due to contractures in her legs. She agreed to undergo chelation therapy in January 2008.

Deferoxamine 500 mg intramuscularly was given daily (except during the weekend) for seven doses. After a weekend break where no adverse events were noted, the dose was increased to 1000 mg/day for five additional doses. Baseline serum and urine samples were collected along with samples during the two treatment periods. Urine gadolinium was measured from 24 h collections. Renal clearance was calculated using the UV/IP method.

Gadolinium was quantified by inductively coupled plasma mass spectrometry (Perkin-Elmer Life and Analytical Sciences, Shelton, CO, USA). Aqueous acidic calibrating standards and patient samples were diluted with...
an aqueous acidic diluent (1% nitric acid) containing two internal standards (terbium and rhodium), with terbium used as an internal standard for quantification. Serum and urine specimens were analysed in duplicate at a 1:25 dilution; negative serum, spiked quality control specimens, and patient samples were diluted in an identical manner.

Serum gadolinium concentrations did not change significantly with deferoxamine treatment; however, urinary excretion rate doubled after deferoxamine (Table 1). Gadolinium clearance was increased from 25 ml/min (baseline) to 51 and 67 ml/min with 500 mg/day and 1000 mg/day of deferoxamine, respectively. Serum ferritin did not change significantly during the treatment. Ferritin was 534 μg/l at baseline, 483 μg/l at the end of treatment and returned to 532 μg/l 1 week after last treatment without iron supplementation. Subjectively, the patient felt that her symptoms had stabilized but no substantial improvement was noted 6 months after deferoxamine treatment. Skin findings and range of motion were also unchanged after treatment. Her most recent serum gadolinium level was 1.6 ng/ml and urine excretion had returned to baseline at 6.5 μg/day after discontinuation of deferoxamine.

Table 1. Serum and urine concentrations at baseline and during treatment with deferoxamine (DFO)

|                | Serum (ng/ml) | Urine (μg/day) | Clearance (ml/min) |
|----------------|---------------|---------------|-------------------|
| Baseline       | 1.7           | 6.0           | 25                |
| DFO 500 mg/day | 1.7           | 11.6          | 51                |
| DFO 1000 mg/day| 1.4           | 13.0          | 67                |

Clearances were calculated using the UV/P method.

Discussion

No standard treatment currently exists as no clinical trial has been conducted for the treatment of NSF. Most would agree that physical therapy should be a part of any treatment programme, and steroids (topical or systemic) are ineffective [5]. Beyond that, controversies exist for nearly every treatment. Available treatments can be sorted into three categories. First is therapies that were reported only once without further confirmation or rebuttal. These medications include pentoxifylline, thalidomide and high-dose intravenous immunoglobulin [6]. The next category is treatments whose success has been challenged in the literature. These include phototherapy (UVA-1, psoralen plus UVA-1, photopheresis), sodium thiosulfate, plasmapheresis, sirolimus, calcipotriene and cyclophosphamide [5–8]. The third category involves therapies that have been confirmed but not refuted. The only medication in this category so far is imatinib, a specific inhibitor of BCR/ABL tyrosine kinase that is approved for treatment of chronic myelogenous leukaemia [9,10]. Activity against systemic sclerosis, a separate chronic fibrotic disease of unknown etiology, in an animal model makes imatinib a promising therapy [11].

Despite the promising results, relapse has been reported when treatment is discontinued [9]. One possibility is that the fibrotic reaction can recur as long as a critical amount of gadolinium remains in the tissue. Elimination or reduction of the gadolinium may be the most effective form of therapy. This explains the reports of spontaneous improvement in NSF after recovery of renal function especially in cases of acute renal failure where the exposure is limited [5]. This may also account for some of the differences in responses reported with some of the therapies.

The results of our study showed that deferoxamine is capable of chelating and increasing the renal clearance of gadolinium by more than twofold. A dose-dependent relationship was also suggested, but unfortunately not enough data were available to perform a statistical analysis. Despite our positive results, deferoxamine is unlikely to be clinically useful because its chelation of gadolinium is too weak. Studies with dimeglumine gadopentetate (Gd-DTPA) showed that patients with a creatinine clearance <20 ml/min only eliminated 63% of the gadolinium-contrast load [12]. The rest (37%) is retained for an extended period of time. Assuming the usual dose (0.1–0.2 mmol/kg) of gadolinium for MRI studies, a 70 kg person would receive between 1 and 2 g of gadolinium. Patients with low renal function would retain 370–740 mg of gadolinium. At a maximum dose of deferoxamine (1000 mg/day) and an excretion rate of 13 μg/day, it would take 78–156 years to rid the body of all gadolinium. On the other hand, our case demonstrates that it is possible to increase the excretion rate of gadolinium with chelation. If a stronger chelator can be identified, a more rapid removal of gadolinium is achievable. A more timely and effective removal of gadolinium could prove useful in the treatment of this devastating disease.

Conflict of interest statement. None declared.

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