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Deferasirox at therapeutic doses is associated with dose-dependent hypercalciuria

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ABSTRACT

Deferasirox is an oral iron chelator used widely in the treatment of thalassemia major and other transfusion-dependent hemoglobinopathies. Whilst initial long-term studies established the renal safety of deferasirox, there are now increasing reports of hypercalciuria and renal tubular dysfunction. In addition, urolithiasis with rapid loss of bone density in patients with β thalassemia major has been reported. We conducted a cross-sectional cohort study enrolling 152 adult patients comprising of β thalassemia major (81.5%), sickle cell disease (8%), thalassemia intermedia (2%), HbH disease (6.5%) and E/β thalassemia (2%). Cases were matched with normal control subjects on age, gender and serum creatinine. Iron chelator use was documented and urine calcium to creatinine ratios measured. At the time of analysis, 88.8% of patients were receiving deferasirox and 11.2% were on deferoxamine. Hypercalciuria was present in 91.9% of subjects on deferasirox in a positive dose-dependent relationship. This was not seen with subjects receiving deferoxamine. At a mean dose of 30.2 ± 8.8 mg/kg/day, deferasirox was associated with an almost 4 fold increase in urine calcium to creatinine ratio (UCa/Cr). Hypercalciuria was present at therapeutic doses of deferasirox in a dose-dependent manner and warrants further investigation and vigilance for osteoporosis, urolithiasis and other markers of renal dysfunction.

1. Introduction

Thalassemia is a disorder of ineffective erythropoiesis and in its most severe form requires chronic blood transfusion and concomitant iron chelation treatment to prevent the complications of iron overload [1]. Thalassemia bone disease is a highly prevalent and severe complication with multiple risk factors including hypogonadism, marrow expansion, kidney stones, iron toxicity and iron chelators [2–4]. Deferasirox is an oral iron chelating agent used widely in the treatment of transfusion-dependent anemia's such as thalassemia major, sickle cell, myelodysplastic syndrome, aplastic and other rare anaemias.

Deferoxamine, the standard of care for the past 40 years, requires subcutaneous or intravenous administration and is associated with poor patient compliance [5]. Deferasirox is highly efficacious and safe in the treatment of iron overload in thalassemia major as demonstrated in large prospective [6,7] and extension studies of up to 5 years duration [8]. A mild dose-dependent reversible increase in serum creatinine was reported in one third of subjects [6,7], but the renal safety was confirmed at deferasirox doses greater than 30 mg/kg/day [9]. However, testing for renal tubulopathy and in particular hypercalciuria was not routinely performed in these early pivotal studies.

Increasing and worrying reports of renal tubular dysfunction including hypercalciuria have emerged with deferasirox [4,10], but this has not been examined systematically. Moreover, hypercalciuria is a possible mechanism linking recent findings of increased urolithiasis with severe osteoporosis in thalassemia major [2,3,11]. We sought to determine the prevalence of hypercalciuria in subjects with transfusion-dependent

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hemoglobinopathies treated with deferasirox or deferoxamine compared to normal controls.

2. Methods

2.1. Cases

We enrolled 152 subjects with transfusion-dependent haemoglobinopathies from a single academic center in Melbourne in 2014. Iron chelator use was documented and dosage expressed as mg/kg/day. Synchronous urine and serum biochemistry was obtained. These comprised of serum creatinine, calcium, phosphate, parathyroid hormone (PTH) and 25(OH)VitD levels. Urine testing for UCa/Cr and tubular protein to creatinine ratios were measured on 2 separate occasions, and the mean value derived. Hypercalciuria was defined as a UCa/Cr greater than 0.40 mol/mol [12]. Hypercalciuria severity was separated into 3 tertiles (normal <0.4 mol/mol, moderate 0.5–1.5 mol/mol and severe 1.5 mol/mol and above). Increased urine protein excretion was defined as a urine protein to creatinine ratio > 0.3 [13].

Bone mineral density was measured using dual energy X-ray absorptiometry (DXA) at a single center. Fractures and kidney stones were defined as those confirmed based on radiological reports or through the medical records as was bisphosphonates use. In the majority of cases, kidney stones were diagnosed radiologically by plain abdominal X-ray or computer tomography (particularly if symptomatic) and abdominal ultrasound. A history of hypogonadism and hypoparathyroidism was documented based on biochemistry [14,15].

2.2. Controls

A control population was selected from subjects in the baseline cohort of the Australian Diabetes, Obesity and Lifestyle (AusDiab) study. Details of the study are described elsewhere [16]. Cases were matched with controls subjects on age, gender and serum creatinine; UCa/Cr was assessed in the same laboratory for both the cases and control subjects.

2.3. Statistics

One-way ANOVA was used to determine the difference between hypercalciuria severity with clinical and biochemical variables; post hoc analysis was performed using the Tukey test. A Kernel density estimation was used to derive a probability distribution of urine Ca/Cr ratio in the deferasirox, deferoxamine and control groups. The relationship between hypercalciuria and iron chelator dosage was determined using uni- and multivariate regression with adjustments for potential confounders (sex, age, creatinine, ferritin, calcium, PTH). Multicollinearity was determined to be present if the variance inflation factor was greater than 10. Analyses were conducted using using Stata 13 (College Station, Texas) and SPSS 20 (IBM, Armonk, NY).

3. Results

The study cohort of 152 subjects comprised of patients with β thalassemia major (81.5%), sickle cell disease (8%), thalassemia intermedia (2%), HbH (6.5%) and E/β thalassemia (2%). The mean age was 34 years and 42% were males. At the time of analysis, 88.8% of patients were receiving deferasirox (mean dose 23.2 mg/kg/day) and 11.2% deferoxamine (mean dose 44.1 mg/kg/day). All subjects had received deferoxamine prior to 2007. Subjects in the deferasirox arm had received continuous deferasirox since 2007; those in the deferoxamine arm were treated with deferoxamine for an average of 5 ± 2 (years ± SD) prior to the commencement of the study in 2014. There was no significant difference in transfusion parameters, serum calcium and vitamin D, hypogonadism, hypoparathyroidism, kidney stones, fractures or bone density between those on deferasirox or deferoxamine at baseline (Table 1).

Table 1
Baseline patient characteristics.

	Deferasirox (n = 134)	Deferoxamine (n = 18)	P value
Gender	M(44%) F(56%)	M(24%) F(76%)	0.1
Age (yrs)	33.5 ± 12.5	37.8 ± 9.1	0.35
Hemoglobin (120–160 g/L)	108.3 ± 10.2	103.1 ± 9.7	0.06
Creatinine (55–105 μmol/L)	67.9 ± 20.2	76.7 ± 47.6	0.69
Ferritin (15–180 μg/L)	1237.4 ± 1401	1738.6 ± 1714	0.1
Calcium (2.20–2.60 mmol/L)	2.28 ± 0.13	2.28 ± 0.10	0.99
Phosphate (0.8–1.5 mmol/L)	1.2 ± 0.25	1.2 ± 0.20	0.79
Parathyroid hormone (1.5–7.0 pmol/L)	1.98 ± 1.24	2.1 ± 1.02	0.56
25 (OH) vitamin D (75–250 nmol/L)	65.4 ± 18.1	72.3 ± 23.9	0.31
Urine calcium/creatinine (≤0.4)	1.20 ± 0.74	0.95 ± 0.66	0.12
Urine tubular protein/creatinine (≤0.3)	0.041 ± 0.08	0.033 ± 0.033	0.34
Fracture	15%	12%	0.74
Hypogonadism	38%	35%	0.84
Hypoparathyroidism	15%	29%	0.21
Kidney stones	23%	18%	0.62
Bisphosphonates	19%	24%	0.62
Lumbar spine Z score	−1.72 ± 1.29	−1.74 ± 1.44	0.6
Femoral neck Z score	−0.93 ± 1.14	−1.138 ± 0.84	0.07

The distribution of UCa/Cr was significantly different in the control, deferasirox and deferoxamine treated subjects (Fig. 1). Hypercalciuria was present in 91.9% of subjects on deferasirox and 83.4% on deferoxamine in the presence of a normal serum creatinine. There was a significant positive association between weight-adjusted deferasirox dosage and hypercalciuria severity which was maintained after adjusting for confounding factors. In contrast, the relationship between deferoxamine dose and hypercalciuria was not significant (Table 2).

4. Discussion

Deferasirox when used in therapeutic dosage is associated with dose-dependent hypercalciuria in patients with thalassemia major. The findings of significant hypercalciuria may explain the increased prevalence of kidney stones [3,11] and associated accelerated bone loss [2] described in the thalassemia cohort since the introduction of deferasirox.

Renal tubular and glomerular dysfunction has been described in the pediatric thalassemia population on deferoxamine and deferasirox [10,17]. Indeed, cases of reversible Fanconi's syndrome, increased

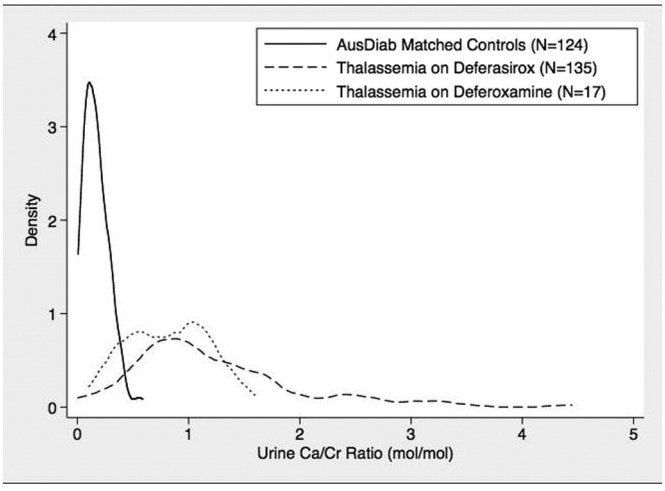

Fig. 1. Kernel density estimation of urine Ca/Cr ratio in subjects treated with either deferasirox or deferoxamine compared to controls.