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BRIEF REPORT

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Hypophosphatemia in children treated with ferric carboxymaltose

In adults, iron-induced hypophosphatemia is an increasingly recognised adverse drug reaction of certain high-dose intravenous iron formulations, particularly ferric carboxymaltose (FCM).[1-3] Data in children are sparse, but severe hypophosphatemia has been reported in adolescents receiving FCM treatment.[4] The aims of this study were to determine the incidence of hypophosphatemia in a larger paediatric collective receiving FCM for treatment of iron deficiency anaemia and to evaluate potential gender differences.

We conducted a systematic electronic query of medical records of all patients admitted to the Department of Pediatrics at Innsbruck University Hospital, Austria, from January 1, 2007, through October 31, 2018. Search terms consisted of the generic term 'ferric carboxymaltose', proprietary brand names and common typographical errors. Patients were included if FCM was administered and plasma phosphate concentrations were determined no longer than 6 months prior to as well as up to 12 months after infusion date. Laboratory parameters were extracted from medical records; results obtained closest to infusion date were used for analyses. Hypophosphatemia was defined as a phosphate concentration below the lower limit of the age- and sex-specific reference interval.[5] Statistical analyses were carried out with SPSS for Windows, version 24 (SPSS Inc, Armonk, NY, USA). Differences in patient and laboratory characteristics between male and female subjects were determined by means of Pearson's chi-square test or Mann-Whitney *U* test. A multiple regression analysis was performed to predict delta phosphate from gender and underlying diagnoses of iron deficiency anaemia. As by Austrian law and confirmed by the local ethics committee, approval from an institutional review board is not required for this type of retrospective observational analysis.

A total number of 36 patients (male: n = 14; female: n = 22) corresponding to 71 FCM doses (single dose: n = 25; multiple doses: n = 11, maximum 10 doses/patient) were included in the study. All patients had normal baseline plasma phosphate concentrations. Baseline characteristics are shown in Table S1.

After the first FCM dose, hypophosphatemia occurred in 6 out of 36 patients (16.7%; age range 8.1-30.1 years; minimum 0.68 mmol/L). Underlying diagnoses in these patients were inflammatory bowel disease (IBD) in four patients (male: n = 1, female: n = 3) and inborn errors of metabolism/mitochondrial disease in two female patients. Laboratory parameters determined after the first FCM dose are displayed in Table S1. Median (interquartile range) delta phosphate was −0.10 (−0.22; 0.10) mmol/L, with statistically significant gender differences (male: 0.08 (−0.18; 0.26) mmol/L; female: −0.14 (−0.31; −0.01) mmol/L; $U = 81.500$, $P = .026$, Mann-Whitney *U* test). Multiple regression analysis revealed that the variables gender and underlying diagnosis category statistically significantly predicted delta phosphate ($F_{(2,32)} = 3.567$, $P = .040$, $R^2 = .182$), with gender adding statistically significantly to the prediction ($P = .017$).

Regarding all doses applied, hypophosphatemia occurred in 8 out of 71 FCM treatments (11.3%). In patients receiving multiple doses, hypophosphatemia occurred in one female patient with IBD receiving FCM after the 1st (0.93 mmol/L), 6th (0.66 mmol/L) and 10th dose (0.57 mmol/L). Between the first dose and the end of the study period, this patient had 25 documented episodes of hypophosphatemia; in eight of these episodes, plasma phosphate concentrations were below 0.80 mmol/L. The nadir of 0.57 mmol/L was reached 42 days after the 10th FCM dose.

Iron-induced hypophosphatemia is now more and more acknowledged as a complication of intravenous iron treatment in adults and seems to be particularly associated with FCM.[1-3] The purported mechanism of FCM-induced hypophosphatemia is reduced cleavage of fibroblast growth factor-23 (FGF23), with elevated intact FGF23 concentrations leading to renal phosphate wasting and secondary hyperparathyroidism.[1] An increasing body of evidence suggests that some patients may develop severe and/or symptomatic hypophosphatemia, leading to both short- and long-term complications.[2]

Our study is the first to report a high incidence of iron-induced hypophosphatemia in children receiving FCM treatment and potential gender effects. In accordance with a previously published case series,[4] it demonstrates that hypophosphatemia is not only common following FCM treatment, particularly after the first dose, but that it might also be pronounced and prolonged. Gender-specific differences were detected in phosphate dynamics following FCM treatment, with girls being more inclined to a decrease in plasma phosphate concentrations after the first dose. In the only randomised trial of intravenous iron-induced hypophosphatemia published so far, gender was not an independent factor influencing hypophosphatemia.[3] This discrepancy might be due to the small sample size and the non-standardised timing of phosphate sampling in our study. Nonetheless, gender aspects might be of interest in future paediatric studies.

The major limitation of our study is its retrospective design. Laboratory assessments were not conducted at pre-specified time points, concomitant urine analyses are not available, and systematic information on signs and symptoms of hypophosphatemia is lacking. This study is a first exploration of this relevant adverse drug reaction in children, which we believe merits and requires further investigation.

To conclude, hypophosphatemia is a common side effect of FCM treatment not only in adults but also in children. Prospective trials evaluating the safety of IV iron formulations in paediatric populations are direly needed.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.