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Case report

Myoglobinuria in two patients with Duchenne muscular dystrophy after treatment with zoledronate: a case-report and call for caution

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Abstract

Rhabdomyolysis with myoglobinuria is a recognized complication of dystrophinopathies. It can be triggered by infections, exercise or volatile anesthetics. To our knowledge, it has never been reported in boys with Duchenne muscular dystrophy (DMD) after the administration of bisphosphonates. We report two patients with DMD who presented an apparent transient rhabdomyolysis with myoglobinuria after zoledronate administration. Possible mechanisms could involve hypophosphatemia, a known dose-dependent side effect of bisphosphonates, and/or direct myotoxicity of biphosphonates. Physicians and families should be aware of rhabdomyolysis with myoglobinuria as a potential uncommon side effect of bisphosphonates in DMD, in particular of zoledronate.

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Keywords: Duchenne muscular dystrophy; myoglobinuria; bisphosphonates; zoledronate.

1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked progressive myopathy due to mutations in the dystrophin gene, affecting one in every 3600–10,000 live male births [1,2]. Boys with DMD typically present with delayed motor milestones and muscle weakness, they progress to loss of ambulation around their teens, and respiratory and heart failure during the second decade. Corticosteroids remain the standard supportive therapy for DMD even though new treatments recently emerged [3–6]. Along with other risk factors that are present in DMD such as progressive weakness, immobility and delayed puberty, chronic corticosteroid therapy increases the risk of low bone mineral density, exposing these patients to fractures, pain and decreased quality of life. Little data is available to guide best practice for bone health management in DMD [7]. However, a consensus exists on the use of bisphosphonates to improve bone mineral density in cases of fractures or bone pain [3,8].

2. Case report

Patient 1 is a 14-year-old boy with DMD due to a deletion of exon 50. He was diagnosed at 5 years; corticosteroids were initiated at 9 years old only, due to parents' concerns about side-effects. Independent walking was lost at 13 years. Bisphosphonates were proposed at 13 years because of intractable bone pain and low bone mineral density on DEXA scan (hip Z-score –3.7 SD, lumbar spine Z-score –2.1 SD). A first infusion of zoledronate (0.04 mg/kg) was well tolerated. A second infusion at the same dose was administrated six months later. Two days after this second infusion, the patient developed flu-like symptoms with diffuse myalgia, vomiting, and dark brown urine. No urine or blood control was performed during the acute phase, since the apparent

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myoglobinuria was reported only after the recovery. Serum electrolytes (notably calcium and phosphate) were normal prior to both infusions. The 25-OH-vitamin D level was 11.9 µg/l before the first infusion and 20.8 µg/l before the second (normal range commonly applied in paediatrics: 20–100 µg/l).

Patient 2 is a 13-year-old boy diagnosed at 4 years with DMD due to a deletion of exons 12–33. Corticosteroid therapy was introduced shortly after diagnosis. He lost ambulation at 11 years. A treatment with bisphosphonates was proposed at 13 years given the low bone mineral density on DEXA scan (hip *Z*-score –5.7 SD, lumbar spine *Z*-score –1.2 SD) and back pain attributed to demineralisation. An intravenous treatment with zoledronate (0.02 mg/kg, corresponding to half the standard dose) was initiated. Serum electrolytes (notably calcium and phosphate) were normal prior to the treatment. Less than 24 h after the infusion, the patient complained of myalgia, fever, nausea, and experienced on the second day a unique episode of dark brown urine. No urine test could be performed during the acute phase, since the episode was reported only after recovery. A blood test done two days after the infusion showed hypophosphatemia (0.82 mmol/l, range: 1.1–2.0 mmol/l) and mild hypocalcaemia (total calcium 2.01 mmol/l, range 2.15–2.55 mmol/l), which recovered after substitution. 25-OH-vitamin D level was 13.9 µg/l (range: 20–100 µg/l).

3. Discussion

In the last years, as the consequences of corticosteroid-associated osteoporosis became more and more evident, growing attention has been paid to the bone health of patients with DMD [8,9]. Corticosteroids affect both bone resorption and bone formation, diminish the gastrointestinal absorption and increase the renal excretion of calcium [9]. Consequently, corticosteroid-treated patients with DMD experience more frequently bone pain due to demineralization and vertebral and long bones fractures [9]. Additional risk factors like progressive muscle weakness, immobilization, delayed puberty, insufficient vitamin D level and possibly inflammatory cytokines increase further the risk for osteoporosis in patients with DMD [8].

Bisphosphonates are the main medical treatment of pediatric osteoporosis, pamidronate being the most frequently used [10,11]. Zoledronate has been introduced more recently. It is much more potent than pamidronate, the infusion time is shorter and it can be administered less frequently [10].

Little data is available to guide the initiation, duration and type of bisphosphonate treatment for patients with DMD [7-9]. Current recommendations for bisphosphonate treatment in pediatric osteoporosis are to start with a stabilization phase during at least two years [10]. In case of persistent risk factors, a maintenance phase can be proposed, although with a lower dose (half-dose or less), until the patient attains his final height [10].

Several retrospective studies and case reports have been published on bisphosphonates for corticosteroid-treated patients with DMD [12–15]. The indications to start treatment were variable, ranging from low bone mineral density, with or without pain, to vertebral fractures. Most of them found an improvement in bone mineral density and Z-scores but effects on pain and fracture risk were less consistent. Some patients continued to have vertebral fractures while on treatment. Prophylactic use of oral bisphosphonates has been described in several studies and showed to stabilize bone mineral density, an effect which seemed to be greater if the treatment was started earlier [13,16].

In our two patients, the indications for treatment initiation were low bone mineral density, defined as a *Z*-score less than or equal to −2.0 SD, and the presence of bone pain [17]. We decided to give zoledronate rather than pamidronate given its shorter infusion time and the longer interval between two infusions. Oral bisphosphonates were not considered as we were concerned about the important gastrointestinal side effects [18]. Consequently, after zoledronate administration both patients developed symptoms that highly suggest transient rhabdomyolysis with myoglobinuria. A limitation of our report is the lack of biochemical evidence for the myoglobinuria. However, in the reported cases, the urine was described as dark brown (cola brown) as it has never been observed before and therefore highly indicative for myoglobinuria in this particular context. Medical attention was not sought during the acute phase because the next urine was less coloured and the episodes were therefore reported only after recovery.

The prescribing information of zoledronate lists flu-like symptoms, myalgias and fatigue among frequent side effects, hypocalcaemia and hypophosphataemia are also mentioned. A risk of rhabdomyolysis is not listed, and to our knowledge no case has been published so far, in particular not in patients with DMD [19]. A case of rhabdomyolysis following zoledronate administration in an adult was however presented at the 2010 meeting of the Endocrine Society, and the World Health Organization's (WHO) global database of reports of suspected drug adverse effects VigiLyze® contains (as of 29 March 2017) 47 reports of rhabdomyolysis involving zoledronate (Uppsala Monitoring Centre, WHO) [20,21].

Possible mechanisms of rhabdomyolysis secondary to bisphosphonates could involve drug-induced hypophosphatemia and/or a myotoxicity of nitrogen-containing bisphosphonates. Hypophosphatemia, as observed in our second patient, is a known dose-dependent side effect of bisphosphonates and a proven risk factor for rhabdomyolysis [22,23]. Regarding myotoxicity, an *in vitro* study has shown that risedronate and alendronate, both nitrogen-containing bisphosphonates, induce apoptosis of rat myoblasts [24]. The inhibition of farnesyl pyrophosphate (FPP) synthase, a key enzyme of the mevalonate pathway, is thought to underlie the observed cytotoxicity. Thus, both a direct cytotoxicity of zoledronate and an indirect metabolic effect (hypophosphatemia), to which a dystrophic muscle might be particularly sensitive, could possibly account for the apparent transient rhabdomyolysis with myoglobinuria observed in our patients.

Other factors could, at least partly, be involved in the observed myoglobinuria. There is a widespread practice of pre-

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scribing calcium supplementation for 5–10 days following the first bisphosphonate infusion [10]. This was not done in our patients, the second case received supplementation but only once hypocalcaemia was confirmed. Further, an optimal vitamin D status during bisphosphonate treatment is known to reduce the risk of side effects [10]. Both our patients had low vitamin D levels.

4. Conclusion

We report two patients with DMD who presented an apparent transient rhabdomyolysis with myoglobinuria after zoledronate administration. Possible mechanisms could involve hypophosphatemia, a known dose-dependent side effect of bisphosphonates, and/or a possible direct myotoxicity as suggested by an animal study. Phosphate supplementation is not currently used in patients after bisphosphonate administration. When considering hypophosphatemia as a possible mechanism for rhabdomyolysis after bisphosphonate infusion, preventive phosphate supplementation could possibly decrease this risk. However, too little data is available to make recommendations regarding prophylactic calcium and phosphate supplementation. Nevertheless, serum electrolytes, in particular calcium and phosphate, and vitamin D levels should be measured and must be in the normal range prior to infusion.

Clinicians should be aware of rhabdomyolysis and myoglobinuria as a potential uncommon side effect of bisphosphonates in DMD, in particular of zoledronate, and accordingly inform the patients and their families.

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