***Intracardiac thrombosis following intravenous zoledronate treatment in a child with steroid-induced osteoporosis***

Short Title: Cardiac thrombosis following zoledronic acid

Samantha J Casea\*, Rebecca J Moona,b\*, Tara Bharuchac, Justin H Daviesa,d

a) Paediatric endocrinology, Southampton Children’s Hospital, University Hospital Southampton NHS Foundation Trust, Southampton, UK

b) MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton, UK

c) Paediatric Cardiology, Southampton Children’s Hospital, University Hospital Southampton NHS Foundation Trust, Southampton, UK

d) Faculty of Medicine, University of Southampton, Southampton, UK

\*SJC and RJM are joint first authors

Corresponding Author:

Dr Rebecca J Moon, NIHR Academic Clinical Lecturer in Child Health

Paediatric Endocrinology

Southampton Children’s Hospital, University Hospital Southampton NHS Foundation Trust

Tremona Road

Southampton, Hampshire, SO16 6YD, UK

E-mail: rm@mrc.soton.ac.uk

Number of Tables: 0

Number of Figures: 3

Word count: 1343

Supplemental Data: None

Keywords: bisphosphonate, intracardiac thrombosis, steroid induced osteoporosis

Abbreviations:

APR, acute phase reaction; DMD, Duchenne muscular dystrophy; LV, left ventricular

**Abstract**

Objectives

Bisphosphonates are used in childhood osteoporosis but can cause an acute phase reaction (APR) and hypocalcemia. We present a child with cardiac thrombosis following zoledronate, a previously unreported complication.

Case Presentation

An 11-year-old with Duchenne muscular dystrophy and steroid-induced osteoporosis presented 48 hours after first zoledronate infusion with fever, tachycardia, tachypnoea and hypoglycaemia. This was managed as acute adrenal crisis and possible sepsis. He also had hypocalcemia, hypophosphatemia, hyponatraemia and hypokalaemia. Echocardiography performed due to persistent chest pain and tachycardia revealed a left ventricular thrombus.

Conclusions

Potential causes for intracardiac thrombosis in this patient include ventricular dysfunction due to acute adrenal crisis or electrolyte disturbance, and hypercoagulability due to the APR. Echocardiography should be considered in children with acute cardiovascular compromise following zoledronate. Stress-dose steroids to cover the APR and a reduced starting dose of zoledronate might have reduced the risk of this complication.

**Introduction**

Bisphosphonates are the currently the only available pharmacological treatment for childhood osteoporosis. Pamidronic acid (pamidronate) and zoledronic acid (zoledronate) are the most commonly used agents, administered as intravenous infusions. Common side effects include an acute phase reaction (APR) following the first infusion and hypocalcaemia occurring a few days following treatment. We present a case of intracardiac thrombosis following zoledronate infusion in a boy with Duchenne muscular dystrophy (DMD) and secondary osteoporosis. To our knowledge, this has not previously been reported as a complication of bisphosphonate therapy.

**Case presentation**

The patient was diagnosed with DMD at 2 years of age following presentation with motor and speech delay. Genetic investigations confirmed an out-of-frame mutation in exon 44 of the dystrophin gene. Oral corticosteroid therapy (prednisolone 0.8 mg/kg/day for 10 days on, 10 days off) was started just after his fifth birthday, and subsequently switched to deflazacort (0.7 mg/kg/day) at age 11 years. Serial echocardiography identified a reduced ejection fraction of 40% at age 11 years 1 month, for which he was commenced on perindopril 2mg daily.

Multiple vertebral fractures were first identified at age 10 years. Dual-energy X-ray absorptiometry scan showed low whole body bone mineral density z-score (-3.3); lumbar spine bone mineral density z-score was not calculated due to mild-moderate wedge deformities in L1, L2 and L4 vertebrae. The patient and his family were counselled on the risks and benefits of zoledronic acid therapy, which was given at age 11 years 4 months. Pre-infusion his serum calcium (2.34 mmol/l), phosphate (1.34 mmol/l), 25-hydroxyvitamin D (88 nmol/l) and renal function were all within normal range. Prior to the infusion, his baseline observations were documented as heart rate 100 beats per minute (bpm), blood pressure 104/68 mmHg, respiratory rate 30 breaths per minute with oxygen saturations of 97% in room air. Zoledronic acid (0.05 mg/kg) was administered intravenously over 45 minutes with prophylactic ondansetron and paracetamol. The infusion rate followed our standard protocol and is slower than that advised in adult patients in whom 4mg can be given over a minimum of 15 minutes (1). The infusion was uneventful and vital sign observations remained within normal limits. He was discharged one hour after the infusion with calcium supplementation (15 mmol twice daily) for 5 days.

He re-presented acutely 48 hours after the infusion with fever, diarrhoea, vomiting, and chest pain. He was hypotensive (blood pressure 91/50 mmHg), tachycardic (heart rate 153 bpm, sinus rhythm) and tachypnoeic with normal oxygen saturations. He was hypoglycaemic with a blood glucose level of 2.2 mmol/l. He was given 100 mg intramuscular hydrocortisone and 2 ml/kg intravenous 10% glucose solution, followed by intravenous hydrocortisone (2 mg/kg), intravenous fluids (initially 10 ml/kg 0.9% saline bolus followed by maintenance fluids) and intravenous ceftriaxone (80 mg/kg) for presumed sepsis on a background of chronic adrenal suppression. A rise in creatinine from a baseline of 22 µmol/l to 34 µmol/l was noted. Perindopril was withheld.

Investigations showed a raised white cell count (18.2 x109L, neutrophils 17.0 x109L) and C-reactive protein (183 mg/L). Blood and urine cultures were negative after 48 hours of incubation. Significant electrolyte disturbances were also noted with hypocalcaemia (corrected calcium 1.92 mmol/L), hyponatraemia (131 mmol/L), hypokalaemia (3.10 mmol/L) and hypophosphatemia (0.35 mmol/L). These were managed with intravenous and subsequently oral replacement of calcium, phosphate and potassium. Progression of biochemical findings are shown in Figure 1. Creatinine peaked at 55 µmol/l on day 5 of admission before returning to baseline.

He was reviewed by the cardiology team on day 3 due to persistent chest pain. Electrocardiogram was unremarkable (Figure 2), and it was felt this pain was unlikely to be cardiac in origin. He continued to have episodes of sinus tachycardia, for which echocardiography was performed on day 6 post zoledronate. Left ventricular (LV) dysfunction similar to the previous echocardiogram performed a month prior to the zoledronate infusion was noted, and additionally new mitral regurgitation. Echocardiography was repeated the following day, which identified a LV thrombus (shown in Figure 3). Anticoagulation was commenced with enoxaparin and warfarin. Repeat echocardiography on days 10 and 11 post zoledronate showed a reduction in size of the thrombus. Surgical management was considered, but a conservative approach was felt more appropriate owing to the risks of surgery in this patient. Further echocardiography on day 16 showed complete resolution of the thrombus. The relative risks and benefits of ongoing anticoagulation was discussed between the cardiologist and family; warfarin was discontinued as it was felt the risk of further thrombus was low. He was discharged on day 16. Further bisphosphonate treatment was declined by the patient and family.

**Discussion**

Zoledronate has been shown in children with steroid-induced osteoporosis to increase bone mineral density compared to placebo (2), but side effects are common. APR consisting of flu-like symptoms within the first few days after infusion, have been reported to occur in up to 77% of bisphosphonate-naïve children (3). These reactions seem to occur more commonly in children with secondary compared to primary osteoporosis (4). Electrolyte disturbances, including hypocalcaemia and hypophosphatemia are also frequently reported (3), usually occuring within 24-48 hours of administration (5). Prolonged hypocalcaemia lasting several weeks after bisphosphonate administration has been reported (6). Prophylactic post-infusion calcium supplementation is recommended to prevent symptomatic hypocalcaemia and seizures. Cardiac thrombosis is not a previously recognised complication of bisphosphonate treatment.

Intracardiac thrombosis is rare in children, most commonly occurring as a complication of central venous catheter placement, sepsis or underlying cardiac disease (7) and typically occurring in the right-sided cardiac chambers. Thrombus formation in the left ventricle is more commonly associated with severe LV dysfunction and arrhythmia (8). Intracardiac thrombosis has not previously been reported in relation to either adrenal crisis or bisphosphonate-related APR in adults or children.

Potential causes for transient deterioration in LV function leading to thrombus formation in our patient include adrenal crisis-related hypotension, dehydration and electrolyte disturbances. Renal impairment was also present in our patient as evidenced by a rise in creatinine from baseline despite a relatively low total serum creatinine (which can result from the myopathy present in DMD). This may have further contributed to electrolyte distrubances. Hypocalcemia is known to cause cardiac arrhythmias including atrial fibrillation, ventricular tachyarrhythmias and prolonged QT intervals; depressed LV function is also reported (9). Both severe hypophosphatemia and hypokalemia may also result in impaired myocardial contractility and tachyarrhythmia (10). The pre-existing LV dysfunction in our patient may have increased his risk for thrombus formation, although it was not severe. Thrombus formation in the left ventricle is generally only seen in patients with severe reduction in LV function, and in patients with a rapid decline in LV function; in one case series of patients with dilated cardiomyopathy, thrombus formation was more commonly seen in those with an ejection fraction < 20% with a rapid deterioration of LV function (8). Ejection fraction was estimated at 40% in our patient the day prior to thrombus visualisation on echocardiogram, representing moderate dysfunction, however it is likely that he had an acute deterioration in ventricular function related to the electrolyte disturbances. It is not possible to speculate when thrombus formation started, although the thrombus may have been present and not visible on echocardiography prior to detection, although retrospective review of the images from earlier in admission confirmed the thrombus was not visible.

The contribution of the APR to a hypercoagulable state through proinflammatory cytokines such as tumour-necrosis factor-α and interleukin-6 (11) might have also increased thrombus formation risk in our patient, although it is unlikely that this alone was the cause as thromboembolic events following bisphosphonate administration have not previously been described. Recently left ventricular thrombi have been reported as a complication of SARS-COV-19 infection in children without significant LV dysfunction (12), highlighting the potential role of the inflammatory hypercoagulation in this process (11). A thrombophilia screen was not undertaken in our patient, but thrombophilia has been shown to increase propensity to intracardiac clot formation (7).

**Learning Points**

We have made several changes to our practice following this case and subsequent review of the literature.

* We now recommend stress dose steroids (7.5 mg/m2 6 hourly hydrocortisone) for all steroid treated patients for 72 hours following bisphosphonate infusion to provide additional steroid-cover for the APR. Interestingly, a randomised controlled trial in adults with osteoporosis found that dexamethasone can reduce the frequency and severity of the APR following bisphosphonate treatment (13).
* Our dosing schedule in bisphosphonate-naïve patients has also been modified to both reduce the risk of APR and hypocalcaemia (3). Our protocol splits the first dose into two administations given on day 1 and half-way through the dosing interval. For example, a 5-18-year-old child would usually be administered zoledronate every 26 weeks; this is administered as half-doses on week 0 and week 13, followed by a full dose on week 26 and every 26 weeks thereafter.
* Cardiac thrombosis is a previously unreported complication of intravenous bisphosphonate therapy, but the recognized side effects of this treatment likely contributed to an increased risk of this outcome. Echocardiography should be considered in patients with significant APR or electrolyte disturbances after bisphosphonate treatment and presenting with arrhythmia or cardiovascular compromise.

**Acknowledgements**

We thank the patient and his family for consent to publish details of their medical case and accompanying images.

###### Author Contributions

SJC and RJM drafted the initial manuscript, critically reviewed, and revised the manuscript. TB and JHD contributed to the care of the patient, critically reviewed and revised the manuscript. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

###### Funding Sources

No specific funding for this study received. RJM is funded by an NIHR Academic Clinical Lectureship.

**Employment or leadership**

None declared.

**Competing interests**

JHD has received travel bursaries from Novo Nordisk, honoraria from Kyowa Kirin. SJC, RJM and TB have no conflicts of interest to declare.

**Statement of Ethics**

###### Written informed consent was obtained from patient and their parent for publication of the details of their medical case and the accompanying images.

**Figure Legends**

Figure 1. Biochemical and echocardiography findings in 11 year old patient with Duchenne Muscular Dystrophy who developed a cardiac thrombosis following zoledronate treatment.

Normal ranges for serum measurements are shown by the shaded grey areas.

Figure 2. Electrocardiogram at time of chest pain and sinus tachycardia

Figure 3. Two-Dimensional echocardiographic image in the four chamber view, demonstrating the thrombus at the apex of the left ventricle.

**References**

1. Electronic Medicines Compendium (EMC). Zoledronic Acid 4 mg/5 ml Concentrate for solution for Infusion. Available from: <https://www.medicines.org.uk/emc/product/13761/smpc>. Accessed 17th October 2022.

2. Ward LM, Choudhury A, Alos N, Cabral DA, Rodd C, Sbrocchi AM, et al. Zoledronic Acid vs Placebo in Pediatric Glucocorticoid-induced Osteoporosis: A Randomized, Double-blind, Phase 3 Trial. J Clin Endocrinol Metab. 2021;106(12):e5222-e35.

3. Munns CF, Rajab MH, Hong J, Briody J, Högler W, McQuade M, et al. Acute phase response and mineral status following low dose intravenous zoledronic acid in children. Bone. 2007;41(3):366-70.

4. Nasomyont N, Hornung LN, Gordon CM, Wasserman H. Outcomes following intravenous bisphosphonate infusion in pediatric patients: A 7-year retrospective chart review. Bone. 2019;121:60-7.

5. Rothenbuhler A, Marchand I, Bougnères P, Linglart As. Risk of Corrected QT Interval Prolongation after Pamidronate Infusion in Children. J Clin Endocrinol Metab. 2010;95(8):3768-70.

6. Peter R, Mishra V, Fraser WD. Severe hypocalcaemia after being given intravenous bisphosphonate. BMJ. 2004;328(7435):335-6.

7. Odaman Al I, Oymak Y, Erdem M, Tahta N, Okur Acar S, Mese T, et al. Assessment of clinical characteristics and treatment outcomes of pediatric patients with intracardiac thrombosis: a single-center experience. Blood Coagul Fibrin. 2022;33(1):34-41.

8. Choi SH, Jeong SI, Yang JH, Kang IS, Jun TG, Lee HJ, et al. A single-center experience with intracardiac thrombosis in children with dilated cardiomyopathy. Pediatr Cardiol. 2010;31(2):264-9.

9. Newman DB, Fidahussein SS, Kashiwagi DT, Kennel KA, Kashani KB, Wang Z, et al. Reversible cardiac dysfunction associated with hypocalcemia: a systematic review and meta-analysis of individual patient data. Heart Fail Rev. 2014;19(2):199-205.

10. Amanzadeh J, Reilly RF. Hypophosphatemia: an evidence-based approach to its clinical consequences and management. Nat Clin Pract Nephr. 2006;2(3):136-48.

11. Thiébaud D, Sauty A, Burckhardt P, Leuenberger P, Sitzler L, Green JR, et al. An in vitro and in vivo study of cytokines in the acute-phase response associated with bisphosphonates. Calcif Tissue Int. 1997;61(5):386-92.

12. Bigdelian H, Sedighi M, Sabri MR, Dehghan B, Mahdavi C, Ahmadi A, et al. Case Report: Acute Intracardiac Thrombosis in Children With Coronavirus Disease 2019 (COVID-19). Front Pediatr. 2021;9:656720.

13. Chen FP, Fu TS, Lin YC, Lin YJ. Addition of dexamethasone to manage acute phase responses following initial zoledronic acid infusion. Osteoporos Int. 2021;32(4):663-70.