AACE Clinical Case Rep. 9 (2023) 32–34

Contents lists available at ScienceDirect

AACE Clinical Case Reports

journal homepage: www.aaceclinicalcasereports.com

Case Report

Adrenal Crisis as An Adverse Reaction to Zoledronic Acid in a Patient With Primary Adrenal Insufficiency: A Case Report and Literature Review

Bryan Kuo, MD [1,*], Alison Koransky, MD [1,2], Cherie Lisa Vaz Wicks, MD [2,3]

[1] Department of Internal Medicine, Temple University Hospital, Philadelphia, Pennsylvania
[2] Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania
[3] Section of Endocrinology, Diabetes, and Metabolism, Temple University Hospital, Philadelphia, Pennsylvania

ARTICLE INFO

Article history:
Received 9 September 2022
Received in revised form
15 November 2022
Accepted 13 December 2022
Available online 17 December 2022

Key words:
adrenal crisis
adrenal insufficiency
bisphosphonate
zoledronic acid

ABSTRACT

Background/Objective: Adrenal crisis is a medical emergency and an acute complication of adrenal insufficiency (AI). It can be triggered by stressors such as infection, dehydration, trauma, or surgery.
Case Report: We present a case of a 70-year-old woman with a history of Addison's disease, who presented in adrenal crisis within 24 hours after receiving her first infusion of zoledronic acid. No trigger was identified after extensive evaluation, making infusion with zoledronic acid the most likely cause of adrenal crisis.
Discussion: Adverse reactions to medications can potentially trigger adrenal crisis. The present case report demonstrates that intravenous bisphosphonates can cause an acute phase reaction that may lead to adrenal crisis. Given the increased risk of osteoporosis in patients with AI there is an increased likelihood of prescription of intravenous bisphosphonates in this patient population.
Conclusion: Patients with AI undergoing infusion with zoledronic acid may require an increased dose of glucocorticoid prior to infusion and may need to undergo monitoring post infusion for possible adrenal crisis.

Introduction

Adrenal insufficiency (AI) is caused by impairment of adrenal gland function leading to a deficiency in adrenal hormones. Primary adrenal insufficiency (PAI) or Addison's disease is due to lack of function of the adrenal glands. The most common cause of PAI is autoimmune adrenalitis, accounting for 68% to 94% of cases.[1,2] Adrenal crisis is a life-threatening complication of AI, with a prevalence of about 5.2-8.3 per 100 patient-years, and mortality of 0.5 per 100 patient-years.[2,3] It can be triggered by an infection, trauma, or other acute stressor and is characterized by hypotension, fever, gastrointestinal symptoms, somnolence, hyponatremia, and hyperkalemia.[1,2] If adrenal crisis is suspected, urgent treatment with parenteral hydrocortisone is required.[2,4]

Patients with PAI are at increased risk for decreased bone mineral density and hip fractures.[5-7] In a Swedish population cohort study, the risk of hip fracture was approximately 2 times greater in patients with PAI when compared to age- and gender-matched controls, likely because many patients with PAI are treated with supraphysiologic doses of glucocorticoid.[5] Increased glucocorticoid intake accelerates bone mass decline through inhibition of osteoblast activity, stimulation of osteoclast activity, and inhibition of calcium absorption.[6,8] In addition, the lack of adrenal androgens in individuals with PAI may increase their risk for osteoporosis.[5,6] Given this increased risk for osteoporosis and hip fractures, patients with PAI are likely to be candidates for bisphosphonate therapy.

We report a case of adrenal crisis which occurred after the first infusion of zoledronic acid was given in a patient with Addison's disease. We describe the work up and successful management of adrenal crisis due to intravenous (IV) bisphosphonate.

Case Report

A 70-year-old woman with a history of Addison's disease, prior COVID-19 infection, thyroid nodule, and osteoporosis was brought to the hospital for altered mental status. She had been diagnosed with Addison's disease 22 years prior and was treated with

Abbreviations: PAI, primary adrenal insufficiency; AI, adrenal insufficiency; APR, acute phase reaction.

* Address correspondence to Dr Bryan Kuo, Department of Internal Medicine, Temple University Hospital, 3401 N Broad Street, Philadelphia, PA 19140.
E-mail address: bryan.kuo@tuhs.temple.edu (B. Kuo).

https://doi.org/10.1016/j.aace.2022.12.003

prednisone 2.5 mg daily for many years. She had previously been treated with 5 mg of prednisone daily which was lowered due to side effects thought to be related to the prednisone. Her other home medications included rosuvastatin 5 mg, vitamin D, and calcium supplementation. She had received treatment for osteoporosis with her first dose of IV zoledronic acid the day prior. Her vitals during the infusion appointment were: (1) blood pressure of 139/61 mmHg, (2) pulse of 70 beats per minute, (3) respiration rate of 16 breaths per minute, (4) temperature of 98.3 °F, and weight of 57.7 kg. Prior to this infusion she was in her usual state of health and had no infectious symptoms during the week leading up to the infusion. She continued to take 2.5 mg of prednisone leading up to and on the day of the infusion. On the same day of the infusion with zoledronic acid, she developed chills at night. The subsequent day, after her family was unable to reach her over the phone, they went to her home and found her confused, lethargic, and incontinent, prompting them to call 911. Emergency medical services found an undetectable glucose on point of care testing. She was treated with an ampule of 10% dextrose and her subsequent glucose was 129. However, her mental status did not improve significantly. On arrival to the emergency department, she was febrile to 103 °F and hypotensive to 85/76 mmHg. Additionally, vitals showed a pulse of 93 beats per minute, respiratory rate of 19 breaths per minute, and oxygen saturation of 95% on room air. Her physical exam was notable for somnolence, diaphoresis, and inability to follow commands. Given her mental status, she was unable to provide additional history regarding the events leading up to presentation. Initial laboratory tests were significant for a leukocytosis of 12.9 K/mm^3 and an elevated lactate of 5.0 mmol/L (Table).

The patient's clinical picture was concerning for an adrenal crisis. In the emergency room, the patient's history of PAI was determined from chart review, and she was treated with IV hydrocortisone 100 mg once, 3 L of isotonic fluid boluses and started on broad spectrum antibiotics. Hypotension improved within 24 hours and lactate normalized to 0.9 mmol/L within 12 hours. She was subsequently placed on hydrocortisone 50 mg IV every 6 hours. Her mental status gradually began to improve during day 1 of hospitalization, and fully returned to baseline by day 2. An extensive infectious workup was performed including blood cultures, urinalysis, lumbar puncture, and computed tomography of the chest, abdomen, and pelvis. Infectious workup returned negative, and antibiotics were discontinued after 24 hours. Hydrocortisone was tapered over the following 3 days, and she was transitioned to physiologic replacement doses of hydrocortisone at 15 mg AM/5 mg PM.

Discussion

The patient presented in adrenal crisis within 24 hours of receiving her first infusion of zoledronic acid. Adrenal crisis was likely provoked by an acute systemic inflammatory reaction to bisphosphonate infusion. Zoledronic acid is an IV bisphosphonate dosed annually that is approved for the treatment and prevention of osteoporosis.[9] Zoledronic acid inhibits bone resorption by blocking the farnesyl pyrophosphate synthase enzyme in osteoclasts resulting in osteoclast apoptosis.[10] Zoledronic acid has been known to cause a transient acute phase reaction (APR) within the first 24-72 h of infusion.[11-13] It is thought that the release of intermediate metabolites from farnesyl pyrophosphate synthase inhibition leads to activation of adjacent γT cells and cytokine release, which in turn causes the APR symptoms.[10] The APR is characterized by flu-like symptoms including fevers, nausea, myalgias, and arthralgias, and the symptoms typically self-resolve by 72 hours after the infusion.[13] Approximately 30% of patients receiving their first dose of zoledronic acid have been shown to experience this reaction, and the incidence of this APR decreases with subsequent infusions[9]; 6.6% of patients have reported this reaction after the second infusion, and 2.8% have reported the reaction after the third infusion.[9,14]

Highlights

- Zoledronic acid may trigger adrenal crisis in those with adrenal insufficiency (AI).
- The prevalence of adrenal crisis after zoledronic acid has not been reported.
- Patients with AI may need increased steroid dosing prior to zoledronic acid.

Clinical Relevance

We report a case of adrenal crisis after zoledronic acid in a patient with primary adrenal insufficiency. This report demonstrates the need for recognizing this phenomenon in patients with adrenal insufficiency receiving IV bisphosphonates, and the possible need for increased steroid dosing to prevent adrenal crisis in this patient population.

Numerous drugs have been noted to induce AI, typically by means of interfering with adrenal function or cortisol availability. The most common cause of drug induced AI is suppression of the hypothalamic-pituitary-adrenal axis by chronic exogenous glucocorticoid administration.[1] Other agents that can induce AI include drugs that increase glucocorticoid metabolism by inducing the CYP3A4 enzyme such as phenytoin, mitotane, and rifampicin, and drugs that inhibit steroidogenic enzymes involved in cortisol production including metyrapone, aminoglutethimide, fluconazole, and etomidate.[1,15] The addition of these drugs that increase cortisol clearance or decrease cortisol production could trigger an adrenal crisis in patients with pre-existing AI.[15] Patients with AI are more prone to adrenal crisis when they are unable to meet cortisol demands in response to physiological stress.[16] Given that an APR is a result of a physiologic stress response, patients with AI could have a provoked adrenal crisis because of an APR to zoledronic acid.

We performed a search for cases of adrenal crisis following IV bisphosphonate therapy. We searched PubMed, ScienceDirect, and BMJ Case Reports. There is one other documented case of adrenal crisis which occurred after infusion of 5 mg zoledronic acid.[17] In that case, the patient, with a past medical history of PAI, had been maintained on a steroid regimen of hydrocortisone 10 mg +5 mg +5 mg for over 15 years. She developed adrenal crisis despite doubling her afternoon hydrocortisone dose to 10 mg on the day of the infusion.[17] This is in contrast to our patient, who had been maintained on a less than physiologic amount of prednisone prior to her zoledronic acid infusion and did not increase her steroid dose during the infusion. There are currently no guidelines for supplemental glucocorticoid administration for adult patients with PAI when receiving bisphosphonate therapy. While there have been smaller studies looking at the use of dexamethasone in the management of the APR, none of these studies included AI as inclusion criteria for their study population.[18,19] Although no recommendations with regards to individuals with AI can be concluded from these studies, this case suggests a possible need for supplemental glucocorticoid administration prior to zoledronic acid infusion in patients with PAI. In addition, both cases of IV bisphosphonate-

Table
Initial Laboratory Tests on Presentation to the Emergency Department

Laboratory tests	Result	Reference value
Chemistry		
Sodium (mmol/L)	136	136-145
Potassium (mmol/L)	3	3.5-5.2
Chloride (mmol/L)	103	101-111
Carbon Dioxide (mmol/L)	21	22-32
Calcium (mmol/L)	9	8.8-10.2
Magnesium (mg/dL)	1.6	1.6-2.4
Blood urea nitrogen (mg/dL)	22	8-20
Creatinine (mg/dL)	1.36	0.60-1.20
Glomerular filtration rate (mL/min/1.73 m^2)	38	>60
Glucose (mg/dL)	122	82-115
Complete blood count		
White blood cells (K/mm^3)	12.9	4.0-11.0
Neutrophils absolute (K/mm^3)	11.5	1.8-7.8
Lymphocytes absolute (K/mm^3)	1.0	1.0-4.8
Monocytes absolute (K/mm^3)	0.5	0.0-0.8
Eosinophils absolute (K/mm^3)	0.0	0.0-0.5
Basophils absolute (K/mm^3)	0.0	0.0-0.2
Red blood cells (K/mm^3)	4.41	4.10-5.10
Hemoglobin (g/dL)	13.1	12.3-15.3
Hematocrit (%)	40	35.9-44.6
Platelets (K/mm^3)	208	150-450
Liver function tests		
Alkaline phosphatase (U/L)	81	45-117
Alanine aminotransferase (U/L)	42	16-61
Aspartate aminotransferase (U/L)	87	15-37
Total bilirubin (mg/dL)	0.9	0.0-1.0
Direct bilirubin (mg/dL)	0.3	0.0-0.6
Urinalysis		
Color	Yellow	Yellow
Clarity	Clear	Clear
Specific gravity	1.018	1.002-1.030
pH	5.0	5.0-8.0
Protein, urine	Trace	Negative
Glucose, urine (mg/dL)	100	Negative
Ketones, urine (mg/dL)	40	Negative
Bilirubin, urine	Negative	Negative
Leukocytes, urine	Negative	Negative
Nitrites, urine	Negative	Negative
Urobilinogen, urine (EU/dL)	0.2	≤1.0
Other		
Lactate (mmol/L)	5.0	0.5-2.0
Troponin (ng/mL)	<0.017	<0.045
Thyroid stimulating hormone (m[iU]/L)	1.28	0.40-4.50

induced adrenal crisis reported so far have occurred in patients with PAI. It is unclear if those with PAI may be at higher risk of developing adrenal crisis compared to those with secondary adrenal insufficiency. More data would be needed to compare the incidence of adrenal crisis in response to zoledronic acid between the 2 conditions.

Conclusion

Adrenal crisis as a reaction to zoledronic acid infusion in patients with AI has not been commonly reported. Further investigation is needed to quantify the frequency and risk factors for adrenal crisis in patients with AI receiving zoledronic acid. With more evidence, consideration should be given to include IV bisphosphonates among the drug induced causes of adrenal crisis in patients with underlying AI. Currently there are no guidelines on the adjustment to the steroid regimen prior to zoledronic acid therapy in patients with AI. This case suggests a possible need for increased glucocorticoid supplementation prior to zoledronic acid therapy, as well as the need for additional research and recommendations regarding preferred steroid dosing to prevent adrenal crisis in patients with AI.

Disclosure

The authors have no multiplicity of interest to disclose.

Acknowledgment

We thank the Temple University Hospital System, Department of Internal Medicine and Section of Endocrinology, Diabetes, and Metabolism.

Funding

Publication of this article was funded in part by the Temple University Libraries Open Access Publishing Fund.

References

1. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. *Lancet Diabetes Endocrinol*. 2015;3(3):216–226.
2. Dineen R, Thompson CJ, Sherlock M. Adrenal crisis: prevention and management in adult patients. *Ther Adv Endocrinol Metab*. 2019;10, 2042018819848218.
3. Alexandraki KI, Grossman A. Diagnosis and management of adrenal insufficiency. In: Feingold KR, Anawalt B, Boyce A, et al., eds. *Endotext*. MDText.com, Inc; 2000.
4. Allolio B. Extensive expertise in endocrinology. Adrenal crisis. *Eur J Endocrinol*. 2015;172(3):R115–R124.
5. Björnsdottir S, Sääf M, Bensing S, Kämpe O, Michaëlsson K, Ludvigsson JF. Risk of hip fracture in Addison's disease: a population-based cohort study. *J Intern Med*. 2011;270(2):187–195.
6. Løvås K, Gjesdal CG, Christensen M, et al. Glucocorticoid replacement therapy and pharmacogenetics in Addison's disease: effects on bone. *Eur J Endocrinol*. 2009;160(6):993–1002.
7. Lee P, Greenfield JR. What is the optimal bone-preserving strategy for patients with Addison's disease? *Clin Endocrinol*. 2015;83(2):157–161.
8. Frey KR, Kienitz T, Schulz J, Ventz M, Zopf K, Quinkler M. Prednisolone is associated with a worse bone mineral density in primary adrenal insufficiency. *Endocr Connect*. 2018;7(6):811–818.
9. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007;356(18):1809–1822.
10. Popp AW, Senn R, Curkovic I, et al. Factors associated with acute-phase response of bisphosphonate-naïve or pretreated women with osteoporosis receiving an intravenous first dose of zoledronate or ibandronate. *Osteoporos Int*. 2017;28(6):1995–2002.
11. Adami S, Bhalla AK, Dorizzi R, et al. The acute-phase response after bisphosphonate administration. *Calcif Tissue Int*. 1987;41(6):326–331.
12. Kennel KA, Drake MT. Adverse effects of bisphosphonates: implications for osteoporosis management. *Mayo Clin Proc*. 2009;84(7):632–637.
13. Tanvetyanon T, Stiff PJ. Management of the adverse effects associated with intravenous bisphosphonates. *Ann Oncol*. 2006;17(6):897–907.
14. Dalle Carbonare L, Zanatta M, Gasparetto A, Valenti MT. Safety and tolerability of zoledronic acid and other bisphosphonates in osteoporosis management. *Drug Healthc Patient Saf*. 2010;2:121–137.
15. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101(2):364–389.
16. Smans LCCJ, Van der Valk ES, Hermus ARMM, Zelissen PMJ. Incidence of adrenal crisis in patients with adrenal insufficiency. *Clin Endocrinol*. 2016;84(1):17–22.
17. Smrecnik M, Kavcic Trsinar Z, Kocjan T. Adrenal crisis after first infusion of zoledronic acid: a case report. *Osteoporos Int*. 2018;29(7):1675–1678.
18. Billington EO, Horne A, Gamble GD, Maslowski K, House M, Reid IR. Effect of single-dose dexamethasone on acute phase response following zoledronic acid: a randomized controlled trial. *Osteoporos Int*. 2017;28(6):1867–1874.
19. 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):663–670.