Potassium Supplementation to Prevent Severe Hypokalemia and Paralysis after High-Dose Methylprednisolone for Ophthalmopathy in Uncontrolled Graves Disease: A Case Report

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Can J Hosp Pharm. 2022;75(3):231-3 https://doi.org/10.4212/cjhp.3145

INTRODUCTION

Graves disease, the most common cause of hyperthyroidism, is an autoimmune disorder in which thyroid-stimulating immunoglobulins or thyroid-stimulating hormone receptor antibodies cause excessive production and systemic release of thyroid hormones.[1] Common pathognomonic signs include diffuse goitre and ophthalmopathy. The latter will manifest in 25%–40% of patients affected with Graves disease.[1,2] Symptoms usually include inflammation, exophthalmos or periorbital edema, blurred vision, diplopia, and reduced perception of colour. The treatment of ophthalmopathy will depend on its severity, the goal being to preserve sight.[1,2] Conservative treatment with topical lubricant to maintain moisture of the ocular surface and restoration of euthyroidism is recommended for patients with mild to moderate symptoms. In severe cases, IV corticosteroids are considered the mainstay of treatment.[2] The standard regimen is usually methylprednisolone 500 mg IV weekly for 6 weeks, followed by 250 mg weekly for another 6 weeks. Higher doses can be used in more severe cases.[3]

Serious adverse effects associated with the use of high-dose corticosteroids in uncontrolled Graves disease include hepatic toxicity, cardiovascular and cerebrovascular events, and rarely thyrotoxic periodic paralysis (TPP). TPP is characterized by the abrupt onset of severe hypokalemia-induced paralysis, with a reported incidence of approximately 2% in Asian populations and an uncertain incidence in Western populations.[4,5] The proposed mechanisms for this reaction are associated with increased expression and activity of sodium–potassium (Na/K) ATPase by both glucocorticoids and thyroid hormones, leading to intracellular shift as well as renal excretion of K.[6] Other mechanisms potentially contributing to an increase in Na/K ATPase activity are an increase in the number and sensitivity of β receptors, which causes catecholamine-mediated K uptake, as well as an increase in androgen levels, the latter being characteristically seen in males.[5,7] Notably, TPP can occur in a thyrotoxic state with or without administration of glucocorticoids, and it is usually reversible with K supplementation.[7-9] It is unclear whether pre-emptive K supplementation and close monitoring of K levels following high-dose corticosteroid use could be beneficial to prevent this adverse event.

We present here a case of severe hypokalemia and paralysis following the use of high-dose methylprednisolone for treatment of ophthalmopathy associated with uncontrolled Graves disease, in which K supplementation was pre-emptively added for the rechallenge.[3]

CASE REPORT

A 29-year-old Thai man presented to the emergency department for bilateral lower-extremity paralysis and bilateral upper-extremity paresis.* Three days before the emergency department visit, Graves disease with diplopia and moderate to severe ophthalmopathy had been diagnosed. At the time of diagnosis, free thyroxine (T4) was 50.2 pmol/L (normal range 8–20 pmol/L), thyroid-stimulating hormone was less than 0.01 mU/L (normal range 0.38–5.33 mU/L), and serum K was 4.4 mmol/L. He had no prior history of chronic illnesses and did not take any medications. He had started therapy with oral methimazole and propranolol.

For the ophthalmopathy, the patient was scheduled to receive methylprednisolone 500 mg IV weekly for 6 doses, then 250 mg weekly for 6 doses (the standard regimen). One day before the emergency department visit, he received his first dose of methylprednisolone at 0900. No reaction occurred during the infusion. At midnight, he experienced

*The patient provided verbal consent for publication of this case report, in accordance with hospital regulations, and his consent was documented in the medical file.

sudden and brief paralysis of his lower extremities while walking, which led to a fall. The paralysis resolved after a few minutes, and he was able to get up and go back to bed. When he woke up the next morning, at 1100, his lower extremities were paralyzed, and his upper extremities were limited in flexion. Emergency services were called, and he was brought to the emergency department that afternoon. Internal medicine and endocrinology were consulted. Laboratory examination showed that serum K level was 1.9 mmol/L and serum creatinine kinase 559 U/L (normal range 30–213 U/L). The results of all other laboratory investigations, including renal function, were normal. Neuromuscular examinations showed lower limb symmetry. He was given potassium chloride (KCl) as an IV bolus (10 mEq over 1 hour), followed by an IV drip (KCl 40 mEq/L at a decreasing infusion rate over 16 hours). His serum K returned to normal, and the paralysis and weakness resolved in less than 24 hours, with no other recurrence.

The patient was scheduled for a rechallenge with methylprednisolone 500 mg IV on an internal medicine unit 1 week later, with planned oral K supplementation. Before the rechallenge, serum K was 3.4 mmol/L and creatinine kinase 43 U/L. T4 was 16.3 pmol/L and thyroid-stimulating hormone less than 0.01 mU/L. The first planned 20 mmol oral KCl tablet was given at the beginning of the infusion. Four hours later, serum K was 4.6 mmol/L, at which time the second planned 20 mmol oral KCl tablet was given. An additional dose of 20 mmol was prescribed to be given the same night, about 11 hours after the start of the infusion. An hour after the last KCl dose, serum K was 4.7 mmol/L. The next day, serum K was 4.3 mmol/L at 0700 and 3.7 mmol/L at 1200 (noon). The patient was discharged with a prescription for K 20 mEq oral tablets to be taken at 1000, 1500, and 2200 on the days of methylprednisolone administration. He was able to complete the treatment without recurrence of TPP or other adverse effects.

DISCUSSION

This report describes a patient with uncontrolled Graves disease who presented with paralysis of the lower extremities and paresis of the upper extremities associated with severe hypokalemia following administration of high-dose methylprednisolone, who received pre-emptive K supplementation for the rechallenge. The administration of methylprednisolone was considered safe with planned oral KCl supplementation consisting of 3 separated doses of 20 mmol each, given over a period of 12 hours around the infusion. A Naranjo score of 6 was obtained for this case, indicating probable causality between administration of methylprednisolone and onset of severe hypokalemia in the context of hyperthyroidism as seen in Graves disease.

Similar cases have been described in the literature.[10-12] Most of these involved young men of Asian descent presenting to the emergency department with abrupt onset of severe paralysis of the lower limbs or all limbs. Laboratory investigations revealed underlying uncontrolled thyrotoxicosis and severe hypokalemia resulting in the diagnosis of TPP, which likely also explains this patient's severe hypokalemia-related paresis.

TPP is due to a transcellular K shift related to increased Na/K ATPase activity in skeletal muscle, due to direct stimulation by thyroid hormone. However, history of the present illness in this patient revealed prior administration of high-dose IV glucocorticoids within 24 hours of symptom onset, which could also have induced hypokalemia-related paresis. Interestingly, glucocorticoids may also increase the Na/K ATPase pool, through steroid-induced hyperinsulinemia (which also stimulates Na/K ATPase action), and by increasing renal K loss.[6] The combination of these mechanisms may explain the severity of the hypokalemia observed in this case. In fact, this hypothesis is supported by the maintenance of normal serum K levels despite rechallenge with high-dose IV corticosteroid by pre-emptive KCl supplementation and a concurrent decrease in T4 levels following methimazole initiation.

Despite the rarity of TPP, health care providers should keep it in mind as a possible complication of Graves disease, and should be aware that concurrent high-dose methylprednisolone administration could further increase the risk of severe hypokalemia-associated paresis. Close monitoring of serum K levels should be considered for these patients. Because severe hypokalemia often occurs within hours of methylprednisolone administration, an overnight hospital stay might also be considered.[9,13] It is unclear whether pre-emptive K supplementation should be prescribed to prevent TPP following the use of high-dose corticosteroids. Data supporting K supplementation in the absence of deficiency are currently unavailable. Although the pre-emptive K supplementation was given only from the second dose of methylprednisolone, at which point T4 levels had greatly declined, we observed maintenance of normal serum K levels in a patient predisposed to TPP in whom T4 levels were still elevated. Therefore, we propose that for this particular case, pre-emptive KCl supplementation and close serum K monitoring might have been beneficial to the patient from the first use of high-dose IV corticosteroid, given his thyrotoxic state. Furthermore, some patients may require high-dose methylprednisolone for other medical conditions or less severe ophthalmopathy. If so, postponing methylprednisolone until normal T4 levels are achieved might be considered if the ophthalmic condition allows it.

CONCLUSION

We have reported a case of TPP in which pre-emptive K supplementation was effective in preventing hypokalemia caused by high-dose methylprednisolone administered for

ophthalmopathy associated with uncontrolled Graves disease. In light of the existing literature and the case reported here, we conclude that pre-emptive K supplementation and close serum K monitoring could be beneficial following the administration of high-dose corticosteroids in patients presenting in a thyrotoxic state. Moreover, delaying corticosteroid use until T4 levels have normalized could be considered if the clinical situation allows.

References

1. Kravets I. Hyperthyroidism: diagnosis and treatment. *Am Fam Physician*. 2016;93(5):363-70.
2. Ginsberg J. Diagnosis and management of Graves' disease. *CMAJ*. 2003; 168(5):575-85.
3. Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, et al. The 2016 European Thyroid Association/European Group on Graves' orbitopathy guidelines for the management of Graves' orbitopathy. *Eur Thyroid J*. 2016;5(1):9-26.
4. Lam L, Nair RJ, Tingle L. Thyrotoxic periodic paralysis. *Proc (Bayl Univ Med Cent)*. 2006;19(2):126-9. Available from: https://pubmed.ncbi.nlm.nih.gov/16609738/
5. Siddamreddy S, Dandu VH. Thyrotoxic periodic paralysis. In: *StatPearls*. StatPearls Publishing; 2020 [updated 2020 Jul 26; cited 2021 Feb 15]. Available from: https://pubmed.ncbi.nlm.nih.gov/32809505/
6. Lin SH, Huang CL. Mechanism of thyrotoxic periodic paralysis. *J Am Soc Nephrol*. 2012;23(6):985-8.
7. Miyashita Y, Monden T, Yamamoto K, Matsumura M, Kawagoe N, Iwata C, et al. Ventricular fibrillation due to severe hypokalemia induced by steroid treatment in a patient with thyrotoxic periodic paralysis. *Intern Med*. 2006;45(1):11-3.
8. Tigas S, Papachilleos P, Ligkros N, Andrikoula M, Tsatsoulis A. Hypokalemic paralysis following administration of intravenous methylprednisolone in a patient with Graves' thyrotoxicosis and ophthalmopathy. *Hormones*. 2011;10(4):313-6.
9. Manoukian MA, Foote JA, Crapo LM. Clinical and metabolic features of thyrotoxic periodic paralysis in 24 episodes. *Arch Intern Med*. 1999;159(6):601-6.
10. Affram KO, Reddy TL, Osei KM. A rare case of thyrotoxic periodic paralysis after epidural steroid injection: a case report and literature review. *Am J Case Rep*. 2018;19:1453-8.
11. Wongraoprasert S, Buranasupkajorn P, Sridama V, Snabboon T. Thyrotoxic periodic paralysis induced by pulse methylprednisolone. *Intern Med*. 2007;46(17):1431-3.
12. Polamaung W, Kongkit J, Yimnoi P, Boonchaya-Anant P, Snabboon T. Thyrotoxic hypokalemic periodic paralysis triggered by dexamethasone administration. *Acta Medica (Hradec Kralove)*. 2020;63(2):91-3.
13. Neki NS. Hyperthyroid hypokalemic periodic paralysis. *Pak J Med Sci*. 2016;32(4):1051-2.

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Competing interests: None declared.

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Funding: None received.