Propranolol-induced hyperkalemia in the management of infantile hemangioma

Huda Al-Rwebah, MBBS,[a] Rayan Alkhodair, MBBS, FRCPC, FAAD,[b] and Sultan Al-Khenaizan, MBBS, FRCPC, DABD[c]
Riyadh, Saudi Arabia

Key words: atenolol; hemangioma; hyperkalemia; propranolol; β-blocker.

INTRODUCTION

Infantile hemangioma is the most common benign vascular tumor of infancy, characterized by its distinctive clinical course of early growth followed by spontaneous regression.[1] Management of infantile hemangioma has been rapidly evolving since the serendipitous discovery of the efficacy of propranolol in 2008.[2] Propranolol, a nonselective β-blocker, was approved by the Food and Drug Administration in March 2014 for the management of infantile hemangioma.[3] Although it has an acceptable safety profile, adverse effects, such as hypotension, hypoglycemia, and bronchospasm, are well known.[4] Furthermore, propranolol-induced hyperkalemia is a rare, potentially life-threatening adverse effect, which was not clearly recognized in the cardiology literature but has been noted in the pediatric dermatology literature.[5-7]

CASE REPORT

A 4-month-old preterm male infant born at 36 weeks' gestation with a birth weight of 2.2 kg was admitted to the hospital with an ulcerated infantile hemangioma measuring 5 × 6 cm on the upper portion of his chest (Fig 1, *A*). He began receiving oral propranolol at 0.5 mg/kg/day divided 3 times a day, which was gradually increased during 4 days to reach 2 mg/kg divided 3 times a day. Four days after initiation of propranolol, he started to develop severe hyperkalemia that was resistant to multiple dose adjustments of propranolol. Hyperkalemia was incidentally detected by the primary team on routine blood investigation to monitor for hypoglycemia. Serum potassium level was initially 5.9 mmol/L and reached 7.3 mmol/L. Propranolol was discontinued and management of hyperkalemia was initiated, including nebulized salbutamol, intravenous fluids, furosemide, and oral sodium polystyrene sulfonate. Two days later, serum potassium levels decreased to 3.7 mmol/L, so propranolol was resumed at a dose of 1 mg/kg divided 3 times a day, but the next day, serum potassium level reached 6.27 mmol/L; therefore, propranolol was discontinued.

Throughout the hyperkalemia episodes, the patient was asymptomatic, with normal blood pressure, vital signs, and electrocardiogram results. Serum potassium level was obtained daily, with the highest one being 7.3 mmol/L. True hyperkalemia was confirmed with repeated nonhemolyzed blood samples obtained from both serum and plasma. Urine output was normal, with a high potassium level (73 mmol/L) and low urine osmolality (70 mOsm/kg). He had normal renal function, serum sodium levels, and serum osmolality, with no evidence of metabolic acidosis. Uric acid level was 215 μmol/L (reference range 120-320 μmol/L), serum phosphate level was 2.04 mmol/L (reference range 1.15-2.15 mmol/L), and serum calcium level was 2.68 mmol/L (reference range 2.25-2.75 mmol/L), ruling out tumor lysis syndrome. A high renin level of 284.7 μIU/mL (reference range: 1-hour supine position 4.2 to 59.7 μIU/mL; 2-hour upright sitting position 5.3 to 99.1 μIU/mL), high aldosterone level of

From the Division of Dermatology, Department of Medicine, King Abdulaziz Medical City, Riyadh[a]; the Division of Pediatric Dermatology, Department of Pediatrics, King Abdullah Specialist Children's Hospital, King Saud Bin Abdulaziz University for Health Sciences[b]; and Division of Pediatric Dermatology, Department of Pediatrics, King Abdullah Specialist Children's Hospital, Riyadh.[c]

Funding sources: None.
Conflicts of interest: None disclosed.

Correspondence to: Rayan Alkhodair, MBBS, FRCPC, FAAD, Division of Pediatrics Dermatology, King Saud Bin Abdulaziz University for Health Sciences, PO Box 3660, Riyadh 11481, Kingdom of Saudi Arabia. E-mail: khodairr@ksau-hs.edu.sa.

JAAD Case Reports 2020;6:359-61.
2352-5126

https://doi.org/10.1016/j.jdcr.2020.01.028

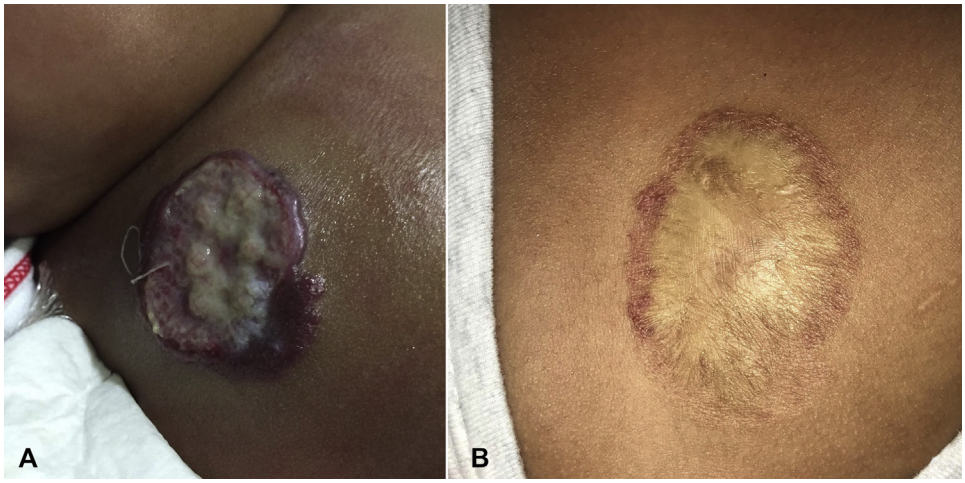

Fig 1. A, Ulcerated infantile hemangioma measuring 5 × 6 cm on the upper portion of the chest before treatment. **B**, Infantile hemangioma completely resolved with only a scar 6 months after initiation of atenolol therapy.

48 ng/dL (reference range: 1-hour supine position <31.0 ng/dL; 2-hour upright sitting position <43.2 ng/dL), normal renin/aldosterone ratio, normal cortisol level, and normal adrenocorticotrophic hormone level ruled out hypoaldosteronism caused by adrenal pathology. The patient was not receiving any other medications, and no history of hyperkalemia was documented. According to our nephrology and endocrinology colleagues, there were no identified renal or endocrine causes of hyperkalemia and no detectable causes of impaired potassium excretion or potassium extracellular shifting, and, in accordance with these findings, propranolol was thought to be the likely cause.

Two days after discontinuation of propranolol, atenolol was introduced as an alternative treatment at 1 mg/kg/day, with no evidence of hyperkalemia, hypotension, or hypoglycemia. The patient was discharged home with normal serum potassium level after being observed for 4 days. On 1-week follow-up, the serum potassium level was 4.8 mmol/L. During the next 6 months, the serum potassium level remained normal; the infantile hemangioma completely regressed, leaving a scar, and atenolol was finally discontinued (Fig 1, *B*).

DISCUSSION

Since it was serendipitously discovered by Léauté-Labrèze et al[2] in 2008, systemic propranolol has been widely used for the management of infantile hemangiomas. Incidence of propranolol-related intolerable adverse effects is approximately 2.1%.[8] The most serious adverse events from propranolol use include atrioventricular block, bradycardia, hypotension, hypoglycemia, and bronchospasm.[4] Moreover, propranolol-induced hyperkalemia is a rare, potentially life-threatening adverse effect and has been reported.[5-7] It was first reported by Pavlakovic et al[5] in a 4-month-old preterm infant who presented with an ulcerated hemangioma on the chest wall. In 2012, propranolol-induced hyperkalemia was reported again by Cavalli et al[6] in a 1-month-old female infant who developed hyperkalemia and hyperphosphatemia 1 day after initiation of oral propranolol for an ulcerated infantile hemangioma over the upper lip. Tumor lysis syndrome, which was linked to oral propranolol treatment, was diagnosed after exclusion of other causes of electrolyte abnormalities. In 2014, hyperkalemia was reported in a 2-year-old male infant known to have intestinal hemangiomatosis.[7] In previously reported cases, oral propranolol therapy was continued because neither electrocardiographic changes nor clinical manifestation of hyperkalemia was noted.[5-7] In contrast, our patient's serum potassium level reached 7.3 mmol/L, which was higher than the previously reported values, and it was persistently high despite several dose adjustments. Fortunately, the cessation of propranolol resulted in a complete normalization of serum potassium level and the use of atenolol resulted in a significant improvement in the ulcerating hemangioma.

The mechanism of propranolol-induced hyperkalemia is thought to be related to the impaired cellular uptake of potassium caused by the reduced sodium-potassium adenosine triphosphatase function, which is primarily mediated through β2-receptor blockage.[9,10] Unlike propranolol,

atenolol has a higher affinity for β1-adrenergic receptors, and it is classified as a selective β1-blocker, which explains the use of atenolol as an alternative therapy for our patient.

Hyperkalemia is also thought to be linked to propranolol-induced abrupt cell lysis, which results in further release of intracellular potassium.[5,6] Moreover, one of the most recognized effects of β-blockers on renal function is their long-term inhibition of renin activity, which results in the suppression of aldosterone release and the subsequent increase in serum potassium level.[11]

In conclusion, propranolol has been widely used for years in dermatology as the first-line treatment of infantile hemangioma. Multiple studies have demonstrated propranolol efficacy, overall good safety profile, and low risk of intolerable adverse effects.[4,8] Propranolol-induced hyperkalemia is an unexpected, potentially life-threatening adverse effect that has been reported in patients with large or ulcerated infantile hemangiomas.[5-7] This case report adds more evidence to the recent literature in regard to this rare serious adverse event, and we propose the use of atenolol as an alternative treatment for patients with propranolol-induced hyperkalemia. There are no guidelines so far recommending serum potassium-level check after initiation of oral propranolol for patients with infantile hemangioma, but we aim to raise the awareness about this potentially serious adverse event and alert dermatologists about its occurrence. Because of the asymptomatic nature of hyperkalemia and its potential for devastating sequelae, further prospective research is needed to investigate its actual prevalence and associated risk factors.

REFERENCES

1. Drolet BA, Esterly NB, Frieden IJ. Hemangiomas in children. *N Engl J Med*. 1999;34:173-181.
2. Léauté-Labrèze C, De la Roque ED, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. *N Engl J Med*. 2008; 358:2649-2651.
3. Fabre Pierre. Pierre Fabre obtains FDA approval to market Hemangeol for the treatment of infantile hemangioma. Available at: http://www.pierre-fabre.com/en/fda-approval-market-hemangeoltm. Accessed December 18, 2016.
4. Léaute-Labrèze C, Boccara O, Degrugillier-Chopinet C, et al. Safety of oral propranolol for the treatment of infantile hemangioma: a systematic review. *Pediatrics*. 2016;138(4): e20160353.
5. Pavlakovic H, Kietz S, Lauerer P, et al. Hyperkalemia complicating propranolol treatment of an infantile hemangioma. *Pediatrics*. 2010;126:e1589-e1593.
6. Cavalli R, Buffon RB, de Souza M, et al. Tumor lysis syndrome after propranolol therapy in ulcerative infantile hemangioma: rare complication or incidental finding? *Dermatology*. 2012; 224:106-109.
7. Belen B, Oguz A, Okur A, et al. A complication to be aware of: hyperkalaemia following propranolol therapy for an infant with intestinal haemangiomatosis. *BMJ Case Rep*. 2014;2014: bcr2014203746.
8. Ji Y, Chen S, Wang Q, et al. Intolerable side effects during propranolol therapy for infantile hemangioma: frequency, risk factors and management. *Sci Rep*. 2018;8(1):4264.
9. Rosa RM, Silva P, Young JB, et al. Adrenergic modulation of extrarenal potassium disposal. *N Engl J Med*. 1980;302(8): 431-434.
10. Reid JL, Whyte KF, Struthers AD. Epinephrine-induced hypokalemia: the role of beta adrenoceptors. *Am J Cardiol*. 1986; 57(12):F23-F27.
11. Weber MA, Drayer JI. Renal effects of beta-adrenoceptor blockade. *Kidney Int*. 1980;18:686-699.