JPPT | Case Report

Temperature Instability in an Infant Treated with Propranolol for Infantile Hemangioma

Betsy Walters Burkey, PharmD; Joshua A Jacobs, PharmD; and Hany Aziz, MS, MD

Infantile hemangiomas are prevalent in the first few months of life and can be associated with risks of scarring, blindness, ulcerations, and airway obstruction depending on the location of lesions. Options for therapy include surgery, laser therapy, or medications. Propranolol is the only US Food and Drug Administration–approved medication option. Propranolol is a nonselective beta-blocker that crosses the blood-brain barrier because of its high lipophilicity, which increases the likelihood of central nervous system effects. In this case, a preterm infant developed infantile hemangiomas on the left forearm, left trunk, left buttock, and nasal tip. The patient was treated with propranolol and concurrently required placement into a heated incubator and was subsequently unable to wean from the incubator. Upon discontinuation of propranolol, temperature instability resolved. Atenolol, a cardioselective beta-blocker that does not cross the blood-brain barrier, was then initiated for the infantile hemangiomas and displayed no adverse effect on the thermoregulation of the infant.

ABBREVIATIONS ADR, adverse drug reaction; AxT, axillary temperature; cGA, corrected gestational age; CNS, central nervous system; EvT, environmental temperature; IH, infantile hemangioma; NICU, neonatal intensive care unit

KEYWORDS adverse drug reaction; infantile hemangioma; propranolol; atenolol; temperature instability

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Introduction

Infantile hemangiomas (IHs) are characterized as benign lesions of the vascular endothelium that tend to rapidly grow prior to birth, just after birth, or up to the first few weeks of life. Approximately 1% to 2% of babies born will have IH, with increasing prevalence in the first year of life.[1] Also, preterm neonates and females have an increased risk of formation, with lesions appearing most frequently on the head or neck. The clinical course ranges from spontaneous resolution to more severe cases, such as blindness, permanent scarring, and ulceration. In particular, hemangiomas that appear on the nasal tip are prone to nasal obstruction and carry a significant risk for facial disfiguration that is difficult to restructure.[2] Treatment, which includes medications, surgery, and laser therapy, is warranted for severe cases of IH that may impair functionality.

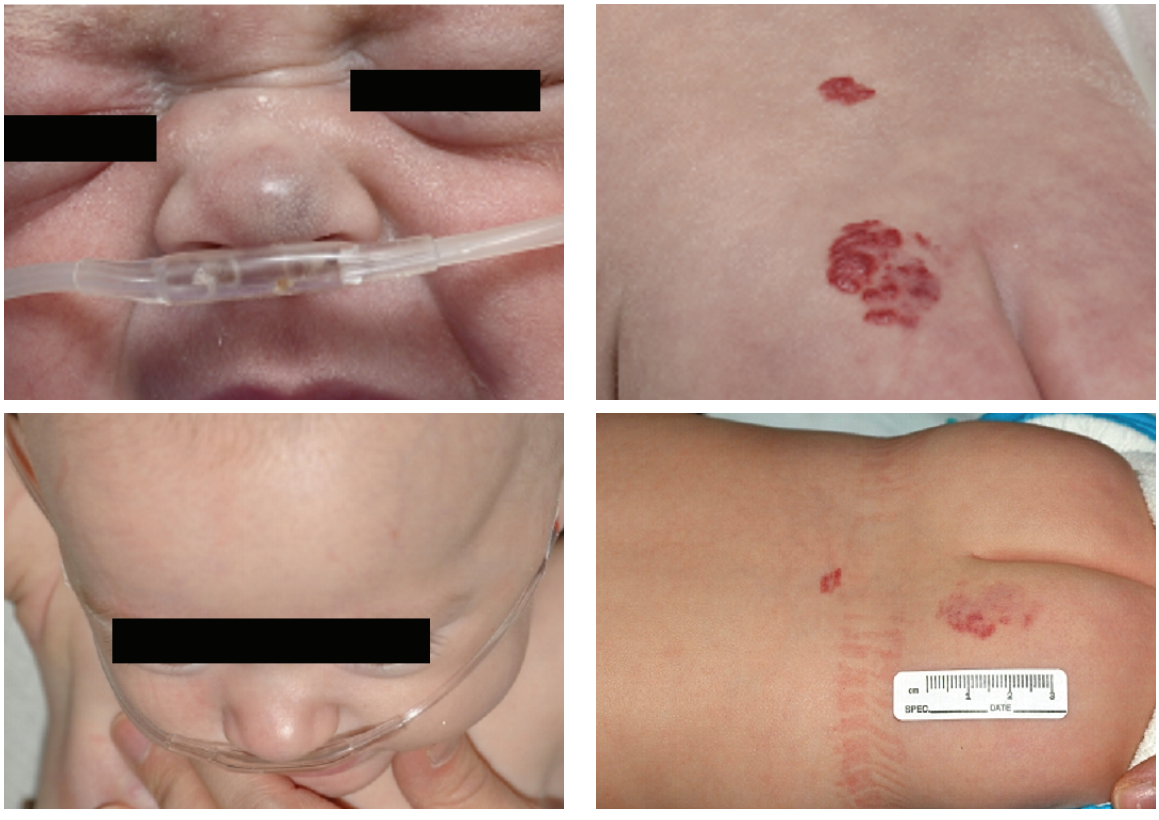
When medications are used, propranolol is the first-line agent because it is the only US Food and Drug Administration–approved medication for IH. The mechanism of action for propranolol use in IH is unclear, but it is theorized to cause suppression of angiogenesis factors via decreased cyclic adenosine monophosphate production and other angiogenesis components, such as matrix metalloproteinase 9, vascular endothelial growth factor, and basic fibroblast growth factor.[3] Common adverse effects with propranolol use are bradycardia, hypotension, hypoglycemia, lethargy, difficulty breathing, and cool, clammy skin. Although cool extremities have been seen with propranolol use, these reported adverse events are likely due to the peripheral vasodilatory properties of propranolol.[4,5] Propranolol is a nonselective beta-blocker, inhibiting both β_1 receptors (primarily myocardium) and β_2 receptors (adipose tissue, pancreas, liver, and smooth muscle). Selective beta-blockers, such as atenolol and metoprolol, are cardioselective by only inhibiting β_1 receptors.

Case

The patient was a 25 1/7-week premature twin girl born by cesarean section. The clinical course in the neonatal intensive care unit (NICU) was significant for respiratory distress syndrome, hyperbilirubinemia, apnea of prematurity, possible sepsis, elevated alkaline phosphatase, feeding problems, and retinopathy of prematurity. After 10 weeks of appropriate therapies in the NICU, the patient was stabilized in an open bassinette.

During week 7 of life, hemangiomas were noted on physical assessment on the left forearm, left trunk, left buttock, and nasal tip. Figure 1 demonstrates the appearance of these skin lesions before the introduction of any IH medications. The patient was in an open bassinet for 12 days prior to the initiation of therapy, with an average axillary temperature (AxT) of 36.7°C and average environmental temperature (EvT) of 23.5°C

Figure 1. Hemangioma lesions associated with beta-blocker therapy. "Cryano nose" (also called Pinocchio nose) is displayed on the left. Images on the right are the 2 lesions on the back and left buttock. Upper pictures are hemangioma lesions prior to propranolol initiation. Lower pictures are hemangioma lesions 3 months after atenolol initiation.



(Figure 2). AxT and EvT are obtained and charted with every "care" time for the infant, which is generally every 3 to 4 hours. When the axillary temperature falls below the minimum value of 36.5°C, the infant is rechecked every hour and the EvT is increased by 0.5°C to 1.0°C until the AxT is 36.5°C to 37.2°C. At 36 5/7 weeks corrected gestational age (cGA) propranolol was initiated at a dose of 0.7 mg orally every 8 hours (1 mg/kg/day). After 3 days of therapy, the AxT declined to an average of 36.4°C, and the patient had to be placed back into a heated incubator.

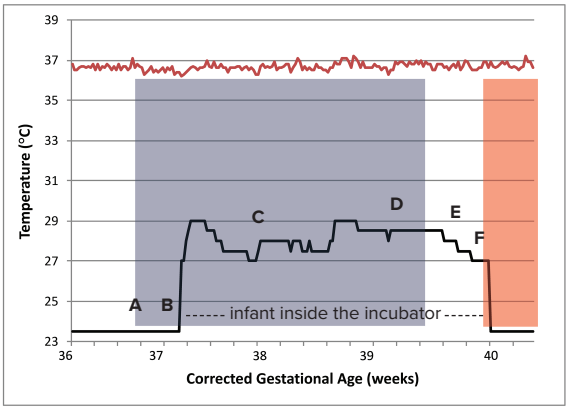
On day 4, the dose of propranolol was increased to 1.4 mg orally every 8 hours (2 mg/kg /day), with an incremental increase in the EvT from 27.5°C to 29.0°C needed to maintain an adequate AxT. Multiple attempts to wean the patient from the incubator were unsuccessful. The managing team excluded other possible causes of the infant's temperature instability, including environmental temperature, equipment malfunction, sepsis, and current gestational age. Even after a reduction in dose by returning to 0.7 mg orally every 8 hours on day 13 of therapy, the temperature instability continued. During propranolol therapy the average AxT was 36.6°C, and the EvT was, on average, 28.0°C.

Ultimately, propranolol was discontinued on day 19 of therapy. Upon consultation with pediatric cardiology, atenolol 0.7 mg (0.5 mg/kg/day) was initiated at a cGA of 39 5/7 weeks, and it was shortly titrated to a dose of 1.4 mg orally twice daily (1 mg/kg/day). After this change, the patient was weaned out of the incubator and stabilized at an AxT of 36.8°C, with an average EvT of 23.8°C. A baby in the NICU will be transitioned from an incubator to a bassinette if the EvT is ≤27.0°C for 24 hours while his or her AxT is stable at 36.5°C to 37.2°C. The patient was discharged home on day of life 104 (40 1/7 weeks cGA), and outpatient follow-up continued to show improvement of the hemangiomas while on atenolol, as seen in Figure 1.

Discussion

Temperature instability has been a rarely recognized adverse effect of beta-blocker therapy in infants, and the evidence of this phenomenon was found with topical timolol (also a nonselective beta-blocker) in IH and congenital glaucoma. One case report exists describing potential hypothermia in patients receiving

Figure 2. Temperature of Infant and Environment During IH Treatment. Axillary temperatures (AxT) denoted in the red line, and environmental temperature (EvT) denoted in the green line. Blue areas denote time when propranolol was being used to treat the IH; red areas denote times when atenolol was used; areas of no color denote the times when no pharmacologic agent was being used. A, Propranolol initiated at 0.7 mg every 8 hrs; B, Propranolol increased to 1.5 mg every 8 hrs; C, Propranolol decreased to 0.7 mg every 8 hrs; D, Propranolol discontinued; E, Atenolol initiated at 0.7 mg every 12 hrs; and F, Atenolol increased to 1.4 mg every 12 hrs.



topical timolol, an alternative treatment for IH.[6] This report describes the potential side effect and possible mechanisms of temperature instability in a premature infant while on topical timolol and subsequently oral propranolol. Also, it supports the emerging treatment of atenolol for IH.

The most common medication therapy for IH is propranolol. The typical dosage regimen is as follows: 0.6 mg/kg twice daily for week 1, 1.1 mg/kg twice daily for week 2, and 1.7 mg/kg twice daily for at least 6 months.[7] Treatment is contraindicated at a corrected age of less than 5 weeks for a term infant and infants weighing less than 2 kg, although no specifications are placed upon the baseline age from which this stipulation is measured in the package insert. Based on a recent randomized trial, treatment success was seen in approximately 38% and 63% of patients treated with propranolol 1 mg/kg/day and 3 mg/kg/day for 6 months, respectively.[8] Within this trial, common side effects were diarrhea, sleep disorders, bronchitis, and even cold hands and feet (1%–10%). Also, a meta-analysis consisting of 324 IH patients compared propranolol and other treatment strategies. Results demonstrated improved efficacy with propranolol compared with other strategies (odds ratio, 9.67; 95% confidence interval, 6.62 – 14.12; $p < 0.001$).[9]

Although propranolol is a first-line treatment, an emerging use of atenolol is showing positive resolution of IH. Studies have shown similar clinical resolutions with atenolol compared with propranolol. One study concluded a 53.8% clinical resolution for atenolol and a 60% resolution for propranolol.[10] Another resulted in 90% clinical involution for atenolol and 100% clinical involution for propranolol.[11] Although these studies were limited in sample size and varied among clinical presentation, the results illustrated clinically relevant outcomes for atenolol. The comparison of the 2 trials can be seen in the Table.

Two possible mechanisms exist regarding the adverse temperature effect seen in propranolol. The first is derived from the centrally acting properties of the medication. Propranolol crosses the blood-brain barrier because of its lipophilic properties, with a volume of distribution of approximately 4 L/kg.[7] Studies in rats illustrate that lipophilic beta-adrenergic antagonists inhibit stress fevers in the central nervous system (CNS), therefore preventing thermoregulation. This mechanism is thought to relate to the nonspecific inhibition of both β_2 and β_3 adrenergic receptors.[12] Propranolol is both highly lipophilic and nonselective, leading to this possible mechanism. This CNS adrenergic mechanism could be seen in humans, ultimately leading to the temperature instability effect of propranolol in this patient.

In addition to the possible CNS activity, another potential mechanism originates from the adrenergic effect on brown adipose tissue. Brown adipose tissue, which is controlled by the adrenergic pathway, is predominantly used for thermogenesis and regulation.[13] Propranolol, which is a nonselective beta blocker, has the ability to inhibit β_2 receptors found on the brown

Table. Study Comparison for Propranolol and Atenolol Use in Infantile Hemangiomas

Study	Patient Population	Interventions	Results
Ábarzúa-Araya et al[10]	Infants 1–15 mo of age (n = 23)	Atenolol 1 mg/kg/day (n = 13) Propranolol 2 mg/kg/day (n = 10)	Clinical resolution after 6 mo: atenolol 7 of 13 (53.8%); propranolol 6 of 10 (60%)
De Graaf et al[11]	Infants with potentially life threatening or posed a functional or anatomic risk (n = 58)	Atenolol 0.5 mg/kg/day to 3 mg/kg/day (n = 10) Propranolol 2 mg/kg/day (n = 28)	Clinical involution after 2 wk: atenolol 27 of 30 (90%); propranolol 28 of 28 (100%)

adipose tissue. Theoretically, inhibition of the β adrenergic pathway, especially in a premature infant, could dysregulate the role of brown adipose tissue thermogenesis, ultimately leading to temperature instability. As described in the case, this infant was born prematurely at 25 weeks and 1 day, and propranolol was initiated 2 days before the cGA of 37 weeks. Thermoregulation through brown adipose tissue is crucial to the survival of a preterm infant; this proposed mechanism of action for propranolol could suppress the adrenergic activity that stimulates crucial brown adipose tissue.

In the case of this infant, propranolol has multiple factors that contribute to the likely causality for the adverse effect seen. Using the Naranjo adverse drug reaction (ADR) probability algorithm, this case is categorized as a probable ADR.[14] It is unlikely that CNS maturity played a role in this, because the patient was stable in an open bassinet for almost 2 weeks prior to the initiation of propranolol, and no other possible cause was identified. Although the temperature of 36.4°C (0.1 degree lower than normal range) may appear insignificant, this value results in the inability to wean infants from the heated incubator, and as the dose was titrated up the incubator temperature also needed to be increased to maintain the infant's temperature within the normal range. Temperature regulation in the neonate (while maintaining the ability to grow at necessary velocity) is one of the final and most important criteria for discharge from the NICU. If a patient cannot thermoregulate effectively, prolonged length of stay and/or growth failure can occur.

This case illustrates that propranolol has the potential to cause temperature instability through multiple mechanisms in an infant. It also emphasizes the emerging role of atenolol for the treatment of IH. Atenolol is a selective β_1 adrenergic inhibitor with low lipophilicity. Without the ability to cross the blood-brain barrier, the likelihood of β receptor inhibition in the CNS is low. Additionally, β_1 receptors are not located on brown adipose tissue, which further reduces the chance of a temperature instability adverse event being present with the use of atenolol.

In conclusion, propranolol has the pharmacology to potentially cause thermodysregulation. Alternatively, atenolol lacks the central and β_2 adrenergic activity of propranolol, while still displaying positive results in the treatment of IH. As more studies become available with atenolol for IH, this side effect should be followed to further support this case observation.

ARTICLE INFORMATION

Affiliations Department of Pharmacy, Fairview Hospital/Cleveland Clinic Children's Hospital, Cleveland, Ohio (JAJ; BWB); Department of Neonatology, Cleveland Clinic Children's Hospital, Cleveland, Ohio (HA)

Correspondence Betsy Walters Burkey, PharmD; bwaltersrph@yahoo.com

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