OBSERVATION

Hypoglycemia in Children Taking Propranolol for the Treatment of Infantile Hemangioma

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Background: Propranolol hydrochloride has been prescribed for decades in the pediatric population for a variety of disorders, but its effectiveness in the treatment of infantile hemangiomas (IHs) was only recently discovered. Since then, the use of propranolol for IHs has exploded because it is viewed as a safer alternative to traditional therapy.

Observations: We report the cases of 3 patients who developed symptomatic hypoglycemia during treatment with propranolol for their IHs and review the literature to identify other reports of propranolol-associated hypoglycemia in children to highlight this rare adverse effect.

Conclusions: Although propranolol has a long history of safe and effective use in infants and children, understanding and recognition of deleterious adverse effects is critical for physicians and caregivers. This is especially important when new medical indications evolve as physicians who may not be as familiar with propranolol and its adverse effects begin to recommend it as therapy.

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PROPRANOLOL HYDROCHLORIDE, a nonselective β-adrenergic blocking agent, has been used for years in infants and children with congenital heart disease, arrhythmias, hypertension, thryotoxicosis, migraines, and behavioral disorders. It has recently been used in the treatment of infantile hemangiomas (IHs) after growth arrest of an infant's hemangioma was incidentally noted when propranolol was started for obstructive hypertrophic myocardiopathy.[1] Given the lack of evidence-based standards for treatment of complicated IHs combined with the risks of other accepted systemic therapies (corticosteroids, vincristine sulfate, interferon), the use of off-label propranolol for IHs has skyrocketed because it is viewed as having a lower adverse-effect profile.

We describe 3 children receiving treatment with oral propranolol for IHs who experienced life-threatening events in association with hypoglycemia and hypothermia. Our purpose is to highlight this idiosyncratic reaction and increase awareness for both the prescribing physician and the emergent care provider who may be caring for the child in an acute setting.

REPORT OF CASES

CASE 1

A healthy 11-month-old girl presented with an unresectable, vision-threatening IH on the upper eyelid. She was started on oral propranolol suspension (20 mg/5 mL), titrating up from 0.3 mg/kg/d to 2 mg/kg/d over a 12-day period. She was taking no other medications and had no history of hypoglycemia. She reached a dose of 2 mg/kg/d divided every 8 hours and was taking that dose without interruption for 3 weeks. The night before hospitalization she was fussy but was otherwise well and ate a normal dinner. On the day of the event she ate breakfast and had no fever, nausea, vomiting, or diarrhea. Because of fussiness she received 1 dose of ibuprofen and a small amount of benzocaine gel to her gums for teething. Two hours after receiving her morning dose of propranolol she became pale, cold, clammy, and increasingly unresponsive, and her father called 911. She was taken by paramedics to the hospital and given intravenous (IV) fluids before arrival at the emergency department (ED). She had an axillary temperature of 34°C in transit. In the ED, her temperature was 36°C, her pulse was 83 beats per minute (bpm), and her blood pressure (BP) was 92/65 mm Hg. Her glucose level was 55 mg/dL. (To convert glucose to millimoles per liter, multiply by 0.0555.) She was rapidly revived with glucose-containing IV and oral fluids. Findings from a computed tomographic scan of the head were normal. She was discharged from the hospital within 24 hours and has done well off all medications, with no apparent sequelae or similar clinical episodes to date (10 months as of time of writing).

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CASE 2

A healthy 18-month-old girl with a nasal tip IH, previously treated with topical clobetasol propionate (at age 2-9 months) was started on propranolol for continued growth of her hemangioma. There was no history of hypoglycemia or other medications. The initial dose of propranolol hydrochloride, 0.5 mg/kg/d, divided and given twice daily, was titrated to 1 mg/kg/d over several weeks. After 2 months there was minimal change in the size of the IH, and the propranolol hydrochloride dosage was increased to 1.25 mg/kg/d, divided and given twice daily. During an intercurrent illness (fever, nausea, vomiting), propranolol was withheld. After 4 days she began eating normally, and propranolol was restarted. The day prior to hospitalization, she ate dinner at 5 PM, had propranolol at 6 PM, and went to bed. The mother found her 13 hours later in bed, cold, clammy, and unresponsive. A 10-minute seizure occurred prior to transport by ambulance to the ED. Her rectal temperature was 35.4°C, her pulse was 84 bpm, and her BP was 98/62 mm Hg. Thirty minutes after arrival, she had another seizure and was given lorazepam. Her blood glucose level was 19 mg/dL, her serum glucose level was 24 mg/dL, and her urine ketones level was 15 mg/dL. She was given 9 mL of a 25% dextrose solution intravenously, which resulted in normalization of her glucose level. She was admitted to the hospital and had no further episodes of hypoglycemia or seizures for the next 48 hours (fingerstick glucose level checked every 2-4 hours). Her organic and amino acid levels were normal.

CASE 3

A healthy 5-week-old, full-term girl presented with a nasal tip IH that was increasing in size rapidly. She was started on oral propranolol hydrochloride suspension (20 mg/5 mL) at 1 mg/kg/d and gradually titrated up to 2 mg/kg/d, divided and given 3 times daily over 4 months. She was taking no other medications and had no history of hypoglycemia. She remained on a dosage of 2 mg/kg/d for 8.5 months without adverse effects and with marked improvement in the appearance of her IH. At 10 months of age, 2.5 hours after having a normal breakfast and receiving her morning propranolol dose, she was found by her mother to be limp, pale, and breathing deeper and faster than usual. Emergency medical services were activated, and the paramedics found her to have a serum glucose level of 20 mg/dL. She was given dextrose intravenously and taken to the ED, where her rectal temperature was 38.7°C. Her parents noted that she had developed a cough and runny nose 1 day prior, but that they felt she had been eating normally. A nasopharyngeal swab for respiratory syncytial virus was taken, and the findings were positive. Findings from chest radiography were normal, and her pulse oximetry level remained above 97% on room air. She was admitted to the pediatric unit, and her propranolol hydrochloride dosing was decreased to twice daily (1.3 mg/kg/d). Albuterol nebulizer treatments and IV fluids were administered. Her blood glucose levels were stable overnight (118, 119, and 82 mg/dL), her oral intake was appropriate for her age, and she was discharged home after 1 day of hospitalization. The parents were instructed to give the propranolol only twice daily until follow-up with the dermatology and cardiology departments was arranged. She has since resumed the 3 times daily dosing of propranolol hydrochloride at 2 mg/kg/d without further difficulty.

COMMENT

Treatment of IHs is designed to control growth, minimize deformity, preserve function, and minimize psychological and emotional stress. Systemic pharmacotherapy is most often used to treat large IHs that present a surgical challenge or those causing functional or life-threatening problems. Well-designed studies evaluating the efficacy and safety of various treatments are lacking, with anecdotal reports and case series leading to currently accepted treatments. Agents traditionally used in treating IHs include oral and intralesional corticosteroids, but other treatments, such as interferon alfa and vinca alkaloids, have also been used.

Propranolol has recently been used in the treatment of IHs after improvement in color, softening, growth arrest, and even regression of an IH was incidentally noted when propranolol was started for treatment of hypertrophic myocardiopathy.[1] Since then, the use of propranolol for IHs has soared because it is viewed as having a lower adverse-effect profile than other systemic therapies used for treating IHs.[2]

Propranolol has been used in children for many years both for cardiac and noncardiac diseases. Although it has been well studied in adults, experience in infants and children has been mainly anecdotal. The most common serious adverse effects of propranolol include bradycardia and hypotension. Bronchospasm can be seen in patients with reactive airway disease. Other adverse effects include congestive heart failure, depression, nausea, vomiting, abdominal cramping, sleep disturbance, and night terrors.

The association between propranolol and hypoglycemia in infants and children is well known and is noted in the product insert. However, this adverse effect is best recognized during the neonatal period with older infants and children considered to be low risk. Because treatment of IHs is typically started outside of the neonatal period, when maintenance of euglycemia is more robust, the risk of hypoglycemia may be overlooked by prescribing physicians. To better define this risk, a literature review of hypoglycemia associated with propranolol therapy in infants and children outside of the neonatal period was performed. Twenty-one cases were identified (**Table 1**). Eleven (52%) were receiving long-term treatment (≥5 days) at doses ranging from 2 to 14 mg/kg/d. The remaining patients received propranolol adjunctively for growth hormone testing (6 patients), intraoperatively (2 patients), and through accidental overdose (2 patients). Seventeen of the 18 identified cases in which the oral intake status was known (94%) occurred after an overnight to 24-hour fast, occasionally in the setting of poor oral intake the preceding day(s). In all but 1 of the patients receiving long-term propranolol therapy, symptoms of hypoglycemia generally occurred in the morning, with a number of the children being unresponsive or unarousable when parents went to check on them in the morn-

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Table 1. Reports of Hypoglycemia Associated With Propranolol Use in Children

Source	Patient Age	Propranolol Hydrochloride Dose	Oral Intake	Symptoms	Glucose Level, mg/dL
Mackintosh[3]	9 y	2 mg intraop Reason not stated	20 h preop fast	Seizure postop	12
McBride et al[4]	2.5 y	4 mg/kg/d	Watery diarrhea 36 h prior, limited intake 24 h prior 16 h preop fast	Unresponsive in morning; seizures, cold, cyanotic, and unresponsive	13 45
Feller[5]	NS	4 mg/kg/d	Poor oral intake followed by NPO from midnight	Unconscious, pale, sweating, myoclonic jerks at 8 AM	15
	NS	4 mg/kg/d	Poor oral intake day prior	Found at 7 AM drowsy, pale, sweating	35 after oral glucose
Hesse and Pedersen[6]	20 mo	Accidental ingestion of unknown amount	Not specified	Stuporous, pale, cyanotic, sweating	14
	3 y	Accidental ingestion of unknown amount	Not specified	Drowsy, sweating	50
Kallen et al[7]	18 mo	4 mg/kg/d	Overnight fast	Unresponsive in morning	38
Pelsor et al[8]	6 children <6 y	20-40 mg adjunctively for GH testing	Overnight fast		
Artman et al[9]	4 y, 2 mo	10 mg/kg/d	Poor oral intake for 3 d		34
Zeligs and Lockhart[10]	27 mo	2 mg/kg/d for 5 d	16 h preop fast	Cool, somnolent, sweating, seizures	44 after glucose water given
Hasan et al[11]	6 mo	4 mg/kg/d	Normal oral intake	Increased somnolence 1 h after dose which improved with oral intake; seizure in ED	25
Bush and Steward[12]	4 y	0.75 mg IV in 0.25 mg divided dose intraop for tachycardia	NPO from midnight pre-op. Total fast close to 24 h	Slept all day postop; unarousable, twitching progressed to seizures at 8 PM	31
Baines and Murrell[13]	16 mo	2 m/k/d	Preop fast from midnight, poor oral intake the day prior	Sweating and lethargic, then had seizure	19.8
Chavez et al[14]	9 y	7.2 m/k/d	No comment about oral intake that morning	Confused, difficulty walking in morning; became unresponsive	27
	6 y	14 m/k/d	Overnight fast	Unarousable in morning	30

Abbreviations: ED, emergency department; GH, growth hormone; intraop, intraoperative; IV, intravenous; NPO, nil per os (nothing by mouth); postop, postoperative; preop, preoperative.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

ing. One patient receiving long-term propranolol therapy had an episode similar to those of 2 of our patients, with development of hypoglycemia, despite normal oral intake, 1 to 2 hours after propranolol was given.[11] Aside from 4 patients who proved to have a growth hormone deficiency, the patients had no known concomitant medical conditions and were not taking medications that could be implicated as the cause of the hypoglycemia. One patient experienced severe cerebral damage and epilepsy,[12] but the remainder recovered without long-term complications.

Although most of the reported patients who developed hypoglycemia were prescribed higher doses of propranolol, 2 of the 3 patients described herein were taking relatively small doses, suggesting that hypoglycemia associated with propranolol may not be dose dependent. While the mechanism by which hypoglycemia develops in some children taking propranolol is not completely understood, normal glucose homeostasis is thought to be impaired through inhibition of β-adrenergic mediated glycogenolysis, gluconeogenesis, and lipolysis. Children and infants seem to be at higher risk for this adverse effect because their glucose utilization rates are higher in the fasting state (as much as 3-fold higher in infants), attributed partly to their greater brain mass relative to their body weight.[15] In addition, glycogen stores are lower in infants and children compared with adults, leading to a reduced fasting ability. This may have been an additional factor in our second case, because glycogen stores may not have been replenished from the previous low intake illness.

Clinical manifestations of hypoglycemia in infants can vary widely:

Early, counterregulatory epinephrine effects (which may be masqueraded by β-adrenergic blockade):
- Sweating
- Shakiness
- Tachycardia
- Anxiety
- Hunger

Late, neuroglycopenia:
- Lethargy
- Stupor
- Poor feeding
- Seizures
- Apnea
- Loss of consciousness
- Hypotermia

Mild hypoglycemia produces symptoms associated with counterregulatory epinephrine action, including sweating, shakiness, tachycardia, anxiety, and hunger.[15] These may be absent or difficult to detect in infants, especially when propranolol-induced β-adrenergic blockade is present. The fussiness seen in our first patient may have reflected this early symptomatic phase. More severe hypoglycemia produces symptoms of neuroglycopenia,

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Table 2. Considerations for Theoretical Increased Risk of Adverse Effects in Patients With Infantile Hemangioma

Population	Adverse Effect	Reason for Concern
<1 y of age, particularly LBW infants	Hypoglycemia	Limited glycogen stores, inability to communicate symptoms
Patients previously treated with systemic steroids	Hypoglycemia	Muted counterregulatory cortisol response secondary to adrenal suppression
Hemangioma-related high output cardiac failure (ie, large liver hemangioma)	Decompensation of HF	Decreased heart rate/contractility limits cardiac response to high output demands

Abbreviations: HF, heart failure; LBW, low birth weight.

including lethargy, stupor, poor feeding, seizures, apnea, loss of consciousness, and hypothermia. The patients in 2 of our 3 cases had clinically significant hypothermia. Permanent neurologic damage is rare.[15]

As the use of propranolol in infants with IHs increases, physicians must be aware of the potential for hypoglycemia. While recognition of signs or symptoms of hypoglycemia may prompt early intervention, measures may be taken to decrease the risk of hypoglycemia. Propranolol should be discontinued during intercurrent illness, especially in the setting of restricted oral intake. For those whose treatment cannot be interrupted, support with glucose-containing IV fluids during perioperative periods is indicated. Preoperative blood glucose levels may identify additional patients whose symptoms might otherwise be masked by preoperative medications and anesthesia.

Particular care should be taken in using propranolol in patients prescribed other medications known to be associated with hypoglycemia or with medical conditions known to produce hypoglycemia. In a review of 1418 cases of drug-induced hypoglycemia, the most common drugs associated with hypoglycemia in patients 10 years or younger (excluding the neonatal period) were alcohol, salicylates, quinine, propranolol, and sulfonylureas (in decreasing frequency).[16]

There are theoretical considerations specific to using oral propranolol for treatment of IH (**Table 2**). Regarding hypoglycemia, most patients will be younger than 1 year, have limited glycogen stores, and a relative inability to communicate, recognize, or treat symptoms. Furthermore, low birth weight, an important risk factor for the development of IH, also confers a greater risk of hypoglycemia. Oral corticosteroids are used frequently for the treatment of IHs; during treatment, there may be some protective effect because steroids inhibit insulin action. However, after prolonged steroid use there may be residual adrenal suppression and subsequent loss of the counterregulatory cortisol response, thus increasing risk of hypoglycemia. Finally, in patients with high-output cardiac failure secondary to a large liver hemangioma, the use of propranolol could result in decompensation secondary to drug-induced suppression of heart rate and contractility. Until the safety of propranolol in these patients can be established and these theoretic concerns allayed, caution should be exercised when prescribing propranolol.

Although propranolol has a long history of safe and effective use in infants and children for the treatment of many conditions, understanding and recognition of deleterious adverse effects is critical for physicians and caregivers. This is especially important when new medical indications evolve as physicians who may not be as familiar with propranolol and its adverse effects begin to recommend it as therapy (as in the treatment of IH). Clearly outlined and safe protocols for initiation and chronic dosage should be developed in conjunction with randomized trials that document efficacy in the treatment of IH.

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