Death Associated With Nadolol for Infantile Hemangioma: A Case for Improving Safety

Eric McGillis, MD,[a] Travis Baumann, MD,[b] Jenna LeRoy, MD[a]

Nadolol is a β-adrenergic antagonist that has been shown to be efficacious in the treatment of infantile hemangioma. It has been suggested that this drug may have fewer side effects compared with the gold standard therapy, propranolol, because it does not exhibit membrane-stabilizing effects and has little ability to cross the blood-brain barrier. However, the pharmacokinetics and safety of nadolol in infants are not well understood, potentially making this therapy dangerous. β-adrenergic antagonist toxicity causes bradycardia, hypotension, hypoglycemia, and even death. We report a case of a 10-week-old girl who was started on nadolol for infantile hemangioma, died 7 weeks later, and was found to have an elevated postmortem cardiac blood nadolol level of 0.94 mg/L. The infant had no bowel movements for 10 days before her death, which we hypothesize contributed to nadolol toxicity. Pharmacokinetics studies show a large fraction of oral nadolol either remains in the feces unchanged or is excreted into feces via the biliary system, allowing continued absorption over time in infants who stool infrequently. Propranolol may be a safer therapy overall. Not only does it have a shorter half-life, but propranolol is hepatically metabolized and renally eliminated, allowing for less drug accumulation in healthy infants with variable stooling patterns. We suggest that if nadolol is selected for therapy, pediatricians should instruct parents to monitor their infants' bowel movements closely and encourage early intervention in the event of decreased stooling. This intervention may greatly improve the safety of nadolol in this vulnerable patient population.

β-blockers have previously been described as efficacious in treating patients with complicated infantile hemangioma (IH).[1] Currently, propranolol is approved by the US Food and Drug Administration for the treatment of IH, and its safety has previously been reported.[2] However, propranolol's short half-life, membrane-stabilizing effects, and ability to easily cross the blood-brain barrier make it inconvenient to administer and predisposes infants to side effects such as sleep disturbances.[3,4] Nadolol, a nonselective β receptor antagonist with a longer half-life than propranolol, has been proposed as an alternative therapy for IH. Small studies have suggested it is effective in the treatment of IH.[1,4] Although these small studies report that nadolol is well tolerated, nadolol's pharmacokinetics have not been fully elucidated in infants. This may lead to harm if physicians are unsure how to properly monitor infants undergoing nadolol therapy. Here, we present the death of a 4-month-old girl undergoing nadolol

abstract

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therapy for IH who was found to have an elevated postmortem nadolol level. Furthermore, we suggest her death may have been prevented by using propranolol as first-line therapy for IH. If nadolol must be used because first-line therapy is not tolerated, we hypothesize that monitoring infants' stooling patterns may make this therapy safer given the discussed pharmacokinetics of nadolol.

CASE

A previously healthy 17-week-old white girl died while on nadolol for facial IH (Fig 1). Her treatment was directed by a board-certified pediatric dermatologist. She was started on nadolol at 10 weeks of age. Her dose was initially 0.25 mg/kg per day divided twice daily (BID) and doubled every 4 days to a dose of 2.0 mg/kg per day divided BID. She tolerated the dose adjustments, and her dose was then increased to 5.5 mg BID 1 month later. Pharmacy records indicate that the medication was formulated correctly.

The infant was exclusively breastfed. Two days before her death, she began to have less interest in feedings, which was characterized by decreased duration of each feeding. The mother decided to not administer the last 3 scheduled doses of nadolol because of the decreased intake. The infant also had a change in her normal stooling pattern.

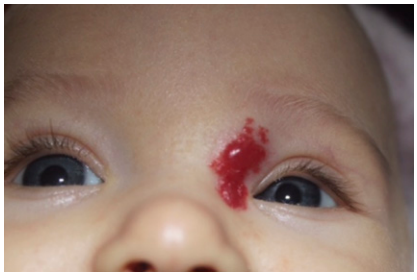

FIGURE 1
Ten-week-old girl with facial IH at the time of initiation of nadolol.

She had not stooled for 10 days before her death. Her mother reported that otherwise, the infant was doing well and did not seem fussy or uncomfortable. On the evening of her death, the infant was noted to be more sleepy than usual in the afternoon. She was fed at 18:30 hours and was put to bed soon afterward. At 22:30 hours, the mother found the infant in her bassinette with perioral cyanosis. She was cold to the touch, and her mother was unable to arouse her. No obvious external obstruction of airway was evident. Cardiopulmonary resuscitation (CPR) was initiated immediately, and emergency services were notified. The police arrived 11 minutes after the emergency services call and drove the mother and infant to the hospital with continued CPR in route. The infant arrived at the emergency department 3 minutes later with fixed and dilated pupils and no cardiac activity. CPR was continued for 9 minutes, and she was subsequently pronounced dead at 17 weeks of age.

The postmortem examination revealed a normally developed, well-nourished, and well-hydrated infant girl. Her growth parameters were within normal limits for her age. There was no evidence of neglect or inflicted injury. No congenital malformations or potentially fatal natural disease was identified. The skeletal survey, histology, and pre- and postmortem metabolic screens were all also normal. Initial toxicological evaluation of cardiac blood for common drugs of abuse, acetaminophen, and salicylates had negative results. Cardiac blood nadolol concentration was 0.94 mg/L (error range 0.58–1.30 mg/L). The immediate cause of death was determined to be unascertained. A time line of the events is presented in Fig 2.

DISCUSSION

To the best of our knowledge, this is the first reported case of a death associated with nadolol therapy for IH. The exact pharmacokinetics of nadolol in infants are not well known. According to the product monograph, the time to peak serum concentration is 3 to 4 hours, it is 30% bioavailable, it is 30% protein bound, and it has an elimination half-life of 20 to 24 hours.[5] Nadolol is not metabolized by humans to an appreciable degree and is excreted unchanged. Approximately 20% of nadolol is eliminated via kidneys, and 70% is eliminated via the gastrointestinal tract.

Original pharmacokinetic studies using radio-labeled nadolol corroborate the product information, demonstrating that less than one-third of the absorbed oral dose is eliminated unchanged in the urine.[6,7] This means more than two-thirds is eliminated via the feces. Even when nadolol is administered intravenously, the study showed that approximately one-third of the dose administered was eliminated in the feces.[6] Fecal elimination and enteric circulation of nadolol is further evidenced by du Souich et al.[8] Healthy volunteers were administered an oral dose of nadolol, and after complete absorption was expected, activated charcoal was given. Activated charcoal increased the overall elimination of nadolol. The proposed mechanism is interruption of the enterohepatic circulation, again suggesting feces as the primary route of elimination.

Because nadolol is eliminated primarily via feces, any process that slows gastrointestinal transit allows more time for enterohepatic recirculation of nadolol. The infant in question did not have a bowel movement for 10 days before her death. It is possible that

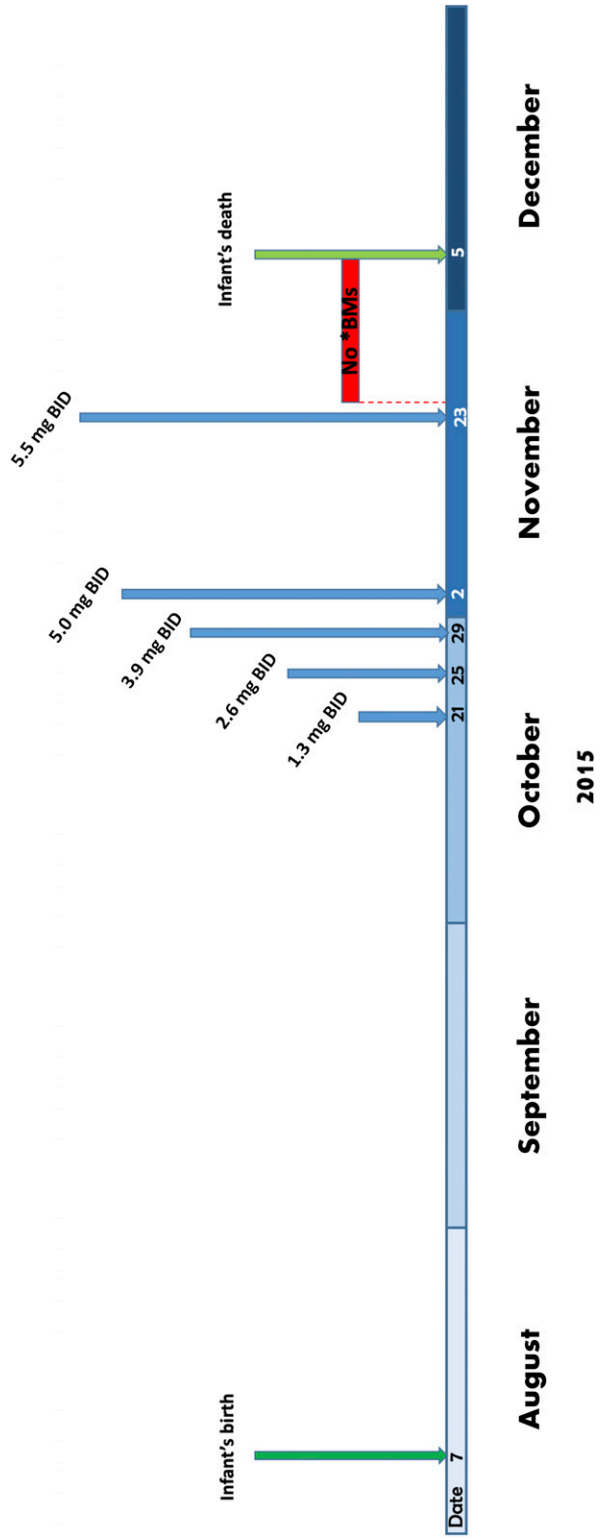

FIGURE 2
Time line of infant's life and nadolol dosing. BM, bowel movement.

her decrease in bowel movements impeded her ability to eliminate nadolol properly, increased enterohepatic recirculation, and therefore led to a supratherapeutic cardiac blood concentration.

A frequently cited pharmacokinetic study of 6 pediatric subjects by Mehta et al[9] is used for justification of BID dosing of nadolol because it suggests that the long half-life of nadolol is shortened in patients <22 months of age. After 22 months, the subjects had an elimination half-life approaching that of adults. In 1 3-month-old subject, nadolol was rapidly distributed to all tissues. In contrast, all of the other 5 subjects, ages 5 months to 14 years, had slower redistribution. This study, although small, suggests that nadolol's pharmacokinetics are unpredictable in early infancy, making appropriate doses challenging for providers. This is concerning for a drug with a narrow therapeutic index. More pharmacokinetic studies are needed in young infants and children to establish the safest dosing strategy for this population.

The pharmacokinetics of nadolol differ greatly from propranolol, the Food and Drug Administration–approved gold standard therapy. After oral ingestion of propranolol, absorption is almost complete and then undergoes extensive first-pass metabolism, with ~25% of the ingested dose entering the systemic circulation.[10] Its time to peak serum concentration is 1 to 4 hours and is 90% protein bound. Propranolol metabolites are largely renally excreted with an elimination half-life of 3 to 6 hours.[10] In contrast, nadolol's extensive fecal elimination and long half-life allow accumulation of the drug via increased enterohepatic recirculation, which can increase toxicity in states of slowed gastrointestinal transit (eg, constipation). Therefore, in healthy young infants with normal hepatic and renal function, in whom stooling patterns or gastrointestinal transit times are variable, propranolol may be the safer choice.

Many complications, although uncommon, have been reported in nadolol administration in the pediatric population. Nadolol has been associated with hypoglycemia in therapeutic dosing in children.[11] It has also been associated with decreased feedings, bradycardia, cold extremities, gastrointestinal symptoms, and wheezing.[1,3,12] In 1 cohort of patients, 2 patients treated with nadolol for IH needed to discontinue therapy because of adverse events.[1] One of them was a 3-month-old with a dose of 1 mg/kg per day who was found lethargic with cold hands and feet. These adverse events are similar to what would occur in propranolol use, both being β adrenergic antagonists. A large French nationwide observational cohort study of oral propranolol use for IH in infants <3 years old further supported the safety profile of propranolol.[2] Large safety studies do not currently exist for nadolol. Unlike nadolol, propranolol crosses the blood-brain barrier and possesses membrane-stabilizing effects. Many researchers have hypothesized that infants would have less neuropsychiatric effects (sleep disturbances) while undergoing therapy with nadolol as opposed to propranolol, although this has not been properly studied.[4]

The cardiac blood concentration of nadolol in our patient was 0.94 mg/L. By comparison, in a previous investigation of 7 adults with mild hypertension given 80 mg of nadolol daily for 13 days, the serum concentration of nadolol was 0.077 ± 0.007 mg/L.[13] Nadolol's monograph states that a mean minimum serum concentration at steady state for a maximum daily dose of 240 mg in adults is 0.131 mg/L.[5] The cardiac concentration found postmortem in this infant was elevated compared with plasma concentrations in adult patients taking therapeutic doses. However, toxic or lethal cardiac concentrations have not been established. Previously, a 61-year-old man who presented with bradycardia, hypotension, and renal failure had an elevated plasma nadolol concentration of 1.3 mg/L.[14] A plasma level of 0.386 μg/L was associated with a 57-year-old woman who intentionally overdosed on nadolol and presented with bradycardia and hypotension that required glucagon and multiple vasopressors.[15]

It is difficult to interpret the cardiac blood concentration in this infant. Cardiac concentrations may be higher than those found in peripheral blood. Postmortem redistribution is not well elucidated for nadolol, and serum levels associated with lethality and toxicity in young children have not previously been reported.

CONCLUSIONS

Nadolol has been shown to be beneficial for IH. However, little is known about its pharmacokinetics and safety in infants. From what we do know about the pharmacokinetics of nadolol based on the most comprehensive studies available, it is probable that the drug accumulated in this infant secondary to her inability to eliminate nadolol in her feces. We suggest propranolol therapy should continue to be first-line therapy given its favorable pharmacokinetics until nadolol's safety is better studied. If propranolol is not tolerated, we suggest that parents with infants undergoing nadolol therapy be educated on the importance of monitoring stool output. This simple action may improve nadolol's safety in this vulnerable population.

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ABBREVIATIONS

BID: twice daily
CPR: cardiopulmonary resuscitation
IH: infantile hemangioma

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