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ISMP Canada Safety Bulletin

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Infantile Hemangioma Treated with Propranolol: Learning from an Infant Death

- *Carefully weigh the harm-to-benefit ratio of beta-blocker treatment for infantile hemangiomas.*
- *Recognize that drug information, including prescribing and monitoring guidelines, is less readily available for off-label use of medications.*
- *Discuss potential harm with parents before prescribing beta-blockers, and support parents with critical drug information (e.g., dosing times related to feeding, signs and symptoms that require medical attention).*
- *Use a simple syrup-based formulation to reduce the risk of hypoglycemia.*
- *Capitalize on opportunities to counsel new and expectant parents on how to reduce the risk factors for sudden infant death.*

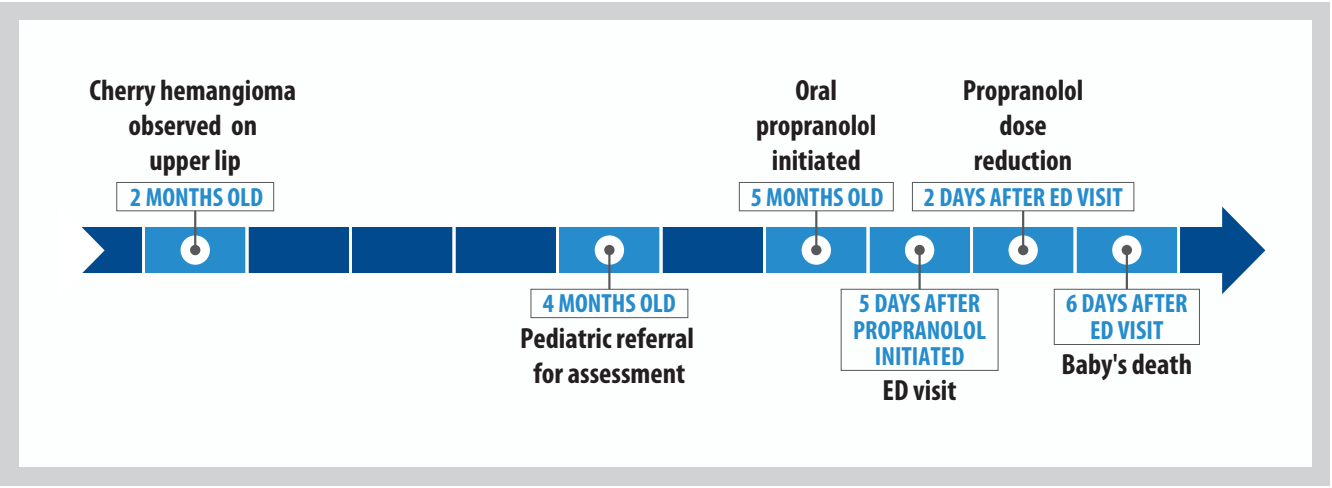
Introduction

Infantile hemangioma (sometimes called a "strawberry birthmark") is a benign vascular, soft-tissue tumour that affects 4% to 10% of infants.[1-4] Most infantile hemangiomas resolve spontaneously, without treatment, but some may warrant medical or surgical treatment because of interference with function, significant disfigurement, or, in rare cases, life-threatening physiologic compromise.[4,5] As part of an ongoing collaboration with a provincial death investigation service, ISMP Canada received a report of the death of an infant who was receiving propranolol for the treatment of infantile hemangioma (an off-label indication for this drug). Although ISMP Canada's review of the use of propranolol in this case found no evidence of a medication error, several learning opportunities were identified and are shared here.

Case Description

A healthy 4-month-old baby girl with an upper lip hemangioma was referred for a pediatric consultation because of concern that the hemangioma was impeding feeding (see Figure 1 for the timeline of events). After a number of assessments and investigations, the pediatrician prescribed oral propranolol 1 mg/kg daily, to be divided into 3 daily doses. The prescription was compounded and filled at a community pharmacy, and the medication was initiated in a hospital clinic, where blood pressure and heart rate were monitored after the first dose. Five days later, the parents brought the baby to the emergency department (ED), reporting reduced fluid intake and lethargy. On examination, the ED physician found that the baby was sucking vigorously on a bottle, appeared to be well hydrated, and was not lethargic. She was later discharged from the ED.

Figure 1. Timeline of events before the baby's death. ED = emergency department.



Two days later, in response to the parents' concern about lethargy, the pediatrician halved the propranolol dose to 0.5 mg/kg daily, divided into 3 daily doses. Five days after the dose reduction, the baby slept most of the day, waking only for feeding. The next morning, she was fed, was awake for awhile, and 2 hours later was placed in her crib. Early that evening the infant was found deceased in the crib with a blanket covering her face. Post-mortem examination did not reveal the cause of death, and serum propranolol levels were well below lethal limits. The cause of death was deemed to be undetermined.

Background

Growth of an infantile hemangioma generally occurs within the first several months of life, and treatment is usually reserved for infants in whom breathing, feeding, vision, or the heart is affected.[4] Systemic corticosteroids were previously considered as first-line treatment, with interferon alfa and vincristine as alternative pharmacological options.[5] However, each of these therapies was limited by serious adverse effects, and they have now fallen out of favour.

Propranolol, a nonselective beta-adrenergic blocker, was discovered serendipitously to be an effective treatment for infantile hemangioma when its beneficial effect on this condition was observed in several infants who were being treated with the drug for cardiac indications.[6] Although the exact mechanism of action is unclear, propranolol is thought to act on beta-adrenergic receptors within the hemangioma resulting in vasoconstriction (which leads to a change in colour and a softening effect).[5] Propranolol also may decrease the release of blood vessel growth-signalling molecules and trigger normal cell death.[7]

A small number of publications on the use of propranolol for infantile hemangioma suggest that it is generally well tolerated, with potential adverse effects similar to those experienced when it is prescribed for other indications. The most concerning adverse effects are hypotension, bradycardia, and hypoglycemia. Hypotension and bradycardia occur most often after the first dose, peaking at 2 hours after administration.[7] Hypoglycemia, on the other hand, is unpredictable, and does not appear to be dose dependent.[7,8] Additional concerns have been expressed about potential long-term cognitive and neurodevelopmental effects of propranolol when used in infants.[9,10]

With the exception of a report from a consensus conference on the use of propranolol, published in 2013,[8] there is a paucity of formal literature to guide the treatment of infantile hemangioma. In general, monitoring of heart rate and blood pressure for 2 hours after dose initiation or increase is

recommended, with slow dose escalation over 1 to 2 weeks to the target dose (1–3 mg/kg daily, given on a 2 or 3 times daily schedule).[8,11] Also recommended is specific monitoring for hypoglycemia in the setting of concomitant administration of a corticosteroid.[12] However, propranolol use alone can increase the risk of hypoglycemia in children and infants, especially preterm infants. Among children up to 2 years old who are taking propranolol, the risk of hypoglycemia may begin after 8 hours of fasting.[7,8] The clinical features of hypoglycemia, with the exception of sweating,[8] are blunted by beta-blockers. Parental education should include monitoring for sweating, appropriate timing of administration of propranolol (during or right after feeding), and information about instances when propranolol should be withheld (e.g., during concurrent illness and restricted oral intake) to help minimize the risk of hypoglycemic events.[8,11]

Findings and Discussion

In the reported case, the cause of death could not be determined. The following issues were considered in the analysis by ISMP Canada.

Indication for Use

Pharmacologic treatment of infantile hemangioma is usually considered when the hemangioma interferes with the infant's normal functions, such as breathing, feeding, vision, or hearing, or is anticipated to result in permanent disfigurement.[8] In this case, the hemangioma was affecting the baby's ability to feed, and therefore, the indication for pharmacologic treatment of the hemangioma was within accepted guidelines.

Patient Monitoring

Propranolol was initiated in a clinic setting, with monitoring of the baby's heart rate and blood pressure. However, it is unknown whether blood glucose monitoring or parental education about the potential for hypoglycemia took place. Although the baby's excessive sleepiness on the day before her death might have been related to hypoglycemia, she did have regular feedings both on that day and on the morning of the day she died. The exact times when propranolol doses were administered are not known, but the prescription label indicated 3 times daily, at least 6 hours apart. The ED visit provided an opportunity to measure blood glucose and identify hypoglycemia, had it been present. Unfortunately, bloodwork was not available for review and hypoglycemia cannot be confirmed using postmortem samples.

Compounded Formulation and Dose-Measuring Device

The prescription required compounding in a community pharmacy. The type of diluent used (simple syrup or a sugar-free liquid) is unknown as pharmacy compounding records were not available at the time of the review. Furthermore, it is not known what type of device the parents used to measure and administer the medication, although pharmacies routinely provide oral syringes to measure liquid medications for children. Overdose, either through a compounding error or a dose measurement error, seems unlikely, given the post-mortem toxicology results, which showed that propranolol levels were below the lethal range.

Safe Sleeping

A great deal of attention has been paid to educating parents about safe sleeping practices and strategies to reduce the risk of sudden infant death. The Public Health Agency of Canada provides literature describing risk factors and strategies for safe sleeping for infants.[13] Several potential risk factors for sudden infant death were identified in this case, but their contribution to the infant's death cannot be determined.

Additional Considerations Related to the Pharmacology of Propranolol

Propranolol is a lipophilic drug that can penetrate the blood–brain barrier; this property can lead to central nervous system (CNS) side effects, such as drowsiness and sleep disturbances.[14] Some large pediatric hospitals in Canada are preferentially using nadolol, a hydrophilic beta-blocker, instead of propranolol to reduce the adverse CNS burden;

nadolol also has a more convenient dosing regimen.[15,16]

Recommendations

Prescribers

- Follow strict patient screening guidelines, and carefully assess the probabilities of harm and benefit before prescribing propranolol; consider obtaining a second opinion prior to initiation, if there is any doubt.
- Provide information to the parents or caregivers about the risks and potential benefits of propranolol therapy. Also advise them that the medication is being prescribed on an off-label basis. Ensure they understand what "off-label" means. Document the information provided as part of a signed consent form.
- For children who are receiving propranolol, perform screening to identify those who are also receiving other medications that may increase the risk of hypoglycemia, such as systemic corticosteroids.
- Create a clear management plan that includes the necessary monitoring.
- Educate parents and caregivers about signs and symptoms that require medical attention, as well as any monitoring requirements (e.g., for hypotension or hypoglycemia).[8,11]
- Reinforce the principles of and strategies for safe sleeping and encourage smoking cessation.

Hospital and Community Pharmacists

- Provide user-friendly measuring devices to facilitate administration of oral liquids, and ask parents to demonstrate the use of these devices to show that they understand how to administer the correct volume.
- Until commercially available pediatric formulations of propranolol and nadolol become available in Canada, compound these medications using a simple syrup diluent, to minimize the risk of hypoglycemia. The formulation of propranolol that is commercially available in the United Sates (Hemangeol) is anticipated to be approved for use in Canada sometime in 2016 (electronic communication: Pierre Fabre Pharmaceuticals Inc., September 18, 2015).
- Instruct parents to administer beta-blockers in association with feeding times, to prevent hypoglycemia.
- Educate parents and caregivers about the important signs and symptoms that require cessation of therapy and/or medical attention (e.g., sweating as a symptom of hypoglycemia).
- Reinforce with new parents the principles of and strategies for safe sleeping. Community pharmacists will often have the opportunity to speak with pregnant patients who smoke, to encourage smoking cessation as a means of creating a safe sleeping environment prior to and after the birth of the baby.

Nurses and Nurse Educators

- Provide continuing education to support recognition of signs and symptoms of concern related to hypoglycemia (e.g., sweating, irritability), bradycardia (e.g., fatigue), or hypotension.
- Reinforce recommended administration times and the principles of and strategies for safe sleeping. Encourage smoking cessation, where applicable.

Conclusion

No medical therapy is without risk of harm. For each patient, all pertinent factors should be carefully considered before treatment with a beta-blocker is initiated, to ensure that the anticipated benefits outweigh the possibility of harm. This caveat is especially important with infantile hemangioma, as it is a condition that often resolves spontaneously over time. In addition, when medications are used on an "off-label" basis, prescribing and monitoring guidance may be limited or not readily available and may change frequently in response to new evidence or case experience. This tragic case has been shared to highlight selected considerations and intervention opportunities associated with the use of propranolol in the treatment of infantile hemangioma.

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This segment of the bulletin describes a recent SafeMedicationUse.ca publication from ISMP Canada's Consumer Program.

January 2016 - Newsletter:

Misconceptions about Medicines That Could Be Deadly: Part 1 – Safe Storage

SafeMedicationUse.ca, ISMP Canada's consumer-focused website, is publishing a 3-part series highlighting common misconceptions that consumers have about medications. The series is based on ISMP Canada's recent analysis of medication errors resulting in deaths outside regulated healthcare facilities (http://www.ismp-canada.org/download/safetyBulletins/2014/ISMPCSB2014-2_DeathsAssociatedwithMedicationIncidents.pdf).

The first article of the series describes a parent observing a young child drink orange juice from a bottle that was inadvertently left within reach by another family member. The parent was not aware that the juice contained methadone, but the next morning, the child could not be awakened and later died in hospital. This incident highlights the importance of properly storing all medications—and emphasizes that even a temporary lapse can lead to a tragic outcome.

Tips for Practitioners:

- Educate patients and caregivers about how to store medications properly and safely.
- Stress the importance of keeping medications in a secure place, away from children and adults who may become confused.
- Discuss with patients any special storage and disposal instructions for individual medications.

Tips to Share with Consumers:

- Never leave a child alone with a medication. If you are interrupted while taking or giving a medication, put the medication in a safe place before attending to the interruption. Alternatively, take the product with you.
- Store all medications in a secure location (e.g., a cabinet with a safety lock or a locked box) out of the reach of children and adults who may become confused. This precaution is especially important for opioids such as methadone. Even a small amount of an opioid can be deadly for a child or for a person who has never taken this type of medicine.
- Teach children to always ***ask an adult*** before eating or drinking anything.

For additional information on the safe storage of medications, read the complete newsletter at: http://safemedicationuse.ca/newsletter/newsletter_Misconception1Storage.html

Consumers Can Help Prevent Harmful Medication Incidents

SafeMedicationUse.ca

5 Questions to Ask about Your Medications

Patients are at high risk of medication errors due to fragmented care at transitions. In collaboration with the Canadian Patient Safety Institute, Patients for Patient Safety Canada, the Canadian Society of Hospital Pharmacists, and the Canadian Pharmacists Association, ISMP Canada developed '5 questions to ask' to help consumers and their caregivers start a conversation about medications with their healthcare provider at transitions in care.

To learn more visit:
www.ismp-canada.org/medrec/5questions.htm

CMIRPS SCDPIM
Canadian Medication Incident Reporting and Prevention System
Système canadien de déclaration et de prévention des incidents médicamenteux

The Canadian Medication Incident Reporting and Prevention System (CMIRPS) is a collaborative pan-Canadian program of Health Canada, the Canadian Institute for Health Information (CIHI), the Institute for Safe Medication Practices Canada (ISMP Canada) and the Canadian Patient Safety Institute (CPSI). The goal of CMIRPS is to reduce and prevent harmful medication incidents in Canada.

HIROC

The Healthcare Insurance Reciprocal of Canada (HIROC) provides support for the bulletin and is a member owned expert provider of professional and general liability coverage and risk management support.

ISMP CANADA

The Institute for Safe Medication Practices Canada (ISMP Canada) is an independent national not-for-profit organization committed to the advancement of medication safety in all healthcare settings. ISMP Canada's mandate includes analyzing medication incidents, making recommendations for the prevention of harmful medication incidents, and facilitating quality improvement initiatives.

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