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Propranolol Treatment for Hemangioma of Infancy: Risks and Recommendations

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Abstract: **Hemangioma of infancy is a condition that may be associated with significant morbidity. While evidence most supports the use of corticosteroids, there is no well-defined or Federal Drug Administration (FDA)-approved systemic therapy for hemangioma of infancy. All currently used treatments have significant risks. Dramatic improvement of complicated hemangioma of infancy to propranolol was recently reported, but details for initiating therapy, monitoring, and potential risks were not included. We present two infants treated with propranolol, who suffered complications and propose a treatment protocol to minimize potential adverse events.**

Hemangiomas of infancy (HOI) are common, benign, self-limited tumors, but a significant percent of these lesions are associated with substantial morbidity in infancy and childhood (1,2). Tumors that often require treatment include those involving the periorbital area, central face, airway, skin folds, and anogenital area, sites at high risk for ulceration, dysfunction, or disfigurement (3). However, there is currently no well-studied or FDA-approved systemic therapy for HOI. While oral prednisolone at 2–5 mg/kg/day has been considered first-line therapy, there is only one small randomized controlled trial of this treatment, comparing it with monthly IV solumedrol (4). While systemic corticosteroids can be effective for high-risk HOI, response is variable and side-effects are insidious, difficult to monitor and potentially serious. Other medications that have been used to treat alarming hemangiomas carry higher risks for adverse effects. This list includes vincristine, interferon alpha, and cyclophosphamide (5,6).

Recently, a small case series of infants with HOI documented a dramatic improvement following treatment with oral propranolol (7). Interestingly, this observed response was serendipitous, discovered with an attempt to treat the adverse cardiac effects that developed as a result of high-dose systemic corticosteroids. This series of 11 patients prompted many pediatric dermatologists to prescribe propranolol for infants with high-risk lesions (8), and triggered a flurry of postings on patient-support Web sites.

Unfortunately, the report did not include a discussion on the details of starting and monitoring propranolol therapy, or the potential risks, which may be distinct in this patient population. The most common serious adverse hemodynamic effects of propranolol are bradycardia and hypotension (9,10). Unlike the index patient treated with propranolol by Leaute-Labreze et al (7) for corticosteroid-induced hypertrophic cardiomyopathy, infants with very large hemangiomas, Posterior fossa

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brain malformation, Hemangiomas of the face, Arterial anomalies, Cardiac abnormalities, Eye abnormalities, Sternal cleft defects (PHACES), or Perineal hemangioma, External genetalia malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, Skin tag (PELVIS) syndrome and especially those with military (diffuse, disseminated) hemangiomatosis, are at risk for high-output cardiac compromise (11). Not only does propranolol have the potential to conceal the tachypnea, hyperhidrosis, and other clinical signs of early cardiac failure, it may also worsen the cardiac performance. Hypoglycemia is another important side-effect that may occur without characteristic jitteriness, because this feature may be blunted by propranolol. Significant long-term neurologic outcomes have been linked to prolonged hypoglycemia in infants (12,13). We report here two infants treated with propranolol, who suffered complications: bradycardia and occult hypoglycemia.

CASE 1

An 8-week-old girl presented with a 2-week history of rapidly growing violaceous tumor on the right upper eyelid. Systemic corticosteroid treatment was initiated at 2.5 mg/kg/day given as a single morning dose, along with ranitidine at 2 mg/kg/dose every 12 hours. The first 2 weeks of therapy were complicated by prolonged episodes of fussiness and continued hemangioma growth. Propranolol was added to her regimen at a total of 2 mg/kg/day given in divided doses every 12 hours. After the first two doses of propranolol she became lethargic and developed cool, clammy hands and feet, prompting evaluation in the emergency room. At that time, her pulse was 87 (average 145 bpm, range 105–185 bpm, age 1–6 mos) and systolic blood pressure 60 mmHg (111 mmHg 95 percentile, 94 mmHg 50 percentile, age 1–5 mos) (14). Blood glucose level was not determined. After 2 hours of monitoring, her pulse and blood pressure returned to normal without specific intervention and propranolol was discontinued. She was referred for intralesional potassium titanyl phosphate laser and intralesional triamcinolone under general anesthesia. Her HOI decreased in size after two treatment sessions and has remained stable without ophthalmologic impairment.

CASE 2

A 36-day-old girl with hemangiomatosis was referred for a second opinion regarding treatment. She was born at 35-week gestation at 6 pounds, 11 oz. following spontaneous early labor. Approximately 20 scattered cutaneous lesions, all < 3 mm, were noted on the first day of life. She was discharged after 6 days, but readmitted at day of life 9–11 for jaundice. She continued to develop new lesions at multiple sites including both eyelids. She was seen by a dermatologist on 25th day of life, when > 100 lesions were noted. The recommended workup was limited to an unremarkable head ultrasound, and a hepatic ultrasound that revealed multiple lesions, in addition to a prominent hepatic artery and portal vein. Ophthalmologic exam detected a lesion on her left iris, but no visual impairment. Vital signs were not recorded. Treatment with propranolol was initiated at 2 mg/kg/day in three divided doses, given every 8 hours. After 10 days of treatment, she was seen for second opinion. She had developed no new lesions, was alert and active, growing along the 50 percentile. Additional evaluation included a complete blood count and thyroid function tests which were unremarkable. Her transaminases were elevated, with ALT 92 IU/L (normal 9–52) and AST 74 IU/L (normal 14–36). The results for her serum glucose were called into the office at a critically low level of 48 mg/dL. Her primary care physician was contacted, but because the patient was asymptomatic and growing well, follow-up glucose was not checked. A subsequent echocardiogram was unremarkable. She was continued on propranolol without dermatology follow-up.

DISCUSSION

Although propranolol has been used for several decades to treat hypertension, ischemic heart disease, arrhythmias, endocrine and neurologic disorders, and eye disorders, FDA-labeling indicates that safety and effectiveness in pediatric patients have not been established. Alternative treatments for alarming HOI include systemic corticosteroids, vincristine, interferon alpha, cyclophosphamide, and surgical excision, therapies that all carry significant risks. We present two patients to report examples of the serious side-effects that may occur when prescribing beta-blockers to infants for HOI. In the absence of a well-defined protocol for initiating and discontinuing propranolol in infancy, we propose a regimen that emphasizes safety.

Propranolol is the prototypical non-selective beta-blocker. It antagonizes both $\beta 1$ and $\beta 2$ receptors equivocally (10). These receptors when activated by epinephrine or norepinephrine result in a variety of actions in a wide variety of tissues. Responses have been much more well-studied in adults than in children. Examples are in the liver where glycogen phosphorylase is activated, and in the heart where calcium influx and sequestration increase. When these receptors are blocked, predictable events occur. These effects may include bradycardia, hypotension, and hypoglycemia.

Clinical signs of these adverse effects include lethargy, restlessness, difficulty breathing, cool clammy skin, delayed capillary refill, and decreased appetite. Propranolol given orally shows significant first pass metabolism with peak absorption at 1–3 hours in adults. The half-life is reported between 3.5 and 6 hours in adults, but effects often last longer than predicted. The mechanism of action for beta-blockers in treating hypertension, ischemic heart disease, arrhythmias, endocrine and neurologic disorders, and eye disorders is not clear. Likewise, the mechanism of action in shrinking HOI remains a mystery. Propranolol's effects on placenta have been demonstrated when used to treat pre-eclampsia (15). Perhaps beta-blockers induce apoptosis by antagonizing Glut-1 receptors or act through other pathways to inhibit growth of the HOI.

Recommendations for instituting treatment with propranolol in infants differ among pediatric subspecialists and academic centers. Like many generic drugs adapted for use in infants, there are no pharmacokinetics data in infants and no prospective, controlled studies describing optimal dosing and monitoring in this age group. Prior to prescribing a beta-blocker for HOI, we suggest devising a local protocol for initiating and adjusting medication with input from local pediatric subspecialists who have experience using this drug. Pediatric cardiologists have the most familiarity with use of propranolol in infants and can also offer expertise in evaluation of infants at risk for coexisting cardiac compromise, including those with large hemangiomas, diffuse hemangiomatosis, and PHACES.

We devised a propranolol protocol that emphasizes patient safety utilizing gradual dose escalation and close monitoring for the first six to eight doses. This may be accomplished on an inpatient basis with a telemetry-equipped hospital bed, with home nursing visits or with close office follow-up. Important variables to consider in recommending inpatient or ambulatory care include the patient's age, history of prematurity, hemangioma subtype, any comorbidities, and level of parental understanding. Infants under 3 months of age are at higher risk of hypoglycemia induced by propranolol, and inpatient induction for closer monitoring in this age group should be considered. Home monitoring for older infants with the assistance of a home health service is possible if the assisting nurse is an experienced pediatric practitioner, and the caregivers have good understanding of the treatment regimen.

After consultation with pediatric cardiologists at several institutions, we developed a basic protocol. Before initiating treatment with propranolol, we obtain baseline vital signs including pulse and blood pressure, fingerstick blood glucose, EKG, and echocardiogram (Table 1). If the echocardiogram or EKG is abnormal, cardiology consultation is requested.

TABLE 1. *Normal Pediatric Vital Signs*

Age	Heart rate (bpm)	Blood pressure (mmHg)	Respiratory rate (bpm)
Premature	120–180	55–75/35–45	40–70
0–3 mos	100–180	65–85/45–55	35–55
3–6 mos	90–180	70–90/50–65	30–45
6–12 mos	80–170	80–100/55–65	25–40
1–3 yrs	70–140	90–105/55–70	20–30
3–6 yrs	65–110	95–110/60–75	20–25
6–12 yrs	60–95	100–120/60–75	14–22
12 yrs	55–85	110–135/65–85	12–18

Infants with large hemangiomas, especially those in a segmental distribution, or hemangiomatosis are at particular risk for extracutaneous complications. All of these subsets are associated with an increased risk of high output cardiac failure and carry the risk of multiple hepatic, gastrointestinal, and central nervous system hemangiomas. If screening abdominal ultrasound is obtained to detect visceral lesions, evaluation for dilatation of the hepatic artery and portal vein may be included. These can provide subtle evidence for early cardiac compromise. Patients with segmental hemangioma suggesting PHACES may also be evaluated with transcranial Doppler and/or magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the head and neck. Coexisting anomalous brain vasculature and insufficient collateral arterial supply could theoretically lead to infarction of brain tissue in the setting of propranolol-induced hypotension. In these cases, consultation with the appropriate pediatric subspecialists is strongly recommended.

The pharmacologically optimal dosing interval for propranolol is every 6 hours, but compliance is easier if the medication is given every 8 to 12 hours. At our institutions, hospitalized infants receive a starting dose of 0.17 mg/kg given at 8-hour intervals (16). Vital signs and blood glucose are monitored 1 hour after each dose, corresponding with peak absorption time. If the first two doses are tolerated, the amount is doubled to 0.33 mg/kg/dose. After two more doses the propranolol is again doubled to 0.67 mg/kg/dose. This is the equivalent of 2.0 mg/kg/day, the dose utilized in most patients by Leaute-Labreze et al (7). Maximum daily doses of up to 5.0 mg/kg have been reported for infants with arrhythmias, but ratio of risk-to-benefit for higher doses is unclear for infants with HOI. For infants less than 3 months of age, we recommend considering slower dose escalation, given increased risk of hypoglycemia. If therapy is initiated on an outpatient basis, we recommend a starting dose of 0.17 mg/kg with a slower dose

escalation, with vital signs and fingerstick blood glucose checked 1 hour after the first dose. If vital signs and glucose are stable, the dose is generally doubled every 3 days with monitoring after every dose increase. When a dose of 0.66 mg/kg is tolerated, we discontinue close monitoring. Frequent feeds, given every 3–4 hours are strongly encouraged. Propranolol is currently available as very concentrated oral solutions, 40 or 20 mg/5 mL. Consider compounding the commercially available preparation to a less concentrated form only if the dose is < 0.1 mL given uncertainty of stability once diluted. It is not optimal to use the 5 mg/5 mL solution intended for intravenous use due to the lack of data regarding stability and absorption if taken orally. Prescribing physicians should educate parents and staff about the importance of double checking the concentration of the dispensed solution to prevent overdosage.

Anticipatory guidance to caregivers about the clinical signs of hypotension, bradycardia, and hypoglycemia should be provided. Frequent feeding, especially in the first 2–3 hours following propranolol administration may help prevent these effects.

Consideration should be given to gradual tapering of propranolol over 2 weeks, rather than abrupt discontinuation (17). Cardiac hypersensitivity may occur 24 to 48 hours after propranolol is stopped, peaking at 4 to 8 days, and diminishing after 2 weeks (17). As with developing an induction protocol, discussion with local pediatric subspecialists prior to discontinuation of propranolol might be helpful.

The impressive response observed by Leaute-Lebreze et al. (7) using propranolol at 2.0 mg/kg/day may represent an effective and possibly safer therapeutic innovation for problematic HOI. However, standard-of-care recommendations cannot be made until more data are available. The potential for significant adverse effects must be recognized, including the bradycardia and hypoglycemia observed in our patients. These two patients were started at 2 mg/kg/day dosing which we believe contributed to the adverse events. In addition, a glucose level was not checked in the first patient, whose symptoms may have been a result of hypoglycemia. As hypoglycemia tends to occur in the first 2–3 hours following propranolol administration, feeding after dosing the medication may blunt these adverse effects. We have safely implemented propranolol using the above conservative protocols for dose escalation in several other patients without problems. Given the lack of data in treating infants with propranolol, especially infants who have HOI rather than cardiac disease, beta-blockers should be used with caution for this indication until there is further understanding of the mechanism of action and optimal dosing. We present the details of a treatment protocol to minimize the risk of adverse events until additional data are available on safety and efficacy of propranolol in the treatment of HOI.

REFERENCES

1. Kilcline C, Frieden IJ. Infantile hemangiomas: how common are they? A systematic review of the medical literature. Pediatr Dermatol 2008;25:168–173.
2. Boye E, Jinnin M, Olsen BR. Infantile hemangioma: challenges, new insights, and therapeutic promise. J Craniofac Surg 2009;20:678–684.
3. Haggstrom AN, Drolet BA, Baselga E et al. Prospective study of infantile hemangiomas: clinical characteristics predicting complications and treatment. Pediatrics 2006; 118:882–887.
4. Pope E, Krafchik BR, Macarthur C et al. Oral versus high-dose pulse corticosteroids for problematic infantile hemangiomas: a randomized, controlled trial. Pediatrics 2007; 119:e1239–e1247.
5. Bruckner AL, Frieden IJ. Hemangiomas of infancy. J Am Acad Dermatol 2003;48:477–493.
6. Michaud AP, Bauman NM, Burke DK et al. Spastic diplegia and other motor disturbances in infants receiving interferon-alpha. Laryngoscope 2004;114:1231–1236.
7. Leaute-Labreze C, Dumas de la Roque E, Hubiche F et al. Propranolol for severe hemangiomas of infancy. N Engl J Med 2008;358:2649–2651.
8. Chang MW. Beta-blocker busts infantile hemangiomas. J Watch Dermatol 2008;6:1.
9. Micromedex R Healthcare Series [Internet database]. Greenwood Village, CO: Thomson Healthcare. Updated periodically. Available at: http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/68E386/DUPLICATIONSHIELDSYNC/C313DB/ND_PG/PRIH/ND_BHCS/SBK/3/ND_P/Main/PFPUI/D5129Kk2E4eFtP/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/6300-v/ContentSetId/30#secN101A6 (accessed on 5 January 2009).
10. Hoffman BB. Adrenoceptor antagonist drugs. In: Katzung BG, ed. Basic and clinical pharmacology, 10th ed. New York: McGraw-Hill, 2007:147–158.
11. Gottschling S, Schneider G, Meyer S et al. Two infants with life-threatening diffuse neonatal hemangiomatosis treated with cyclophosphamide. Pediatr Blood Cancer 2006;46:239–242.
12. Inder T. How long can I go? The impact of hypoglycemia on the immature brain. Pediatrics 2008;122:440–441.
13. Burns CM, Rutherford MA, Boardman JP et al. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. Pediatrics 2008;122: 65–74.
14. Park MK. Pediatric cardiology for practitioners, 5th ed. Philadelphia: Mosby, 2008.
15. Rouget C, Barthez O, Goirand F et al. Stimulation of the ADRB3 adrenergic receptor induces relaxation of human placental arteries: influence of pre-eclampsia. Biol Reprod 2006;74:209–216.
16. Lexi-Comp ONLINE. Propranolol Hydrochloride. Hudson, OH: Lexi-Comp; c1978-2009. Available at: http://www.crlonline.com/crlsql/servlet/crlonline?a = doc&bc = chiat_f&id = 218768 (accessed on 14 March 2009).

17. MicromedexR Healthcare Series [Internet Database], Greewood Village, CO: Thomson Healthcare. Updated periodically. Available at: http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/FD86B3/DUPLICATIONSHIELDSYNC/A57282/ND_PG/PRIH/ND_B/HCS/SBK/3/ND_P/Main/PFPUI/6DTTNe2E3UQuC/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/2119/ContentSetId/31/sectionId/adverseReactionsSection/SearchTerm/propranolol%20/SearchOption/BeginWith#ip8 (accessed on 5 January, 2009).