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Oral Propranolol for Hemangiomas of Infancy

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In the June 12, 2008 issue of *The New England Journal of Medicine*, Christine Léauté-Labrèze and colleagues from the Bordeaux Children's Hospital reported their preliminary experience with propranolol in the treatment of severe hemangiomas of infancy.¹ Their brief Letter to the Editor described 11 infants with capillary hemangiomas: ten with facial lesions and one a hemangioma on the forearm. The first four infants had failed to respond to prednisolone. Average age at the onset of therapy was 3.2 months (range 2-6 months). The first patient was treated with an oral propranolol dose of 3 mg/kg/day, while the remaining patients received 2 mg/kg/day. All patients demonstrated improvement in the size and color of their hemangiomas, with ultrasound confirmation of a reduction in size available in four of the infants. The average duration of treatment in the ten patients who had completed therapy at the time of publication was 9.8 months. At follow-up, seven of the ten infants who completed treatment continued to have regression in the color and thickness of their lesions while the others remained stable.

The effectiveness of a commonly used, older drug for this condition was unexpected. It provided clinicians with an alternative to drugs with more significant adverse effect profiles (corticosteroids, interferon alfa, cyclophosphamide, and vincristine) and quickly became a first-line therapy. Propranolol, approved by the Food and Drug Administration on November 13, 1976, was the first beta-adrenergic receptor-blocking agent introduced in the United States and has been used in a wide variety of disease states.^{2,3} This issue of *Pediatric Pharmacotherapy* will provide a brief review of the pharmacology of propranolol and focus on recent case reports of its use in treating infantile hemangiomas.

Additional Clinical Experience

Shortly after the initial case series appeared, several other case reports and small case series were published describing the successful use of

propranolol.⁴⁻¹¹ Bonifazi reported another 5 infants treated with propranolol at a dose of 2 mg/kg/day (divided and given orally 3 or 4 times daily).⁴ In 2009, Maturo and Harnick gave propranolol to two infants with hemangiomas involving the airway.⁵ The patients, a 3-month-old with an isolated paraglottic hemangioma and a 5-month-old subglottic hemangioma, were treated with propranolol as their sole therapy. The infants were initially started on a dose of 0.5 mg/kg and titrated over the next 24 hours to 2 mg/kg/day (divided and given orally twice daily). Both patients were asymptomatic at follow-up, with a plan to continue treatment for one year.

Earlier this year, Truong and colleagues treated another infant with a subglottic and mediastinal hemangioma using a combination of oral propranolol (2 mg/kg/day) and prednisolone (3 mg/kg/day).⁶ Despite having failed previous attempts at surgical resection, the patient's stridor resolved within two days of starting drug treatment. An MRI performed a week later revealed a 50% reduction in the size of the mass. Prednisolone was tapered off at that time, while the propranolol was continued for 5 months. It was tapered off with no recurrence of symptoms.

In a letter published in the *British Journal of Dermatology*, Manunza and colleagues briefly described their experience with propranolol in 30 infants with hemangiomas between July 2008 and April 2009.⁷ The average patient age at the start of therapy was 5.8 months (range 1.2-13.5 months). Ten patients had facial hemangiomas, nine had periocular lesions, six had nasal lesions, and three had subglottic lesions. Nine of the patients were treated after failure to respond to corticosteroids. Two were treated with both prednisolone and propranolol, while the rest received only propranolol. Oral propranolol solution was initiated at a dose of 1 mg/kg/day (divided into three daily doses). Heart rate, blood pressure, and blood glucose were monitored in all patients. If tolerated, the dose was increased to 2 mg/kg/day after 1 week. Doses were adjusted for weight increases every

month on follow-up. Treatment continued for 1 year unless complete resolution occurred earlier, and therapy was tapered off over the last month. At publication, 19 infants had successfully completed treatment and the remaining patients had demonstrated significant improvement. The majority of patients responded within a week of initiating propranolol. No significant adverse effects were reported.

After reporting on their initial experience with propranolol in 2009⁸, Buckmiller and colleagues published a retrospective study of 32 infants treated at the Arkansas Children's Hospital in the April 2010 issue of *Laryngoscope*.⁹ Fifteen of the patients had experienced a complication related to their hemangioma, including ulceration, bleeding, and visual or airway obstruction. Patients were treated with propranolol 2 mg/kg/day (divided and given orally three times daily), after a thorough history, physical examination, and baseline electrocardiogram (ECG). Doses were adjusted for growth at monthly follow-up. Treatment was continued for one year, tapered at completion by reducing the dose by 50% for 1-2 weeks. Ninety-seven percent of the patients had a positive response to treatment (50% were considered excellent responders, 47% partial responders, and 3% non-responders). Adjunct therapy for partial and non-responders consisted of laser treatment, intralesional corticosteroid injection, or surgical resection. Minor adverse effects included somnolence in 27% of patients, gastroesophageal reflux in 9%, respiratory syncytial virus exacerbation or rash in 4.5%. Additional case series have reported similar success with propranolol for isolated orbital and hepatic hemangiomas.^{10,11}

In addition to these reports, the authors of the original case series subsequently published data from a larger group of patients.¹² A total of 32 infants received propranolol at oral doses of 2-3 mg/kg/day after ECG, echocardiography, and baseline heart rate and blood pressure were assessed. Ultrasound evidence was used to supplement clinical observation in determining regression. As in their earlier paper, the authors noted improvement in hemangioma color and growth in all patients. The patients were treated for a mean duration of 6.1 months. Propranolol was well tolerated, with one patient requiring discontinuation of therapy for wheezing.

Clinical Trials

Six trials of oral beta-adrenergic blocking agents for treatment of infantile hemangiomas are listed

on the National Institutes of Health clinical trials registry, www.clinicaltrials.gov (accessed 7/31/10). Five of the trials are currently enrolling patients, including four randomized comparison trials with propranolol and a trial evaluating the efficacy of nadolol. Two placebo-controlled propranolol studies are being conducted by Léauté-Labrèze and colleagues, authors of the initial case series. The first study is scheduled to conclude patient enrollment by the end of the year. A larger international study, The Study to Demonstrate the Efficacy and Safety of Propranolol Oral Solution in Infants with Proliferating Infantile Hemangiomas Requiring Systemic Therapy, is also currently enrolling patients.

Additional studies comparing oral propranolol to prednisone or prednisolone are being conducted at Seattle Children's Hospital, Children's National Medical Center in Washington D.C., and the University of Sao Paulo in Brazil. The Hospital for Sick Children in Ontario, Canada is studying the utility of nadolol, another non-selective beta-adrenergic blocking agent, in this patient population. Expected completion dates range from December 2010 to July 2013. The results of these clinical trials should provide more definitive information on the efficacy and safety of this therapeutic class in the treatment of hemangiomas.

Mechanism of Action

Within hours of starting therapy, propranolol produces vasoconstriction, resulting in a reduction in the color of the hemangioma. Its primary effect, however, appears to be alteration in the progression of angiogenesis in the hemangioma. Regulation of hemangioma growth involves basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). Léauté-Labrèze and colleagues theorized that propranolol may decrease expression of bFGF and VEGF. Based on examination of hemangioma tissue, Truong and coworkers have also speculated that beta-adrenergic antagonists may ablate catecholamine receptor signaling, decreasing cyclic AMP and reducing levels of VEGF. In addition, propranolol may promote involution of hemangiomas by triggering apoptosis in endothelial cells.^{1,6}

Pharmacokinetics

Propranolol is well absorbed after oral administration, but undergoes significant first-pass metabolism by the liver. Peak plasma concentrations occur 1-4 hours after an oral dose. Administration with protein-rich foods increases

bioavailability. Propranolol is highly protein bound (90%); in adults, the volume of distribution is approximately 4-5 L/kg. It is extensively metabolized via aromatic hydroxylation, N-dealkylation, and direct glucuronidation to primarily inactive metabolites. Propranolol is a substrate for cytochrome P450 (CYP) 2D6 and 1A2. It is a weak inhibitor of CYP2D6. The average elimination half-life in adults is 2-6 hours.^{2,3}

Contraindications and Precautions

Infants with large hemangiomas or diffuse (miliary) hemangiomatosis are at risk for high-output cardiac compromise. Propranolol may further reduce cardiac function in these patients and should be instituted with close monitoring.¹³ Propranolol should be used with caution in patients with renal or hepatic dysfunction, underlying cardiovascular disease, asthma, diabetes, or glaucoma.^{2,3}

Adverse Effects

Treatment with oral propranolol has been well tolerated in most of the cases of infantile hemangioma published to date. The primary adverse effects reported with propranolol use in infants have been somnolence, hypotension, bradycardia, bronchospasm, and hypoglycemia.¹⁴ These reactions typically respond to dose reduction and may not require discontinuation of therapy. Lawley and colleagues reported lethargy, bradycardia, and hypotension in an 8-week-old infant with an eyelid hemangioma after two doses of propranolol and hypoglycemia (with a blood glucose level of 48 mg/dL) after 10 days of propranolol in a 36-day-old infant with multiple hemangiomas.¹⁵ Both infants were being treated with an oral propranolol dose of 2 mg/kg/day.

Bonifazi and colleagues reported severe hypoglycemia and a resultant seizure upon waking in an infant who had been received oral propranolol 2 mg/kg/day for 5 months to treat diffuse hemangiomatosis.¹⁶ The patient was hospitalized and closely monitored, but no further episodes occurred. Propranolol was restarted the following day at 1.5 mg/kg/day. The patient was able to continue treatment for another 5 months without further adverse effects.

Drug Interactions

Administration of pentobarbital, phenobarbital, phenytoin, or rifampin may increase the rate of propranolol metabolism and reduce serum concentrations, potentially decreasing the effectiveness of treatment. Concomitant use of

calcium channel blockers, chlorpromazine, cimetidine, ciprofloxacin, diphenhydramine, flecainide, fluconazole, haloperidol, hydralazine, isoniazid, propylthiouracil, quinidine, ritonavir, selective serotonin receptor agonists (triptans), selective serotonin reuptake inhibitors (SSRIs), teniposide, terbinafine, theophylline, tricyclic antidepressants, and zileuton with propranolol may increase serum propranolol concentrations and increase the risk for toxicity.^{2,3}

Propranolol should be administered with caution in patients receiving other antidiabetic, antiarrhythmic or blood pressure-regulating drugs. It may reduce the effectiveness of sympathomimetics in the management of patients with asthma. Concurrent use of propranolol may increase serum concentrations of diazepam or warfarin. It may reduce concentrations of lovastatin and pravastatin. Propranolol should not be given with ergot derivatives or monoamine oxidase inhibitors.^{2,3}

Dosing Recommendations

In a follow-up letter to the initial publication by Léauté-Labrèze and colleagues, Siegfried, Keenan, and Al-Jurcidi first described a treatment protocol for oral propranolol in infants with hemangiomas.¹³ General treatment guidelines have been developed based on their recommendations and those of subsequent authors.^{1,4-12,15} Prior to the start of treatment, a complete family history should be obtained (with attention to cardiovascular disease), along with a thorough physical examination, serum chemistries, and a baseline assessment of heart rate and blood pressure. Most centers obtain a baseline ECG as well.

Therapy is typically initiated with a propranolol dose of 0.5-1 mg/kg/day (divided and given orally three times daily). If tolerated, the dose may be increased to 2-3 mg/kg/day. Treatment is typically continued for 6-12 months, with doses adjusted for weight gain on a monthly basis. At the conclusion of treatment, propranolol should be tapered off, with a 50% reduction in dose for 1-2 weeks prior to discontinuation.

All propranolol doses provided in the published case reports and case series, as well as in this review are for oral (enteral) administration.

Propranolol oral and intravenous (IV) doses are NOT equivalent and these recommendations do not apply to IV dosing.^{2,3}

At this time, there are no recommendations to guide parenteral propranolol dosing for infants with hemangiomas.

Cardiovascular parameters and blood glucose should be closely monitored after the initial dose or any dosing change. Manunza and colleagues monitored their patients for changes in heart rate or blood pressure every 30 minutes over a 4-hour period at initiation and whenever the dose was increased.⁷ These parameters were also measured twice weekly during the first week and weekly thereafter. Maturo and Hartnick describe as similar protocol, with hourly blood pressure and heart rate checks for 4 hours.⁵

Availability

Propranolol (Inderal[®] and others) is available in tablet, liquid, and injectable formulations. Roxane Laboratories produces 4 mg/mL and 8 mg/mL oral propranolol solutions. Both are strawberry-mint flavored and dye-free. Multiple manufacturers produce the 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg tablets, as well as 60 mg, 80 mg, 120 mg, and 160 mg extended release capsules. There is also a 1 mg/mL injection, available in 1 mL vials.^{2,3}

Summary

Based on the successful results of numerous case series, oral propranolol has earned a role as a first-line therapy in the management of infantile hemangiomas. Although controlled clinical trials are still underway, the efficacy of propranolol in reducing the size of facial, orbital, and airway hemangiomas, as well as its mild adverse effect profile, have made it a preferable choice over traditional treatments. Recent case reports have also suggested a potential role for propranolol in the management of hepatic hemangiomas and diffuse hemangiomatosis as well.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 7/23/10:

1. Alglucosidase alfa (Lumizyme[™]) was added to the Formulary for the treatment of late-onset Pompe disease in patients 8 years of age and older who do not have evidence of cardiac hypertrophy. The usual dosing regimen is 20 mg/kg given as an IV infusion every 2 weeks.
2. Gadofosveset (Ablavar[™]), a gadolinium-based contrast agent for magnetic resonance angiography, was also added to the Formulary.
3. Velaglucerase alfa (VPRIV[™]) was added for long-term enzyme replacement therapy in children and adults with type I Gaucher disease. The usual dose is 60 units/kg given by IV infusion every other week.

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