



December 2011: Volume 3, Issue 3

Infantile Hemangiomas: Update on Therapy

In this Issue...

As the most common tumor of childhood, infantile hemangioma is an important entity in pediatric and general dermatology. Great heterogeneity in size, location, growth, and sequelae has in the past rendered difficult a clear understanding of the optimal management of these tumors. The advent of propranolol as a treatment option for infantile hemangiomas has altered dramatically the traditional therapeutic algorithm. Currently, considerable controversy exists regarding whether corticosteroids or beta-blockers represent the safer, more efficacious therapy. In the absence of comparative clinical trials, the practitioner must interpret the literature and decide on a case-by-case basis which treatment to use.

In this issue, we discuss the debate over corticosteroids versus propranolol, describe the side effects of each, and review a potentially new addition to the available beta-blocker treatment armamentarium.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Discuss current controversies in the management of infantile hemangiomas,
- Describe the potential side effects associated with the use of propranolol and prednisolone therapy for infantile hemangiomas,
- Recognize factors that place infants at high risk for experiencing side effects from treatment with propranolol.

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1 hour
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December 15, 2011

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■ [ATENOLOL FOR THE TREATMENT OF INFANTILE HEMANGIOMAS](#)

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Guest Faculty Disclosures

Katherine B. Puttgen MD discloses that she has no financial relationship with commercial supporters.

Unlabeled/Unapproved Uses

The author has indicated her presentation today will include references to the unlabeled or unapproved uses of propranolol, prednisolone/prednisone in the treatment of infantile hemangioma.

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COMMENTARY

The treatment algorithm for infantile hemangiomas has changed dramatically over the last 3½ years, with the introduction of propranolol as a novel therapeutic agent for the subset of hemangiomas that require intervention. The publication of a letter to the editor by Léauté-Labrèze and colleagues in 2008 was widely read and cited in the dermatology literature, resulting in the widespread use of this nonselective, lipophilic beta-blocker for the treatment of problematic infantile hemangiomas. The excitement generated by this serendipitous discovery has led to concerns over potential overuse and undermonitoring of the medication, perhaps inadvertently fostered by the fact that this initial publication offered little instruction on drug initiation or monitoring. Currently—although without the use of comparative, randomized, controlled trials—propranolol is rapidly gaining first-line status in the treatment armamentarium for infantile hemangiomas among many experts in the field of vascular anomalies. Some respected clinicians still favor a slower, more cautious approach to propranolol use, however, and prefer corticosteroids as first-line therapy, given their >40 years of use and good tolerability in most patients.

Since comparative, head-to-head trials are yet to be published (although, it should be noted, they are under way), clinicians treating children with symptomatic infantile hemangiomas must cull the literature carefully to determine the best treatment option for their patients. Since the initial report by Léauté-Labrèze,¹ there have been >110 English-language publications about propranolol and hemangiomas. Not too far back in many experienced clinicians' minds is the story of interferon, which was initially heralded as an exciting treatment alternative to corticosteroids but was later shown to be associated with up to a 20% risk for spastic diplegia, with the highest risk reported in infants <12 months of age.²

When prednisolone is used to treat infantile hemangiomas, the agent must be administered at high doses, with most clinicians recommending 2 to 3 mg/kg/day.³ In the study by Greene and Couto (reviewed in this issue), the investigators use 3-mg/kg/day dosing, with their choice based on a meta-analysis that showed a significantly greater response at this higher dose.⁴ The authors admit that most patients have residual



hemangioma at the end of prednisolone therapy, which is an important difference from infants described in most propranolol treatment reports. Although the mention of treatment until "complete involution" in the paper by Sans and coworkers (reviewed in this newsletter) is likely an overstatement of effect, in my clinical experience, it is true that the degree of involution observed during propranolol therapy is often greater than that noted with corticosteroid use. What remains unclear, however, is whether this greater degree of change in hemangioma size is due to a truly differing drug effect or whether it may be related, in part, to the fact that most clinicians attempt to taper prednisolone as early as possible, given their concern over potential side effects. Propranolol, on the other hand, is considered by many to be the more innocuous of the two agents, is often continued for longer periods of time, and, as such, perhaps overlaps with some natural involution. In addition, it is very important to recognize that many infants are now being treated with propranolol who, in the past, would likely have been managed expectantly (ie, medical intervention is now offered to many patients with disfiguring or cosmetically sensitive, but not truly function- or life-threatening lesions, so we may not be comparing the same with the same). What does appear to be no longer debatable, however, is that propranolol has the ability to induce involution in hemangiomas that are beyond the early proliferative phase of growth. The Sans and Hogeling papers, both reviewed in this issue, report on such patients. In comparison, prednisolone is generally accepted to be effective primarily in the early proliferative phase of hemangioma growth, which occurs in the first 3 to 5 months of life.⁵

In the study by Greene and Couto, the strongest assertion is the authors' observation that corticosteroids have a long track record of safe use, and although their potential side effects are well known and numerous, the majority of steroid-treated infants with hemangiomas do very well and experience transient, if any, adverse effects. Medication is administered on an outpatient basis in all cases, and no expensive monitoring or testing is required. In contrast, propranolol, although associated with few side effects in most patients treated over the last 3 years, does have the potential for such rare, but truly life-threatening, adverse effects as hypoglycemia (including hypoglycemic seizure), hypotension, bradycardia, and bronchospasm. Many clinicians advocate, as I do, inpatient admission for initial propranolol dosing for certain patients, including the very young and those at high risk for potential complications (eg, those with PHACE [an acronym that describes a neurocutaneous syndrome encompassing the following features: posterior fossa brain malformations, large facial hemangiomas, arterial anomalies, cardiac anomalies and aortic coarctation, and eye abnormalities⁶] syndrome or with heart failure), which adds a considerable expense.

Currently, the greatest need exists for large head-to-head studies that compare the traditional treatment standard, corticosteroids, with the new alternative, propranolol. The other great limitation that affects all studies of infantile hemangiomas, especially those discussed in this newsletter, is the lack of a validated outcome measure. Hemispheric measurements with tape measures fail to document fully the extent of most lesions and are poorly reproducible by different providers. With ultrasound, it is difficult to compare the same lesion over time, and even excellent medical photography systems fail to fully appreciate the clinical extent of many hemangiomas, especially when normal growth of the infant is taken into account. There is much fertile ground for continued research. Just as it is difficult to believe that the patients in the study by Greene and Couto experienced no side effects, it is equally difficult to believe the 100% efficacy reported by Sans and collaborators. The truth about both therapies likely lies somewhere in the great between, and it is, as always, the task of the clinician to navigate those often murky waters.

Commentary References

1. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taïeb A. [Propranolol for severe hemangiomas of infancy](#). *N Engl J Med*. 2008; 358(24):2649-2651.
2. Michaud AP, Bauman NM, Burke DK, Manaligod JM, Smith RJ. [Spastic diplegia and other motor disturbances in infants receiving interferon-alpha](#). *Laryngoscope* 2004;114(7):1231-1236.
3. Frieden IJ, Haggstrom AN, Drolet BA, et al. [Infantile hemangiomas: current knowledge, future directions. Proceedings of a research workshop on infantile hemangiomas, April 7-9, 2005, Bethesda, Maryland, USA](#). *Pediatr Dermatol*. 2005;22(5):383-406.
4. Bennett ML, Fleischer AB Jr, Chamlin SL, Frieden IJ. [Oral corticosteroid use is effective for cutaneous hemangiomas: an evidence-based evaluation](#). *Arch Dermatol* 2001;137(9):1208-1213.

- Chang LC, Haggstrom AN, Drolet BA, et al; [Hemangioma Investigator Group. Growth characteristics of infantile hemangiomas: implications for management.](#) *Pediatrics*. 2008;122(2):360-367.
- Metry DW, Dowd CF, Barkovich AJ, Frieden IJ. [The many faces of PHACE syndrome.](#) *J Pediatr*. 2001;139(1):117-123.

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ORAL PREDNISOLONE FOR INFANTILE HEMANGIOMAS

Greene AK, Couto RA. **Oral prednisolone for infantile hemangioma: efficacy and safety using a standardized treatment protocol.** *Plast Reconstr Surg*. 2011;128(3):743-752.

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Greene and Couto conducted a chart review of 25 consecutive patients treated at a single institution over a 4-year period, between 2007 and 2010, with oral prednisolone 3 mg/kg/day administered in a single daily dosing for the treatment of problematic infantile hemangiomas. The objective of the study was to determine the safety and efficacy of oral prednisolone for the treatment of infantile hemangiomas. Infants included in the study received oral prednisolone 3 mg/kg/day for 1 month and were then gradually tapered by 0.5 mL every 2 to 4 weeks, based on treatment response and age. Regression was defined as any decrease in size, stabilization by cessation of further growth, and treatment failure was defined by continued growth. No additional medications were administered prophylactically.

Treatment with oral prednisolone was initiated at an average age of 12.1 ± 7.2 weeks for 32.2 ± 10.0 weeks' duration. All hemangiomas involved the head and neck, with the largest number ($n=12$) affecting the cheek. Moreover, all treated hemangiomas either regressed (88.0%) or stabilized (12.0%), exhibiting no further growth. Overall, 20% of patients developed a cushingoid appearance that resolved after treatment ended. Rebound growth during taper was observed in 2 patients and responded to an increase in prednisolone dose. The authors reported no drug-related side effects.

Based on their chart review, Greene and Couto concluded that oral corticosteroids in the form of prednisolone, administered once daily at a 3-mg/kg/day dose, are both safe and effective for the treatment of symptomatic infantile hemangiomas. The treatment criteria included visual axis or airway obstruction; damage to a structure such as the lip, nose, or eyelid that is likely to result in permanent deformity; and a lesion that is large enough to leave behind significant fibrofatty residuum. The population comprised infants <5 months of age—an indication that all subjects were within the early proliferative phase of hemangioma growth.¹ The paper cites regression in 88.0% of treated infants, but does not comment on the degree of regression or attempt to further delineate response in either quantitative or qualitative terms. The investigators also state that aside from cushingoid appearance, which they do not list as a complication, no side effects were reported. They did not measure or document blood pressure, blood glucose, weight, height, complaints of gastric upset, gastroesophageal reflux, irritability, or fussiness, however, which are all known potential side effects of oral corticosteroid use. No infections were noted during treatment. The authors maintain that in comparison to propranolol, which is associated with side effects that could potentially be life-threatening (hypotension, bradycardia, hypoglycemia, seizure, and bronchospasm), oral corticosteroids have a more-than-40-year

track record of safe and effective use for the treatment of hemangiomas when administered during the proliferative phase, and should remain the first-line therapeutic option.

References

- Chang LC, Haggstrom AN, Drolet BA, et al; [Hemangioma Investigator Group. Growth characteristics of infantile hemangiomas: implications for management.](#) *Pediatrics*. 2008;122(2):360-367.

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FOLLOW-UP REPORT ON PROPRANOLOL FOR THE TREATMENT OF INFANTILE HEMANGIOMAS

Sans V, de la Roque ED, Berge J, et al. **Propranolol for severe infantile hemangiomas: follow-up report.** *Pediatrics*. 2009;124(3):e423-e431.

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This is an observational pilot study from the French group that reported on the initial serendipitous discovery of propranolol as an effective treatment for infantile hemangiomas.¹ The authors of the current study report on 32 children (including the initial 11 patients in the 2008 pilot study) with problematic infantile hemangiomas who were treated with open-label propranolol at starting doses of 2 mg/kg/day (28 cases) to 3 mg/kg/day (4 cases), divided into 2-times-daily or 3-times-daily dosing. Although not explicitly stated, the investigators imply that many, and perhaps most, of the patients were treated with twice-daily dosing. Compared with the initial publication, the current group provides more details on their treatment protocol, which involved either a 24-hour hospitalization or a 6-hour monitoring session. Blood pressure and heart rate were measured every hour during the 6-hour sessions. Patients were reevaluated at day 10 and then monthly. Ultrasounds were performed in 11 of 32 patients at baseline and at day 60.

Of the 32 patients evaluated, 27 were 1 to 12 months of age (mean, 4.2 months) and 5 were 18 to 48 months of age (mean, 31 months). A total of 21 patients were female. Overall, 13 infants had previously received oral corticosteroids, with either no response or stabilization only. The authors report color change and softening of all hemangiomas within 24 hours of propranolol initiation. Most notably, they report a 100% response rate, which was documented with serial photographs, and, in 11 patients, reduced maximal thickness and increased resistivity index (indicating lower vascularity) on ultrasound at day 60 compared with ultrasound at day 0. At the time of the report, 17 patients were still taking propranolol. Of the 15 subjects who discontinued propranolol, the mean duration of treatment was 9.4 months. Rebound growth was noted in 6 cases as either recoloration or regrowth, and responded to reinitiation of the medication. Side effects included 1 asymptomatic episode of hypotension that resolved when the child awoke, and 1 patient discontinued treatment because of wheezing after 3 months of therapy.

The authors of the study concluded that propranolol is safe and effective for the treatment of symptomatic infantile hemangiomas, and is well tolerated. Most notably, their patients exhibited a response rate of 100%, demonstrating not only stabilization of growth but also continued regression until what they describe as "complete involution" was achieved, thereby shortening by several years the natural growth cycle of the hemangiomas. The study does not attempt to further quantify or qualify the degree of improvement. The subset of patients who underwent ultrasound investigation showed resistivity indexes similar to those observed in late-stage, involuting hemangiomas. Another notable finding is the fact that response was not limited solely to patients in the early proliferative phase of the hemangioma but was also seen in those 5 infants in the involutorial phase (18 to 48 months of age). This finding is distinct from the results reported with the use of oral corticosteroids, which are generally noted to act only in the proliferative phase of the hemangioma.² This study provides additional, but not complete, details on the treatment protocol for drug initiation and shows in a larger group of patients the effectiveness of propranolol for the treatment of infantile hemangiomas with minimal toxicity.

References

1. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taïeb A. [Propranolol for severe hemangiomas of infancy.](#) *N Engl J Med*.2008; 358(24):2649-2651.
2. Bennett ML, Fleischer AB Jr, Chamlin SL, Frieden IJ. . [Oral corticosteroid use is effective for cutaneous hemangiomas: an evidence-based evaluation.](#) *Arch Dermatol*.2001;137(9):1208-1213.

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FIRST RANDOMIZED, CONTROLLED TRIAL OF PROPRANOLOL FOR THE TREATMENT OF INFANTILE HEMANGIOMAS

Hogeling M, Adams S, Wargon O. **A randomized controlled trial of propranolol for infantile hemangiomas.** *Pediatrics*.2011;128(2):e259-e266.

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This study is the first report of a randomized, placebo-controlled, double-blinded trial that examined the safety and efficacy of propranolol for the treatment of infantile hemangiomas. Study participants were randomized in a 1:1 ratio to propranolol 2 mg/kg/day, divided 3 times daily, or placebo at identical dosing. Baseline examinations included measurement of vital signs, electrocardiogram (ECG), echocardiogram, complete blood count, and comprehensive metabolic panel (including blood glucose). Propranolol was administered at 1 mg/kg/day, divided 3 times daily for 1 week, then increased to 2 mg/kg/day, divided 3 times daily for weeks 2 to 24. Infants <6 months of age were monitored for 4 hours with hourly blood pressure, heart rate, and blood glucose measurements at the start of week 1 and week 2. Repeat ECGs were obtained at week 2, and patients were then followed at monthly intervals. Outcome measures included percent change in volume at monthly intervals, and blinded examination and scoring of photographs.

A total of 40 patients were enrolled, with 1 patient excluded from the study because of baseline liver enzyme elevation; therefore, 19 patients were included in the propranolol group and 20 in the placebo group. Three patients in the placebo group discontinued because of lack of efficacy. At enrollment, there were 27 girls and 12 boys, ranging in age from 11 weeks to 4 years. Stabilization of growth in all propranolol-treated patients occurred before week 4. In addition, a significant difference existed between the groups with respect to percent change in volume at all time points, with the largest difference noted at week 12. In the active treatment group, percent change in volume declined steadily at all time points. Improvements in redness and elevation, but not blueness, occurred at weeks 12 and 24, as documented in photographs. Adverse events included bronchiolitis, upper respiratory tract infection, and disrupted sleep. No cases of hypotension, bradycardia, or hypoglycemia were reported.

This study represents the first reported randomized, controlled trial of the use of propranolol for the treatment of infantile hemangiomas, and corroborates earlier case reports and case series, which have shown propranolol to be efficacious and generally well tolerated. Importantly, the investigators attempt to quantify degree of regression in a way in which the authors of the first two studies reviewed above (Greene and Couto, and Sans and colleagues) do not, which lends greater weight to their conclusions. They also present a detailed treatment protocol, which was lacking in initial reports.¹ In the active treatment group, there were 2 patients who were considered nonresponders, 1 patient with a periocular hemangioma with small volume decrease and stabilization of growth, and 1 patient had an ulcerated hemangioma that required 2 months to heal. It is important to note that according to the definition set forth by Greene and Couto, the patient who experienced stabilization would have been considered a responder. Additionally, based on the definition

by Sans and coworkers, the ulcer that took 2 months to heal would likewise have been considered to be a positive response, indicating that the authors of the current study used a somewhat higher threshold for a good response. This study was also rigorous in its documentation of adverse events, including those that were potentially related (eg, sleep disturbance, cold hands and feet, bronchiolitis) and likely unrelated (eg, streptococcal infection, viral gastroenteritis, ulceration, visual compromise) to the medication.

References

1. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taïeb A. [Propranolol for severe hemangiomas of infancy.](#) *N Engl J Med*.2008; 358(24):2649-2651.

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ADVERSE EVENTS ASSOCIATED WITH PROPRANOLOL TREATMENT OF INFANTILE HEMANGIOMAS

de Graaf M, Breur JM, Raphaël MF, Vos M, Breugem CC, Pasmans SG. **Adverse effects of propranolol when used in the treatment of hemangiomas: a case series of 28 infants.** *J Am Acad Dermatol.* 2011; 65(2):320-327.

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De Graaf and colleagues conducted an open-label, unblinded, apparently prospective study of the use of propranolol for symptomatic or disfiguring infantile hemangiomas in a group of 28 children, with a focus on adverse events encountered during therapy. The protocol for drug initiation and monitoring included a baseline ECG. Dosing was begun in an inpatient setting for infants <1 month of age; those considered by the investigators to be at risk for hypoglycemia, hypotension, or bradycardia; and those with relative contraindications to propranolol. Inpatients were discharged after 10 doses of propranolol or on day 5 of hospitalization. All other infants were treated as outpatients. Propranolol was started at 1 mg/kg/day, divided into 2 or 3 doses, and titrated to 2 mg/kg/day after a minimum of 5 doses. Doses were increased up to a maximum of 4 mg/kg/day. Patients were evaluated monthly for up to 12 weeks.

Of the 28 patients studied, 21 (75%) were female. Notably, 1 patient had PHACE syndrome with significant cerebral vascular anomalies and did not experience any side effects. The age range at drug initiation was 2 to 43 months (median, 6 months). Propranolol was dosed between 1.8 and 4 mg/kg/day. At the time of publication, only 6 patients had completed treatment. Two patients experienced symptomatic hypoglycemia, 1 of whom was simultaneously on a prednisolone taper. Three patients experienced bronchial hyperreactivity associated with viral infections, and propranolol was later reinitiated in 2 of the 3. Asymptomatic hypotension was the most common side effect, reported in 15 patients, and 1 patient experienced symptomatic hypotension associated with vomiting and decreased oral intake. One patient experienced an unobserved episode thought to be consistent with a seizure, although no electroencephalogram, blood pressure, heart rate, or blood glucose measurements were recorded; propranolol was later reinitiated in this patient without incident. Sleep disturbance (8 patients), constipation (3 patients), and cold extremities (3 patients) were also observed. Four patients in the cohort were >12 months of age and were noted to exhibit a good response.

This report of 28 patients, 22 of whom were still receiving therapy at the time of this writing, is intended to focus less on efficacy and more on potential adverse events associated with propranolol use. Of note, the authors report the use of higher doses of propranolol (up to 4 mg/kg/day) than do most other publications, and they also report more side effects compared with other case series. According to the investigators, the symptomatic hypoglycemia reported in 2 patients was unrelated to the propranolol dose, but 1 of the 2 patients received a maximum propranolol dose of 4 mg/kg/day and the other

experienced hypoglycemia during a simultaneous taper of prednisolone. This patient has been described elsewhere as well.¹ It is important to note that patients treated simultaneously with corticosteroids and propranolol are at greater risk for hypoglycemia. In a hypoglycemic state, counterregulatory hormones (glucagon, cortisol, epinephrine, growth hormone) work to increase blood glucose. But in a patient receiving both propranolol and prednisolone, the beta-blockade inhibits epinephrine and endogenous cortisol is low because of iatrogenic adrenal insufficiency, making symptomatic hypoglycemia more likely to occur. Thus, these patients must be monitored very closely. This study points out that propranolol is not an innocuous medication, but rather one that requires close monitoring and clear parent education about potential side effects.

References

1. Breur JM, de Graaf M, Breugem CC, Pasmans SG. [Hypoglycemia as a result of propranolol during treatment of infantile hemangioma: a case report.](#) *Pediatrics.* 2011;28(2):169-171.

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ATENOLOL FOR THE TREATMENT OF INFANTILE HEMANGIOMAS

Raphaël MF, de Graaf M, Breugem CC, Pasmans SG, Breur JM. **Atenolol: a promising alternative to propranolol for the treatment of hemangiomas.** . *J Am Acad Dermatol.* 2011;65(2):420-421

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This letter to the editor documents the successful use of atenolol, a hydrophilic β 1-selective blocker, for the treatment of 2 patients with infantile hemangiomas who required discontinuation of propranolol due to bronchial hyperreactivity and hypotension (patient 1) and restless sleep (patient 2). For both patients, atenolol was initiated during inpatient hospitalization at 0.5 mg/kg/day for 7 days and increased to a target dose of 1 mg/kg/day thereafter. Both patients were still on the medication at the time of this writing.

Both patients exhibited a response to atenolol without the side effects encountered during treatment with propranolol. The authors state that the time to response was slower in these atenolol-treated patients than the responses they have seen in propranolol-treated patients; most notably, these patients did not demonstrate the rapid softening and purple coloration observed in propranolol-treated patients.

This letter to the editor is the first publication on the use of atenolol for the treatment of infantile hemangiomas. The pulmonary effects of beta-blockers are mediated through β 2-receptor blockade, and atenolol is a β 1-receptor blocker; the authors postulate that this is why patient 1 was able to tolerate atenolol without any difficulty. Compared with atenolol, propranolol is lipophilic and more easily crosses the blood-brain barrier, which the investigators suggest may be associated with possible nightmares and hallucinations in propranolol-treated patients (although this effect is difficult to quantify in infants). The authors admit that the response to atenolol is less dramatic than that observed with propranolol, particularly early in the course of treatment—a finding they attribute to the β 2-receptor blockade properties of propranolol.

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