Clinical Policy Bulletin: Infantile Hemangioma

Number: 0817

Policy

Aetna considers treatment for hemangiomas of infancy medically necessary when the lesion:

- is associated with Kasabach-Merritt Syndrome;
- results in a documented functional impairment;
- compromises vital structures (e.g., nose, eyes, ears, lips or larynx);
- is symptomatic (e.g., bleeding, painful, ulcerated, prior infection, or pedunculated and symptomatic)

When medical necessity is met as outlined above, the following treatments are considered medically necessary alone or in combination:

- Sclerosing therapy
- Laser therapy
- Surgical excision
- Cryosurgery/Cryotherapy
- Embolization
- Radiotherapy
- Intralesional steroids

Aetna considers oral propranolol medically necessary for infants who have severe life- or vision-threatening hemangiomas.

Note: A hospital stay may be medically necessary to monitor infants’ blood pressure, glycemic control and heart rate for possible unwanted reactions (e.g., bradycardia, hypoglycemia and hypotension).

Inpatient initiation of propranolol is considered medically necessary for infants who:

- Are less than or equal to 8 weeks (corrected age*); or
- Lack adequate social support; or

*Corrected age is used when the child is preterm and/or is less than 6 months of age at birth.
Have co-morbid conditions affecting the cardiovascular system, the airway system (including symptomatic respiratory hemangiomas), or blood glucose maintenance.

Inpatient admission is considered medically necessary until the target does of propanolol is tolerated for 2 hours. For inpatients, it is suggested that propranolol be initiated at 0.33 mg/kg orally 3 times daily (TID); and BP and HR are checked 1 and 2 hours after each administration. If 3 doses are tolerated, propranolol is increased to the target of 0.66 mg/kg TID (2 mg/kg/day) with similar BP and HR monitoring. Once the target dose is tolerated for at least 2 hours, the patient may be discharged. If dose initiation or escalation is not tolerated, it is recommended the dosage be reduced and then gradually increased until tolerated.

* Corrected age and chronological age are not synonymous in preterm infants. "Corrected age" (or "adjusted age") represents the age of the child from the expected date of delivery. Corrected age is calculated by subtracting the number of weeks born before 40 weeks of gestation from the chronological age (AAP, 2004).

See also CPB 0031 - Cosmetic Surgery for medically necessary indications for removal of hemangiomas (port wine stains) located on the face and neck.

**Background**

Nguyen and Fay (2009) noted that infantile hemangiomas are common vascular tumors of childhood with a propensity for the head and neck. In the peri-ocular region, they can cause functional and cosmetic deformity. The proliferation and involution of hemangiomas are controlled by complex interactions of molecular, cellular, and hormonal regulators. There is no single uniformly safe and effective treatment option. Various modalities, including local and systemic pharmacologic agents, lasers, surgery and embolization, are employed to halt growth and to induce regression.

Buckmiller (2009) stated that infantile hemangiomas are the most common benign tumors of infancy and the majority of them occur in the head and neck. Recent literature has described propranolol for the treatment of these vascular tumors. Propranolol was serendipitously found to induce early involution in hemangiomas even during the proliferative phase of the hemangioma cycle. First reported in June 2008, and presented at the International Society for the Study of Vascular Anomalies meeting in Boston that same month, propranolol has stirred much interest in the physicians who treat these types of lesions. Early case report data are now appearing in the literature, and are verifying the findings of the initial studies as an effective treatment for hemangiomas. The author’s institution has the privilege of maintaining a high volume vascular center and has begun treating patients with problematic hemangiomas with propranolol as well. The present article reviewed the literature and give some of our preliminary experience with the drug. The author concluded that research regarding propranolol is in its infancy but, should the initial results and safety record be borne out, it is likely to revolutionize how infantile hemangiomas is managed.
Leaute-Labreze and colleagues (2008) published a case series in the New England Journal of Medicine, which observed that propranolol could inhibit the growth of infantile capillary hemangiomas. In several of the 11 cases, the infants were administered corticosteroids, with no improvement.

Maturo and Hartnick (2010) described the initial use of propranolol as the sole treatment for focal infantile airway hemangiomas, and reported on available literature describing the use of propranolol for airway lesions. This retrospective case series was carried out at a tertiary pediatric medical center. These researchers obtained the following results: 2 children demonstrated significant response to oral propranolol therapy and avoided not only invasive surgical procedures, but also long-term administration of oral corticosteroids. This was the first report of treating infantile airway hemangiomas with only propranolol without additional surgical intervention or corticosteroid use. Review of literature reveals initial case series with similar, successful results using propranolol as an adjuvant treatment along with other medications and surgical interventions. The authors concluded that the initial use of propranolol as the sole treatment for infantile airway hemangioma is promising. Literature review reveals that propranolol as the sole treatment for most head and neck hemangiomas shows significant promise based on early case reports. They stated that further studies are needed to determine the long-term effectiveness, dosing strategies, and side effect profile of propranolol treatment for hemangiomas.

Buckmiller et al (2010) explored the impact of propranolol on both proliferative and involuting hemangiomas at a tertiary vascular anomalies center. These investigators reviewed children treated with propranolol for problematic hemangiomas followed by a blinded prospective analysis of serial photographs taken during the course of their therapy. Parental questionnaires were obtained to evaluate perceived therapeutic response and complications to oral propranolol. A total of 32 children with complete photo documentation were treated with oral propranolol for infantile hemangiomas between September 2008 and June 2009 were included in this analysis. Twenty-seven patients began therapy during the proliferative phase of their lesions (mean age of 4.9 months), whereas five patients began during the involutional phase (mean age of 19.4 months). Ninety-seven percent of patients displayed improvement in the quality of their hemangiomas during propranolol therapy. Patients were determined to be excellent responders (n = 16, 50 %), partial responders (n = 15, 47 %), or non-responders (n = 1, 3 %). Partial and non-responders received adjuvant therapy (75 %, laser therapy; 31 %, steroid injections). Ten patients experienced minor but reportable side effects to propranolol, including somnolence (27.2 %), gastroesophageal reflux (9.1 %), respiratory syncytial virus exacerbation (4.5 %), and rash (4.5 %). The authors concluded that propranolol may revolutionize the treatment of problematic hemangiomas that cause imminent functional or cosmetic sequelae. At therapeutic doses, propranolol is safe and effective in the majority of patients. Adjunctive therapies may still be required. Minor side effects, expected from beta-blocker therapy, are common but easily managed.

Leboulanger et al (2010) provided preliminary assessment of the efficacy of propranolol on subglottic hemangioma in children on a nation-wide scale (multi-
centric, retrospective study of clinical files of 14 children; pre- and post-treatment endoscopies). Mean age at diagnosis was 2.3 (0.7 to 4) months. Mean percentage of airway obstruction was 68 % (15 to 90) before propranolol introduction. Propranolol was started at 5.2 (0.7 to 16) months of age. This treatment was effective in all cases with a mean regression of the stenosis to 22 % after 2 weeks and 12 % after 4 weeks. Other medical treatments (steroids) could be stopped. In 1 patient, a side effect of propranolol motivated the switch to another β-blocker. In 4 patients, treatment was stopped after 5.2 (1 to 10) months with a relapse in 2 (50 %) cases. One of these 2 patients developed a resistance to propranolol and required a surgical procedure by external approach. The authors concluded that this preliminary nation-wide survey confirms propranolol high effectiveness against airways’ localization of infantile hemangiomas. Propranolol also allows alleviation or cut-off of previous medical treatments. However, recurrences are possible after early treatment interruption.

Guldbakke et al (2010) reported a case and presented a short review of the literature on the use of propranolol used in treatment of infantile hemangioma. The patient responded quickly to propranolol, with a clinical response within few days. Literature described reduced size and changes in the color of hemangiomas within 24 to 48 hours. The authors’ experience is in line with that reported in the literature. Propranolol treatment of this patient group has only been documented in observational studies of small groups and no prospective clinical studies have been reported. The authors concluded that propranolol seems to be an effective treatment of infantile hemangiomas. They stated that prospective controlled studies are needed to document optimal dosing, need for monitoring, side effects and duration of therapy.

Georgountzou, et al. (2012) reported that propranolol, as first-line treatment, yielded excellent results in patients with problematic, proliferative phase infantile hemangiomas, with very good clinical tolerance and also seems to be effective in relapses. The investigators administered oral propranolol, a dose of 2 mg/kg/day, to 28 children. Cardiologic evaluation was performed before treatment initiation. Hemodynamic variables and blood glucose levels were monitored during the first 24 hours of treatment, while the children were hospitalized. Clinical response and tolerance were assessed every month, along with photographic documentation. Macroscopic regression was considered the reduction greater than 90% in the size of the infantile hemangiomas. The investigators reported that effects on color and growth were observed within the first month in all cases. Twenty-four of the 28 subjects completed treatment after a mean duration of 7.56 months, and their hemangiomas were successfully regressed. Propranolol was administered again, with satisfactory results, in three patients (12.5%) because of hemangioma regrowth. Satisfactory response is noticeable in ongoing cases. Episodes of hypotension were noted in four patients. The investigators reported that there were no treatment interruptions because of side effects. The investigators stated that the optimal duration of propranolol treatment remains to be defined by long-term observation.

Hogeling, et al. (2011) reported that propranolol hydrochloride, administered orally at 2 mg/kg per day , reduced the volume, color, and elevation of focal and segmental infantile hemangiomas in infants younger than 6 months and children...
up to 5 years of age. The investigators randomly assigned 40 children between the ages of 9 weeks and 5 years with facial infantile hemangiomas or infantile hemangiomas in sites with the potential for disfigurement to receive propranolol or placebo oral solution 2 mg/kg per day divided 3 times daily for 6 months. Baseline electrocardiogram, echocardiogram, and laboratory evaluations were performed. Monitoring of heart rate, blood pressure, and blood glucose was performed at each visit. Children younger than 6 months were admitted to the hospital for monitoring after their first dose at weeks 1 and 2. Efficacy was assessed by performing blinded volume measurements at weeks 0, 4, 8, 12, 16, 20, and 24 and blinded investigator scoring of photographs at weeks 0, 12, and 24. The investigators reported that infantile hemangioma growth stopped by week 4 in the propranolol group. The investigators saw significant differences in the percent change in volume between groups, with the largest difference at week 12. Significant decrease in infantile hemangioma redness and elevation occurred in the propranolol group at weeks 12 and 24 (p = 0.01 and 0.001, respectively). The investigators reported that no significant hypoglycemia, hypotension, or bradycardia occurred. One child discontinued the study because of an upper respiratory tract infection. Other adverse events included bronchiolitis, gastroenteritis, streptococcal infection, cool extremities, dental caries, and sleep disturbance.

Fuchsmann et al (2011) reported the efficacy of propranolol as first-line treatment of head and neck hemangiomas in children and to present an optimized protocol for treating hemangiomas. A total of 39 children with head and neck infantile hemangiomas were treated. Propranolol was the sole treatment in 60 % of patients and was started at a mean age of 4.1 months (age range of 1 to 11 months) for early interventions among 33 of 39 patients. Propranolol therapy resulted in lightening and reduction of hemangiomas at 37 of 39 locations within 2 days to 2 weeks. One subglottic hemangioma and 1 nasal tip hemangioma did not respond or showed only a partial response; in these patients, propranolol therapy was delayed and followed other treatment failures. After successful therapeutic regression, 6 recurrences occurred; when re-introduced, propranolol was again effective. Recurrences were avoided by prolonged treatment. Twenty-six hemangiomas occurring at locations for which corticosteroid treatment previously would not have been initiated (nose, lips, and parotid area) unless a complication had occurred were treated with propranolol and were rapidly controlled. The mean duration of propranolol therapy was 8.5 months. No instances of β-blocker discontinuation because of complications occurred, but propranolol was substituted by acebutolol in 5 patients because of trouble sleeping. The authors concluded that propranolol is an effective treatment of head and neck infantile hemangiomas, especially when started early within the rapid growth phase, and is first-line treatment of orbit and larynx hemangiomas. The efficacy and tolerability of propranolol led us to treat some hemangiomas in patients whom we previously would have observed rather than subject to corticosteroid therapy. Relapse was avoided if treatment was prolonged after theoretical involution (age 12 months). Questions remain about optimal dosing and age at treatment cessation.

Peridis et al (2011) studied the effectiveness of propranolol in infantile airway hemangiomas and compared the effectiveness of propranolol versus different therapies. A literature search of Ovid, Embase, the Cochrane database, Google™ Scholar, and Medline using PubMed as the search engine was performed to
identify studies that analyzed the effect of propranolol treatment in children with airway hemangiomas. Random-effect meta-analytical techniques were conducted for the outcome measures. A total of 13 studies, comprising 36 patients were included in the analysis. Propranolol was found to be an effective intervention for the resolution of infantile airway hemangiomas ($p < 0.00001$). Meta-analysis of effectiveness of propranolol versus steroids, CO(2) laser, or vincristine showed that propranolol is the most effective treatment. The authors concluded that this meta-analysis demonstrated that propranolol should be recommended as a first-line treatment in infantile airway hemangiomas. However, because of the possible side effects of propranolol, current infantile hemangioma treatment centers recommend a full cardiovascular and respiratory review be performed prior to initiation of therapy.

Spiteri Cornish and Reddy (2011) examined the evidence base for the use of propranolol administered orally in the management of peri-ocular capillary hemangioma, and use this information to guide future research. A systematic review of literature was carried out by 2 independent reviewers using the search strategies highlighted below. A total of 100 cases of oral propranolol use in peri-orbital or orbital capillary hemangiomas have been documented in the literature. Of the 85 cases that had details of previous treatment, it was used as first-line treatment in 50 (58.8 %). The commonest dose used was 2 mg/kg/day. Adverse events were documented in 1/3 of cases; in most cases these were minor. Improvement or complete resolution of the lesions occurred in 96 % of cases. Recurrence was noted in 1/5 of cases.

El-Essawy et al (2011) determined the effectiveness and possible side effects of using propranolol for the treatment of orbital and peri-orbital infantile hemangiomas. Infants with peri-orbital or orbital hemangiomas who had not received either local or systemic corticosteroids were recruited. The changes in tumor size, color, and texture, and any side effects of the drug were recorded. A total of 15 infants with a mean age of 8.13 +/- 4.7 months were treated according to the set protocol. A change in the color and texture of the hemangioma occurred in the first week following treatment. Mean duration of treatment was 7.67 +/- 3.96 months. The size of hemangiomas decreased from a mean of 2.4 +/- 0.9 cm to a mean of 1.6 +/- 1.0 cm 3 months after treatment ($p = 0.001$). One patient had to stop the drug because of peripheral vascular ischemia. Another case had the dose reduced to control a mild hyperglycemia. Serious side effects were not observed. A single case of tumor re-growth (8.3 %) was recorded. The authors concluded that treatment of 1-2 mg/kg/day propranolol proved to be effective and associated with minimal side effects. It is likely to replace steroids as the first-line of treatment of hemangiomas in infants.

Jin et al (2011) prospectively evaluated the safety and effectiveness of propranolol as a first-line treatment for problematic infantile hemangioma in China. From March 2009 to February 2010, a total of 78 patients with problematic infantile hemangioma were included in the prospective study. The characteristics of the tumor, including sex, age, site, complications, were recorded. The response to treatment at 1 week, at 1 month and at the end of treatment was evaluated. The efficacy of treatment was graded as no response, stabilization, or accelerated regression. The indications for treatment, side effects and relapse after treatment were documented. The mean follow-up period was 16.7 months (range of 12.1 to
Oral therapy was initiated at a mean age of 3.7 months (range of 1.1 to 9.2 months) as first-line therapy. The mean age at the end of treatment was 11.2 months (range of 5.2 to 22.3 months). The treatment was lasted for 7.6 months (range of 2.1 to 18.3 months). One week after treatment beginning, the hemangioma growth was controlled in all the patients. The accelerated regression was achieved in 88.5 % (69/78) of patients after 1 week of treatment, and 98.7 % (77/78) of patients after 1 month of treatment and at the end of treatment.

Ulceration occurred in 14 cases before treatment, which was healed after treatment for 2 months. Minor side effects were happened in 15.4 % (12/78) of patients. Rebound growth of lesion was noticed in 35.9 % (28/78) of patients. The authors concluded that propranolol is effective in the treatment of infantile hemangioma with minor side effect. They suggested that propranolol should be used as the first-line treatment.

Price et al (2011) examined if propranolol therapy is safe and effective and superior to oral corticosteroids for treating infantile hemangiomas (IHs). The percentage of clearance was quantified by documented serial global photography and clinical examinations (length, height, and width) to segregate patients into 2 groups: (i) patients who had clearance of 75 % or more and (ii) patients who had less than 75 % clearance. The mean duration of treatment was 7.9 months for propranolol and 5.2 months for oral corticosteroids. Fifty-six of 68 patients (82 %) who were receiving propranolol achieved clearance of 75 % or more compared with 12 of 42 patients (29 %) who were receiving oral corticosteroids (p < 0.01). Adverse effects were minimal in the propranolol group: 1 patient had hypoglycemia and 2 patients had a non-specific skin eruption that was not associated with propranolol therapy. All 42 patients in the corticosteroid group had 1 or more adverse effects (p < 0.01). Relapse after discontinuation of propranolol therapy occurred in 2 of the 68 patients; however, both patients responded to propranolol therapy on re-initiating of treatment. Surgical referrals after treatment were required in 8 patients (12 %) in the propranolol group and 12 patients (29 %) in the oral corticosteroid group (p < 0.01). The authors concluded that propranolol therapy was more clinically effective and more cost-effective than oral corticosteroids in treating IHs. It also resulted in fewer surgical interventions and demonstrated better tolerance, with minimal adverse effects, compared with oral corticosteroids. Therefore, propranolol should be considered a first-line agent given its safety and efficacy in the treatment of IHs.

Bertrand et al (2012) shared their experience using propranolol for problematic IH and to evaluate the efficacy of this treatment modality. A retrospective chart review analysis was performed for 35 consecutive children treated with propranolol as an oral solution on an outpatient basis in the authors' dermatology/vascular anomalies clinic. A protocol was established with the help of pediatric cardiologists, including pre-treatment electrocardiography and echocardiography. Medical photographs taken after 2 months of treatment were rated by 2 independent evaluators. These researchers treated 31 girls and 4 boys with a median age of 3.5 months. Rapid improvement was reported in the first days of treatment in 34 patients. Mean improvement after 2 months was 61.5 %. No serious adverse effects were reported. The authors concluded that propranolol was effective in controlling the proliferative phase of problematic IH. It was well-tolerated in this study. Outpatient treatment is possible if parents follow strict
guidelines. Propranolol should be a first-line treatment for problematic IH in carefully selected patients.

Mawn (2013) evaluated the potential risks and benefits of the various modalities for peri-ocular IH. A literature search was conducted for IH and propranolol, steroids, and surgery. The pertinent published literature on surgical resection of IH were reviewed and summarized. A retrospective analysis was also performed of the Vanderbilt Children's Hospital (VCH) surgical case series of 12 children who underwent surgical resection of a sight-threatening IH. A total of 7 articles reported 20 or more patients treated with propranolol for IH. Many of these patients only had a partial response to propranolol in spite of months of treatment. In addition to the impact on IH, propranolol has been demonstrated to block neural pathways critical for learning and memory. Twelve children underwent surgical resection of a visual-threatening IH at VCH. Two of these children had failed treatment with oral propranolol. The average time of surgery was 80 minutes. All 12 children had immediate resolution of the visual compromise. The authors concluded that early surgical intervention can successfully and quickly result in excellent visual and anatomic outcomes. Propranolol may have unrecognized neurocognitive impact and should be reserved for those lesions unamenable to surgical or local steroid injection.

Gomulka et al (2013) noted that historically the 1st-line of treatment for IHs has been oral corticosteroids, but because of recent discoveries recognizing the effectiveness of oral and topical beta-blockers, IH management is dynamically changing. With these new treatment options, some physicians are altering the way they manage IHs despite having little evidence-based data on the treatment methods. High-lighting treatment changes at a single large tertiary pediatric referral center, the authors concluded that despite the numerous studies already published on this topic, more reliable prospective studies are needed to determine the safety, effectiveness, and best treatment algorithms for the use of topical and oral beta-blockers for the treatment of IHs.

Broeks and colleagues (2013) stated that IHs in the airway may be potentially life-threatening during the proliferative phase. Available treatments like oral corticosteroids (OCS) and chemotherapeutic agents usually showed variable responses and serious side effects. Propranolol is a new and promising treatment option. These investigators reported the findings of a case-series study of 5 IH patients with airway involvement, supplemented with a review of literature. Propranolol treatment (2.0 to 3.0 mg/kg/day) was initiated between 3 weeks and 6 months of age. Three cases were treated with propranolol monotherapy, 2 cases with OCS primarily and propranolol secondarily, in which treatment with OCS could be reduced rapidly. In this case-series study, a dramatic, fast response was observed in all cases, with a permanent effect after discontinuation in 4 cases. In 1 patient a relapse of airway problems occurred 2 months after discontinuation of propranolol at 16 months of age; this resolved after re-start of propranolol. Review of literature together with these 5 cases showed 81 patients with airway IHs treated with propranolol. Propranolol was effective in 90% of the cases and 7 patients were classified as non-responders. Eight IHs relapsed while weaning of propranolol or after discontinuation; dose adjustment or re-start was effective in most cases, but 1 patient appeared resistant to therapy. The authors concluded that propranolol appeared to be a rapidly effective and safe treatment strategy for
most IHs obstructing the airway. Because of the fast and important effects of propranolol, randomized controlled trials are hardly justifiable for this specific, relatively rare but, acute treatment indication. Despite the effectiveness of propranolol, close monitoring of the patients with an airway IH is needed, considering the risk of relapse of symptoms during or after treatment and the reported resistance to propranolol in at least 9% of the published cases. The dose and duration of treatment should be high and long enough to prevent relapse. They stated that further research should focus on the optimal treatment protocol; the actual percentage of non-responders as well as the mechanism of resistance to propranolol are unknown and need to be ascertained.

Patel and Bauman (2014) stated that “current evidence supports that propranolol is safe to use for otherwise healthy infants with IH with appropriate screening, cautious dosing, and thorough caretaker education following the above-mentioned guidelines. Outpatient monitored initiation may be considered for infants over 48 weeks post-conceptual age, with adequate social support and without relevant comorbid cardiac, pulmonary, or blood glucose conditions. For other infants, including those with PHACES (posterior fossa abnormalities, hemangioma, arterial lesions, cardiac and eye anomalies), inpatient initiation is advised”.

According to a consensus conference (Drolet, et al., 2013), inpatient initiation is recommended for infants who:

- Are less than or equal to 8 weeks (corrected gestational age); or
- Lack adequate social support; or
- Have co-morbid heart, lung, or glucose pathology

For inpatients, propranolol is initiated at 0.33 mg/kg orally 3 times daily (TID); and BP and HR are checked 1 and 2 hours after each administration (Patel and Bauman, 2014). If 3 doses are tolerated, propranolol is increased to the target of 0.66 mg/kg TID (2 mg/kg/day) with similar BP and HR monitoring. Once the target dose is tolerated for at least 2 hours, the patient is discharged. If dose initiation or escalation is not tolerated, the dose is reduced and gradually increased until tolerated.

Outpatient initiation (Drolet, et al., 2013) may be considered by experienced physicians for infants who:

- Are greater than 48 weeks post-conceptual age; or
- Have adequate social support; or
- Do not have concerning co-morbid conditions.

Outpatient initiation should be performed with cardiovascular monitoring for at least 2 hours after the 1st dose and after each escalation to capture peak changes in HR and BP (Patel and Bauman, 2014). Propranolol is initiated at 0.33 mg/kg, and BP and HR are checked at 1 and 2 hours. If the initial dose is tolerated, the patient may be discharged on 0.33 mg/kg TID, with a minimum of 6 hours between doses. Once 0.33 mg/kg TID is tolerated for 3 to 7 days, the dose can be increased to 0.5 mg/kg TID with BP and HR checks at 1 and 2 hours after the 1st dose. After 3 to 7 days, the dose may be similarly increased to target dose of 0.66 mg/kg TID with BP and HR checks at 1 and 2 hours after the 1st dose.
CPT Codes / HCPCS Codes / ICD-9 Codes

**There are no specific codes for Oral Propranolol:**

CPT codes covered if selection criteria are met:

- 11400
- 11446
- 17106
- 17108
- 17110
- 17111
- 11900
- 11901
- 77401

Other CPT codes related to the CPB:

- 77402
- 77403
- 77404
- 77406

ICD-9 codes covered if selection criteria are met:

- 228.00 - Hemangioma(s)
- 228.09
- 757.32 - Vascular hamartomas

Other ICD-9 codes related to the CPB:

- 287.39 - Other primary thrombocytopenia [Kasabach-Merritt syndrome]
- 707.00 - Chronic ulcer of skin
- 707.9

The above policy is based on the following references:


