Propranolol Treatment for Infantile Hemangiomas: Inpatient Protocol (for Indiana Only)

Guideline Number: CS333IN.02
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Instructions for Use

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Related Policies
None

Application

This Utilization Review Guideline only applies to the state of Indiana.

Coverage Rationale

This clinical guideline addresses the use of oral propranolol for the treatment of infantile hemangiomas (IH) and the potential need for up to a two day inpatient stay to monitor certain patients for heart rate, blood pressure and blood sugar levels.

Inpatient admission in a licensed acute care hospital to initiate oral propranolol for treating Infantile Hemangiomas (IH) according to U.S. Food and Drug Administration (FDA) labeled indications may be indicated when the following criteria are met:

- For infants 2 months of age and younger, an inpatient admission up to two days (48 hours) to monitor heart rate, blood pressure and blood sugar levels
- For children over 2 months of age, an inpatient admission for up to two days (48 hours) when the member has medical comorbidities that require closer monitoring when initiating oral propranolol, including but not limited to:
  - Small for gestational age (SGA)
  - Prematurity requiring apnea monitoring
  - Cardiac disease
  - Reactive airways
  - Associated congenital anomalies
- Comorbidities requiring a longer stay must be identified, with an anticipated length of inpatient stay
- Any requests for an extension of the inpatient stay beyond two days must be clinically reviewed

Note: Medical management is highly individualized and treatment with oral propranolol is considered in the presence of ulceration, impairment of a vital function, (ocular compromise or airway obstruction), or risk of permanent disfigurement.

Definitions

Infantile Hemangioma (IH): A benign neoplasm that commonly develops in neonates within their first few months of life. These vascular tumors are more common in Caucasians, and girls are three to five times more likely than boys to have a hemangioma. Most IHs undergo rapid initial proliferation beginning in the first few weeks of life and continuing over several months followed by involution that begins in the last few months of the baby's first year. In most cases, involution dramatically decreases after 4 years of age, but significant sequelae of the lesions may persist permanently (Léaute-Labrèze et al., 2015).

Description of Services

The treatment of Infantile Hemangioma (IH), the most common childhood tumor with an incidence of 4-5%, has undergone a revolution since the observation in 2008 of dramatic regression of IH with oral propranolol, a nonselective β-adrenergic receptor–blocking agent. Although most IHs resolve naturally without treatment, approximately 10% to 15% cause complications requiring intervention (Léaute-Labrèze et al., 2016). It is suggested that medical intervention be initiated as early in the course of the disease as possible if such complications are to be avoided.

The mechanism of action of propranolol on IH has yet to be clearly defined. Some of the proposed hypotheses include vasoconstriction, decreased renin production, inhibition of angiogenesis, and stimulation of apoptosis (Drolet et al., 2013).

In April 2014, the U.S. Food and Drug Administration (FDA) approved oral Hemangeol (propranolol hydrochloride) solution for the treatment of proliferating IH requiring systemic therapy. For additional information see the following website: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=205410. (Accessed March 25, 2021)

Clinical Evidence

Léauté-Labrèze et al. (2015) performed a randomized controlled trial of oral propranolol in 460 infants aged 1 to 5 months with infantile hemangiomas (IH). Patients administered a dose of 3.4 mg/kg per day exhibited a 60% rate of successful treatment (complete or nearly complete resolution of the target hemangioma), compared with a 4% rate among those treated with placebo.

Hogeling et al. (2011) conducted a randomized controlled trial in 40 children between the ages of 9 weeks and 5 years with facial IHs. Children younger than 6 months were admitted to the hospital for monitoring after their first dose at weeks 1 and 2. No significant hypoglycemia, hypotension, or bradycardia occurred. IH growth stopped by week 4 in the propranolol group. Significant decrease in IH redness and elevation occurred in the propranolol group at weeks 12 and 24 (P = .01 and .001, respectively). The authors concluded that propranolol hydrochloride administered orally at 2 mg/kg per day reduced the volume, color, and elevation of focal and segmental IH in infants younger than 6 months and children up to 5 years of age.

Georgountzou et al. (2012) evaluated the effectiveness, safety and tolerability of propranolol as single-agent treatment in 28 patients with problematic, proliferative-phase IHs. Oral propranolol was administered at a dose of 2 mg/kg/day. 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. The authors observed that propranolol as a first-line treatment, yielded excellent results with very good clinical tolerance. The optimal duration of the treatment remains to be defined by long-term observation.

Patel and Bauman (2014) conducted a literature review to evaluate best practices in the management of propranolol in the treatment of IH. Although there is a lack of consensus between routine outpatient or inpatient initial administration, inpatient initiation is suggested for infants who are ≤ 8 weeks (corrected gestational age), lack adequate social support, or have comorbid heart, lung, or blood glucose conditions. For inpatients, propranolol is initiated at 0.33 mg/kg orally three times daily (TID); and blood pressure (BP) and heart rate (HR) are checked 1 and 2 hours after each administration. If three 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.

Based on a consensus conference on the use of propranolol for treatment of IH, Drolet et al. (2013) recommend that inpatient initiation be done in infants 8 weeks of gestationally corrected age, or any age infant with inadequate social support, or any age infant with comorbid conditions affecting the cardiovascular system, the respiratory system including symptomatic airway hemangiomas or blood glucose maintenance.

Clinical Practice Guidelines

American Academy of Pediatrics (AAP)

The AAP clinical practice guideline for the treatment of infantile hemangiomas (IH) recommends early intervention and/or referral (ideally by 1 month of age) for infants who have potentially problematic IHs. When systemic treatment is indicated, propranolol is the drug of choice at a dose of 2 to 3 mg/kg per day. Treatment typically is continued for at least 6 months and often is maintained until 12 months of age (occasionally longer) (Krowchuk et al., 2019).

References

Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. Pediatrics. 2013 Jan;131(1):128-40.

Georgountzou A, Karavitakis E, Klimentopoulou A, et al. Propranolol treatment for severe infantile hemangiomas: a single-centre 3-year experience. Acta Paediatr. 2012;101(10): e469-e474.

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

Krowchuk DP, Frieden IJ, Mancini AJ, et al. American Academy of Pediatrics. Clinical practice guideline for the management of infantile hemangiomas. Pediatrics. 2019;143(1).

Léaute-Labrèze C, Boccara O, Degrugillier-Chopinet C, et al. Safety of oral propranolol for the treatment of infantile hemangioma: a systematic review. Pediatrics. 2016 Oct;138(4). Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. N Engl J Med. 2015 Feb 19;372(8):735-46.

Patel NJ, Bauman NM. How should propranolol be initiated for infantile hemangiomas: Inpatient versus outpatient? Laryngoscope. 2014;124(6):1279-1281.

Guideline History/Revision Information

Date	Summary of Changes
06/01/2021	Supporting Information • Updated *Clinical Evidence* and *References* section to reflect the most current information • Archived previous policy version CS333IN.01

Instructions for Use

This Utilization Review Guideline provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this guideline, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Utilization Review Guideline is provided for informational purposes. It does not constitute medical advice.

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