PROPRANOLOL TREATMENT FOR INFANTILE HEMANGIOMAS: INPATIENT PROTOCOL

Guideline Number: MMG112.G

Effective Date: March 1, 2019

Table of Contents

<table>
<thead>
<tr>
<th>Table of Contents</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVERAGE RATIONALE</td>
<td>1</td>
</tr>
<tr>
<td>DEFINITIONS</td>
<td>1</td>
</tr>
<tr>
<td>DESCRIPTION OF SERVICES</td>
<td>1</td>
</tr>
<tr>
<td>CLINICAL EVIDENCE</td>
<td>2</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>2</td>
</tr>
<tr>
<td>GUIDELINE HISTORY/REVISION INFORMATION</td>
<td>3</td>
</tr>
<tr>
<td>INSTRUCTIONS FOR USE</td>
<td>3</td>
</tr>
</tbody>
</table>

COVERAGE RATIONALE

Introduction
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.

- Oral propranolol is indicated for treating Infantile Hemangiomas (IH) according to U.S. Food and Drug Administration (FDA) labeled indications.
- An inpatient admission up to two days (48 hours) in a licensed acute care hospital may be indicated for treating IH with oral propranolol in infants 2 months or younger. The purpose of the inpatient admission is to monitor heart rate, blood pressure and blood sugar levels.
- Children over 2 months of age with medical comorbidities that require closer monitoring when initiating oral propranolol (e.g., small for gestational age [SGA], prematurity requiring apnea monitoring, cardiac disease, reactive airways, associated congenital anomalies) may be treated as inpatients for the same 2-day protocol unless the medical issues require longer monitoring. In that event, comorbidities requiring a longer stay must be identified, with an anticipated length of inpatient stay.
  - 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.
  - Any requests for an extension of the inpatient stay beyond two days must be clinically reviewed.

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 vascular tumor with an incidence of 3% to 10%, 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, ideally early in the proliferative phase of growth (Léaute-Labrèze et al., 2016).
The mechanism of action of propranolol on IH is 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: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=205410. (Accessed January 24, 2019)

**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 (completely 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.

**Professional Societies**

**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**


**GUIDELINE HISTORY/REVISION INFORMATION**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
</tr>
</thead>
</table>
| 03/01/2019 | • Reorganized policy template:  
|            | o Simplified and relocated Instructions for Use  
|            | o Removed Benefit Considerations section  
|            | • Updated supporting information to reflect the most current clinical evidence and references; no change to coverage rationale  
|            | • Archived previous policy version MMG112.F |

**INSTRUCTIONS FOR USE**

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

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare West Medical Management Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Member benefit coverage and limitations may vary based on the member’s benefit plan Health Plan coverage provided by or through UnitedHealthcare of California, UnitedHealthcare Benefits Plan of California, UnitedHealthcare of Oklahoma, Inc., UnitedHealthcare of Oregon, Inc., UnitedHealthcare Benefits of Texas, Inc., or UnitedHealthcare of Washington, Inc.