Hemangiomas and β-Blockers: On the Rebound

Anthony J. Mancini, MD

Infantile hemangioma (IH) is the most common tumor of childhood, and although most lesions eventually involute, the proliferative phase may be associated with complications, such as ulceration, bleeding, functional compromise, and anatomic disfigurement. Rarely, IH can have major or life-threatening consequences, such as airway obstruction, high-output congestive heart failure, and consumptive hypothyroidism. It is for reasons such as these that therapy may be indicated.

Propranolol, a nonselective β-adrenergic receptor antagonist, has been used off-label in children for years in the treatment of cardiac dysrhythmias, congestive heart failure, and hypertension. In 2008, Léauté-Labrèze et al1 reported their discovery of its benefits against IH, an observation confirmed in their follow-up report of 32 infants 1 year later.2 Oral propranolol (OP) has evolved to become the standard of care for IH therapy. In 2014, a pediatric formulation was approved by the US Food and Drug Administration (March) and the European Medicines Agency (April).3, 4 The results of the multicenter, randomized, double-blind, adaptive phase 2-3 trial assessing its efficacy and safety in treating IH were published in 2015.5

Although the precise mechanisms of action of OP in the treatment of IH remain unclear, once initiated, the effects in most lesions are unmistakable: lightening of color, softening and flattening of the tumor, and improvement in functional compromise (ie, mechanical ptosis or astigmatism). One limitation that has become clearer with accumulating clinical experience, though, is that of potential rebound IH growth after OP, estimated to occur in 6% to 25% of children.2, 5-9 Understanding the phenomenon of postpropranolol rebound, and being able to predict or (better yet) prevent it, will increase clinical success and parental satisfaction with OP therapy and, in some instances, help prevent morbidity (such as airway blockage resulting from subglottic IH rebound).

In this issue, Shah and colleagues10 report their findings of a retrospective cohort study of 980 patients with IH treated with OP, in which they assessed the incidence of rebound growth, IH characteristics, and treatment factors. They distinguished major rebound growth (need for dose adjustment or treatment reinitiation) from minor rebound growth (no change in therapy necessary), and used a visual analog scale as a proxy for IH response. The incidence of rebound growth was 25.3%, with 15.7% of patients experiencing major rebound. The odds ratios for rebound were highest when OP was discontinued or tapered before 12 months of age (and especially before 9 months), and also in the infants who were older than 15 months of age. The lowest rebound was noted in the group that had OP discontinued or tapered between 12 and 15 months of age. When duration of OP therapy was stratified by quartiles, there was a trend toward decreasing rebound with >12 months of therapy, but this factor was statistically insignificant when comparing the “rebound” and “no-rebound” groups. The authors...
assessed predictive clinical factors for rebound, and identified head and neck lesions, segmental IH, deep or mixed IH, and female gender. Maximum OP dosing did not correlate with rebound risk, but most of this cohort (as acknowledged by the authors) was treated with a similar dose range (1.5–2.5 mg/kg per day). Rebound was more likely in patients who abruptly discontinued OP (versus those who were tapered).

The findings of Shah et al confirm the findings of others, and expand our understanding of this phenomenon. Their finding of increased rebound in deep or mixed IH and segmental IH is consistent with other reports, as is the increased risk of rebound observed in girls. The aforementioned hemangioma subtypes may represent a unique subpopulation of IH programmed to proliferate longer.

In a series of IH with prolonged growth by Brandling-Bennett et al, all 23 lesions were on the head and neck, another feature found in the current study; in that series, nearly 40% of IH involved the parotid gland, a detail not included in the current report. The data from Shah et al expand the published observations on rebound as a function of duration of OP therapy and age at the time of discontinuation or taper. Several previous studies report a higher rebound rate with shorter durations of OP therapy, although in others this association is less clear. The optimal duration of OP therapy for IH remains undetermined, and is likely influenced by multiple patient and IH variables.

Several important questions remain. Is there a dose-response relationship between OP and IH rebound? Should varied recommendations (weight-based dose and/or treatment duration) be used for IH of different rebound risk? Does OP therapy prolong the proliferative potential of IH? Does the duration of therapy needed to minimize rebound correlate with age at treatment initiation? The field is ripe with opportunities for further study. In the meantime, the results of this large cohort review by Shah et al will help guide clinicians in optimizing OP therapy and minimizing rebound growth in select higher-risk lesions.

**ABBREVIATIONS**

IH: infantile hemangioma  
OP: oral propranolol

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