Propranolol for Infantile Hemangiomas: A Review

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Abstract Infantile hemangiomas (IHs) are the most common vascular tumors of infancy. Since it was discovered several years ago, propranolol hydrochloride has become a very popular and successful treatment for complicated and aesthetically disfiguring IHs. The recent literature on propranolol is reviewed, including a summary of larger studies, discussion of adverse effects, and the use of propranolol in complicated IHs, such as ulcerated IHs, airway, and hepatic IHs.

Keywords Propranolol · Infantile hemangioma · Adverse effects · Airway hemangioma · Ulcerated hemangioma · Hepatic hemangioma · PHACE syndrome · Topical beta blockers

Abbreviations

IH Infantile hemangioma

Introduction

Infantile hemangiomas (IHs) are the most common vascular tumors of infancy affecting approximately 4 % of Caucasian infants [1]. IHs generally are not present at birth and subsequently proliferate with the most rapid growth period, particularly of superficial IHs occurring between 1 and 2 months of age [2]. The majority of IH growth is completed by 5 months of age [3]. The rapid growth during early infancy is followed by slowed growth and gradual involution. Although many IHs do not require treatment, in certain anatomic areas IHs may cause disfigurement or threaten vital functions (such as visual,

oral, or airway function). IHs may become complicated with painful ulceration or, rarely, bleeding.

Propranolol hydrochloride is a nonselective B-blocker that was serendipitously discovered to inhibit growth of IHs in 2008 when children with IHs were treated with propranolol for cardiac indications [4]. Since that time, there have been an outpouring of reports describing the use of propranolol, including numerous case series and a small, randomized, controlled trial supporting the safety and efficacy of propranolol [5]. Other beta blockers, such as nadolol, acebutolol, atenolol, and topical timolol, have been reported to be beneficial; however, the majority of reports are of propranolol. Although there are no FDA-approved treatments for infantile hemangiomas, the advent of propranolol is a major advance for the field of Pediatric Dermatology. The advantages of propranolol are that it has a rapid onset resulting in clinical improvement, appears to have less serious side effects than systemic corticosteroids, can be used for IHs beyond the proliferative phase, and is inexpensive. A large, international, randomized, controlled trial is underway. Propranolol has become the first-line treatment for IHs, eclipsing systemic corticosteroids as the preferred treatment for IHs. This review article summarizes the recent literature for propranolol as a treatment for infantile hemangiomas.

Discussion

Pharmacology

Propranolol hydrochloride is used to treat hypertension, migraine headaches, anxiety, and tremor. In infants, it has primarily been used for cardiac indications and neonatal hyperthyroidism. Propranolol has not been FDA approved for any pediatric indication; however, in other countries propranolol is licensed for pediatric use in migraine prophylaxis, arrhythmias, thyrotoxicosis, and tetralogy of Fallot

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[6]. Propranolol acts on beta-1 (cardiac) and beta-2 (bronchial, vascular smooth muscle) receptors. Beta-1 blockade produces decreased heart rate and decreased myocardial contractility during periods of high sympathetic activity, resulting in decreased cardiac output. Blockade of beta receptors in cardiac conduction tissue results in slowing AV conduction and suppression of automaticity. Beta-2 blockade is responsible for many of the adverse effects of propranolol, including bronchospasm, hypoglycemia, and peripheral vasoconstriction. Propranolol has been well studied in adults and has a therapeutic half life of 3–6 hours [7].

Mechanism of Action

The mechanism of propranolol acting on infantile hemangiomas is being investigated. Beta adrenergic receptors are present on endothelial cells. Mechanisms, such as vasoconstriction, endothelial cell apoptosis, and decreased angiogenesis, have been proposed to explain how propranolol affects IHs.

Beta blockers inhibit vasodilation, which is caused by adrenaline interacting with beta receptors, resulting in nitrous oxide synthesis and release. Vasoconstriction leads to immediate changes in the IH due to decreased blood flow from the capillaries feeding the IH and can be observed as color lightening and softening within the first 3 days of initiating treatment [8•].

Angiogenic growth factors are important in endothelial cell proliferation. Beta blockers are proposed to downregulate angiogenic growth factors, such as VEGFA, matrix metalloproteinases (MMP-2 and MMP-9), and IL-6.[9] Chim et al. treated proliferating and regressing IH endothelial cells with propranolol and found that propranolol induces a cytotoxic effect on IH endothelial cells through HIF 1alpha mediated inhibition of VEGF-A [10].

Propranolol Studies

All studies to date have indicated that propranolol is effective for treating infantile hemangiomas [5•, 11•, 12–17]. Most studies evaluating propranolol for infantile hemangiomas have involved small patient numbers with dosages of 1–3 mg/kg/day divided bid to tid (Table 1). In young infants, less than 1–2 months of age, some physicians initiate therapy during a brief hospitalization. In older patients, propranolol is usually administered on an outpatient basis. Some centers gradually titrate the dosage over a 1- to 2-week period, versus others who initiate the full dose of oral propranolol at 2 mg/kg/day. Duration of treatment ranges from 3 to 9 months. Propranolol has been used to treat children of different ages with IHs in the proliferative phase, as well as stable IHs. Most studies for propranolol established a protocol, including pretreatment cardiac evaluation

(sometimes with EKG and echocardiogram), followed by monitoring of vital signs, and sometimes glucose levels or ultrasound measurements of the IH. Most studies have excluded patients with PHACE syndrome and arterial abnormalities by performing MRI/MRA on infants with large facial IHs. Some groups admit patients to the hospital for monitoring hemodynamic parameters after the first dose, whereas in clinical dermatology practice propranolol is usually initiated on an outpatient basis. A consensus conference recently convened to standardize the approach to propranolol use in infantile hemangioma. These results have not yet been published. Discontinuing propranolol is recommended by tapering the dosage over a 2-week period to prevent rebound tachycardia. Rebound IH growth tends to occur in children younger than 12 months [5•]. A recent meta-analysis of greater than 1,000 patients treated with propranolol for IH with a mean dose of 2.1 mg/kg/day showed a high rate of efficacy (average 97 %) and very low rate of serious adverse events. The most common adverse events were sleep disturbances and acrocyanosis. Serious adverse events were rare, with reports of symptomatic hypotension in five patients, symptomatic bradycardia in one patient, and hypoglycemia in four patients, one of which presented with hypoglycemic seizures [18]. Larger, prospective, randomized, controlled trials are expected to provide more information about the optimal dosage, efficacy, and safety profile of propranolol.

Comparing Propranolol and Systemic Corticosteroids

Propranolol seems to be superior to systemic corticosteroids. This has been assessed in two, small, comparative trials. A retrospective case control study, matched 12 pairs of infants who received propranolol with those that had received systemic corticosteroids, by IH size, location, and age. They found that at 6 months of treatment, all of the children in the propranolol group showed good-to-excellent response, whereas nine children in the corticosteroid group showed slight-to-moderate response. The response in the propranolol group was faster and showed greater clinical improvement [19].

A retrospective comparison of 68 children who received propranolol for their IHs with 42 patients that received corticosteroids for their IHs, found that 81 % of the propranolol group achieved 75 % improvement in their IH compared with 29 % of the corticosteroid group with 75 % improvement. Additionally, the cost of propranolol was less, and there were fewer complications in the propranolol group [20].

Ulcerated IHs

Propranolol is a promising treatment for ulcerated IHs. The most common complication of infantile hemangiomas is

Table 1 Summary of larger studies of Propranolol for IH

Authors	Type of study	No. of patients	Dosage mg/kg/day	Duration	Efficacy	Side effects	Monitoring
Manunza	Case series	30	2 tid	7 months mean	All improved clinically	3 hypotension	Protocol for initiation and monitoring
Sans	Case series	32	2–3 bid or tid	6.1 months mean	40 % regression by 60 days on U/S, nearly 100 % clinical improvement	1 hypotension 1 wheezing 2 insomnia 2 agitation 1 nightmares 1 night sweats 1 cold hands	Initial EKG, Echo, inpatient monitoring first day, HR, BPchecks, some U/S measurements
Bagazgoitia	Case series (multicenter retrospective)	71	2 bid	3–5 months	60 % reduction in IH by 20 weeks	10/71 sleep disturbance 1 stridor 1 breath-holding spells	Cardiol exam, EKG, BP, glucose in some, MRI as needed
Schupp	Case series	55	2 tid	6 months mean-younger pts longer	83 % partial regression	2 asthma 6 acrocyanosis 1 fatigue 6 rebound 3 exanthem/skin 2 GI probs	Initial hospitalization, EKG, BP, glucose in <1 month olds
Bertrand	Retrospective case series	35	2–3 tid	8.9 months mean	61 % after two months of tx	1 bradycardia 1 shortness of breath 8 sleep disturbance 6 drowsy 4 benign infections 3 GI symptoms 2 irritability 1 poor weight gain 2 changes in appetite	Initial EKG, Echo, outpatient management, home BP monitoring, Vital signs at clinic visits
Hogeling	Randomized trial	40	2 tid	6 months	60 % mean % change in volume at 24 weeks	4 bronchiolitis 2 sleep disturbance 1 cold hands/feet 1 strep infection 1 viral URTI 1 viral gastro 1 elevated alk phos 1 dental caries	Baseline labs, echo, EKG, inpatient observation of 4 hours for <6 months, monitoring of BP, HR, glucose
Holmes	Case series	31	3 ?	3 months mean	87 % significant regression	1 hypotension 1 GERD 1 restlessness 1 bronchiolitis	? cardiovascular pre tx workup
Buckmiller	Case series	32	2 tid	Not reported	97 % improved	6 somnolence 2 GERD 1 psoriasis-like rash 1 RSV exacerbation	?

ulceration, in up to 15–25 % of IHs in a tertiary care setting [21, 22]. Treatment of ulceration includes general wound care measures with debridement of crust via saline soaks, application of topical antibiotics, pain medications, and wound dressings. Medical and surgical treatments employed for ulcerated IHs include becaplermin gel, pulsed dye laser therapy, and surgical excision of the ulcerated IH. There are reports of propranolol being effective in the healing process

of ulcerated IHs. Propranolol was effective in treating 33 infants with problematic ulcerated hemangiomas in a retrospective review [23]. The mean time to healing was 4.3 weeks, and head and neck location of the IH correlated with faster healing. Children also were reported to have significantly reduced pain within days of starting propranolol treatment. In a case-control study of 20 infants with ulcerated IHs treated with propranolol matched to historical

controls, the propranolol group healed faster than the control group 8.7 vs 22.4 weeks. Starting propranolol at an earlier stage of disease tended to result in shorter ulceration duration [24]. In six infants with complicated ulcerated IHs treated with propranolol, the ulcerations healed within 2–6 weeks of starting propranolol [25]. These reports all used a dosage of 2–2.5 mg/kg/day divided tid. Bagazgoitia et al. included eight ulcerated IHs in their study where they used 2 mg/kg/day divided bid; all ulcerations healed within 2 weeks of propranolol [11•]. In contrast, Manunza et al. reported that two of their patients with deep ulcerations deteriorated despite treatment with propranolol [14]. Although larger confirmatory studies are likely required, some authors are recommending propranolol as a first-line treatment for ulcerated IH. It may be helpful for the clinician to identify and treat high-risk IHs (such as a large superficial component, located on mucosal surfaces, the perineum, or in areas of high friction, and with early white or greyish surface discoloration) to try to avoid ulceration.

Hepatic IH and Propranolol

The liver is the most common extracutaneous site of IH involvement. Hepatic infantile hemangiomas can be classified as focal, multifocal, and diffuse. Similar to cutaneous IHs, liver IHs are usually small, localized, and do not require treatment. Certain liver IHs can result in life-threatening complications, such as high-output cardiac failure or liver enlargement leading to hypothyroidism. Hypothyroidism is due to deactivation of thyroxine by type 3 iodothyronine deiodinase produced by hemangioma tissue where the IH replaces most of the liver or in very large IHs [26]. The presence of numerous cutaneous IH can be an important clue to the diagnosis of hepatic IH, and abdominal ultrasound is recommended if five or more cutaneous IHs are identified. Diffuse hepatic infantile hemangiomas (a rare subtype) have been treated successfully by using propranolol in combination with other medical therapies, such as systemic corticosteroids and vincristine [27]. Mhanna et al. successfully treated three infants with multifocal and diffuse intrahepatic hemangiomas with propranolol at a dosage range of 1.5–2 mg/kg/day [28]. Mazereeuw-Hautier described eight patients with hepatic IH, three of whom were experiencing heart failure who were treated with propranolol. All of the reported patients experienced clinical or radiographic improvement, or both, including resolution of the associated hypothyroidism in three patients with diffuse hepatic lesions [29]. The use of propranolol to treat symptomatic hepatic IH requires further study to determine optimal dosage and use as a monotherapy or to be used in conjunction with steroids and vincristine.

PHACE Syndrome and Propranolol

PHACE syndrome (posterior fossa abnormalities, hemangioma, arterial/aortic anomalies, cardiac anomalies, eye abnormalities, and sternal/supraumbilical raphe) is an uncommon neurocutaneous disorder where infants present with large (>5 cm), facial hemangiomas.

Propranolol use in PHACE syndrome remains controversial, because there is concern that propranolol could increase the risk for stroke in this patient population. A recent poster described propranolol use in 32 patients with PHACE syndrome with cervical and intracranial artery anomalies. These children were treated with an average dose of 1.8 mg/kg/day divided tid or bid. One of 32 patients developed a change in neurologic status. Recommendations were to use the lowest possible dosage of propranolol, slow titration, tid dosing to minimize abrupt changes in BP, and close patient follow-up [30]. PHACE syndrome is not an absolute contraindication to propranolol use, but must be considered and monitored carefully, particularly if the child has aberrant cerebrovasculature.

Airway IH and Propranolol

Airway hemangiomas can be life-threatening. Children with IHs in the beard or mandibular distribution (facial segment S3) are at risk of developing airway IHs. Children with PHACE syndrome have been recently reported to have up to 52 % risk of airway hemangiomas [31]. Rarely, IHs in other locations can be associated with airway IHs, and these children present with stridor, hoarse cry, or difficulty breathing in the first 4–12 weeks of life. Traditional treatment of airway IHs is with systemic corticosteroids, laser surgery performed by ENT, and rarely tracheostomy. There are case reports and case series of propranolol successfully treating airway IHs [11•, 14, 15, 32]. A meta-analysis of 36 infants with airway IHs concluded that propranolol should be recommended as a first-line treatment in infantile airway hemangiomas. A full cardiovascular and respiratory evaluation is recommended before initiation of propranolol in these children, and inpatient monitoring is likely required for children with respiratory symptoms [33].

Propranolol Used to Treat IH Beyond the Proliferative Phase

Propranolol is effective to treat IHs beyond the proliferative phase. A retrospective multicenter study of 49 patients confirmed that propranolol is effective to shrink IH that are beyond the proliferative phase, including effectiveness in a 10-year-old child. The authors suggest using propranolol in older infants before surgical intervention, because it may minimize the need for plastic surgery or result in a smaller excision [34•]. Propranolol

was as effective in children older than age 6 months as it was in children younger than age 6 months in the largest, retrospective, multicenter, case series to date [11•]. Propranolol was effective in children older than age 6 months who were treated in a randomized, controlled trial [5•].

Safety/Adverse Effects

Since the advent of systemic propranolol therapy for IH, pediatric dermatologists and those caring for infants with IH have become familiar with the side effects and contraindications of beta adrenergic blocking medications (Table 2). The adverse effects of propranolol are well known and include bradycardia, hypotension, bronchospasm, hypoglycemia, sleep disturbance, nightmares, and acrocyanosis. Gastroesophageal reflux, nausea, vomiting, diarrhea, somnolence, hyperkalemia, tumor lysis syndrome, psoriatic drug rash, respiratory syncytial virus exacerbation, and dental caries have been reported [35–38]. Propranolol is contraindicated in patients with asthma, heart block, and sinus bradycardia, and it is recommended not to be used during episodes of bronchiolitis. Caution is advised in patients with PHACE syndrome and cervical or intracranial arterial abnormalities. The most serious side effect of propranolol is hypoglycemia. Propranolol is thought to cause hypoglycemia by inhibiting glycogenolysis, glyconeogenesis, and lipolysis. Children have lower glycogen stores and higher glucose consumption rates when fasting and, therefore, are more susceptible to hypoglycemia than adults [39•]. It is suggested to administer propranolol with feeds to reduce the risk of hypoglycemia. Therapy should be temporarily discontinued in the event of intercurrent illness, such as vomiting, diarrhea, decreased oral intake, somnolence, or bronchiolitis. An uncontrolled case series showed a high rate (64 %) of mostly minor side effects in 18 of 28 infants treated with propranolol for IHs [40].

Table 2 Side effects of propranolol

■ Hypotension
■ Bradycardia
■ Hypoglycemia
■ Bronchospasm
■ Peripheral vasoconstriction
■ Gastrointestinal disturbances
■ Behavioural changes/sleep disturbances
■ Rashes-psoriatic
■ Diarrhea
■ Hyperkalemia
■ Dental caries

Controlled studies will be helpful to further delineate adverse events attributable to propranolol in this patient population.

Rebound Growth of IH

Pediatric dermatologists have noticed that when propranolol treatment is ceased, there may be rebound growth of the IH or changes, such as increased redness and elevation of the IH.

One case series has specifically looked at this issue and found that 5 of 24 patients (19 %) had rebound IH growth within 0 to 6 months of stopping oral propranolol. Early cessation of treatment or a prolonged IH proliferative phase may be the reason for rebound growth, but the exact mechanism remains unknown. It was mainly the deep component that recurred [41]. The patients in this study also mainly had deep segmental IH, which have been known to have a prolonged proliferative phase [42]. It is important to follow-up with patients after discontinuing propranolol (for up to 6 months) to assess for potential rebound and intervene as necessary, especially if the children are younger than 1 year of age. In my experience, if you have access to an experienced ultrasonographer, performing an ultrasound before stopping propranolol in patients with deep IHs may be helpful to assess a residual deep component with high blood flow, which is likely to rebound.

In a randomized, controlled trial, increased redness and increase in volume was noted after discontinuing propranolol. This was more common in children younger than 1 year of age [5•].

Topical Beta Blockers

Timolol is a topical nonselective beta-blocker that is the most commonly prescribed therapy for childhood glaucoma. Timolol in its ophthalmic administration is contraindicated in patients with asthma, sinus bradycardia, atrioventricular block, or overt cardiac failure. Timolol has showed therapeutic promise for IH in a few case reports and small pilot studies. For superficial (thin) hemangiomas, at least, topical timolol may be effective. The largest study to date provides encouraging results. It describes the use of timolol maleate 0.5 % or 0.1 % gel forming solution for small, superficial IH retrospectively in a multicenter study involving 73 children. The majority (85 %) were treated with the 0.5 % solution twice daily without occlusion for approximately 3–6 months. All children improved except one, and one child had sleep disturbances. No rebound growth occurred after 3–6 months of follow-up [43]. The mechanism of timolol is presumably similar to that of propranolol. Given intravenously, timolol has been shown to be eight times as potent as propranolol. Topical timolol gel is thought to be less bioavailable for systemic absorption than topical timolol

solution. A recent commentary cautions those prescribing topical timolol to be aware of side effects and systemic absorption, which may be even more pronounced in certain locations, such as mucosal surface and thinner skin sites, such as periocular, oral, perineal, perianal, and ulcerated IH. Using a topical medication also may delay use of a systemic medication in cases where systemic agents would be more appropriate. Recommendations include telling parents to use an exact number of drops, such as 1–2 drops per application to help avoid overdose, as well as monitoring for fussiness, poor circulation, and hypothermia [44]. Because systemic absorption likely occurs with topical timolol, patient's vital signs should be monitored. Two small studies have assessed topical 1 % propranolol applied bid or tid to superficial IHs and found that it was effective [45, 46]. Randomized, controlled studies of the safety and efficacy of topical beta-blockers for IH are in process. Future studies should address the optimal dosage concentration, duration of treatment, systemic absorption of topical timolol and topical propranolol, and mode of application. Until we know more, systemic therapy should probably remain first-line therapy for time-sensitive problematic hemangiomas, such as those that threaten vision.

Conclusions

Treating IHs with oral propranolol hydrochloride 2 mg/kg/day divided bid to tid until the end of the proliferative phase appears to be very effective, and the evidence to date supports its use as a first-line option for potentially disfiguring or complicated IHs. Larger dose-finding studies are required to confirm the optimal dosage of propranolol. Due to the heterogeneous nature of IHs, duration of treatment with propranolol will likely need to be individualized depending on the child's type of IH and response to treatment.

Guidelines for initiating treatment with propranolol and therapeutic monitoring vary widely between institutions. Until consensus practice guidelines for propranolol and IHs are published, it is recommended that dermatologists communicate with their local pediatric cardiologists to establish their practice parameters. There may be unknown side effects of propranolol used for the indication of infantile hemangiomas and regular follow-up visits are advised. Although there may be pressure from parents to treat uncomplicated, nondisfiguring IHs, propranolol is not without side effects, and it is important to weigh the risks and benefits of treatment, as well as to reassure parents about the natural history of IHs and eventual involution. Evidence from

larger, controlled trials should be helpful to answer outstanding questions about propranolol, particularly safety profile.

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