

# Treatment of infantile hemangioma with propranolol

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Infantile hemangiomas are proliferative vascular disorders that occur in the pediatric airway, potentially causing airway narrowing and respiratory stress. It appears in 1 out of 10 children, more frequently in girls. Hemangiomas are benign tumours that usually appear on the head or neck but may also occur in deep organs. Until recently, the most common medical therapy used was high-dose systemic corticosteroids, which often resulted in significant adverse effects (hypertension, irritability, and Cushing-like conditions). In 2008, propranolol, which was used for treating cardiovascular diseases, was accidentally found to be successful in the treatment of intractable diffuse lymphangiomatosis. Propranolol apparently causes down-regulation of the Raf mutagen-activated protein kinase-signalling pathway, with reduced expression of vascular endothelial growth factor. Propranolol inhibits lymphangiogenesis and reduces lymphatic malformation growth by inhibition of vascular endothelial growth factor. It could have a beneficial effect on lymphatic malformation and in diffuse lymphangiomatosis, and may exert its effects on growing hemangiomas by three different molecular mechanisms: vasodilation, inhibition of angiogenesis and induction of apoptosis. This is a review of the pharmacology of propranolol as it relates to the treatment of hemangiomas.

**KEYWORDS:** hemangiomas; infants; propranolol.

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## ■ INTRODUCTION

Lymphangioma is a rare congenital malformation of the lymphatic system, which usually occurs in children before the age of 2 years.<sup>1</sup> Infantile hemangioma is the most common tumor in infants.<sup>2</sup> It occurs in 1 out of 10 children<sup>2</sup> and is more frequent in children of Caucasian race, and is three times more common in girls.<sup>3</sup> Untreated, these lesions carry a mortality rate of nearly 50%.<sup>4,5</sup>

Propranolol, a  $\beta_1$  and  $\beta_2$  adrenergic receptor blocker, accelerates regression of proliferating infantile hemangiomas, but does not affect non-involuting congenital hemangiomas and non-proliferating in infantile hemangiomas.<sup>6</sup>

Infantile hemangiomas are proliferative vascular tumours that occur in the pediatric airway, potentially causing airway narrowing and respiratory stress.<sup>7</sup> They are composed of endothelial cells with high mitotic rates and stromal components such as fibroblast, mast cells and pericytes.<sup>8</sup> The natural history of the hemangioma characteristically goes through a rapid growth phase during infancy followed by gradual involution.<sup>9</sup> About 80% of hemangiomas are located in the head and neck regions.<sup>10</sup>

Over the last few years, propranolol has become a popular and successful treatment for infantile hemangiomas. However, further research on its safety is needed if it is going to be used more frequently.<sup>11</sup> At present propranolol is awaiting licensing by the European Medicines Agency for

use of hemangiomas but is licensed for other pediatric conditions. If it is to be used more frequently for hemangioma treatment, its efficacy and safety profile must be investigated in more detail. Starkey and Shahidullah<sup>11</sup> aimed to review the evidence on propranolol therapy for infantile hemangiomas with a particular focus on its safety profile.

Propranolol is a non-selective beta blocker that is used for the treatment of a variety of cardiovascular diseases. Lèauté-Labréze et al.<sup>12</sup> widely used propranolol for the first-line treatment of infantile hemangioma. Successful treatment of intractable diffuse lymphangiomatosis was also reported by Ozeki et al.<sup>13</sup> Propranolol is thought to cause down-regulation of the Raf mitogen-activated protein kinase signalling pathway, with reduced expression of vascular endothelial growth factor.<sup>14</sup>

Multiple lesions with increased vascular endothelial growth factor staining have been reported in lymphatic malformation specimen histological factors. Therefore, propranolol could have a beneficial effect on lymphatic malformations as it does in diffuse lymphangiomatosis.<sup>13</sup> The vascular endothelial growth factor family is involved in the development and growth of the vascular endothelial system.<sup>13</sup>

## ■ BIBLIOGRAPHIC RESEARCH

The bibliographic search was performed electronically using PubMed and EMBASE databases as search engines;

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May 2014 was the cut-off point. The following key words "propranolol neonate", "propranolol metabolism", "propranolol therapy neonate", "propranolol pharmacokinetics neonate", "management of infantile hemangiomas" and "propranolol citrate adverse effects neonate" were used. In addition, the books NEOFAX: a Manual Used in the Neonatal Care by Young and Mangum<sup>15</sup> and the Neonatal Formulary<sup>16</sup> were consulted.

## ■ RESULTS

### Dose of propranolol in infants

Young and Mangum<sup>15</sup> suggest giving a starting oral dose of 0.25 mg/kg per dose every 6 hours, and increase as needed up to a maximum of 3.5 mg/kg every 6 hours. The starting intravenous dose should be 0.01 mg/kg every 6 hours; increase as needed to a maximum of 0.15 mg/kg every 6 hours. Elective dosage requirements will vary significantly. Propranolol is the most widely used non-selective  $\beta$ -blocker in infants. Neonatal Formulary<sup>16</sup> suggests using from 0.25 up to 0.75 mg/kg every 8 hours by mouth for neonatal thyrotoxicosis, and combining with hydralazine in order to control dangerous hypertension. It is sometimes used to control arrhythmia, to manage the long QT syndromes and, experimentally, in the management of severe infantile hemangiomas.<sup>16</sup> For arrhythmia, give 0.02 mg/kg intravenously over 10 min with ECG monitoring and increase this, in steps, to a cumulative.

### Monitoring of propranolol in infants

Monitoring of propranolol should be done by continuous electrocardiogram during acute treatment of arrhythmias, during inhibition treatment, and after dosage changes. Measurements of systemic blood pressure should be performed frequently. Measure blood glucose during initiation of treatment and after dosage changes. Assess for increased airway resistance.<sup>15</sup> Treatment of neonatal hypertension should be started with 0.25 mg/kg every 8 hours by mouth together with hydralazine to a maximum of 2 mg/kg per dose. The therapeutic levels of propranolol blood should range between 20 and 100  $\mu$ g/ml.<sup>15</sup>

### Pharmacokinetics of propranolol in infants with hemangioma

Although propranolol pharmacokinetics have been studied extensively in adults, little is known about the effect in infants. Filippi et al.<sup>17</sup> measured the propranolol concentrations after oral administration in 4 term and 32 preterm neonates. Propranolol was administered at the dosage of 0.5 or 0.25 mg/kg every 6 hours. After 0.5 mg/kg per hour, the mean  $\pm$  SD level of propranolol was 60.8  $\pm$  25.0 ng/ml, the time of maximal concentrations was 2.6  $\pm$  0.9 hours and the area under the plasma concentration was 364.7 + 150.2 ng/ml per hour. The half-life was 14.9  $\pm$  4.3 and 15.6  $\pm$  6.1 hours after the dose of 0.5 and 0.25 mg/kg per hour, respectively. The apparent clearance was 27.2  $\pm$  13.9 and 31.3  $\pm$  13.3 ml/kg per min, after 0.5 and 0.25 mg/kg doses, respectively. In infants, the bioavailability is 30% to 40%.<sup>15</sup> In adults, the bioavailability is 26  $\pm$  10%, the clearance is 16  $\pm$  5 ml/min/kg, the half-life is 3.9  $\pm$  0.4 hours and the peak plasma concentrations is 49  $\pm$  8 ng/ml.<sup>18</sup>

In adults, the use of propranolol has been well studied, and when taken orally it shows significant first-pass metabolism with a peak absorption within 1 to 3 hours and

a half-life of around 3.5 to 6 hours.<sup>18</sup> In infants, the dosage ranges between 1 and 3 mg/kg/day.<sup>11</sup> The age interval at initiation of therapy ranges from 2 months and 2.5 years.<sup>15,16</sup>

### Development and classification of infantile hemangiomas

Infantile hemangiomas are the most common tumours of infancy, occurring in 3% to 5% of all infants.<sup>19</sup> Chang et al.<sup>2</sup> state that the infant lymphoma occurs in 1 out of 10 children. Infants 2 months old have a distinct pattern of proliferation and involution, and express the glucose transporter (GLUT)-1, a protein normally found in erythrocytes and endothelial blood-tissue barriers.<sup>20</sup> Most infantile hemangiomas are present as solitary tumours affecting the skin, multifocal infantile hemangioma may be present as solitary tumours affecting the skin. Multifocal infantile hemangiomas<sup>21</sup> are not rare and may be associated with extracutaneous involvement, particularly affecting the liver.<sup>21</sup>

Spiteri et al.<sup>22</sup> reviewed the use of propranolol in the management of periocular capillary hemangioma. Capillary hemangiomas, or infantile hemangiomas, are the most common congenital vascular alteration in the periocular region. Several treatment modalities have been documented, with variable degrees of success. Propranolol has been recently reported to be an effective and safe alternative. The aim of Spiteri's review<sup>22</sup> was to exanimate the evidence base for the use of orally administered propranolol in the management of periocular capillary hemangioma; this information is useful to guide future research. Rarely, a capillary hemangioma can be acquired at or before puberty.<sup>23</sup>

In 2007, Christians-Lagay et al.<sup>24</sup> proposed that hepatic hemangiomas could be classified into three categories: focal, multifocal and diffuse hemangiomas. Diffuse infantile hepatic hemangiomas are frequently associated with abdominal compartment syndrome and conjunctive hypothyroidism, with a high risk of mortality or need for liver transplantation as a life-saving therapy. Focal hepatic hemangiomas are large solitary tumours and most are probably not infantile hemangioma. Unlikely infantile hemangiomas are often present at time of birth; most are not associated with skin lesions, and when tested, most have been GLUT-1 negative.<sup>25</sup> In contrast, multifocal and diffuse hepatic hemangiomas are in most cases true infantile hemangiomas involving the liver.<sup>26</sup> Multifocal infant hepatic hemangiomas are present as multiple spherical tumours, and many remain completely asymptomatic, resolving spontaneously without sequelae.

## ■ ADVERSE EFFECTS

The potential side effects of propranolol include bradycardia, hypotension, bronchospasm, hypoglycaemia, peripheral vasoconstriction, gastrointestinal disturbances, behavioural changes, sleep disturbances, rashes, profuse sweats and diarrhoea, hypocalcaemia, rashes, gastrointestinal discomfort/reflux, fatigue, and bronchospasm, all of which tend to be quite rare and are seen at doses > 2 mg/kg/day.<sup>11,27,28</sup> A side effect of propranolol is hypoglycaemia,<sup>5</sup> which has also been reported in infants with hemangiomas.<sup>29,30,31</sup> Propranolol is thought to cause hypoglycaemia by inhibiting glycogenolysis, gluconeogenesis and lipolysis.<sup>32</sup> Twenty-one cases of hypoglycaemia were reported by Holland et al.<sup>31</sup> Fifty-two percent of patients were receiving

long-term treatment for over 5 months at doses ranging from 2 to 14 mg/kg/day. Children were more susceptible to hypoglycaemia for two reasons. Firstly, they have lower glycogen stores leading to reduced fasting ability and secondly, they have higher glucose utilisation rates when fasting.<sup>33</sup>

$\beta$ -Blockers can mask the early sympathetic signs of hypoglycaemia such as tachycardia, sweating and palpitation. It is therefore advised that propranolol should be temporarily discontinued in those with reduced calorie intake or inter-current illness.<sup>32</sup> This suggests that there may be an additional risk of hypoglycaemia secondary to adrenal suppression from long-term steroid use.<sup>30</sup>

Propranolol inhibits the sympathetic nervous system by blocking the  $\beta$ -receptors in the the sympathetic nervous system as well as reducing cardiac contractility, thus causing bradycardia and reduced blood pressure, respectively.

$\beta_2$  Adrenoreceptors are located in the lungs and so non-selective  $\beta$ -blockers such as propranolol act on the airways. This can cause bronchospasm which usually only occurs in patients with a known reactive airways disease. In one study on infantile hemangiomas, a child developed wheezing 3 months after initiating propranolol but symptoms resolved after treatment was stopped.

Supraventricular tachycardia, with atrioventricular re-entry being the underlying mechanism, is the most frequent tachycardia rhythm, requiring medical treatment in infants with no cardiac disease. The acute treatment of a single episode of supraventricular tachycardia generally has an excellent prognosis. An antiarrhythmic prophylaxis of supraventricular recurrences is usual recommended during the first year of life. Although many efficient drugs are available for the supraventricular treatment, a careful risk-benefit analysis of each single case should the correct drug choice.

## ■ DISCUSSION

Use of oral propranolol for treatment of infantile hemangiomas was first reported in 2008 on 2 children who showed rapid regression of their lesions after being started on this medication for cardiovascular issues. Since then, the effectiveness of oral propranolol for infantile hemangiomas of all types has been demonstrated in multiple publications.<sup>2,32,34</sup> Typically, improvement in cutaneous infantile hemangioma can be observed in 24 to 48 hours of administration of the initial dose of propranolol.<sup>35</sup> Complete regression is sometimes observed by the end of the sixth month of treatment, both objectively and by Doppler ultrasound.<sup>36,37</sup> Oral propranolol was noted to resolve stridor caused by subglottic airway hemangiomas in 24 to 48 hours of the initial dose.<sup>38</sup>

Propranolol has also been successfully used for treatment of segmental infantile hemangiomas in PHACES syndrome without reduction of brain perfusion.<sup>39</sup> However, many clinicians are reluctant to use propranolol in this setting because of concern regarding stroke risk in patients with agenesis or dysgenesis of the carotic circulation.<sup>39,40</sup> Propranolol has also been successfully used for treatment of segmental infantile hemangiomas in PHACES syndrome without reduction of brain perfusion.<sup>39</sup>

The most serious side effect of propranolol is hypoglycaemia,<sup>31</sup> which has also been reported following its use for infantile hemangioma.<sup>28,30,32</sup>

While propranolol's general mechanism of action is well established as an orthostatic antagonist of  $\beta_1$  and  $\beta_2$  adrenergic receptors, its mechanism of action on infantile hemangiomas remains uncertain. It has been suggested that propranolol may exert its effect via vasoconstriction of the high-flow blood vessel feeding the infantile hemangioma tumour or through inhibition of angiogenesis via hypoxia-inducible factor  $\alpha_1$ -mediated inhibition of vascular endothelial growth-A,<sup>41</sup> matrix metalloproteinases and IL-6 (proangiogenic cytokine). It has also been proposed that propranolol acts by suppressing renin production, which in turn leads to reduction in angiotensin II levels, which leads to reduced vascular endothelial growth factor from mesenchymal stem cells, and a shift from vasculogenesis to adipogenesis.<sup>42</sup> Lymphangiomas are a rare congenital pathology that appears preferentially in the face or neck. Lymphangiomas are the most common tumours of childhood. They are composed of endothelial cells with high mitotic rates and stromal components such as fibroblast, mast cells and pericytes.<sup>8,41</sup> Infantile hemangiomas occur in 1 out of 10 children<sup>20</sup> and are characterized by rapid growth during the first year of life (proliferating phase) and a slow regression that is usually completed by 7 to 10 years of age (involuting phase). Infantile hemangiomas are proliferative vascular tumours potentially causing airway narrowing and respiratory stress.<sup>42</sup>

The course of infantile hemangiomas includes three stages: proliferating, involuting and involuted. In 30% of neonates, infantile hemangiomas are evident at birth.<sup>8</sup> At 3 to 6 months of life, the growth phase begins and continues until 9 to 12 months of age. In many infants, the growth phase of an infantile hemangioma begins just after birth; involution may start as soon as 3 to 6 months. The appearance of a superficial infantile hemangioma changes during the involuting phase. Most infantile hemangiomas are in anatomically neutral locations and involute without intervention. Prevention of life-threatening complications or permanent disfigurement and avoidance of aggressive or scarring treatments are the goals of management. Treatment of ulceration is also important.<sup>43</sup> Therapy depends on several factors, including the presence of associated anomalies and life-threatening or function-threatening complications.<sup>8</sup> Indications for early medical intervention include large facial infantile hemangiomas or those located in the nose, airway or eyes. In these instances, early medical therapy may prevent life-threatening complications, severe pain or visible scars.<sup>8,44,45,46</sup>

The appearance of infantile hemangiomas depends in their location within the skin. Those situated in the superficial dermis because of their appearance as bright-red, raised nodules, are commonly termed strawberry hemangiomas. Infantile hemangiomas deep in the reticular dermis give the appearance of soft masses with a blue tone and normal overlying skin. In some instances, this neoplasm may have both superficial and deep elements.

Lèauté-labréze<sup>12</sup> treated 11 infants with propranolol at the dosage of 3 mg/kg/day and found a significant change of colour and softness of hemangiomas within 24 hours. The age range promising results ranges considerably.<sup>11</sup>

Individual  $\beta$ -blockers vary with regard to their  $\beta$  receptor selectivity, intrinsic stimulatory activity, lipid solubility and membrane-stabilising effects. Stimulation of  $\beta_1$  receptors increases inotropy, chronotropy and automaticity in the



heart, while  $\beta_2$  receptor stimulation results in bronchodilation and enhanced gluconeogenesis. Most infant hemangiomas are in anatomically neutral locations and involute without intervention. Treatment of anatomical ulceration is also important.<sup>43</sup>

Most groups have used a dose of 1 to 3 mg/kg/day for the treatment of infantile hemangiomas. The majority performs baseline cardiology investigations prior to commencing propranolol in outpatients.<sup>27,47</sup>

Currently, propranolol is widely used and is recommended as the first-line treatment for infantile hemangiomas in some sites, especially the airway.<sup>48</sup> Treatment of intractable infantile hemangiomas is still challenging, especially in patients with cervical infantile hemangiomas. In this case, partial resection and sclerotherapy was used, but the patient's mixed-type infantile hemangiomas had not regressed after 1 year.

There are several therapies for the treatment of infantile hemangiomas (Table 1). The first-line therapy to treat infant hemangiomas is cortisol or propranolol. In 50 out of 85 patients (85%), propranolol was used as the first-line therapy. However, propranolol has also been successfully used for treatment of segmental infantile hemangiomas in PHACES syndrome without reduction of brain perfusion.<sup>39</sup> However, many clinicians are reluctant to use propranolol in this setting because of concern regarding stroke risk in patients with agenesis or dysgenesis of the carotid circulation.<sup>39,40</sup>

While propranolol's general mechanism of action is well established as an orthostatic antagonist of  $\beta_1$  and  $\beta_2$  adrenergic receptors, the mechanism of action on infantile hemangioma remains uncertain. It has been suggested that propranolol may exert its effective via vasoconstriction of the high-flow blood vessels feeding the infant hemangioma tumor or through inhibition of angiogenesis via hypoxia-inducible factor (HIF)  $-\alpha$  mediated inhibition of VEGF-A,<sup>41</sup> matrix metalloproteinase and ILA6 (proangiogenic cytokine). It has also been proposed that propranolol acts by suppressing rennin production, which in turn leads to reduced VEGF secretion from mesenchymal stem cells, and a shift from vasculogenesis from mesenchymal stem cells, and a shift from vasculogenesis to adipogenesis.

In pediatric cardiology practice, propranolol is used to treat tachycardia, congestive heart disease, and symptoms related to congenital heart disease. Doses as high as 17/mg/day are used in these settings. The use of propranolol for the treatment of infantile hemangiomas has been used for the first time by Léauté-Labrèze et al.<sup>12</sup> Further research is required to ensure that the doses recommended for the treatment of infantile hemangiomas are evidence-based. Such research may result in an improvement in the efficacy of propranolol in neonates.

**Table 1 - Drugs used to treat hemangiomas**

Management options	
First-line therapy	Corticosteroids (topical, intralesional, systemic) propranolol
Second-line therapy	Interferon-alpha (2a-2b), laser therapy, surgical therapy
Other therapy	Cyclophosphamide, imiquimod, vincristine, timolol maleate solution

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## RESUMO

Hemangiomas infantis são desordens vasculares proliferativas que ocorrem na via aérea de crianças, potencialmente causando o estreitamento das vias aéreas e estresse respiratório. Ocorre em uma de cada dez crianças, mais frequentemente em meninas. Os hemangiomas são tumores benignos que geralmente aparecem na cabeça ou no pescoço, mas também podem ocorrer em órgãos profundos. Até recentemente, a terapia médica mais comum era a ministração de doses elevadas de corticosteroides sistêmicos, que muitas vezes resultavam em efeitos adversos significativos (hipertensão, irritabilidade e condições "Cushing-like"). Em 2008, o propranolol, utilizado para o tratamento de doenças cardiovasculares, foi acidentalmente usado com sucesso para o tratamento de linfangiomatose difusa intratável. Aparentemente o propranolol induz infra-regulação da via de sinalização da proteína quinase mutagênica Raf-ativada, com reduzida expressão do fator de crescimento vascular endotelial. O propranolol inibe a linfo-angiogênese e reduz o crescimento de malformações linfáticas por inibição do fator de crescimento vascular endotelial. Pode ter um efeito benéfico sobre a malformação linfática e em linfangiomatose difusa e pode exercer os seus efeitos sobre os hemangiomas por três mecanismos moleculares distintos: vasodilatação, inibição da angiogênese e indução de apoptose. Esta é uma revisão sobre a farmacologia de propranolol, focando especificamente no tratamento de hemangiomas.

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