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# Propranolol for infantile haemangiomas: a review

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**ABSTRACT**

Infantile haemangiomas are the most common benign tumour of infancy. However the majority are self-resolving and only a small minority of cases require treatment, with various different medications being used in the past. Over the last few years, propranolol, a non-selective  $\beta$ -blocker, has become a popular and successful treatment for infantile haemangiomas. However, further research on its safety is needed if it is going to be used more frequently. This article summarises the current literature on propranolol for haemangioma treatment with emphasis on its toxicity and adverse event profile.

**INTRODUCTION**

Infantile haemangiomas are commonly seen in paediatrics with a small number being a challenge to manage. Over the last few years, propranolol has become increasingly popular as a successful medication choice with fewer side effects than other current treatments. At present propranolol is awaiting licensing by the European Medicines Agency for use for haemangiomas but is licensed for other paediatric conditions. If it is to be used more frequently for haemangioma management, then its efficacy and safety profile must be investigated in more depth. It is important when any drug is used for a new indication that those who are not familiar with prescribing it understand the potential adverse effects. This article aims to review the evidence on propranolol therapy for infantile haemangiomas with a particular focus on its safety profile.

Articles were found through a literature search using MedLine and EMBASE. MeSH terms used included 'haemangiomas' and 'propranolol' and the subheadings 'drug therapy', 'toxicity' and 'adverse events'.

**EPIDEMIOLOGY AND NATURAL HISTORY**

Infantile haemangiomas are the most common benign tumours in infancy affecting 5–10% of the population.<sup>1</sup> They are seen less commonly in African American and Asian compared to Caucasian children and occur more frequently in females with a female:male ratio of 3:1.<sup>2</sup> The head and neck region is the most frequently involved area (60%), followed by the trunk (25%) and the extremities (15%).<sup>3</sup>

Infantile haemangiomas have a predictable natural history. The majority are not present at birth. However, a minority may have a precursor lesion such as a vascular patch or area of pallor. Soon after birth infantile haemangiomas undergo significant growth (proliferative phase) for several months followed by gradual involution which usually occurs over several years. Regression is

complete in 50% of 5-year-old patients and 90% of 9-year-old patients.<sup>4</sup>

The majority of children with infantile haemangiomas require no treatment as the lesions regress over time and produce no long term scarring. In approximately 10% of cases, depending on their anatomical site, there can be serious or life threatening complications requiring treatment (see table 1).<sup>5</sup> At present there are no gold standard systemic treatments for infantile haemangioma. The current approach for complicated infantile haemangiomas includes the use of systemic or intralesional corticosteroids, chemotherapeutic agents such as  $\alpha$  interferon and vincristine, laser therapy, surgical resection or a combination of these treatments.<sup>6</sup> At present there are no published comparative studies of these approaches.

**PROPRANOLOL AND INFANTILE HAEMANGIOMAS**

In 2008, a child with obstructive hypertrophic cardiomyopathy was treated with propranolol at 3 mg/kg/day. This child was noted to have a co-existing nasal haemangioma and there was a coincidental improvement of the haemangioma while the child was on propranolol. The same authors studied a series of 11 patients and found a significant change in both the colour and softness of haemangiomas within the first 24 h on propranolol, with all haemangiomas improving.<sup>7</sup> Subsequently, numerous other case reports and small studies have been undertaken showing promising results as seen in table 2. The age range for starting propranolol varies in the literature.<sup>6–17</sup> Current evidence shows more predictable shrinkage of the tissue with propranolol, but unlike other treatments propranolol also has an effect on the tissue once the involution phase commences.<sup>7</sup>

**PHARMACOKINETICS**

Individual  $\beta$ -blockers vary with regard to their  $\beta$  receptor selectivity, intrinsic stimulatory activity, lipid solubility and membrane-stabilising (sodium channel) effects. Stimulation of  $\beta_1$  receptors increases inotropy, chronotropy and automaticity in the heart, while  $\beta_2$  receptor stimulation results in bronchodilatation and enhanced gluconeogenesis.<sup>18</sup>

At present in the UK, propranolol is licensed in children for use in migraine prophylaxis, arrhythmias, thyrotoxicosis and tetralogy of Fallot.<sup>19</sup> It is a non-selective  $\beta$ -adrenergic antagonist that demonstrates equal affinity for both  $\beta_1$  and  $\beta_2$  receptors and therefore acts on multiple tissues. The use of propranolol has been well studied in adults and when taken orally it shows significant first pass metabolism with peak absorption within 1–3 h and a half life of around 3.5–6 h.<sup>20</sup> There are no

published pharmacokinetic studies on propranolol in infants or children.

### MECHANISM OF ACTION

Haemangiomas are composed a number of cell types including endothelial cells. Recent studies have found that capillary endothelial cells express  $\beta_2$  adrenergic receptors.<sup>21</sup> Propranolol is thought to exert its effects on growing haemangiomas by three different molecular mechanisms: vasoconstriction, inhibition of angiogenesis and induction of apoptosis.<sup>20</sup>

The autonomic nervous system and epinephrine play key roles in the control of vascular tone. Epinephrine can cause both vasoconstriction and vasodilatation by activating both the  $\alpha_1$  receptors and  $\beta_2$  receptors, respectively.  $\beta$ -Blockers without  $\alpha$ -antagonistic effects like propranolol inhibit epinephrine mediated vasodilatation and this leads to vasoconstriction of endothelial cells.<sup>22</sup>

During the growth phase of haemangiomas, there is increased expression of two major proangiogenic factors:

basic fibroblast factor and vascular endothelial growth factor (VEGF). Recent publications have found that the expression of VEGF is reduced by  $\beta$ -blockers which thus leads to inhibition of angiogenesis.<sup>23</sup>

Apoptosis is regulated by a number of pathways, with the  $\beta_1$  adrenoreceptor being the probable receptor involved. It has been hypothesised that by blocking the  $\beta_1$  adrenoreceptor, propranolol induces apoptosis at an increased rate.<sup>24</sup>

### THERAPEUTICS

Most groups have used a dose of 1–3 mg/kg/day (table 2) for the treatment of infantile haemangiomas. However, the duration of treatment ranges widely from 3 to over 12 months. Some continue the medication until regression starts or there is complete haemangioma resolution.<sup>14</sup> The majority perform baseline cardiology investigations prior to commencing propranolol in outpatients.<sup>6–14</sup> However, some are still cautious and admit their patients to hospital for heart rate and blood pressure monitoring.<sup>13</sup> All the groups discussed their protocol with their local cardiology service; it is important to hold discussions with the relevant specialities involved in looking after such children. The current literature supports the tapering of propranolol at the end of the course over a 2–3-week period,<sup>6–21</sup> presumably to prevent the known problem of rebound tachycardia.<sup>25</sup>

### OUTCOME

Studies have shown that haemangioma relapse rates vary after propranolol is stopped (see table 2) with some studies showing no relapse,<sup>11–13</sup> while others have reported that some minor changes reoccurred requiring some patients to restart propranolol.<sup>7–8</sup> One study found that 47% of patients showed some

**Table 1** Sites at high risk for complications of infantile haemangioma<sup>5</sup>

Sites	Complications
Head, neck, perineum, lip	Ulceration
Airway	Airway obstruction
Eye	Astigmatism, amblyopia, tear duct obstruction, proptosis, ptosis, strabismus and myopia
Lumbosacral region	Spinal dysraphism, tethered spinal cord and genitourinary anomalies
Liver	Hepatomegaly, congestive heart failure, thyroid abnormalities

**Table 2** Propranolol dosing, duration and outcome in infantile haemangiomas

Author	Country of study	Number of patients	Dose range (mg/kg/day)	Age range (median, months) at initiation (months)	Location of haemangioma	Duration of treatment (months)	Outcome
Buckmiller <i>et al</i> <sup>6</sup>	USA	41	2	1.5–30 (7.1)	Multiple sites	Not reported	16 excellent responders 15 partial responders 1 non-responder
Leaute-Labreze <i>et al</i> <sup>7</sup>	France	11	2–3	2–6 (3.2)	Facial: 10 Forearm: 1	4–12	All regressed or stabilised
Sans <i>et al</i> <sup>8</sup>	France	32	2–3	2–41 (4.2)	Multiple sites	3–10	10 regressed 6 mild relapse 9 treatment ongoing
Denoyelle <i>et al</i> <sup>9</sup>	France	2	2–3	4 and 11	Phases: 1 Subglottic: 1	7	Both responded with no regression
Rosbe <i>et al</i> <sup>10</sup>	USA	3	1–2	3 weeks–8 months (4.9)	Subglottic	7–18	2 completely responded
Marsciani <i>et al</i> <sup>11</sup>	Italy	1	1–2	2	Hepatic	Not reported	Excellent response
Li <i>et al</i> <sup>12</sup>	Australia	4	2	11 weeks–2.5 years (10.5)	Orbital	6–12 months	All improved
Manunza <i>et al</i> <sup>13</sup>	UK	30	2	1.2–13.5 (5.8)	Facial	3.5–15	All improved
Haider <i>et al</i> <sup>14</sup>	USA	17	Initially 0.5, increased slowly to 2	3 weeks–12 months	Periocular	Until resolution or 9–11 months of age	10 excellent responders 6 good response 1 fair response
Maturo <i>et al</i> <sup>15</sup>	USA	2	2	3 and 5	Airway	Not reported	Both responded
Nauouri <i>et al</i> <sup>16</sup>	France	4	1–2	5 weeks–5 months (3.0)	Ulcerated Lip: 1 Body: 2 Skull: 1	92 ongoing treatment	3 excellent response 1 relapsed off treatment
Qin <i>et al</i> <sup>17</sup>	China	58	1–1.5	1–12 (4)	Multiple	2–5	10 excellent response 35 good response 12 moderate response 1 poor response

Box 1 Side effects of propranolol<sup>8 19</sup>

- ▶ Bradycardia
- ▶ Hypotension
- ▶ Bronchospasm
- ▶ Hypoglycaemia
- ▶ Peripheral vasoconstriction
- ▶ Gastrointestinal disturbances
- ▶ Behavioural changes/sleep disturbances
- ▶ Rashes – purpura, psoriatic type
- ▶ Profuse sweats
- ▶ Diarrhoea

success on propranolol but needed further therapy for resolution of the haemangiomas.<sup>6</sup> A minority of patients may not respond to propranolol treatment.<sup>6 17</sup> Given that the majority of the literature is based on small numbers of patients, further research is needed to provide more accurate relapse and non-responder rates. The methods for quantifying change in haemangiomas are also an area for further investigation.

## TOXICITY

β-Blockers have a well documented safety and side effect profile. The common side effects are listed in box 1. There has been one reported death in children related to β-antagonists. This followed ingestion of a significant overdose of propranolol by a 7-year-old girl.<sup>26</sup> A further review revealed that in 40 years of clinical use at therapeutic doses in children less than 7 years of age, there have been no cases of mortality and no serious cardiovascular events.<sup>27</sup>

The most serious side effect of propranolol is hypoglycaemia,<sup>28</sup> which has also been reported following its use for infantile haemangiomas.<sup>14 29 30</sup> Holland *et al* reviewed 21 cases of hypoglycaemia related to propranolol use.<sup>31</sup> Eleven (52%) patients were receiving long term treatment for over 5 months at doses ranging from 2 to 14 mg/kg/day. Some 94% of the episodes occurred after a period of fasting with the majority occurring in the early morning. There have been a few cases with low doses (<4 mg/kg/day) suggesting that the hypoglycaemia may not always be dose dependent.<sup>31</sup> Propranolol is thought to cause hypoglycaemia by inhibiting glycogenolysis, gluconeogenesis and lipolysis.<sup>28</sup> Children seem to be 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>31</sup>

Another concern is that β-blockers can mask the early sympathetic signs of hypoglycaemia such as tachycardia, sweating and palpitations. It is therefore advised that propranolol should be temporarily discontinued in those with reduced calorie intake or inter-current illness.<sup>28</sup>

A recent case report has also described an infant who developed hypoglycaemia after starting propranolol while on a tapering dose of corticosteroids. This suggests that there maybe an additional risk of hypoglycaemia secondary to adrenal suppression from long term steroid use.<sup>29</sup> This may have implications for the treatment of infantile haemangiomas given that current practice is to use steroids as first line therapy in complicated haemangiomas.

There is limited evidence on the incidence of adverse events or drug reactions with β-blockers used within their clinical indication. A study reporting on paediatric β-blocker toxicity

Table 3 Side effects reported in infantile haemangioma studies

Author	Number of patients	Dose range (mg/kg/day)	Number of side effects reported	Side effects
Buckmiller <i>et al</i> <sup>6</sup>	41	2	10	Somnolence: 6 Gastro-oesophageal reflux: 2 Allergic reaction: 1 RSV exacerbation: 1
Sans <i>et al</i> <sup>8</sup>	32	2–3	9	Insomnia: 2 Agitation: 2 Nightmares: 1 Profused sweats: 1 Asthma onset: 1 Cold hands: 1 Reduction in blood pressure: 1
Haider <i>et al</i> <sup>14</sup>	17	2	6	Gastrointestinal upset: 2 Intermittent fatigue: 1 Spitting: 1 Shaking episodes if dose missed: 1
Holland <i>et al</i> <sup>31</sup>	3	1.25–2	3	Hypoglycaemia: 3
Abott <i>et al</i> <sup>32</sup>	3	1	3	Diarrhoea: 3
Qin <i>et al</i> <sup>17</sup>	58	1–1.5	58	Diarrhoea: 37 Sleep change: 18 Bradycardia: 58

RSV, respiratory syncytial virus.

revealed no significant cardiovascular morbidity.<sup>26</sup> However, 4.3% (nine cases) of children in this study reported minor symptoms including lethargy, disorientation and wakefulness.<sup>26</sup> Table 3 shows the side effects reported in studies on infantile haemangiomas.<sup>6 8 14 17 31 32</sup> Diarrhoea has been reported in the literature in both adults and children on propranolol.<sup>17 32 33</sup> Three infants in one centre developed diarrhoea on 1 mg/kg of propranolol for infantile haemangiomas, with two improving on cessation of treatment.<sup>32</sup> In another study in China almost two thirds of children (64% 37/58) with infantile haemangiomas being treated with propranolol developed diarrhoea while on treatment.<sup>17</sup> It has been suggested that the children were either more susceptible to propranolol than adults or alternatively, that the diarrhoea was secondary to maltitol in the propranolol suspension causing osmotic diarrhoea.<sup>32</sup>

Propranolol inhibits the sympathetic nervous system by blocking the β-receptors on the nerves of the sympathetic system as well as reducing cardiac contractility, thus causing bradycardia and reduced blood pressure, respectively. The majority of patients have no side effects from this mechanism, but a survey from multiple US poison centres found 8/378 children less than 7 years of age having had a β-blocker overdose had associated cardiovascular instability, some requiring intravenous medication and fluids. Of these eight children with symptoms, three had taken propranolol in doses ranging from 5 to 12 mg/kg/dose.<sup>29</sup> There is also some concern about its use in some large haemangiomas, that lowering the heart rate and contractility with propranolol may cause decompensated cardiac failure.<sup>31</sup> Those with large haemangiomas should therefore be referred to a paediatric cardiologist before commencing propranolol.

$\beta_2$  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 known reactive airways disease. In one study on infantile haemangiomas, a child developed wheezing 3 months after initiating propranolol but symptoms resolved after treatment was stopped. The wheezing was thought to be undiagnosed allergic asthma as the child had a history of atopic dermatitis and no concomitant infection.<sup>8</sup> There have been reports of bronchospasm in adults with no asthma history being treated with propranolol.<sup>34</sup> Theoretically, premature infants with chronic lung disease may be at more risk from bronchospasm from propranolol given their sensitive airways; however there is currently no evidence to support this hypothesis.

## CONCLUSIONS

There is clear evidence that propranolol is an effective treatment for infantile haemangiomas. Propranolol has been used for a number of decades for cardiovascular disease in children with a reasonable safety profile. Steroids are associated with greater toxicity, including more serious side effects such as stunted growth, hypertension and hypertrophic obstructive cardiomyopathy. Given the encouraging response rates and low risk of adverse events, many centres are now using propranolol as first line treatment for haemangiomas.<sup>35</sup>

There are some concerns that must be addressed if propranolol is going to become the mainstay treatment of haemangiomas. Firstly, propranolol should only be used in complicated haemangiomas. With the advent of easy access to information, there is pressure from families to use propranolol for children with simple haemangiomas, particularly for cosmetic reasons. This would not be justified given that the majority of these haemangiomas resolve spontaneously. Not only would the costs rise but children would be placed at unnecessary risk from the potential side effects of propranolol.

Secondly, further research on propranolol safety and efficacy needs to be carried out given its increased popularity, and indeed dose range studies are underway. At present many dermatologists are using propranolol as first line treatment despite there being no published studies showing that it is as effective as or better than steroids for infantile haemangiomas. This is especially true for those rapidly growing lesions found in cosmetically sensitive areas (eg, the nose). A couple of studies are underway comparing these steroids and propranolol, but until this data is available it would seem prudent to reserve propranolol as second line treatment. However, the indications for propranolol use may change with the results of these studies. For those centres which continue to use propranolol as first line therapy, emphasis must be on producing written guidance by all interested parties so that treatment can be given safely until such time there are acceptable protocols based on trial evidence.

**Competing interests** None.

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