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Oral propranolol in the treatment of proliferating infantile haemangiomas: The British Society for Paediatric Dermatology consensus guidelines

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Abstract

Background

Infantile haemangiomas (IH) are the most common vascular tumours of infancy. Despite their frequency and potential complications, there are currently no unified UK guidelines for the treatment of IH with propranolol. There are still uncertainties and diverse opinions regarding indications, pre-treatment investigations, its use in PHACES syndrome, and cessation of treatment.

Methods

This study used a modified Delphi technique, which involved an international treatment survey, a systematic evidence review of the literature, a face-to-face multidisciplinary panel meeting and anonymous voting.

Results

The expert panel achieved consensus on 47 statements in 8 categories including indications and contraindications for starting propranolol, pre-treatment investigations, starting and target dose, monitoring of adverse effects, the use of propranolol in PHACES syndrome and how to stop treatment.

Conclusions

This consensus guideline will help to standardise and simplify the treatment of IH with oral propranolol across the UK and assist in clinical decision-making.

Introduction

Infantile haemangiomas (IH) are the most common vascular tumours, affecting around 4% of infants.[1] They are more common in premature or low birth weight infants, females and Caucasians.[2] Placental anomalies are an important risk factor.[1] IH typically appear in the first few weeks of life and grow rapidly for the first few months. However, slow proliferation can continue for the first 6-12 months.[3] Due to their spontaneous involution, the majority of IH do not require treatment. Nonetheless, about 15% of IH result in complications, such as obstruction of airway and vision, ulceration or disfigurement, and require therapeutic intervention.[4] In 2008, the first report of the successful use of propranolol radically changed the treatment of IH and since then propranolol has become the first-line therapeutic agent in the management of complex IH.[5] Studies have shown that propranolol is a safe and effective treatment for IH in most patients.[6-9]

The exact mechanisms of action of propranolol on IH are still not completely understood. Recent studies have offered evidence for variety of mechanisms, including pericyte mediated vasoconstriction[10], the inhibition of vasculogenesis[11,12], catecholamine induced angiogenesis[13,14] and downregulation of the renin-angiotensin-aldosterone axis.[15]

Despite the high frequency of propranolol use and potential complications, there are currently no UK guidelines for the treatment of IH with propranolol. Our recent European treatment survey indicated differing approaches to the management of IH, for instance with regard to pre-treatment investigations, treatment dose, length of treatment, use in PHACES syndrome, and cessation of treatment.[9] In addition, many

UK dermatology departments have formulated their own propranolol guidelines for the treatment of IH. US and European round table expert consensus statements published in 2013 and 2015 have provided guidance on best practices to standardise the approach to the use of propranolol for treatment of complicated IH but the European recommendations did not include a survey of current practice, and the US recommendations did not follow a Delphi and anonymous voting approach.[16,17]

The purpose of the British Society for Paediatric Dermatology guideline is to provide evidence-based guidance on the use of propranolol in the treatment of IH, with a view to assisting clinical decision making and standardising care. These guidelines are based on an international survey of how oral propranolol is currently used in clinical practice, a systematic review of the literature and a Delphi consensus process to produce specific guidance for practicing clinicians.[9]

Methods

As a first step to inform the treatment guidelines, we conducted an international survey of current practice in 8 European countries, involving review of 1,100 IH patients on oral propranolol with regard to treatment efficacy and safety (Propranolol In the Treatment of Complex infantile Haemangiomas (PITCH) Taskforce).[9] This was followed by a systematic review of the literature and both were used to develop statements relating to the use of oral propranolol in the treatment of IH. In addition, all members of the British Society for Paediatric Dermatology (BSPD) were invited to send in their local guidelines on the use of oral propranolol in the management of IH. We received guidelines from 19 centres and produced a summary document, highlighting differences in management.

Two meetings held by LS, MG, and CF, taking the above evidence into account, led to the generation of 70 statements, which were circulated to the expert members of the guidelines panel (all co-authors on this paper), prior to the face-to-face meeting. All panel members also received the treatment survey paper previously published in the BJD[9], and the document highlighting the differences between existing departmental treatment guidelines.

Nineteen experts from 14 different institutions (15 paediatric dermatologists, 2 paediatricians, a paediatric cardiologist and a paediatric ENT specialist) attended the face-to-face guidelines meeting. One non-voting panel member acted as independent facilitator (SML). Free discussion preceded anonymous voting on all statements. Each statement required 80% agreement from the panel to be accepted or rejected. Using these rules, agreement was reached on 47 statements in 8 categories (Table 1).

After the meeting, the statements were circulated to all BPSD members for comments. The consensus paper was written and sent to all expert panel members for final approval. In addition, the statements were posted on the BSPD website, inviting critical review and online comments from the wider UK paediatric dermatology community. We adhered to the Agree II guidance for guideline development.[18]

Table 1. Consensus statements

I. Indications for starting propranolol for infantile haemangiomas (IH):

1. IH causing/likely to cause vision compromise
2. Airway IH with potential or actual airway compromise
3. Nasal IH with actual or potential obstruction
4. Lip IH causing potential or actual functional impairment and/or disfigurement
5. Auditory canal involvement causing recurrent infection
6. Ulcerated IH, especially where topical treatment would not be appropriate or has not been effective
7. Risk of permanent disfigurement
8. Spinal cord compression by IH
9. Liver IH in conjunction with cutaneous IH in selected cases in collaboration with other specialists

II. Contraindications

A. Relative

1. Frequent wheezing
2. Blood pressure outside normal range for age – treatment in conjunction with paediatrician
3. Heart rate outside normal range for age – treat in conjunction with paediatrician

B. Absolute

1. Hypoglycaemic episodes, recent or on-going
2. Heart block, second and third degree
3. Hypersensitivity to propranolol

III. Pre-treatment investigations

1. Cardiovascular and respiratory examination by a competent practitioner is required before starting propranolol (auscultation, peripheral pulses, abdominal examination for potential liver enlargement)
2. Pre-treatment ECHO needed in selected cases
3. Pre-treatment ECG needed in selected cases
4. Routine pre-treatment FBC, renal, liver and thyroid profiles are not required before starting propranolol.
5. Baseline glucose is only required in selected cases (see also under IV. Starting Propranolol)
6. Paediatric cardiology assessment in selected cases

IV. Starting propranolol

1. Propranolol preparation 5mg/5 ml to be used
2. BAD/BSPD patient information leaflet provided
3. Post first dose monitoring not routinely needed
4. Where observation needed (HR and BP), there should be 30 minutes between observations
5. Total length of observation 2-4 hours
6. Glucose to be checked only in patients at risk of hypoglycaemia (pre-term, low weight, faltering growth, neonates, history of hypoglycaemia)
7. Starting dose 1 mg/kg/day
8. Maintenance dose for uncomplicated patients 2 mg/kg/day
9. Minimum time interval between dose increases 24 hours
10. Clinical photographs to record baseline appearance and treatment response

V. Propranolol treatment in patients with comorbidities/pre-term/low weight

1. For children with comorbidities that are likely to lead to hypoglycaemia (e.g. hyperinsulinism)/pre-term/low weight) the propranolol starting, maintenance and incremental dose schedules will need to be more cautious than for children with no comorbidities/term birth/normal weight. Individual dosing regimens to be determined by the supervising dermatologist/paediatrician.

VI. Propranolol treatment in patients with facial segmental IH (suspected PHACES syndrome)

1. Ideally, brain MRI-MRA should be done before starting the full dose of propranolol in patients with segmental IH of the head and neck.

2. The starting dose before brain MRI/MRA for patients with segmental IH of the head and neck is 0.5 mg/kg/day.
3. All patients with suspected PHACES syndrome should have ECHO and ECG interpreted by a paediatric cardiologist or paediatrician with a special interest in cardiology.
4. If brain MRA shows arterial stenosis or agenesis discuss with paediatric neurologist regarding treatment with propranolol and propranolol dosing.

VII. During treatment with propranolol

1. Dose can be adjusted for weight at clinic visits, by the GP or by parents with written instruction
2. Dose of propranolol for non-segmental IH can be divided in two or three daily doses at the discretion of the treating clinician
3. Maximum dose for non-responders is 3 mg/kg/day
4. A drug dosing card is recommended to aid dose adjustment and avoidance of dosing errors.
5. Routine follow-up for a patient on a stable treatment dose, without complications, should be at intervals of 2-3 months.
6. BP and HR do not need to be monitored between appointments if the infant is well.

VIII. Stopping propranolol

A. Temporary cessation required if:

1. Significantly reduced oral intake(due to risk of hypoglycaemia)
2. Wheezing requiring treatment

B. End of treatment

1. In many cases treatment can be stopped at one year of age, and the majority of IH patients do not need treatment beyond 17 months of age. It is safe to stop propranolol abruptly (rather than weaning patients off treatment gradually) during or at the end of therapy.
2. After treatment has been completed, routine follow up is not required.

Consensus recommendations

1. Indications for treatment of IH with propranolol

The majority of IH do not require treatment because spontaneous involution without significant complications or sequelae can be expected. Indications for treatment can be divided into three main categories: ulceration, risk of disfigurement and functional impairment (Table 1).

Ulceration

Ulceration is a common complication, occurring in nearly 16% of patients with IH, most often by 4 months of age, during the rapid growth phase.[19] This risk is much higher (approximately 50%) for IH involving the lower lip and perineum.[19] Ulcerations can be very painful and often result in scarring. Ulcerated IH require treatment with

propranolol if topical treatment has not been effective or is not appropriate (eg. large IH that cannot be treated with topical timolol maleate). Ulcerated IH beyond the growth phase do not require treatment with propranolol. Very rarely, propranolol can worsen the ulceration of IH, possibly reflecting reduced blood flow causing peripheral ischaemia. In such cases, a reduction in the propranolol dose can be helpful. Treatment with topical timoptol can be a suitable alternative[20], but this should only be undertaken in specialist settings.

Functional impairment

Vision

Peri-ocular IH warrant early treatment with propranolol if causing or likely to cause visual impairment. Failure to treat vision threatening IH can lead to severe and permanent visual disturbances by occluding the visual axis, compressing the globe, or expanding into the retrobulbar space.[21] Complications such as amblyopia, significant refractive errors, and strabismus are seen in up to 80% of patients with untreated peri-ocular IH.[22] These patients need to be reviewed by an ophthalmologist.

Feeding

IHs of the lip may have an adverse impact on feeding, particularly if ulcerated.[23] Nursing care of the ulceration is important as an adjunct therapy.

Breathing

Infants are obligatory nasal breathers and so nasal IH blocking the nostril may impact on feeding as well as breathing. Airway IH can develop in infants who do not

have cutaneous lesions. However, the risk of airway IH is higher with segmental IH located in a mandibular, cervicofacial or "beard" distribution. The possibility of airway IH must be suspected in any infant with hoarseness and stridor. These patients need to be managed in conjunction with ENT specialist.

Ear

Treatment is warranted for IH causing symptomatic obstruction of the ear canal (most commonly recurrent infections).

Risk of disfigurement

IH affecting the central face and ears are particularly likely to lead to disfigurement, through distortion of important anatomic landmarks. Even relatively small IH of the nose, lips and ears can lead to permanent and stigmatizing skin changes. IH with a stepped border of the superficial component and those with a cobblestoned surface are associated with higher risk of disfigurement than those with a progressive border and a smooth surface and are more prone to leave anetodermic and redundant skin on regression.[24] IH of ears, nose, lips, forehead and cheek, and thick IH with stepped border on the face require a low threshold for treatment with propranolol.

2. Absolute and relative contraindications to treatment with propranolol

Before initiation of propranolol for IH, a prescribing physician should perform screening for risks associated with oral propranolol. Contraindications to treatment of IH with propranolol are listed in Table 1. A thorough cardiovascular and respiratory history should be obtained, with particular attention to wheezing, as well as specific enquiry about hypoglycaemic episodes and poor feeding. In patients with a heart

rate and/or blood pressure outside normal range for age (Table 2 and 3)[25], treatment needs to be initiated in conjunction with a paediatrician/paediatric cardiologist.

3. Pre-treatment investigations

The prescribing physician should take a thorough history and perform a comprehensive physical examination, including auscultation, palpation of peripheral pulses, abdominal examination for liver enlargement, and measurement of heart rate and blood pressure. A pre-treatment ECG is not required routinely, but should be performed in patients with a heart rate outside the normal range for age[25] (Table 2), a strong family history of sudden death/arrhythmia, episodes of loss of consciousness and maternal history of connective tissue disease. A pre-treatment ECHO is required in patients with heart rate outside the normal for age (Table 2), a heart murmur detected on auscultation, and in patients with segmental IH. A cardiology assessment is only required if indicated by examination findings or in patients with segmental IH. No screening blood tests are required routinely before starting propranolol. Baseline glucose is required if the infant is pre-term, small for dates, feeding poorly or has a history of hypoglycaemic episodes.

4. Starting propranolol

Initiation and escalation of propranolol

Treatment with propranolol can be initiated on an outpatient basis without monitoring of heart rate or blood pressure for infants older then 4 weeks, with no significant comorbidities, born at term, with normal birth weight, established feeds and appropriate weight gain.

The starting dose of propranolol is 1 mg/kg/day in 3 divided doses. The dose can be increased after 24 hours to 2 mg/kg/day in three divided doses. For pre-term patients and those with comorbidities, such as hyperinsulinism previous episodes of hypoglycaemia, respiratory, cardiac, metabolic and neurological disorders or cerebrovascular abnormalities, the propranolol starting, maintenance and incremental dose schedules may need to be modified. Under such circumstances, a typical starting dose is 0.5mg/kg/day, but individual dosing regimens are down to the local paediatrician/dermatologist.

Patients younger than 4 weeks, who are pre-term, with faltering growth, feeding difficulties, and/or significant comorbidities, such as hyperinsulinism, previous episodes of hypoglycaemia, respiratory, cardiac, metabolic or neurological disorders require admission for 2-4 hours on initiation and for dose increments greater than 0.5 mg/kg/day. Heart rate and blood pressure measurements should be done immediately before the first dose, and then every 30 minutes for 2-4 hours after the first dose. The blood glucose needs to be checked only in patients at risk of hypoglycaemia (pre-term infants, low weight, faltering growth, neonates, poor feeding, and history of hypoglycaemia). Parents should ensure that their child is fed regularly to reduce the risk of hypoglycaemia. If feeding is reduced, for instance because the child becomes unwell, then propranolol needs to be stopped until the child is feeding normally. (The initiation of propranolol in patients with PHACES syndrome is described in the next section.)

Formulations of propranolol

Propranolol is currently commercially available as propranolol hydrochloride oral solution. We recommend the 5 mg/5 mL preparation, as this is the concentration

least likely to be associated with dosing errors. Other concentrations should only be used if a patient cannot tolerate the required volume of 5 mg/5 mL preparation. Hemangeol™ (4.28 mg/ml, $612.76 for 120 ml[26]) was approved by the FDA and EMA in 2014, but is not available in the UK. According to the British National Formulary, the price for generic propranolol oral solution 5 mg/5 ml 150 ml is £18.50.[27] There is no advantage in prescribing the non-generic formulation, as the treatment efficacy is deemed similar.

Documentation

Clinical photographs should be taken at initiation of treatment to record the baseline appearance for the purpose of treatment response monitoring.

Parents should be given verbal and written information about the treatment and potential adverse effects, reinforced with a patient information leaflet, including contact details of the clinical team. Such a leaflet is available from the BSPD website (http://www.bspd.org/IHleaflet/)

5. Propranolol treatment in patients with cervicofacial segmental IH (suspected PHACES syndrome)

Cervicofacial segmental IH can be associated with PHACE association (Posterior fossa anomalies, Haemangioma, Arterial anomalies, Coarctation of the aorta/Cardiac anomalies and Eye anomalies). This group of patients pose a distinctive treatment challenge, as they frequently require prompt treatment for airway and peri-ocular IH, but propranolol may increase the haemodynamic risks associated with an otherwise asymptomatic cerebral arteriopathy.[28,29]

All patients with segmental IH of the head and neck require cardiac assessment, including ECG and ECHO interpreted by a paediatric cardiologist, before starting propranolol. Ideally, a cerebral magnetic resonance angiogram (MRA) should also be performed, before propranolol treatment is initiated. If it is not possible to obtain an urgent MRA, the starting dose of propranolol should be no more than 0.5 mg/kg/day in three divided doses. If MRA shows arterial stenosis, discussion with a paediatric neurologist is required prior to starting or increasing the dose of propranolol.

6. During treatment with propranolol

The patient should be reviewed 2-3 months after starting treatment. Patients with complicated IH might be reviewed sooner than that. The dose of propranolol can be adjusted for weight either at clinic visits, by the GP, or by the parents with written instructions. After treatment initiation, the total daily dose of propranolol can be divided into two or three daily doses in patients with non-segmental IH at the discretion of the treating clinician. Blood pressure and heart rate do not have to be monitored for well patients between follow-up visits. If the IH is not responding adequately to treatment, the dose can be increased to a maximum of 3 mg/kg/day.

7. Stopping propranolol

Propranolol should be temporary discontinued in the setting of significantly reduced oral intake or if the patient has wheezing that requires treatment. Treatment of IH should extend beyond the proliferative period of IH to avoid rebound growth, and the decision when to stop treatment will have to be guided by clinical features. Premature cessation of propranolol may lead to rebound growth. There is no uniform

cut off age that determines the risk of rebound growth, although our recent European study suggested that children age 17 months or older had a significantly lower risk of rebound growth compared to younger age groups.[9] In most patients, however, the treatment can be safely stopped at 12-14 months of age.[8,30]

Discussion

Our guidelines aim to unify and simplify the treatment of IH with oral propranolol across the UK and beyond, providing guidance on previously identified uncertainties regarding indications, pre-treatment investigations, its use in PHACES association, and cessation of treatment (Figure 1). The management consensus statements were reached using an international survey of current practice across eight European countries and a systematic review of the literature to formulate guideline statements, followed by a modified Delphi technique with anonymous voting to develop clinical management recommendations. Statements were also posted on the BSPD website to allow every BSPD member to comment on the statements before implementation.

Despite our systematic approach, there were a few areas that required extensive discussion during the consensus meeting, such as the need for blood glucose measurements and which children require hospital admission as well as the propranolol starting dose, as there is currently a lack of controlled studies to base clinical decision making on.

Our guidelines are limited to oral propranolol, rather than whole treatment modalities, such as other systemic beta-blockers, including nadolol and atenolol[31], and the topical beta-blocker timolol.[32] We accept that some aspects, such as the statement on generic propranolol, are UK-specific, but we nevertheless hope the guidelines will help to standardise practice internationally. As the guidelines are primarily based on

expert consensus, revision of these guidelines will be required if new information on propranolol in the treatment of IH becomes available, for instance with regard to treatment dose. Another area of current research is the theoretical concerns regarding neurodevelopmental or cognitive side effects of propranolol have been raised, as propranolol has the ability to cross the blood-brain barrier.[33] Nevertheless, propranolol has by far the best documented safety profile[34], even if possible long-term effects remain to be fully evaluated, which will have to be addressed in a large observational study assessing long-term outcomes. Should new evidence become apparent over time, this will be worked into the planned revision of the current guidelines by our multi-disciplinary group in two years.

Figure 1. Treatment flowchart

Table 2. Normal heart rate by age (beats/minute)

Normal heart rate by age (beats/minute)		
Age	Awake Rate	Sleeping Rate
Neonate (<28 d)	100-205	90-160
Infant (1 mo-1 y)	100-190	90-160
Toddler (1-2 y)	98-140	80-120

Table 3. Normal blood pressure by age (mm Hg)

Normal blood pressure by age (mm Hg)			
Age	Systolic Pressure	Diastolic Pressure	Systolic Hypotension
Birth (12 h, <1000 g)	39-59	16-36	<40-50
Birth (12 h, 3 kg)	60-76	31-45	<50
Neonate (96 h)	67-84	35-53	<60
Infant (1-12 mo)	72-104	37-56	<70
Toddler (1-2 y)	86-106	42-63	<70 + (age in years x 2)

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Authors' contributions:

The international PITCH survey was initiated and led by Carsten Flohr (CF) and adopted by the BSPD as an official taskforce. The BSPD propranolol guidelines project was initiated and led by CF, following approval by the BSPD Executive Committee. Mary Glover (MG) acted as Co-Lead. Lea Solman did most of the ground work, including the conduct of the systematic literature search and organisation of the consensus meeting. She also wrote the guidelines paper drafts under the guidance of CF and MG. All co-authors attended the face-to-face consensus meeting and approved the guidelines paper prior to submission.

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