

Paper

# Propranolol for infantile haemangioma: A review of current dosing regime in a regional paediatric hospital.

Pauline McGee, Sophie Miller, Claire Black, Susannah Hoey

Accepted 24 October 2012

## INTRODUCTION

Cutaneous infantile haemangiomas affect approximately 1 in 10 children. They tend to follow a natural course of rapid proliferation during the first year of life and subsequently regress over 5-10 years. Most haemangiomas are non-problematic, but a few become problematic, through ocular, airway or functional impairment, or ulceration. Oral propranolol therapy has been observed to inhibit the proliferation and incite regression of these lesions during their proliferative phase. At present there are no nationally agreed guidelines on propranolol use in paediatric patients with infantile haemangioma, our unit follows a similar pre screening and dose initiation regimen to that of other paediatric hospitals such as Great Ormond Street Hospital for Children.

## METHODS

A retrospective chart review was performed on patients with infantile haemangiomas treated with oral propranolol at the Royal Belfast Hospital for Sick Children (RBHSC) between April 2009 and June 2011. Using a proforma, data was collected on dosing, efficacy and adverse effects.

## RESULTS

Twenty four patient notes were identified and reviewed. All 24 patients underwent the work up prior to initiation of therapy. Infant age at start of treatment ranged from 8 weeks to 17 months. Overall, 22/24 infants had improvement in their lesions with propranolol. 23/24 ( 95.8%) of patients were commenced on the standard dosing regimen of 1mg/kg/day in divided doses. 22/23 of these infants tolerated treatment well and had their dose titrated to 2mg/kg/day. The one child who did not tolerate the initial dose was bradycardic and dose reduced then titrated without further problems. On the 2mg/kg/day dose 3/24 infants had side effects: lethargy in two and disturbed sleep in one. Two of these infants had their dose reduced with good effect.

## CONCLUSION

Oral propranolol is an effective treatment for infantile haemangiomas for the indications described. Improvement was noted in the majority of our patients' haemangiomas using the current dosing regimen. A low incidence of side effects was reported. This contributes to the growing evidence

that low dose oral propranolol is a safe, efficacious treatment for problematic haemangiomas and we hope, in due course that regional and national guidelines can be developed for this purpose.

## INTRODUCTION

Infantile haemangiomas are the most common benign tumours of infancy. They affect approximately one in ten infants.<sup>1</sup> They are more common in Caucasian populations and in female infants. The male to female ratio is variable with some reports suggesting the condition is up to four times more common in females.<sup>2</sup> A higher incidence is observed in premature babies<sup>3</sup> and those who were subject to chorionic villous sampling in utero.<sup>2,3</sup>

The majority of haemangiomas are located in the head and neck region with lesions on the trunk and extremities being less common.<sup>1</sup> The cutaneous lesions present soon after birth and are characterised by rapid proliferation during the first year of life, followed by a gradual involution over the next five to ten years. Whilst most haemangioma are non-problematic, requiring no treatment, approximately 10% cause significant morbidity predominantly through airway obstruction, ocular compression, functional impairment or ulceration.<sup>4</sup> Until recently treatment options for problematic haemangioma have included intralesional and systemic steroids, chemotherapeutic agents including vincristine and interferon-alpha, laser therapy or surgical intervention.<sup>5</sup>

Propranolol is a non selective beta blocker; in the UK it is currently licensed for treatment of arrhythmia, hypertension, Tetralogy of Fallot thyrotoxicosis in children and migraine prophylaxis.<sup>6</sup> In 2008 regression of a facial haemangioma was noted in a child being treated with propranolol for obstructive hypertrophic cardiomyopathy.<sup>7</sup> Since then propranolol has been introduced as a primary treatment for complicated haemangioma. This case series examines the indications, dosing regimen, and observed outcomes for children with infantile haemangioma, treated with propranolol, in Northern Ireland.

---

Department of Dermatology and Plastic Surgery, Royal Belfast Hospital for Sick Children, 180 Falls Road, Belfast BT12 6BE.

Correspondence to Pauline McGee

pauline\_magee@hotmail.com

To date there are no national pre-screening guidelines for the use of propranolol in the treatment of paediatric haemangioma. In our unit we follow the same pre-screening assessment as many other UK units including that at Great Ormond Street Hospital for Children. Children are admitted to the ward as a day-case for baseline investigations (Figure 1). A dosing regimen of 1 mg/kg/day is commenced initially which is increased to 2mg/kg/day at one week if this is well tolerated.

**METHODS**

- Full clinical examination including cardiovascular and respiratory assessment
- Full blood picture, urea & electrolytes, blood glucose
- Thyroid function test
- Dipstick urine test for glucose
- Electrocardiogram and echocardiogram
- Abdominal Ultrasound (in patients with multiple lesions)
- Medical Photography

*Fig 1. Pre-treatment screening investigations*

A retrospective chart review was performed, for paediatric patients with infantile haemangioma, treated with propranolol at the Royal Belfast Hospital for Sick Children between April 2009 and June 2011. Patients had been managed by specialist paediatric dermatology or plastic surgery teams. A proforma was used to collect information on patient demographics, indication for propranolol, dosing regimen undertaken, and observed outcomes. Treatment benefit was measured by subjective assessment of lesion regression by the medical team at clinic review. Improvement was documented objectively by serial photography by the medical photography department, providing a permanent record for parents and staff of the improvement in size, shape, colour, contour and residual deformity of lesions. Outcome of airway lesions was observed by appearance of haemangioma at repeat bronchoscopy.

Indication	Number of patients	Percentage (%)
Ocular involvement	7	29.1
Airway obstruction	4	16.7
Presence of ulceration	3	12.5
Functional impairment	5	20.8
Ulceration and functional impairment	5	20.8

*Fig 2. Indication for propranolol therapy*

**RESULTS**

Twenty six patients were identified and of these, 24 patient notes were retrieved. Hence, two patients were excluded as chart retrieval was not possible.

Of the 24 patients, 5 were male and 19 female, giving a male:female ratio of 1:4. All 24 were Caucasian.



*Fig 3a. Ulcerated hand lesion prior to propranolol treatment.*



*Fig 3b. Appearance of hand lesion after 4 weeks of propranolol therapy*



Fig 4a. Extensive ulcerated facial haemangioma prior to propranolol treatment

All children underwent work up, as illustrated in figure 1 before commencing therapy. Patients were monitored closely when starting therapy and during dose escalation. Regular review was arranged throughout the treatment period.

The indications for therapy were ocular involvement, airway compromise, presence of ulceration, functional impairment or a combination of the above. Figure 2 outlines the indications for commencement of propranolol therapy in our population. Ocular compromise was present in seven infants, airway obstruction in four and the presence of ulceration alone in a further three children. Functional impairment was the sole feature in five infants. A further five babies were commenced on propranolol due to ulceration in combination with a functional impairment.

Four out of 24 infants had received prior treatment or were receiving concurrent therapy with oral corticosteroids. The indication was airway obstruction in 3 of these patients and functional impairment in the other child. This is current routine practice for patients with airway obstruction.<sup>8</sup>

The age at the start of therapy ranged from 8 weeks to 17 months, with the median age for commencing therapy being 12 weeks.

### **DOSING REGIMEN**

The standard initial dose of 1mg/kg/day was used in 23/24 (95.8%) children. This was given in three divided doses per day. One patient was commenced on a lower dose (0.5mg/kg/day). This child had PHACES syndrome, and hence cautious dosing was instigated due to cardiac disease. The treatment was well tolerated in this child and the dose gradual escalated in keeping with the standard regime.

Of children commenced on 1mg/kg/day dose, 22/23 (95.6%) had tolerated treatment well at the end of the first week. All but one of these children had their dose escalated to 2mg/kg/day at one week, in keeping with the protocol. Dramatic improvement was noted on the initial dose of 1mg/kg/day in one child and therefore dose escalation was not undertaken.

The one child who had not tolerated the initial 1mg/kg/day



Fig 4b. Appearance of lesion after 10 weeks of propranolol therapy

of propranolol was bradycardic on commencement of the drug, and hence had their dose halved to 0.5mg/kg/day from day 1. A week later however, the treatment was being well tolerated without bradycardia and the dose titrated to 1mg/kg/day and ongoing, as per protocol, without problems. This child also had underlying congenital hypothyroidism and was on thyroxine replacement therapy.

### **EFFICACY AND DURATION OF THERAPY**

22/24 (91.6%) patients had documented regression of their haemangiomas with propranolol therapy.

10/24 patients had completed their course of propranolol at the time of data collection. Duration of therapy ranged from 3.5 to 14 months (median 10.5 months). Treatment for two of these infants was discontinued after 3.5 and 6 months due to failure to respond to therapy. Of note these children were commenced on therapy at an older age of 17.5 and 11 months respectively. The remaining 8 children responded well to therapy. One of these children did not attend follow up after completion of treatment. No recurrence was observed when the propranolol was discontinued in all 7 children who attended follow up appointments.

14/24 patients were still receiving propranolol at the time our data was compiled. Duration of therapy in this group ranged from 1 to 14 months to date. All 14 patients were demonstrating positive changes in the appearance of their haemangiomas.

### **ADVERSE REACTION**

There were few reported side effects in our group of infants. On the dose of 2mg/kg/day, poor sleep was reported in one child, and lethargy was reported in two children. One child with poor sleep and one child with lethargy had their dose reduced back to 1mg/kg/day in view of the side effects. One child had bradycardia, as above.

### **DISCUSSION**

Propranolol has been used for decades in the practice of paediatrics for the treatment of cardiovascular disease at a dose as high as 8mg/kg/day. Results from our case series



*Fig 5a.* Ulcerated lip and forehead haemangioma prior to treatment



*Fig 5b.* Lesions 6 weeks into propranolol therapy. Note the previously ulcerated lip lesion has healed.

indicate that propranolol at a dose of 2mg/kg/day is effective in promoting regression and reducing morbidity from problematic cutaneous infantile haemangiomas.

This dose (2mg/kg/day) has been reported as effective in other centres.<sup>9</sup> A higher dose of 3mg/kg/day has been used in Alderhey Hospital, and has been shown to be effective and well tolerated.<sup>10</sup>

Various strengths of propranolol suspension are available. In our unit we prescribe 10mg per 5ml strength. It is important that repeat prescriptions issued in the primary care setting are of the same strength to ensure accurate and safe dosing. We generally advise that propranolol should be given with feeds to reduce the risk of hypoglycaemia and to withhold treatment if the child is vomiting or generally unwell.

Prior to treatment children should undergo some baseline investigations, at present there is huge variation amongst centres in the UK in terms of pre treatment screening tests. We have modified our protocol to include key baseline measurements of pulse, blood pressure and blood glucose. Children with multiple lesions should have an abdominal ultrasound to exclude hepatic involvement and children with suspected cardiac disease require further investigation with ECG, ECHO and input from a paediatric cardiologist.

Children with segmental and large high risk facial lesions should have a MRI of the region to delineate local extension. All children should have medical photography prior to initiation of treatment and regularly throughout treatment to document response to therapy.

The demographics in our small patient population demonstrated characteristics that were consistent with the literature: all our patients were Caucasian and haemangioma affected more females than males. A low incidence of side effects was reported in our patient group, namely disrupted sleep, lethargy and bradycardia. We wonder if the child with bradycardia was prone to this, given the underlying congenital hypothyroidism. Lethargy and sleep disturbance are recognised side effects of propranolol.<sup>11</sup> Well documented side effects not observed in our group but reported elsewhere include hypoglycaemia,<sup>12</sup> gastrointestinal upset and bronchospasm.<sup>1</sup> The children who did not gain benefit from propranolol in our series were those who commenced treatment at an older age. This illustrates the importance of primary care education to ensure children are identified and treated promptly, ideally within the first six months of life.

The effect of propranolol on infantile haemangiomas

was discovered incidentally and little is known about its precise mechanism of action in these tumours. The possible mechanisms include vasoconstriction, inhibition of angiogenesis and induction of apoptosis.<sup>3</sup>

Propranolol is effective during the proliferative phase of growth. Patients who had a poor response to propranolol were those who were commenced on therapy at an older age. This highlights the need for prompt early referral of infants with problematic haemangiomas, for consideration of propranolol therapy. When started at the proliferative stage, the growth of the lesion is inhibited and regression promoted. It may be that the children who did not benefit from the therapy had passed this proliferative stage.

Research is ongoing in this field, looking at efficacy, safety profile and most appropriate dosing regimen for propranolol, in the treatment of complicated infantile haemangioma. At present in Northern Ireland, the use of propranolol for cutaneous haemangiomas is reserved for those which are problematic, and all children are managed at a regional centre under the care and close supervision of a specialist team. Results so far have been promising. In the future its use may be rolled out for non problematic lesions with the aim of reducing the volume of redundant skin when these lesions regress naturally, impacting on cosmetic outcome. Another option maybe the application of topical propranolol to superficial haemangiomas, and a recent paper has reported this novel approach safe and effective.<sup>13</sup>

This case series contributes to the growing evidence that oral propranolol is efficacious and safe, with a careful dosing and monitoring regimen; in time we hope that guidelines will be developed for regional and national use.

The authors have no conflict of interest.

## REFERENCES

1. Zimmermann AP, Wiegand S, Werner JA, Eivazi, B. Propranolol therapy for infantile haemangiomas: Review of the literature. *Int J Ped Otorhinolaryngol*. 2010; **74(4)**:338-42
2. Schwartz RA, Sidor MI, Musumeci ML, Lin RL, Micali G. Infantile haemangiomas: a challenge in paediatric dermatology. *J Eur Acad Dermatol Venereol*. 2010; **24(6)**:631-8
3. Storch CH, Hoeger PH. Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action. *Br J Dermatol*. 2010; **163(2)**:269-75
4. Starkey E, Shahidullah H. Propranolol for infantile haemangiomas: a review. *Arch Dis Child*. 2011; **96(9)**:890-3.
5. Leonardi-Bee J, Batta K, O'Brien C, Bath-Hextall FJ. Interventions for infantile haemangiomas (strawberry birthmarks) of the skin. *Cochrane Database Syst Rev*. 2011 May 11;(5):CD006545.
6. The Paediatric Formulary Committee. BNF for Children. London: BMJ Publishing Group, The Royal Pharmaceutical Society of Great Britain. RCPCH Publications Ltd. 2012. p 89.
7. Leaute-Labrese C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taleb A. Propranolol for severe hemangiomas of infancy. *N Engl J Med*. 2008; **358(24)**:2649-51
8. Morton NS. Large airway obstruction in children. Part 1: Causes and Assessment. *Update Anaesth*. 2004; **18(13)**:44-9. Available online from: [http://www.nda.ox.ac.uk/wfsa/html/u18/u1813\\_01.htm](http://www.nda.ox.ac.uk/wfsa/html/u18/u1813_01.htm). Last accessed Nov 2012.
9. Manunza F, Syed S, Laquida B, Linward J, Kennedy H, Gholam K. Propranolol for complicated infantile haemangiomas: a case series of 30 infants. *Br J Dermat*. 2010; **162(2)**:466-8
10. Holmes WJ, Mishra A, Gorst C, Liew SH. Propranolol as first-line treatment for rapidly proliferating infantile haemangiomas. *J Plast Reconstr Aesthetic Surg*. 2011; **64(4)**: 445-51
11. Love JN, Howell JM et al. Lack of toxicity from paediatric beta blocker exposures. *Hum Exp Toxicol*. 2006; **25(6)**:341-6
12. Holland KE, Frieden IJ, Frommelt PC, Mancini AJ, Wyatt D, Drolet BA. Hypoglycaemia in children taking propranolol for the treatment of infantile haemangioma. *Arch Dermatol*. 2010; **146(7)**:775-8
13. Kunzi-Rapp K. Topical propranolol therapy for infantile hemangiomas. *Pediatr Dermatol*. 2012; **29(2)**: 154-9