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ORIGINAL ARTICLE

Use of propranolol for treatment of infantile haemangiomas in an outpatient setting

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Introduction: Propranolol has recently emerged as an effective drug treatment for infantile haemangiomas. The side effect profile of the drug and the safety of administering propranolol in outpatient settings in this age group remain uncertain. We report our experience with 200 infants and children prescribed propranolol to treat infantile haemangiomas, including 37 patients considered to have a poor response to treatment.
Method: Patients were prescribed propranolol (1 mg/kg/dose bd) as outpatients at the Vascular Anomalies Service at the Royal Children's Hospital, Melbourne.
Results: The median age at commencement was 4 months (range 5 days–7 years). Twenty patients were older than 12 months at commencement. The median duration of treatment was 8 months. About 80% of treated haemangiomas were on the face. Approximately 50% of patients were considered to have an excellent response, 30% to have a good response and 20% to have a poor response. All segmental facial haemangiomas responded well. In contrast, 25% of focal facial haemangiomas responded poorly. Sleep disturbance was the most common side effect. Gross motor abnormalities including delayed walking were observed in 13 patients.
Conclusion: Propranolol appears to be an effective treatment for infantile haemangiomas, particularly large segmental facial lesions. A poor response was seen in 20% of patients. Treatment has been provided in an outpatient setting without major complications and with excellent parental compliance. The side effect profile appears to be favourable, but further follow-up is required to identify unexpected long-term side effects.

Key words: haemangioma; haemangioma of infancy; PHACES syndrome; propranolol; vascular birthmark.

What is already known on this topic

1 Propranolol appears to be effective in treating infantile haemangiomas.
2 Propranolol has an excellent safety record in children.

What this paper adds

1 In our study of 188 infants with infantile haemangiomas who were treated as outpatients with propranolol, 20% responded poorly.
2 Focal facial haemangiomas responded poorly considerably more often than other types of haemangiomas. All segmental facial haemangiomas had a good or excellent response to treatment.
3 Sleep disturbance was the most common side effect in this study group. Gross motor abnormalities were reported, and gross motor development should be monitored.

Introduction

Infantile haemangiomas are the most common tumour of childhood, affecting 5–10% of all infants.[1] They classically appear after birth as pale or red patches that grow for months. After their growth period, most haemangiomas gradually resolve over several years without causing problems. Some haemangiomas persist and some cause major problems. For example, large facial haemangiomas can lead to temporary or lifelong disfigurement. Any haemangioma likely to cause significant problems requires treatment. The mainstay of treatment for two decades has been oral corticosteroids. Laser, vincristine and/or interferon-alpha have also been used.

In June 2008, Leaute-Labreze *et al.* published the first report of haemangiomas responding to oral propranolol.[2] Several case reports and small series have subsequently been reported (e.g.[3–8]). A recent randomised controlled trial of propranolol

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in 40 children up to 5 years concluded that propranolol is well tolerated and effective for infantile haemangiomas.[9] Virtually all patients in reported series are described as 'responders'. Three of the larger series reported only one non-responder from 32 patients,[7] 58 patients[8] and 19 patients[9], respectively.

Although propranolol has been widely used for treatment of hypertension in adults over a long period, experience in infants is less extensive. Possible side effects of propranolol in infants include hypoglycaemia, hypotension and exacerbation of asthma. It is also possible that other, unpredicted complications may occur. This has led to some caution in the use of propranolol, with some centres admitting patients for a period of inpatient monitoring during initiation of treatment. This study is a review of the use of propranolol for the treatment of infantile haemangiomas in an outpatient setting.

Methods

Patient selection

All patients prescribed propranolol for infantile haemangiomas by the Vascular Anomalies Service at Royal Children's Hospital (RCH), Melbourne, from June 2008 to April 2011 were included in the study, which has been approved by the RCH Human Research Ethics committee. Indications for propranolol treatment were the established indications for pharmacological treatment, that is: threat of compression of a vital structure such as eye, risk of long-term disfigurement, large size, or presence of a complication such as ulceration. As the effectiveness and safety of treatment became clearer over the course of the study, propranolol became our first-line treatment for all patients requiring treatment and was used to treat many haemangiomas that would not previously have been treated with oral corticosteroids.

Treatment protocol

Infants who were thriving were treated on an outpatient basis (>85% of patients). Investigations were not performed unless specifically indicated. Infants with risk factors such as prematurity, poor feeding, large segmental facial haemangioma or abnormal findings on clinical examination received investigations that might include blood pressure and/or blood glucose monitoring, electrocardiogram, echocardiography and/or imaging of the neck and intracranial vasculature as appropriate.

No licensed preparation of liquid propranolol is available in Australia. Parents were offered a choice of dissolving commercially available propranolol tablets in water or a compounded syrup made up by the pharmacy. The great majority of parents opted to prepare the tablets themselves. For well infants treated as outpatients, propranolol treatment was commenced at 0.5 mg/kg/dose bd for 3 days, then increased to 1 mg/kg/dose bd from then on, given with feeds. The parents were given written instructions to stop propranolol if their child was unwell or not feeding well for any reason. All infants continue to be reviewed at regular intervals.

Most patients received no treatment apart from propranolol. Thirty-seven patients received one or more other treatments before or during propranolol treatment. Twenty-two patients treated in the early part of the study also received oral prednisolone with limited response leading to the introduction of propranolol. Pulsed dye laser was used on 23 patients, mainly those with larger segmental facial lesions.

Assessment

Patients were reviewed 1 month and 4 months after commencement of treatment, and then each several months. Detailed clinical data (including an assessment of response and any side effects) were maintained for all infants. Assessment of outcomes was determined using high-quality photographs taken at each visit. In order to minimise bias, all assessments were performed after all patients had been treated and by the same investigator. Each haemangioma was rated on two parameters, the percentage reduction in size (bulk) and the percentage loss of colour. The assessment for each haemangioma was taken as the mean of these two values. Patients were divided into three groups as follows: (i) <30% improvement = poor response; (ii) 30% to <70% improvement = good response; (iii) 70% or more improvement = excellent response. Results are presented in table form and analysed using Pearson's χ^2 test on StatXact software v4.01 (Cytel Corporation, Cambridge, MA, USA). Where numbers were large, a Monte Carlo estimate was used. A *P*-value of less than 0.05 was considered significant.

Results

Patient demographics

Two hundred children were prescribed propranolol. Twelve infants were found at review to have never received any propranolol. Of the 188 children who actually took propranolol, 76% were female and 80% of hemangiomas were on the face. The median age at commencement was 4 months (range 5 days–7 years). Thirteen patients were between 1 and 2 years old at commencement, and seven were older than 2 years. The median duration of treatment was 8 months (range 10 days–30 months).

Outcome of treatment

Approximately 50% of patients were considered to have an excellent response (Fig. 1), 30% to have a good response and 20% to have a poor response. When the type of haemangioma (focal, mixed or segmental) is taken into consideration, it can be seen that focal facial lesions are considerably overrepresented in the non-responder group (Table 1). Among patients with focal facial haemangiomas, 25% had a poor response (Figs 2,3) compared with 12% of all other patients combined. In contrast, no segmental or mixed facial lesions had a poor response and over 80% had an excellent response (Figs 4,5). Of the 17 patients with segmental facial lesions, five patients had associated intracranial, cardiac or sternal abnormalities consistent with PHACES (Posterior fossa anomalies, Haemangioma, Arterial lesions, Cardiac abnormalities/aortic coarctation, Eye abnormalities, Sternal abnormalities) syndrome. Thirteen of these 17 patients also received multiple treatment with pulsed dye laser.

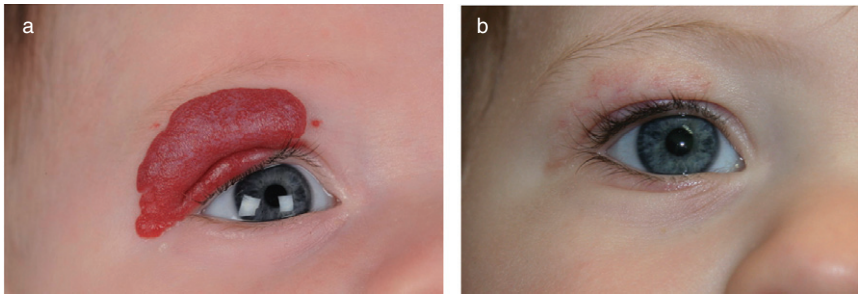

Fig. 1 Excellent response to propranolol. Patient 1 at (a) 4 months of age, starting propranolol and (b) at 12 months of age after 8 months of propranolol treatment.

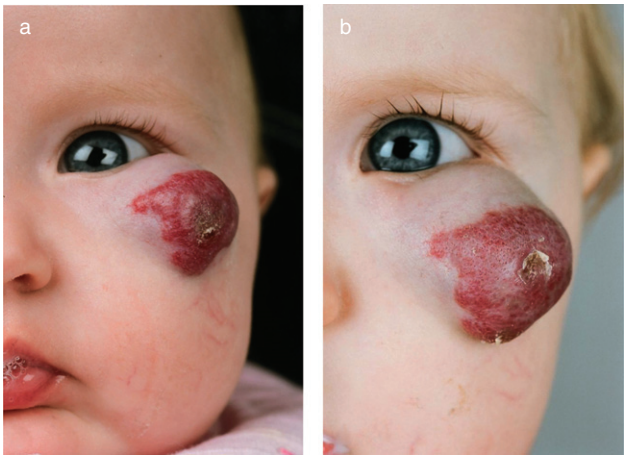

Fig. 2 Poor response to propranolol. Patient 2 at (a) 4 months of age and (b) at 9 months of age after 5 months of prednisolone and propranolol treatment and prior to surgery.

Table 1 Response to propranolol treatment based on type and location of haemangioma

	Poor	Good	Excellent	Total
Face – focal	27	34	45	106
Face – mixed	0	2	11	13
Face – segmental	0	3	14	17
Other† – focal	7	17	15	39
Other† – mixed	0	1	2	3
Other† – segmental	3	1	6	10

(Overall $P = 0.007$. When face and 'other' lesions are analysed separately: face $P = 0.001$, 'other' are not significant $P = 0.33$, Pearson's χ^2, Monte Carlo estimate) †'Other' includes all non-face lesions.

To assess the effect of the age of commencement on outcome, patients were divided into five groups (Table 2). There is a clear trend to worse outcomes as the age at commencement increases. If treatment was started before 2 months of age, only 7% had a poor outcome. Between 2 and 18 months, 20% did poorly. After 18 months of age, 45% showed a poor response.

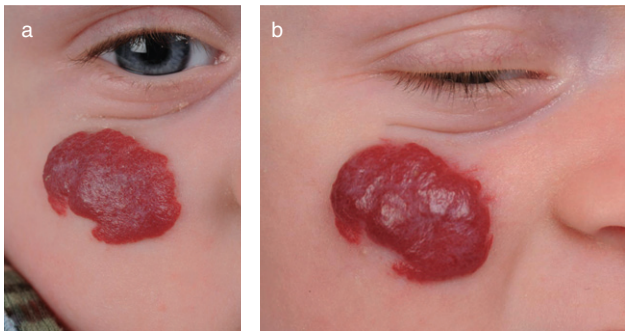

Fig. 3 Poor response to propranolol. Patient 3 at (a) 3 months of age and prior to propranolol treatment and (b) at 7 months of age after 4 months of propranolol treatment.

Side effects and dosing errors

Fifty-one families reported possible side effects. Potentially serious side effects were noted at home in two infants. One became less active and anorexic, and the parents continued to give propranolol for 2 days despite feeding having stopped. The other infant developed vomiting and diarrhoea and was less active after starting propranolol. This resolved with cessation, and recurred when propranolol was restarted by the parents. In both cases, propranolol was ceased without medical intervention and complete recovery occurred within a day.

The most common side effect was sleep disturbance. Twenty-six infants (14%) had sleeping symptoms such as waking screaming at night only when they were taking propranolol. Several of these children slept well after the evening dose of propranolol was ceased. Six children ceased propranolol because of sleeping problems.

Gross motor abnormalities were noted in 13 children. One child at 7 months was weight bearing when supported but stopped this after propranolol was started. Two other walking children were noted to be unsteady on their feet in the morning while on propranolol. One child on propranolol was noted to be able to walk at 11 months for the first time when propranolol was stopped for a week for gastroenteritis but ceased walking after propranolol was restarted. Delayed walking (commencing between 17 and 20 months) was observed in seven other children on long-term propranolol. Four of these seven had no other problems that might have contributed to delayed walking. All walked normally by 20 months. Two children were

Fig. 4 Excellent response to propranolol. Patient 4 with PHACES syndrome with airway and spinal cord obstruction and an extensive disfiguring facial tumour despite high-dose prednisolone. Within 14 h of his first propranolol dose, his signs of spinal cord obstruction resolved, and his oxygen requirements dropped. Over the next 8 months, he was weaned off prednisolone and no longer needed a tracheostomy tube. (a) At 5 months of age when propranolol was started. (b) At 11 months of age. (c) At 23 months of age, weaned off propranolol.

described as unusually passive for the months they were on propranolol, becoming noticeably more active within a day of stopping medication.

A few infants had episodes of bronchiolitis while on propranolol. Medication was only interrupted if the wheezing was moderate or severe. One infant was given 40 mg tablets instead of 10 mg tablets for four doses due to a pharmacy error at a prescription refill, without any observable sequelae.

Regrowth of haemangioma after cessation of treatment

It has previously been observed that there can be a slight recurrence of haemangioma after stopping propranolol.[2,3] We found noticeable regrowth of haemangioma in 30 (22%) of the 136 patients who had stopped their propranolol and been subsequently reassessed. In 17 patients, regrowth was sufficiently significant that propranolol was restarted.

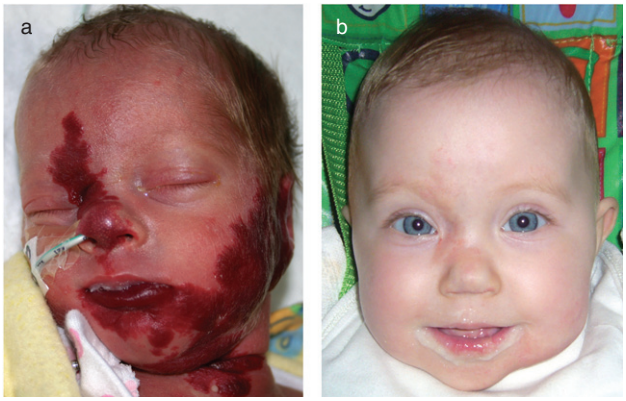

Fig. 5 Born 8 weeks premature with minor sternal changes consistent with PHACES syndrome, patient 5 developed an extensive, rapidly growing facial haemangioma after birth. She was commenced on propranolol alone at day 13 of life. She responded dramatically and has remained on propranolol. During her treatment, she has also had a short course of prednisolone and repeated laser treatments. (a) On day 13 of life, starting treatment with propranolol alone. (b) At 7 months of age, still on propranolol.

Table 2 Effect of age of starting treatment on outcome

Age at start (months)	Poor Number (% of total)	Good Number (% of total)	Excellent Number (% of total)	Total
0–2	2 (7)	9 (31)	18 (62)	29
2–4	18 (22)	18 (22)	46 (55)	82
4–8	7 (15)	20 (43)	19 (41)	46
8–18	5 (25)	6 (30)	9 (45)	20
18–72	5 (45)	5 (45)	1 (9)	11

$P = 0.017$, Pearson's χ^2, Monte Carlo estimate.

Discussion

The discovery in 2008 that propranolol can reduce the size of infantile haemangiomas has led to a substantial change in the way this condition is managed. Impressive anecdotal results have led many centres to change primary treatment for this condition from corticosteroids to propranolol. There is considerable uncertainty about optimum dosage and duration of treatment and about which haemangiomas will not respond to treatment. In this study, most children were treated as outpatients, and monitoring by both medical staff and parents has continued for up to 3 years.

The findings presented here support previously published data indicating that propranolol appears to be an effective treatment for infantile haemangiomas. However, in contrast to previously published results, there was a significant subset (20%) of infants who did not respond to propranolol treatment. In particular, a quarter of focal facial lesions responded poorly (e.g. Fig. 2). No other factors were identified that might predict which lesions would not respond. In particular, non-response

could not be attributed to the age at starting treatment, as 18 of the 27 focal facial non-responders commenced treatment before 4 months of age. Non-responders were subsequently managed with surgery or waiting for the natural involution process as appropriate to their individual circumstance.

The group who responded most favourably to propranolol were infants with large segmental facial haemangiomas. Many were also treated with pulsed dye laser, but this usually began after significant shrinking had already occurred after commencement of propranolol treatment. Some of these children had extraordinary responses (e.g. Figs 4,5). In infants with this presentation, it is important to consider the possible diagnosis of PHACES syndrome. As such, these infants have a small risk of having a significant intracranial arteriopathy. Imaging of the cardiac, neck and head vasculature is recommended. In particular, there is a theoretical risk that propranolol might increase the likelihood of intracranial ischaemia in patients with intracranial arteriopathy by lowering blood pressure. If imaging has been done, the nature of the arterial pathology can be taken into account in deciding whether to start propranolol. The potential for severe disfigurement in these patients if untreated and the excellent response to propranolol observed in our centre shifts the balance towards treatment in these cases.

The safety of outpatient treatment with propranolol has been supported by this study. In total, 11 children (6%) stopped propranolol because of side effects, usually sleeping problems. No child in this study appeared to have any significant ongoing problems from propranolol. Two children may have had an episode of hypoglycaemia at home associated with poor intake and continued dosing with propranolol; both recovered rapidly without any intervention after the parents stopped giving propranolol. Diarrhoea was reported in 3% of families, much lower than the 64% in one previous report.[8] One possible reason for this difference might be that most children in our study were given propranolol tablets in water, rather than compounded syrup.

Gross motor abnormalities were observed in 13 infants. This finding may be coincidental as some abnormalities are expected when monitoring any large group of infants and toddlers. However, the number of otherwise normal children with delayed walking in this study (three at 18 months, one at 17 months, out of about 146 older than 16 months at the end of the study) is outside the expected range (97th centile 16.0 months, 99th centile 17.6 months[10]). Moreover, some parents reported striking changes in gross motor function that commenced within days of starting propranolol and/or ceased within a day of stopping. In each case, parents did not report any concomitant changes suggestive of hypoglycemia or hypotension such as decreased alertness or change in general behaviour. All children with delayed walking have eventually walked normally and one has mild cerebral palsy, as might be expected in a group of this size. The development of all children is continuing to be monitored.

Thirty-two patients had ulceration at the start of propranolol treatment. After commencement of propranolol, healing varied from a week to several months. Two infants required surgery for ulceration. Four infants developed small ulcers while on treatment. Ulceration was managed with standard treatments including topical anaesthesia, topical and/or oral antibiotic and wound dressings. No evidence that propranolol has an effect on ulcer healing could be adduced from this study.

Most families involved in this study made up a propranolol solution at home from commercially available tablets. They found this method rapid, simple and cheap. When made up this way, the solution is slightly cloudy and some families were initially concerned that significant propranolol might be undissolved and that dosing might therefore be unpredictable. Analysis of these home-made mixtures has confirmed that this is not a problem.[11]

Conclusion

Data from 188 infants with haemangioma treated with propranolol in an outpatient setting showed that most haemangiomas had a good or excellent response. The most dramatic effects were seen with large segmental facial lesions. Overall, 20% of haemangiomas did not respond to treatment. Treatment was stopped because of side effects in 6% of children. Sleep disturbance was the most frequent side effect noted.

Preliminary summary results were presented at the 2010 meeting of the International Society for the Study of Vascular Anomalies in Brussels.

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