Propranolol: a promising new treatment for infantile haemangioma

ANNIKA SMITH MB BS(Hons), FRACP, MPHTM
ORLI WARGON FACD, MClinEd

Propranolol has revolutionised treatment of infantile haemangiomas. GPs need to understand the role of propranolol in this context and be able to refer patients appropriately to paediatric or paediatric dermatology services.

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Infantile haemangiomas (IHs) are the most common vascular tumours of infancy, affecting 5 to 10% of the population.[1] They occur predominantly in Caucasian children; there is a female predominance.[2] The lesions have a predictable natural history of rapid growth during early infancy (over several months), followed by slower growth and gradual involution (over several years).[3] Regression is complete in 50% of 5-year-old and 90% of 9-year-old patients.[4]

The majority of IHs require no treatment and undergo spontaneous regression over time. However, spontaneous involution is no guarantee of a satisfactory cosmetic result.[5] IHs in certain locations (eye, nasal tip, mouth and airway) may impair vital functions or cause disfigurement, requiring prompt intervention. Large, segmental or multifocal lesions pose systemic complications, and the local complication of painful ulceration can lead to scarring. Approximately 10% of children require treatment for IHs because of life-threatening locations, local complications, or cosmetic/functional risks.[6,7]

In the past there has been no gold standard in the systemic treatment of IH. Therapeutic options have consisted of systemic and intralesional corticosteroids, chemotherapeutic agents (such as vincristine, interferon alfa), laser treatment and surgical resection.[8] To date, there have been no published comparative studies of these approaches. The mainstay of treatment for high-risk IHs has been systemic corticosteroids, an option limited by variable efficacy and common adverse effects, such as cushingoid features, adrenal suppression, weight gain, behavioural changes, gastric irritation, hypertension, immunosuppression and growth impairment.[5] Second-line therapies, including vincristine and interferon alfa, also have significant adverse effects (e.g. peripheral neuropathy, spastic diplegia).[9]

PROPRANOLOL: A NEW THERAPEUTIC OPTION

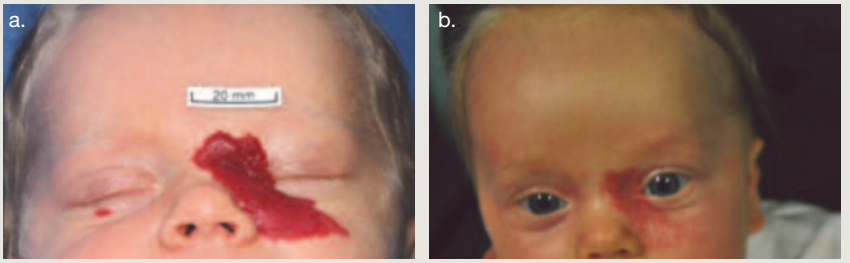
In 2008, French investigators made the serendipitous discovery that propranolol, a nonselective β-blocker traditionally used for treating hypertension, tachycardia and congestive cardiac failure, can induce dramatic regression of IHs. Their observation has radically changed the therapeutic approach to these tumours.

Subsequent reports confirming the impressive efficacy and safety of propran dol for IHs have been met with growing optimism.[10-12] In a multicentre retrospective study of 110 infants with IH, propranolol was significantly more effective than oral corticosteroids, with 82% of patients treated with propranolol achieving at least 75% clearance of the lesion compared with 29% of patients treated with oral corticosteroids ($p<0.01$).[5] None in the propranolol group suffered serious adverse effects. All patients (100%) treated with corticosteroids experienced adverse

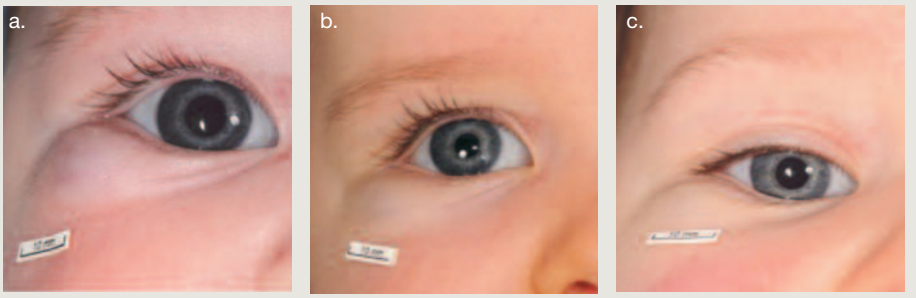
Dr Smith is Dermatology Registrar at Sydney Children's Hospital and Prince of Wales Hospital, Sydney.

Dr Wargon is Conjoint Associate Professor at the University of NSW. She is also Head of the Department of Paediatric Dermatology, Sydney Children's Hospital, Sydney, NSW.

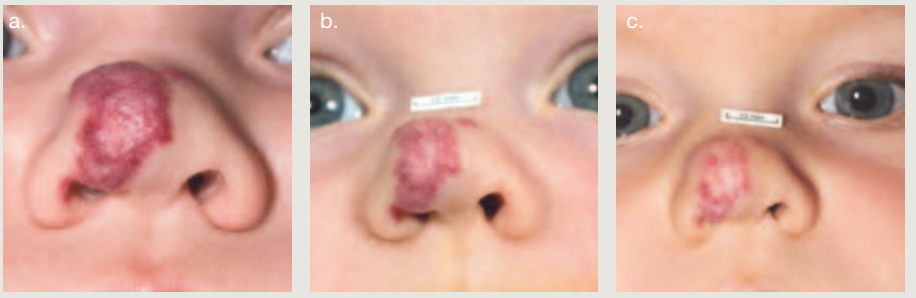
INFANTILE HAEMANGIOMAS AND PROPRANOLOL THERAPY



Figures 1a and b. A 4-week-old infant with a segmental IH of the left inner canthus, shown before (a) and after 12 weeks (b) of propranolol therapy.



Figures 2a to c. A 6-month-old girl with a deep periocular IH, shown before treatment (a) and after 12 weeks (b) and 24 weeks (c) of propranolol therapy.



Figures 3a to c. A 4-month-old boy with a nasal tip IH, shown before treatment (a) and after 12 weeks (b) and 24 weeks (c) of propranolol therapy.

effects. After treatment, 12% of infants in the propranolol group required surgery compared with 29% of those in the corticosteroid group. The authors of the study suggested that propranolol be first-line treatment for symptomatic and disfiguring IH, even when treatment is initiated after the first year of IH growth. As corticosteroids act by halting IH proliferation rather than inducing tumour shrinkage, their use is limited to the early proliferative phase (first six months, a narrow window of opportunity for treatment in which many still fail to respond).[5]

In addition, a small randomised controlled trial in Australia showed that propranolol (2 mg/kg/day) reduced the volume, colour and elevation of IHs in infants younger than 6 months and up to 5 years of age.[11]

It is important to remember that propranolol has not yet been approved for use in treating IH. However, this situation is likely to change as larger multicentre trials provide more detailed information regarding optimum dosing in different age groups and safety and relapse rates after discontinuation (results expected to be published soon). Many physicians are prescribing propranolol as first-line treatment of IHs (off label). Propranolol has been well studied in adults and has been used for decades to treat children with cardiovascular disorders. The pharmacokinetics and side effects are well known and it has a good safety profile.[13]

Some examples of the use of propranolol to treat IHs are shown in the box on this page (Figures 1 to 3).

MECHANISM OF ACTION

The exact mechanism of action of propranolol in the involution of IH is unknown. However, it is thought to exert its effects on proliferating endothelial cells in IH by three different molecular mechanisms:

- vasoconstriction (by decreasing the release of nitric oxide, with immediate changes in visible colour and palpable softening of the tumour)
- inhibition of angiogenesis (through inhibition of proangiogenic signals – decreased expression of vascular endothelial growth factor and basic fibroblast factor, which explains the progressive improvement in the haemangioma), and
- induction of apoptosis (of endothelial cells).[14]

ADVERSE EFFECTS

Known adverse effects of propranolol include hypotension, bradycardia, hypoglycaemia, bronchospasm, sleep disturbance, diarrhoea and hyperkalaemia.[6,13] On the basis of case reports and case series, oral propranolol treatment appears to

have a favourable safety profile in children. Reports of death or acute heart failure associated with propranolol initiation have been limited to the settings of intravenous administration or drug overdose.[13] Further, a review found that in 40 years of clinical use of β-blockers in children less than 7 years old there had been no deaths and no serious cardiovascular events.[15] The risk of propranolol-related side effects can be minimised with monitoring (pre-treatment cardiac assessment and monitoring for bradycardia, hypotension and hypoglycaemia at initiation of treatment and on serial review).[13]

ADMINISTRATION

Consensus protocols on the use of propranolol for treating IHs, developed after review of existing data by a multidisciplinary team, were published earlier this year.[13] These consensus protocols recommend a target dose of 1 to 3 mg/kg/day, with most members of the team advocating 2 mg/kg/day, the median dose reported in the literature.[7,13] There are data to suggest that monitoring for potential side effects while initiating oral propranolol can be performed safely in an outpatient setting. However, the consensus guidelines suggest inpatient hospitalisation for initiation of treatment for infants 8 weeks of age or younger, and for infants of any age with inadequate social support or comorbid conditions affecting the cardiovascular or respiratory system or blood glucose maintenance. According to the guidelines, cardiovascular monitoring should include heart rate and blood pressure measurements at baseline, 1 and 2 hours after receiving the initial dose, and after significant dose increments (>0.5 mg/kg/day). It should also include one set of measurements after the target dose has been achieved.[13]

Despite the widespread use of propranolol and numerous reports of the successful treatment of IH, there is still uncertainty regarding safety monitoring, dose escalation, duration of treatment and long-term outcomes. The consensus protocols aim to address some of these issues.[13] In this context, it is important that detailed information regarding proper administration of the medication and warning signs of potential side effects be provided to parents and carers. This need was highlighted in a recent paper detailing guidance for the parents and carers of infants who are being treated with propranolol for IH.[16] It is important that GPs understand the role of propranolol in the context of IHs and be able to refer patients appropriately to paediatric or paediatric dermatology services.

KEY POINTS

- IH is the most common vascular tumour of infancy.
- In certain locations, IHs may impair vital functions or cause disfigurement and require prompt intervention.
- Propranolol, a nonselective β-blocker, has been found to induce dramatic IH regression in case series and randomised controlled trials.
- Known adverse effects of propranolol include hypotension, bradycardia, hypoglycaemia, bronchospasm, sleep disturbance, diarrhoea and hyperkalaemia.
- Propranolol has been found to be rapidly effective for IH, well tolerated and better than previous therapies at inducing regression.
- Propranolol has revolutionised treatment of IHs. Results from larger multicentre trials will provide more detailed information regarding its use. MT

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