Clinical opinion

A revolution in the management of infantile haemangiomas

M Rademaker
Hon. Associate Professor, Dermatology Department, Waikato Hospital, Hamilton, New Zealand

AUTHORS Léauté-Labrèze C, Dumas de la Roque E, Hubiche T et al.
TITLE Propranolol for severe hemangiomas of infancy
DECLARATION OF INTERESTS No conflict of interests declared.

SUMMARY

In a letter to the editor, Léauté-Labrèze and colleagues describe the chance observation of the significant beneficial effects of propranolol on infantile haemangiomas (IH). A child, aged four months, had a large nasal IH, which had not responded to standard treatment with oral prednisolone (3 mg/kg/day). Coincidentally, the infant developed hypertrophic obstructive cardiomyopathy and was commenced on propranolol, 3 mg/kg/day. Within 24 hours, the IH was observed to be regressing and had completely flattened by 14 months of age.

A second infant, with an extensive IH affecting the entire right upper limb and face, had also not responded to high-dose prednisolone. He developed high cardiac output so was initiated on propranolol, 2 mg/kg/day. Within seven days there was marked improvement in the haemangioma. The systemic steroids were discontinued at four months of age, but the haemangioma continued to improve.

With informed consent, the authors then treated an additional nine infants (11 in total) with severe or disfiguring IHs with propranolol (2–3 mg/kg/day). Within 24 hours, a change in the haemangioma from intense red to purple was apparent in all infants; this change was associated with a palpable softening of the lesions.

A subsequent paper described the results of treating 32 children (21 girls; mean age at onset of treatment: 4.2 months) with large IHs with propranolol. Immediate effects on colour and growth were noted in all cases and were especially dramatic in haemangiomas complicated by dyspnoea, haemodynamic compromise or palpebral occlusion. In ulcerated haemangiomas, complete healing occurred within two months.

OPINION

Infantile haemangiomas, previously called capillary haemangiomas, are the most common soft-tissue tumours of infancy. They are benign vascular neoplasms with a characteristic clinical course. During the proliferative phase (birth to 12 months), rapidly dividing endothelial cells are responsible for the enlargement of the IH. This is followed by an involutional phase, such that most IHs have clinically resolved by age 7–9 years. While it is estimated that 10–12% of children may develop an IH, the majority are small and require no treatment. Unfortunately, a few impair vital or sensory functions, or cause significant permanent disfigurement.

The aetiology of IH remains unclear. A significant advance was the classification of haemangiomas and vascular malformations based on endothelial cell characteristics. It has since been hypothesised that during the third trimester of fetal development, immature endothelial cells coexist with immature pericytes, which maintain their proliferative capacity for a limited period during postnatal life. Angiogenic peptides, including vascular endothelial growth factor (VEGF), beta-fibroblast growth factor (bFGF) and proliferating cell nuclear antigen, may induce proliferation of these immature cells, resulting in the development of the IH. As the endothelial cells differentiate, mast cells migrate into the IH, releasing interferon and transforming growth factor, which terminate this proliferation. Involution of the haemangioma then occurs through senescence of these endothelial cells.

Prior to June 2008, rapidly growing IHs causing functional problems were treated with protracted courses of very high-dose prednisolone (2–5 mg/kg/day, often for 4–8 months), interferon-α, or vincristine. Adverse effects often limited their use.

The observation by Léauté-Labrèze and colleagues has been met with great excitement by those who treat IHs, and has already revolutionised the management of this condition. Precise details of the most appropriate dosage, length of treatment and which haemangiomas respond best are still to be clarified. It would be nice to see randomised placebo-controlled studies, but the speed and magnitude of the response of IHs to propranolol may make this difficult. However, there is already a trend to treat smaller, non-complicated IHs, which should be resisted until such studies have been performed.
The mechanism of action of propranolol in IHs is unknown, but it may include simple vasoconstriction, decreased expression of VEGF and βFGF genes through downregulation of the RAF-mitogen-activated protein kinase pathway or triggering of apoptosis of endothelial cells.

It is rare for a single observation to lead to a major paradigm shift in treatment. This one certainly has, and emphasises the value of careful clinical observation.

REFERENCES

Exclusive offer for RCPE Collegiate Members

50% discount on Fellowship subscriptions

We are pleased to offer a significant discount in annual subscription rates for eligible Collegiate Members who are consultants and wish to progress to Fellowship.* Collegiate Members of four years’ standing who are successful in their nomination for Fellowship will be able to obtain a 50% discount on their first year’s Fellowship subscription and a 25% reduction on their second year’s subscription, offering savings of up to £300.

Please access details of our reduced subscription rates, including concessionary elements for Fellows working less than half-time or on maternity leave, at: www.rcpe.ac.uk/join/fellowshipoffer.php

Fellowship confers a range of additional benefits and opportunities:

- International peer and public recognition through the use of the ‘FRCP Edin’ post-nominals.
- Professional support for revalidation/recertification.
- The opportunity to participate in projects and working groups to determine the future direction of education and clinical medicine.
- The opportunity to help maintain national and international clinical standards by acting as an MRCP (UK) examiner.
- The opportunity to inform College responses to external policy consultations in your specialty.
- The opportunity to participate in the governance of the College through election to committees and to Council.

*Eligible candidates should normally have held a substantive Consultant post or equivalent for at least 11 months. If you hold such a post and are interested in being considered for Fellowship, the principal method is nomination by an existing Fellow. Please e-mail Avril Harries at a.harries@rcpe.ac.uk for a list of Fellows in your area. Alternatively, you may wish to discuss nomination with one of our Regional Advisers or consider self-nomination.