

Prolonged tumour growth after treatment of infantile haemangioma with propranolol

Roderic J Phillips^{1,2}, Catherine M Crock¹, Anthony J Penington^{1,3}, Philip S Bekhor¹

Infantile haemangioma is the most common tumour of infancy, sometimes requiring treatment because of the risk of functional impairment or permanent scarring. Growth usually ceases by 12 months of age, and the tumour gradually regresses. In 2008, a review of all patients previously seen in seven international treatment centres identified only five children in whom any haemangioma growth was seen beyond 2 years of age, and none beyond 4 years.¹

Since 2008, the treatment of choice for haemangiomas has been oral propranolol for several months, for up to 18 months with segmental lesions. When commenced early, propranolol usually leads to rapid cessation of growth and tumour involution that is much more rapid than without treatment.² We have previously reported our experience with outpatient propranolol treatment of 200 infants.³ We now report a subset of 20 children for whom treatment with propranolol was initially effective and had ended, but was followed by progressive regrowth of the tumour, in some cases over many years. It is recognised that some regrowth is possible after stopping propranolol treatment, but it is usually self-limiting, although it may require a few additional months of treatment. Regrowth rarely occurs after 3 years of age.⁴ In our series, regrowth occurred in children more than 2 years old; six were over 3, and regrowth in two children continued beyond 5 years of age.

One of these children was born at 32 weeks' gestation and developed a rapidly growing extensive facial haemangioma (Box). She responded superbly to oral propranolol, which was ceased at 10 months of age. Regrowth was slow but progressive over the next 4 years, forming several clumps of recurrent tumour in conjunction with increased numbers of superficial vessels. (Box, D). Some surface clearing was noted before her 7th birthday, but also further regrowth of lip haemangioma that occurred despite oral propranolol (3 mg/kg/day), topical timolol, pulsed dye laser, and topical sirolimus. Different patterns of regrowth were noted in some other children, including recurrence of the tumour mass or a gradual increase in the density of surface telangiectatic vessels.

In our series, propranolol treatment of several children was ceased but then resumed after significant regrowth was seen. This usually, but not always, stopped or reversed regrowth. The oldest children also had a brief period of oral prednisolone treatment during infancy (standard practice in 2008) and some children had had pulsed dye laser therapy. Neither of these treatments has been associated with prolonged haemangioma regrowth as described here. It has been suggested that being female, deep lesions, and

A. Patient 1 at 13 days of age, before treatment. B. At 10 months, almost complete clearing after treatment with oral propranolol, together with brief oral prednisolone and pulsed dye laser therapy. C. At 2 years, redevelopment of surface vessels despite continuing propranolol (3 mg/kg/day). D. At 5.5 years, progressive thickening of haemangioma in the lip and several clumps, despite treatment with propranolol, laser, and topical timolol and sirolimus



early discontinuation of propranolol might increase the risk of regrowth.⁴ In our series, the mean age at cessation of propranolol was 20 months, later than currently recommended.

Prolonged tumour growth of this nature has not previously been described. Propranolol may act by blocking β -adrenergic receptors on haemangioma stem cells.⁵ In addition to stopping proliferation and hastening involution of infantile haemangioma, propranolol may have the unwanted side effect in some children of interfering with the natural mechanisms for clearing tumour stem cells.

Competing interests: No relevant disclosures. ■

© 2017 AMPCo Pty Ltd. Produced with Elsevier B.V. All rights reserved.

- 1 Brandling-Bennett HA, Baselga E, Lucky AW, et al. Infantile hemangiomas with unusually prolonged growth phase. *Arch Dermatol* 2008; 144: 1632-1637.
- 2 Leaute-Labreze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. *N Engl J Med* 2015; 372: 735-746.

- 3 Phillips RJ, Penington AJ, Bekhor PS, Crock CM. Use of propranolol for treatment of infantile haemangiomas in an outpatient setting. *J Paediatr Child Health* 2012; 48: 902-906.
- 4 Shah SD, Baselga E, McCuaig C, et al. Rebound growth of infantile hemangiomas

after propranolol therapy. *Pediatrics* 2016; 137: e20151754.

- 5 Munabi NC, England RW, Edwards AK, et al. Propranolol targets hemangioma stem cells via cAMP and mitogen-activated protein kinase regulation. *Stem Cells Transl Med* 2016; 5: 45-55. ■