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REVIEW

The use of propranolol in the management of periocular capillary haemangioma—a systematic review

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Abstract

Capillary haemangioma or infantile haemangioma (IH) is the most common congenital vascular tumour in the periocular region. Several treatment modalities have been documented, with variable degree of success. Propranolol has recently been reported to be an effective and safe alternative. The aim of this systematic review is to examine the evidence base for the use of propranolol administered orally in the management of periocular capillary haemangioma, and use this information to guide future research. A systematic review of literature was carried out by two independent reviewers using the search strategies highlighted below. A total of 100 cases of oral propranolol use in periorbital or orbital capillary haemangiomas have been documented in the literature. Of the 85 cases that had details of previous treatment, it was used as first-line treatment in 50 (58.8%). The commonest dose used was 2 mg/kg/day. Adverse events were documented in one-third of cases; in most cases these were minor. Improvement or complete resolution of the lesions occurred in 96% of cases. Recurrence was noted in one-fifth of cases. Propranolol has shown a lot of promise in the therapy of IH and further research in the form of properly designed randomized trials is certainly warranted. Treatment guidelines based on literature available to date is included in this review.

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Keywords: propranolol; beta-blocker; capillary haemangioma; haemangioma; orbital; periocular

Introduction

Capillary haemangioma or infantile haemangioma (IH) is the most common congenital vascular tumour of the periorbital region,[1] affecting approximately 10% of all infants.[2] They are benign tumours of vascular endothelial cells that are defined and distinguished from other vascular tumours and malformations by their unique histology and evolution (as highlighted in the Mulliken and Glowacki classification). The natural history of the haemangioma characteristically goes through a rapid growth phase during infancy followed by gradual involution. The former phase consists of endothelial hyperplasia and increased number of mast cells, whereas the involutional phase is characterized by fibrosis, diminished cellularity, and normal mast cell count.[3]

Rarely, a capillary haemangioma can be acquired at or before puberty.[1] About 80% of haemangiomas are located in the head and neck regions.[4] Around the eye, an IH can cause significant functional and cosmetic deformity, with 43–60% incidence of amblyopia when either eyelid or orbit is affected. This is as a result of astigmatism or mechanical ptosis causing visual deprivation.[5,6] Orbital involvement can lead to proptosis, exposure keratopathy, and compressive optic neuropathy. Although the natural history of an IH is spontaneous regression during the first decade of life, a high proportion of children with periocular IH will need treatment.[7] Ocular indications for treatment include obstruction of visual axis by the haemangioma or high degrees of astigmatism causing amblyopia,[8] exposure keratopathy secondary to proptosis, compressive optic neuropathy or rarely bleeding from the lesion.[7] Several treatment

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modalities have been used in the management of haemangiomas, including intralesional or systemic steroids, surgery, embolization, radiation, interferon therapy, and laser therapy[6,9–11] with variable efficacy and safety. Propranolol was serendipitously found to induce early involution in haemangiomas[12] and is now considered as a highly promising pharmacologic agent for the treatment of periocular capillary haemangiomas, especially in deep orbital lesions.

Methodology

Search strategy

Ovid MEDLINE (1948 to February Week 4 2011), CINAHL, and EMBASE were searched using the medical subject headings 'capillary hemangioma', 'adrenergic beta-antagnonists' and 'propranolol', and the following free text terms: 'periocular', 'orbital', 'capillary hemangioma', 'periocular hemangioma', 'eyelid hemangioma', 'capillary hemangioma', 'infantile hemangioma', 'stork bite', 'propranolol', 'beta blocker', 'haemangioma', 'capillary haemangioma', 'infantile'. The relevant keywords were linked using the Boolean operators AND/OR. The Cochrane database was searched for randomized controlled trials (RCT), systematic reviews, and meta-analyses using the same search strategy, as indicated above. Two independent reviewers analyzed the search results and the corresponding full articles. All case reports, retrospective or prospective case series, or randomized control trials reporting the use of propranolol in the management of periocular haemangioma were included. Articles that described use of propranolol for haemangioma elsewhere in the body were also analyzed to pick up cases of periocular haemangioma. Animal studies, unpublished abstracts/conference proceedings were excluded. The reference lists of included articles were studied to identify additional potentially relevant reports. Only articles/studies published in English language were included.

Inclusion criteria for this review

The primary objective of this review is to determine the evidence base of using propranolol in the management of periocular or orbital capillary haemangiomas. All forms of relevant literature, including case reports and case series, were included in the review. Any patient with a capillary haemangioma in the periocular area or orbit treated with propranolol was included. Any other skin lesions or capillary haemangiomas that were not treated with any beta-blockade therapy were excluded.

Results

Literature search

The electronic searches, including reference lists of the retrieved articles, found 96 titles and abstracts. Articles were read in full and the decision about inclusion of an article was not based solely on titles or abstracts. A total of 77 references were not relevant to the scope of the review, because they dealt with haemangiomas that were not periocular or orbital. The remaining 19 references are summarized in Table 1. There are no published RCTs on the efficacy and safety of propranolol in the treatment of periocular IH. Our search revealed a total of 100 patients that have been treated with oral propranolol for periocular or orbital IHs.

Patient demographics

The youngest child treated was 1 week of age, and the oldest 18 months, with a mean age of 4.8 months.

Haemangiomas had an orbital extension in 11 cases. The rest were superficial periorbital. More detailed description of the location of the superficial haemangioma was given in 40 of the 89 periorbital cases. A small proportion of these patients also had haemangiomas elsewhere, such as ear, jaw and chin. The main indication for treatment of the lesion was amblyopia, which was either visual deprivation, anisometropic or astigmatic. Management of the haemangioma was also combined with appropriate treatment for amblyopia.

The other five patients had an intraconal or orbital haemangioma resulting in one or more of the following: proptosis, exposure, anisometropia, globe displacement, strabismus, and compressive optic neuropathy.

Diagnosis was based on the typical appearance of the lesion in all cases of superficial periocular IHs,[12–17,19] and in one case of orbital lesion,[13] where a right anterior orbitotomy was performed and the appearance of the lesion was typical of a capillary haemangioma. Imaging in the form of computerized tomography or magnetic resonance imaging was performed to diagnose all intraconal masses (11 cases in this review). Where diagnosis couldn't be made with this information, a biopsy was obtained (one case).[5]

Previous treatment

Details of previous treatment before commencing propranolol were given in 85 of the 100 patients.

In 50 out of these 85 patients (58.8%), propranolol was used as first-line treatment. Five patients (5.0%) had received previous intralesional steroids. The rest, 36.5%, were previously treated with systemic prednisolone at a dose of 1–5 mg/kg/day (most cases on 2 mg/kg/day).

Table 1 Patient demographics and details of propranolol use

Reference (please refer to main bibliography)	*Number of patients*	*Location of IH*	*Age at presentation (months)*	*Mean age at presentation (months)*	*Dose of propranolol (mg/kg/day)*	*Duration of Rx (months)*	*Mean duration of Rx (months)*
Léauté-Labrèze *et al*[12]	7	Periocular	2–6	3.3	2	7–10	6.4
Haider *et al*[13]	17	Periocular	1–12	5.8	2	9–11	7.6
Sans *et al*[14]	14	Periocular	1–18	4.2	2–3	6	6.6
Milet *et al*[15,a]	18[b]	Periocular	N/A	N/A	N/A	N/A	N/A
Al Dhaybi *et al*[8,a]	17[b]	Periocular	N/A	6.5	2–3	N/A	5.5
Lawley *et al*[16]	2	Periocular	1–2	1.5	2	0.5	
Holmes *et al*[17]	5	Periocular	1–10	3.9	3	3	3.1
Fay *et al*[5]	1	Orbital	4	4	2	8	8
Bang *et al*[18]	1	Orbital	0.5	0.5	2	8	8
Tan *et al*[19]	2	Periocular	1–8.5	2.7	1.5–2	12	N/A
Taban *et al*[20]	1	Orbital	1.5	1.5	2	6	6
Holland *et al*[21]	1	Periocular	11	11	2	0.5	0.5
Li *et al*[22]	4	Orbital	2.75–29	10.1	2	6–14	9.75
Arneja *et al*[23]	2	Orbital	2–3	2.5	2	8	8
Manunza *et al*[24]	9	Periocular	1.2–13.5	6.5	1–2	3.5–15	5.5
Cheng *et al*[25]	10	Periocular Orbital	1–11	4.2	2	3–10.5	8.2
Chik *et al*[26]	2	Periocular	0.25–0.5	0.375	2	3–4	3.5
Fabian *et al*[27]	3	Periocular	3–8	6.3	2	3–4	3.3
Mishra *et al*[28]	7	Periocular	N/A	N/A	3	N/A	N/A

Abbreviations: IH, Infantile hemangioma; kg, kilogram; mg, milligram; Rx, treatment.
[a]Published abstracts only.
[b]Similar cases published in two different papers.

Intralesional or systemic steroids were found to be slightly effective at first in some cases, but did not halt progression and were not free of side effects. Alternative treatment was required as haemangioma growth persisted despite steroid treatment, and anisometropia and astigmatism needed to be addressed, possibly using occlusion. Certain centres used propranolol as first-line treatment for capillary haemangiomas based on their own experience, but no further details of specific cases was described.[29]

Dosage and safety

Propranolol in the dosage range of 1–3 mg/kg/day has been used in all documented cases, with 2 mg/kg/day as the most common dose. Duration of treatment varied between 2 weeks to 1 year with a mean duration of 6.9 months (Table 1).

Adverse effects with propranolol for infantile periocular capillary haemangiomas were documented in 26 of the 100 cases (Table 2). However, many of these were not serious enough to warrant stopping or amending the dose of propranolol. In fact, propranolol was only discontinued in five cases (5%).

One episode of bronchospasm was documented in this literature review. The child had been previously diagnosed with atopic dermatitis and the wheezing condition was later diagnosed as asthma. Propranolol was stopped, and wheezing stopped a few days after.[14]

Table 2 Adverse effects of treatment

Author	*Number of patients*	*Adverse reactions*
Tan *et al*[19]	1	Hypotension
Haider *et al*[13]	6	Fatigue Transient GI upset Regurgitation
Sans *et al*[14]	9	Hypotension Asthma onset Insomnia Agitation Nightmares Sweats Cold hands
Lawley *et al*[16]	2	Hypotension Bradycardia Hypoglycaemia
Holmes *et al*[17]	1	Hypotension
Holland *et al*[21]	1	Hypoglycaemia
Al Dhaybi *et al*[8]	6	Diarrhoea Sleep disturbance Agitation

Hypoglycemia was documented in two cases in this review,[16,21] a 36-day-old and an 11-month-old girl. The latter had to be hospitalized for a day, after which propranolol was stopped, whereas the former had no sequelae.

Hypotension was documented in four cases where propranolol was used for periocular IHs.[14,16,19] The first case was an 8-week-old girl who had systolic blood pressure of 60 mm Hg after 2 weeks of treatment. After 2 h of monitoring, her pulse and blood pressure returned to normal without any intervention. Propranolol was discontinued.[16] The second case was a premature infant who had borderline asymptomatic diastolic hypotension. Propranolol in this case was slowly incremented over 2 months to 2 mg/kg/day and no further intervention was required. It was not stopped and there was successful involution of the haemangioma. Low-dose propranolol administered in divided doses with gradual increase is therefore advocated by the authors.[19] In the third case, blood pressure decreased 3 h after the first dose to 62/25 mm Hg while the child was sleeping, and resolved spontaneously without any therapeutic intervention. Propranolol was not discontinued.[14] Other documented side effects (Table 2) were minor and self-limiting. Finally, hypotension was documented as being a transient self-limiting asymptomatic event that did not require premature termination of treatment.[17]

Cardiac hypersensitivity has been reported to occur 24–48 h after stopping propranolol, peaking at 4–8 days, and diminishing after 2 weeks.[30] There were no cases of cardiac hypersensitivity after stopping propranolol. Tapering the dose over a 2-week period has been reported to be safer.[16] Early termination of treatment might be advisable in certain cases.[17]

Haider *et al*[13] reported problems with compliance to treatment in nearly one-fourth of their patients. Luckily, this did not have any effect on efficacy and none of the patients had serious adverse effects.

Efficacy

Clinical outcome in the majority of cases reported was qualified as being either successful or not. No standard method of defining success was used in these reports. Haider *et al*[13] has attempted to define various grades of success. An 'excellent' result was qualified as more than 50% reduction in size of the haemangioma, 'good' result as decrease in size of $<50\%$, 'fair' result as no further growth, and 'poor' result as continued growth or intolerable adverse effects.

All cases of orbital haemangiomas resolved after 2–4 months of treatment.[5,12,13,18,20,25] In patients with periocular IHs, blanching, softening, and early regression of the lesions started within the first 3 days of treatment. The earliest visible response to treatment varied from 1 week[6,13,31,] to 6 weeks[12] after initiation of treatment.

Improvement or resolution of the lesion was observed in 96 of the 100 documented cases. In the other four cases, propranolol was discontinued because of hypotension ($n=1$),[16] asthma onset ($n=1$),[14] hypoglycaemia ($n=1$),[21] or no effect on astigmatism ($n=1$).[25] Propranolol was therefore effective in 96 out of the 97 cases as it was discontinued in three cases for adverse events, and in one for lack of an adequate response to the drug.

Recurrence of the haemangioma occurred in 15% after withdrawal of propranolol. This did not seem to be related to the duration of treatment or the age of the patient. Recurrences were in the form of mild recolouring in seven cases[12,14] and rebound growth in eight cases.[12,17] Treatment was re-started in six of the latter eight 'regrowth' cases, for a further 6–54 weeks (mean 9.3 weeks),[17] and all of these responded well. The rest of the cases of recurrences did not require retreatment with propranolol.

Other beta blockage for periocular capillary haemangiomas

Acebutolol, a selective β-adrenergic receptor blocking agent has been used in one patient of 2 months of age with hemifacial haemangioma causing ocular occlusion, with no response to systemic prednisolone. A dose of 10 mg/kg/day was used for 10 months, causing regression and resolution of ocular occlusion.[32] There is no further documentation of use of this drug in management of periocular IHs.

Limitations of this review

Only 100 cases have been reported to date. While every effort was made to include all relevant published literature, unpublished reports could be a source of publication bias. Publication bias due to unfavourable results is another potential limitation of any systematic review. Furthermore, only articles published in English language have been reviewed.

Discussion

Various treatment modalities have and are still being used for the management of periocular IHs. Systemic corticosteroids can be effective but may be accompanied by significant systemic adverse effects, and rebound growth can occur upon cessation of treatment.[33] Other agents used include vincristine sulphate, cyclophosphamide, imiquimod cream, and interferon.[6,34–36] Intralesional corticosteroids (triamcinolone) are sometimes used. Radiation, laser,[10] embolization,[9] and surgical excision[6,11] are other more invasive options, and the latter might have to be an earlier option in periocular IHs to minimize likelihood of amblyopia.[6]

Propranolol is used by paediatric cardiologists in children as young few weeks to treat tachydysrhythmias, idiopathic hypertrophic subaortic stenosis, paroxysmal hypoxaemic spells, long Q-T syndrome, and congenital heart failure at doses up to 8 mg/kg/day in divided doses.[26] It is used at a lower dose for treatment of periocular IHs. A 40-year review of propranolol toxicity in children found no cases of mortality,[28] and in all cases, adverse effects resolved either spontaneously or when the drug was stopped.[37]

The known side effects of propranolol include bronchospasm,[14] hypoglycaemia,[16,21,38] mood disturbances, somnolence,[39] bradycardia, and hypotension.[14,16,17,19] Bronchospasm is usually seen as an exacerbation in patients with underlying reactive airway diseases. It is therefore important to question parents about previous atopic or wheezing conditions.[14] Hypoglycemia can occur as propranolol decreases lipolysis, glycogenolysis, and gluconeogenesis.[38] In addition, it can also mask hypoglycaemia symptoms. The potential for the above adverse events requires adequate education of the parents and caution on the part of the prescribing physician.[4] Hypoglycemia associated with propranolol is best recognized during the neonatal period, especially in low-birth weight newborns, with older infants and children considered to be low risk.[21] This adverse event may not be dose dependant. While recognition of signs or symptoms of hypoglycemia is essential, adequate care is needed decrease the risk of such an adverse event. It is recommended that propranolol be discontinued during intercurrent illness, especially in the setting of decreased oral intake. If this is not possible, glucose containing intravenous fluids are indicated.[40] Blood glucose levels should be monitored before and during treatment.

The difficulty in defining outcomes is apparent in the review. Haider *et al*[13] have reported their attempt at such a definition. This remains one of the drawbacks. Volumetric assessment documented either by ultrasonography or magnetic resonance imaging of the lesion is probably the best quantitative method to assess the response to treatment.

Protocol for use of propranolol

Protocols have been suggested by several authors.[16,24] Manunza *et al*[24] suggested a protocol where baseline investigations are done before treatment including an echocardiogram, ECG and abdominal ultrasound. Heart rate and blood pressure are monitored every half hour for the first 4 h of treatment, after which they are checked twice weekly for two weeks, and once weekly thereafter. Lawley *et al*[16] has called for a more intensive monitoring as an inpatient. The dose is increased in gradual increments every 3 days. As risk of hypotension and hypoglycemia is higher in premature and young infants, slower dose escalation is recommended in these selected cases. The treatment is continued until the proliferative phase has ended (6–12 months of age) or until stabilization of refraction on consecutive follow-up visits, if the haemangioma causes astigmatism.[23]

Areas for future research

The response to propranolol therapy seen in many reports may represent the natural history of evolution of the haemangioma. The recurrence seen in some reports when propranolol was stopped, and subsequent resolution in re-initiation of propranolol therapy does provide some proof that propranolol has an effect on the haemangioma (challenge–rechallenge).

It is evident from this review that, to date, there are no published RCTs evaluating the efficacy of propranolol in the management of IH. Designing a proper RCT could prove extremely difficult, especially as various treatment modalities exist and head-to-head comparisons might not be possible. It is also evident from the review that published reports varied tremendously in terms of baseline parameters such as location and size of lesion, age at intervention, indication for treatment, previous therapy, and standardized method of monitoring response and adverse effects. Furthermore, the high success rate reported so far makes it extremely difficult for power calculation for a randomized trial. Duration of therapy also needs further investigation as almost one fifth of children treated for at least 6 months had a recurrence when propranolol was stopped. Recurrence did not seem to be related to duration of treatment so maybe this decision would have to be done on a patient individual basis.

Propranolol is a non-selective beta-blocker and may be more prone for adverse effects. There is scope for other more selective beta-blockers such as acebutolol to be introduced into trials. Mode of administration of beta-blockers is another avenue for further research. Although there are reports of topical application of timolol gel in the treatment of superficial periocular haemangioma,[41] details are vague and further evidence is required to understand their value.

In summary, propranolol has shown a lot of promise in the therapy of IH and further research in the form of properly designed RCT with well defined outcome measures is warranted, although one must appreciate that designing a proper RCT in this case might prove extremely difficult.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

KSC and ARR contributed to the design and conduct. KSC wrote the article and ARR revised the review.

References

1 Gard R, Gupta N, Sharma A, Jain R, Beri S, D'Souza P. Acquired capillary haemangioma of the eyelid in a child. *J Paediatr Ophthalmol Strabismus* 2009; **46**: 118–119.
2 Drolet BA, Esterly NB, Frieden IJ. Haemangiomas in children. *N Engl J Med* 1999; **341**: 173–181.
3 Finn MC, Glowacki J, Mulliken JB. Congenital vascular lesions: clinical application of a new classification. *J Pediatr Surg* 1983; **18**: 894–899.
4 Cruz OA, Siegfried EC. Propranolol treatment for periocular capillary haemangiomas. *J AAPOS* 2010; **3**: 251–256.
5 Fay A, Nguyen J, Jakobiec FA, Meyer-Junghaenel L, Waner M. Propranolol for isolated orbital infantile haemangioma. *Arch Ophthalmol* 2010; **128**: 256–258.
6 Maguiness SM, Frieden IJ. Current management of infantile haemangiomas. *Semin Cutan Med Surg* 2010; **29**: 106–114.
7 Tambe K, Munshi V, Dewsbery C, Ainsworth JR, Willshaw H, Parulekar MV. Relationship of infantile periocular haemangioma depth to growth and regression pattern. *J AAPOS* 2009; **13**: 567–570.
8 Al Dhaybi R, Milet A, McCuaig C, Ospina L, Powell J. Treatment of periocular infantile haemangioma with propranolol: review of 17 cases. *Pediatr Dermatol* 2009; **26**: 665–666.
9 Ceisler E, Bleij F. Ophthalmic issues in haemangiomas of infancy. *Lymphat Res Biol* 2003; **4**: 321–330.
10 Apfellberg DB, Maser MR, White DN, Lash H, Lane B, Marks MP. Benefits of contact and non-contact YAG laser for periorbital haemangiomas. *Ann Plast Surg* 1990; **24**: 397–408.
11 Tronina SA, Bobrova NF, Khrinenko VP. Combined surgical method of orbital and periorbital haemangioma treatment in infants. *Orbit* 2008; **27**: 249–257.
12 Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F. Propranolol for severe haemangiomas of infancy. *N Engl J Med* 2008; **358**: 2649–2651.
13 Haider KM, Plager DA, Neely DE, Eikenberry J, Haggstrom A. Outpatient treatment of periocular infantile haemangiomas with oral propranolol. *J AAPOS* 2010; **14**: 251–256.
14 Sans V, Dumas de la Roque E, Berge J, Grenier N, Boralevi F, Mazereeuw-Hautier J *et al*. Propranolol for severe infantile haemangiomas: follow-up report. *Pediatrics* 2009; **124**: 423–431.
15 Milet A, Al Dhaybi R, Superstein R, Powell J, Hamel P, Chevrette L *et al*. Propranolol for the treatment of periocular capillary haemangiomas. *J AAPOS* 2010; **14**: e5.
16 Lawley LP, Siegfried E, Todd JL. Propranolol treatment for haemangioma of infancy: risks and recommendations. *Pediatr Dermatol* 2009; **26**: 610–614.
17 Holmes WJM, Mishra A, Gorst C, Liew SH. Propranolol as first-line treatment for rapidly proliferating infantile haemangiomas. *J Plast Reconst Aesth Surg* 2010; **125**: 420–427.
18 Bang G. Propranolol in treatment of capillary haemangiomas. *Pediatric Ophthalmology Grand Rounds*, University of Illinois Eye and Ear Infirmary, http://www.uic.edu/com/eye (accessed on 31 October 2010).
19 Tan ST, Itinteang T, Leadbitter P. Low-dose propranolol for infantile haemangioma. *J Plast Reconst Aesth Surgery* 2011; **64**: 292–299.
20 Taban M, Goldberg RA. Propranolol for orbital haemangioma. *Ophthalmology* 2010; **117**(1)**:** 195–195.e4.
21 Holland KE, Frieden IJ, Frommelt PC, Mancini AJ, Wyatt D, Drolet BA. Hypoglycemia in children taking propranolol for the treatment of infantile haemangioma. *Arch Dermatol* 2010; **146**: 775–778.
22 Li YC, McCahon E, Rowe NA, Martin PA, Wilcsek GA, Martin FJ. Successful treatment of infantile haemangiomas of the orbit with propranolol. *Clin Experiment Ophthalmol* 2010; **38**(6): 554–559.
23 Arneja JS, Pappas PN, Shwayder TA, Cullen ML, Becker CJ, Hamzavi FH *et al*. Management of complicated facial haemangiomas with beta-blocker (propranolol) therapy. *Plast Reconstr Surg* 2010; **126**(3): 889–895.
24 Manunza F, Syed S, Laguda B, Linward J, Kennedy H, Gholam K *et al*. Propranolol for complicated infantile haemangiomas: a case series of 30 infants. *Br J Dermat* 2010; **162**: 452–468.
25 Cheng JF, Gole GA, Sullivan TJ. Propranolol in the management of periorbital infantile haemangioma. *Clin Exp Ophthalmol* 2010; **38**: 547–553.
26 Chik KK, Luk CK, Chan HB, Tan HY. Use of propranolol in infantile haemangioma among Chinese children. *Hong Kong Med J* 2010; **16**: 341–346.
27 Fabian ID, Ben-Zion I, Samuel C, Spierer A. Reduction in astigmatism using propranolol as first-line therapy for periocular capillary haemangioma. *Am J Ophthalmol* 2011; **151**: 53–58.
28 Mishra A, Holmes WJM, Gorst C, Liew SH. Role of propranolol in the management of periocular haemangiomas. *Plast Refract Surg* 2010; **2**: 671.
29 Ernemann U, Kramer U, Miller S, Bisdas S, Rebmann H, Breuninger H *et al*. Current concepts in the classification, diagnosis and treatment of vascular anomalies. *Eur J Radiol* 2010; **1**: 2–11.
30 MicromedexR Healthcare Series. (Internet Database), Greewood Village, CO: Thomson Healthcare. Updated periodically. Available at: http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/FD86B3/DUPLICATIONSHIELDSYNC/A57282/ND_PG/PRIH/ND_B/HCS/SBK/3/ND_P/Main/PFPUI/6DTTNe2E3UQuC/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/2119/ContentSetId/31/sectionId/adverseReactionsSection/SearchTerm/propranolol%20/SearchOption/BeginWithip8 (accessed 31 October 2010).
31 Haik BG, Karcioglu ZA, Gordon RA, Pechous BP. Capillary haemangioma (infantile periocular haemangioma). *Surv Ophthalmol* 1994; **38**: 399–426.
32 Bigorre M, Van Kien AK, Valette H. Beta-blocking agent for treatment of infantile haemangioma. *Plast Reconstr Surg* 2009; **6**: 195e–196e.
33 Buckmiller LM. Propranolol treatment for infantile haemangiomas. *Curr Opin Otolaryngol Head Neck Surg* 2009; **6**: 458–459.

34 Laquer V, Hoang V, Nguyen A, Kelly KM. Angiogenesis in cutaneous disease: Part II. *J Am Acad Dermatol* 2009; **61**: 945–958.
35 Tucci FM, De Vincentiis GC, Sitzia E, Giusio L, Trozzi M, Bottero S. Head and neck vascular anomalies in children. *Int J Paed Otorhinolaryngol* 2009; **73S**: S71–S76.
36 Boye E, Jinnin M, Olsen BR. Infantile haemangioma: challenges, new insights, and therapeutic promise. *J Craniofac Surg* 2009; **20**(Suppl 1): 678–684.
37 Love JN, Sikka N. Are 1-2 tablets dangerous? Beta-blocker exposure in toddlers. *J Emerg Med* 2004; **26**: 309e14.
38 Léauté-Labrèze C, de la Roque ED, Taïeb A. More on propranolol for haemangiomas of infancy. *N Engl J Med* 2008; **26**: 2846–2847.
39 Buckmiller LM, Richter GT, Suen JY. Diagnosis and management of haemangiomas and vascular malformations of the head and neck. *Oral Dis* 2010; **5**: 405–418.
40 Halamek LP, Stevenson DK. Neonatal hypoglycaemia, part II: pathophysiology and therapy. *Clin Pediatr (Phila)* 1998; **1**: 11–16.
41 Pope E, Chakkittakandiyil A. Topical timolol gel for infantile haemangiomas: a pilot study. *Arch Dermatol*. 2010; **5**: 564–565.