International Journal of Pediatric Otorhinolaryngology 74 (2010) 338–342

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

Review article

Propranolol therapy for infantile haemangiomas: Review of the literature

A.P. Zimmermann *, S. Wiegand, J.A. Werner, B. Eivazi

Department of Otolaryngology, Head and Neck Surgery, Philipps University, Marburg, Germany

ARTICLE INFO

Article history:
Received 6 October 2009
Received in revised form 30 December 2009
Accepted 5 January 2010
Available online 1 February 2010

Keywords:
Propranolol
Haemangioma
Beta-blocker
Pharmacologic therapy

ABSTRACT

Objectives: Haemangiomas are the most common tumors of infancy affecting approximately 1 in 10 children. Unlike other tumors, haemangiomas enter an involution phase, during which they usually regress over the next several months to years. Sometimes intervention is required due to proliferative growth which is complicated by ulceration, bleeding, persistent aesthetic deformity or infection.
Methods: Review of the literature.
Results: Propranolol, a nonselective beta-blocker, has recently been introduced as a novel modality for the treatment of proliferating haemangiomas. The exact mechanism of action of propranolol in the treatment of haemangiomas remains unclear, but vasoconstriction, down-regulation of angiogenic factors such as VEGF and bFGF and up-regulation of apoptosis of capillary endothelial cells may be responsible for the reduction of haemangiomas. Besides, an inhibition of MMP-9 and HBMEC expression by propanolol is discussed as possible mechanism influencing the growth of haemangiomas. However, there are different case reports of successfully treated infants in the current literature.
Conclusion: There is the obtain that propranolol will detach steroids in the therapy for infantile haemangiomas.

Contents

1. Introduction

Haemangiomas are the most common tumors of infancy affecting approximately 1 in 10 children [1]. Haemangiomas are more common in Caucasians, being evident in up to 12% of all children and occurring more frequently in females than in males, in a ratio of 3:1. Sixty per cent of haemangiomas are located in the head and neck area, whereas 25% occur on the trunk and 15% on the extremities [2]. Usually 80% of all haemangiomas are single lesions, but 20% of affected infants develop multiple tumors. Infantile haemangiomas are characterized by an inconspicuous appearance at birth, but undergo rapid and intermittent growth throughout the first year of life. By the age of 5 years usually 50% of the lesions have involuted. This increases to nearly 70% by the age of 7 years and about 90% by the age of 9 years. Nevertheless, in 40–50% of all affected children teleangiectatic cutaneous vessels, fibrous-fatty tissue or scar formations can be observed as a residue of the lesions [3,4].

Although general outlines of haemangioma growth characteristics have long been recognized, specific details about haemangima growth and information regarding differences in growth patterns between haemangioma subtypes are lacking. There are different theories on the origin of infantile haemangiomas. These include suggestions of placental origin, intrinsic defect or somatic endothelial mutation, and extrinsic factors creating a conductive milieu for growth. However, no current hypothesis explains all the characteristics of infantile haemangiomas. In the last several years, much has been learned about molecular features of haemangioma

* Corresponding author at: Department of Otolaryngology, Head and Neck Surgery, University Hospital Giessen & Marburg, Campus Marburg, Deutschhausstr. 3, 35037 Marburg, Germany. Tel.: +49 6421 5866478; fax: +49 6421 5866367.
E-mail address: anzimmer@med.uni-marburg.de (A.P. Zimmermann).

0165-5876/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijporl.2010.01.001

and haemangioma-derived endothelial cells cultured in vitro. Haemangioma endothelial cells exhibit constitutive vascular endothelial growth factor signalling the endothelial cells comprising infantile haemangiomas show intense and persistent immunoreactivity for a number of tissue-specific markers that is highly characteristic of placental microvasculature like GLUT-1. Therefore there is the hypothesis that haemangiomas possibly stem from placental tissue or resemble it [3,4]. Infantile haemangiomas vary tremendously from small, benign growth to large, function-threatening tumors. Most require no treatment, but treatment is needed if dramatic aesthetic, and/or functional impairment as visual or airway obstruction or ulceration arises [5]. Until now oral corticosteroids are considered as first-line therapy for such troublesome and severe haemangiomas. Systemic steroids have proven effectiveness, but the risks of long-term and high dose use include growth disturbances and immune system dysfunction as well as ulcerations up to severe tissue loss. Moreover, there are cases of fast growing infantile haemangiomas which show no response to steroid therapy. Other therapeutic options as interferon alpha and vincristine are used less often because of side effects and toxicity [6]. In cases of life-threatening haemangiomas and haemangiomatosis cyclophosphamide was also reported to offer promising results [7]. However, the serious side effects of cyclophosphamide like avascular necrosis, cardiomyopathy, pulmonary fibrosis, gonadal damage, and subsequent malignancies [8] have to be kept in mind and therefore the application of cyclophosphamide in the therapy of infantile haemangiomas needs to be carefully considered. Reported successful invasive treatments, especially for airway haemangiomas, include intralesional steroid injection, endoscopic and open excision, laser therapy, and tracheotomy. The treatment plan depends on many factors, including the size and extent of the lesion, social situations, and surgeon's comfort or experience with any given treatment modality.

The use of propranolol in the treatment of haemangiomas was serendipitously discovered last year in 2 children who showed rapid regression of disease when treated for cardiopulmonary conditions [9]. The treatment course occurred during the proliferative phase of growth, but the impact of propranolol on persistent disease remains unknown. After this notification [9] several groups worldwide initiated propranolol therapy in children with haemangiomas and gained experiences with this treatment. Therefore it was necessary to summarize the results. This review presents the current knowledge on propranolol therapy in infantile haemangiomas and the assumptions regarding the possible mechanism of propanolol in haemangioma therapy.

2. Propranolol for haemangiomas—mode of action and side effects

Propranolol was the first clinically useful beta adrenergic receptor antagonist. Invented by Sir James W. Black, it revolutionized the medical management of angina pectoris and is considered to be one of the most important contributions to clinical medicine and pharmacology of the 20th century [10]. Beta-blockers may also be referred to as beta-adrenergic blocking agents, beta-adrenergic antagonists, or beta antagonists.

Propranolol is a nonselective beta-blocker. The levorotatory isomer of propranolol binds reversibly with β1- and β2-adrenoreceptors; both receptors have membrane stabilizing activity. By this mechanism propranolol leads to a reduction of the heart rate and of the cardiac output; however, initially the effect is delayed because of peripheral vasoconstriction. The AV nodal conduction time and the AV refractoriness are prolonged and blood flow and pressure decreases in most vascular territories. The drug is also characterized as an adrenoreceptor partial agonist, especially the S-(−) enantiomer. Probably owing to the effect at the α1-adrenoceptor, the racemate and the individual enantiomers of propranolol have been shown to substitute for cocaine in rats with the most potent enantiomer being S-(−)-propranolol. Research has also shown that propranolol has inhibitory effects on the norepinephrine transporter, stimulates norepinephrine release and partially agonizes serotonin receptors, the two former indirectly while the latter directly. Both enantiomers of the drug have local anaesthetic (termed topical) effect.

Propranolol is almost completely absorbed from the gastrointestinal tract and there is significant first pass metabolism and hepatic tissue binding with up to 90% of an oral dose being eliminated. At least one metabolite shows biological activity but the effect on overall activity is unknown. Metabolites and a small amount of unchanged propranolol are excreted in the urine. Propranolol is highly protein-bound (80–95%). It is widely distributed throughout the body with highest levels occurring in the lungs, kidney, brain and heart.

The response of infantile haemangiomas to propranolol reported in the New England Journal of Medicine by Léauté-Labrèze et al. [9] catapulted the use of this treatment to first-line status among physicians managing this disease [11,12].

Regulators of haemangioma growth and involution are poorly understood. Infantile haemangiomas are composed of a complex mixture of clonal endothelial cells associated with pericytes, dentric cells, and mast cells. Haemangiomas usually appear a few weeks after birth and grow more rapidly than the infant does. This proliferative phase of haemangiomas is characterized histologically by plump endothelial cells with frequent mitosis, an increased number of mast cells and multilaminated basement membranes. Two major proangiogenetic factors are involved: basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). This period is followed by spontaneous slow involution which shows apoptosis, and is morphologically characterized by flat, inactive and normal-appearing endothelial cells in a matrix of the so-called "fibrous-fatty tissue" [4,6].

Potential explanations for the therapeutic effect of propranolol on haemangiomas include vasoconstriction, which is immediately visible as a change in colour, associated with a palpable tissue softening. Other included suggestions are a down-regulation of angiogenetic factors such as VEGF and bFGF and an up-regulation of apoptosis of capillary endothelial cells [2,9]. There are also data published which indicate a selective role of propranolol in inhibiting the expression of MMP-9 (angiogenic and extracellular matrix degrading enzyme) and HBMEC (human brain microvascular endothelial cells). These facts may potentially add to propranolol's anti-angiogenetic properties. HBMEC play an essential role as structural and functional components in tumor angiogenesis [13]. A further interesting issue is the fact that haemangiomas are more frequent in premature infants. Up to now there is no explanation for this observation. Pregnant women with premature contractions receive tocolytics. Tocolytics are vasodilatory beta-sympathomimetic drugs, the antidote of beta-blockers. As a result of the knowledge that beta-blockers are effective for treatment of haemangiomas, it seems possible that tocolytics may contribute to their incidence in premature infants [14].

Propranolol has a well-documented safety and side effect profile. Its use in children has been limited to hypertention and cardiovascular diseases as a psychopharmaceutical agent [5]. Although serious side effects have been reported in new borns after intrauterine exposure to beta-blockers including propranolol, post-natal exposure seems to have no adverse effects. After more than 40 years of clinical use in infants with cardiac findings, there is no case of life-threatening complications as direct result of exposure to propranolol. Potential side effects of beta-blockers include bradycardia, hypotension, hypoglycemia, rash, gastroin-

testinal discomfort/reflux, fatigue and bronchospasm, all are rare and observed at higher doses (>2 mg/kg/day).

A treatment protocol for propranolol use was developed by several groups [5,11] to optimise drug safety and its comparability to other drugs. A careful history and physican examination are obtained. In the absence of cardiac conditions and airway diseases the patient is considered as a candidate for therapy.

3. Review of case reports (Table 1)

Léauté-Labrèze et al. [9] treated a child with propranolol at a dose of 3 mg/kg of body weight per day because of its obstructive hypertrophic myocardiopathy. Simultaneously the child had a nasal haemangioma. This showed a coincidental impressive improvement during this therapy. A second child with pathological cardiac findings and a facial haemangioma was treated with propranolol at a dose of 2 mg/kg of body weight per day and showed a clear resolution of the haemangioma. Because of this positive effect propranolol (2 mg/kg/day) was given to 9 additional children who had severe disfiguring infantile haemangiomas of the face (8/9) and forearm (1/9). In all patients a regression of the haemangioma was observed.

Theletsane et al. [15] reported a case of a 2 weeks old girl with a facial–oropharyngeal–laryngeal haemangioma and features of the PHACES syndrome. During high dose systemic steroid therapy several side effects like ulcerations occurred. There was no regression after 4 weeks of steroid therapy. In the other 11 cases they started a propranolol therapy with a dose of 2 mg/kg/day. They observed an immediate improvement of the respiratory symptoms and a complete healing of all skin lesions after 6 months.

Itani and Fakih [16] described the case of a 4-month-old female with facial haemangioma which responded also promptly response to low-dose oral propranolol. A clinical response was noticed few days after the start of the treatment and there were no major side effects.

Bigorre et al. [17] treated 1 infant with a parotid haemangioma diagnosed at 6 weeks of age, 2 other 2-month-old patients with hemifacial haemangiomas and 1 13-month-old child with a perineal haemangioma. After an ineffective therapy with steroids respectively after the occurrence of complications such as ulceration or ocular occlusion they were successfully medicated with acebutolol (beta-blocker) 10 mg/kg/day.

In the report of Denoyelle et al. [18] 2 infants with subglottic haemangiomas, which were resistant to other established medical treatments got beta-blockers. Both haemangiomas responded dramatically to systemic propranolol. In the first case the girl was treated for 7 months with a dose of 3 mg/kg/day. In case 2 a girl was still treated with propranolol 2 mg/kg/day (>2 month) as the article was published.

Bonifazi et al. [19] treated 11 infants with facial, parotideal and metameric haemangiomas. The therapy was started between 1, 5 and 3 months of age. Five of the children were treated with oral propranolol dose of 2 mg/kg/day divided in 4 doses. The other 6 infants were treated with 1% topical propranolol for several months. After several days of therapy in all cases a improvement was noticeable. However the topical therapy with propranolol showed only an improvement of the superficial component.

Sánchez Pérez et al. [20] gave an account of a 3 months old child with a bilateral facial haemangioma of the forhead, lips and retroauricular region. Initial treatment began with a dose of 0.5 mg/kg/day propranolol. This dose was boosted up to 2 mg/kg/day and the child was treated for 11 months without any side effects.

Buckmiller et al. [5] reported a case of a nearly 2-year-old female with a facial and subglottic haemangioma. The patient showed stridor and agitation. Several intralesional steroid injections, debulking with CO_2 laser, and systemic therapy with vincristine failed to improve the clinical symptoms. Following cardiology approval and obtaining parental consent for off-label use, the patient was provided oral propranolol at 2 mg/kg/day

Table 1
Characteristics and treatment dose of all reported cases.

Case	Sex/age	Location of IH	Dose (mg/kg/day)	Duration	References
1–11	4M/2–4 months 7F/2–6 months	10 facial (nose, forhead, periorbita), 1 forearm	2 (10/11) 3 (01/11)	Not reported	[9]
12	F/2 months	Facial, oropharynx, larynx and PHACES syndrome	2	Not reported	[15]
13	F/4 months	Upper eyelid	Low dose	Not reported	[16]
14–18	1, 5–13 months	3 facial (parotideal, hemifacial), 1 perineal	10 (acebutolol)	Not reported	[17]
19–20	2F/0–2 months	Subglottic (one with PHACES syndrome)	3 (1/2) 2 (1/2)	2 month/not reported	[18]
21–25	3F/2M 1, 5–3 months	Nose, lip, forehead, oral cavity, cheek, parotideal	2	Not reported/several months	[19]
26–31	2F/3M 1, 5–2 months	Nipple, ankle, nose, parotideal, hand and forearm, metameric	1% topical	Not reported/several months	[19]
32	3 months	Facial	2	9 months	[20]
33	24 months	Facial/subglottic/tracheal	2	Not reported	[5]
34	F/1, 5 months	Parotideal	2	4 months	[21]
35–36	2F/ 8 weeks, 36 days	Eyelid, haemangiomatosis	2	One 24 h and one not reported	[22]
37–68	21F/11M 1–48 months	Face, forearm, thorax, neck, parotideal	2 (28/32) 3 (04/32)	Not reported/several months	[23]

divided into 3 doses. After 6 weeks of treatment all baseline airway symptoms have been resolved. The patient remained asymptomatic and was continuing propranolol therapy until all cervical-facial lesions have resolved.

There is a further report of a 6-week-old female with a parotideal haemangioma. Our own group [21] started a therapy with systemic steroids (5 mg prednisolon/kg/day) and reduced the dose over 4 weeks. We monitored not only no progression but also no regression on that condition. After another 6 weeks we observed new proliferation of the haemangioma. The propranolol therapy was started with an initial dose of 1 mg/kg/day. This was boosted up to 2 mg/kg/day divided into 3 units for 7 months. A nearby complete regression of the haemangioma during the treatment period with propranolol could be shown.

Lawley et al. [22] described the cases of 2 girls. An 8-week-old child presented with a 2 week history of a rapidly growing tumor on the right upper eyelid and a 36 days old girl with haemangiomatosis were treated with a daily dose of 2 mg/kg. The first child became lethargic and developed cool after the first 2 doses. Because of the cardiac side effects the therapy was discontinued. The results for the serum glucose of the other girl were called into the office at a critically low level of 48 mg/dL. Because the patient was asymptomatic and growing well, follow-up glucose was not checked and therapy was continued.

In the follow-up report of Sans et al. [23] 32 children with haemangiomas got beta-blockers. The drug was given in 28 cases at a starting dose of 2 mg/kg/day, in 2 or 3 divided doses. In 4 cases, the initial dosage was 3 mg/kg/day to maximize efficacy, because of cardiac indications, dyspnoea, and ulcerations. The children were re-evaluated after 10 days and then every month. In all cases rapid therapeutic effects were noted and haemangiomas responded dramatically to systemic propranolol: change of colour, softening of lesion, regression of dyspnoea, healing of ulcerations, etc. Ultrasound examinations after 60 days showed regression in maximal thickness and lower vascular activity within the haemangiomas.

Cremer et al. [14] reported of the largest collective of treated patients. They performed this therapy to more than 60 infants with haemangiomas. The initial dose at the first day was 1 mg/kg/day and raised to 2 mg/kg/day for 3–6 months. All infants were treated with resounding success. However, due to missing detailed analysis of the cases this patient group was not included into the present evaluation.

No relevant side effects were noted during the treatment course of all reported cases.

4. Conclusion

The recent report of dramatic response of haemangiomas to propranolol was initially a discovery by chance in patients who had cutaneous lesions associated with cardiac disease [9]. All reported cases of cutaneous, subglottic and oropharyngeal haemangiomas demonstrate a significant regression after the therapy with propranolol/beta-blockers without any relevant side effects. In all cases the therapy with propranolol showed a prompt effect also after ineffective therapy with systemic steroids or laser therapy.

Oral corticosteroids have been the mainstay of therapy for problematic infantile haemangiomas for decades. High dose systemic steroids are used for severe life-threatening haemangiomas. They show a variable response, and sometimes they are associated with significant long-term adverse effects. A safer, easier, and more predictable therapy is sorely needed. Propranolol is an enticing agent to consider.

Propranolol has a well-documented safety and side effect profile and is established in the therapy of infant cardiovascular diseases since decades. However the therapy with propranolol for haemangiomas is an off-label-indication and the parents have to be well informed and to assent.

Up to now the following treatment protocol for propranolol is established [11]: baseline echocardiography and 48-h hospitalisation or home nursing visits to monitor vital signs and blood glucose levels. Medication is given every 8 h, with an initial dose of 0.16 mg/kg of body weight. If the vital signs and glucose levels remain normal, the dose is incrementally doubled to a maximum of 0.67 mg/kg (up to a maximum daily dose of 2 mg/kg). Propranolol should gradually tapered over a period of 2 weeks.

To sum up all case reports, 2–3 mg/kg/day propranolol should be administered, divided in 2–4 doses per day. This therapy should be continued through the proliferative phase of haemangioma growth or until no further improvement occurs. Instead of abrupt discontinuation a gradual tapering of propranolol over 2–3 weeks is recommended. If a rebound effect occurs patients are placed back on propranolol.

In all, propranolol appears to be an effective treatment for infantile haemangiomas and should now be used as a first-line treatment in haemangiomas when intervention is required. In this context, controlled studies with a significant collective will be possible to investigate both the safety and efficacy of propranolol in addition to establishing appropriate dose and treatment duration.

References

[1] L.C. Chang, A.N. Haggstrom, B.A. Drolet, E. Baselga, S.L. Chamlin, M.C. Garzon, et al., Growth characteristics of infantile hemangiomas: implications for management, Pediatrics 122 (2008) 360–367.

[2] C. Léauté-Labrèze, A. Taieb, Efficacy of beta-blockers in infantile haemangiomas: the physiopathological significance and therapeutic consequences, Ann. Dermatol. Venerol. 135 (2008) 860–862.

[3] B. Eivazi, M. Ardelean, W. Bäumler, H.P. Berlien, H. Cremer, R. Elluru, et al., Update on haemangiomas and vascular malformations of the head and neck, Eur. Arch. Otorhinolaryngol. 266 (2009) 187–197.

[4] J.A. Werner, A.A. Dünne, B.M. Lippert, B.J. Folz, Optimal treatment of vascular birthmarks, Am. J. Clin. Dermatol. 4 (2003) 745–756.

[5] L. Buckmiller, U. Dyamenahalli, Richter GT, Propranolol for airway hemangiomas: case report of novel treatment, Laryngoscope (2009) (Epub ahead of print).

[6] J. Nguyen, A. Fay, Pharmacological therapy for periocular infantile haemangiomas: a review of the literature, Semin. Othalmol. 24 (2009) 178–184.

[7] A. Vlahovic, R. Simic, D. Djokic, C. Ceran, Diffuse neonatal hemangiomatosis treatment with cyclophosphamide: a case report, J. Pediatr. Hematol. Oncol. 31 (2009) 858–860.

[8] S. Gottschling, G. Schneider, S. Meyer, H. Reinhard, D. Dill-Mueller, N. Graf, Two infants with life-threatening diffuse neonatal hemangiomatosis treated with cyclophosphamide, Pediatr. Blood Cancer 46 (2006) 239–242.

[9] C. Léauté-Labrèze, E. Dumas de la Roque, T. Hubiche, F. Boralevi, J.B. Thambo, A. Taieb, Propranolol for severe haemangiomas of infancy, N. Engl. J. Med. 358 (2008) 2649–2651.

[10] M. Helfand, K. Peterson, T. Dana, Drug Class Review on Beta Adrenergic Blockers, 2007 http://www.ohsu.edu/drugeffectiveness/reports/final.cfm.

[11] E.C. Siegfried, W.J. Keenan, S. Al-Jureidini, More on propranolol for haemangiomas of infancy, N. Engl. J. Med. 359 (2008) 2846–2847.

[12] K. Frazer, in: Proceedings of the 67th Annual Meeting of the American Academy of Dermatology, San Francisco California, USA, 6–10 March, 2009;
K. Frazer, Am. J. Clin. Dermatol. 10 (2009) 205–210.

[13] B. Annabi, M.P. Lachambre, K. Plouffe, R. Moumdjian, R. Béliveau, Propranolol adrenergic blockade inhibits human brain endothelial cells tubulogenesis and matrix metallopteinase-9 secretion, Pharmacol. Res. (2009) (Epub ahead of print).

[14] H.J. Cremer, W. Kachel, C. Kosel, Propranolol in der Behandlung problematischer Hämangiome, Kinder- und Jugendarzt 40.Jg, 2009 (Nr. 7).

[15] T. Theletsane, A. Redferjn, O. Raynham, T. Harris, N.S. Prose, N.P. Khumalo, Life-threatenting infantile haemangioma: a dramatic response to propranolol, J Eur Acad Dermatol Venerol (2009) (Epub ahead of print).

[16] M.H. Itani, H. Fakih, Response of facial haemangioma to oral propranolol, BMJ Case Rep. (2009).

[17] M. Bigorre, A.K. Van Kien, H. Valette, Beta-blocking agent for treatment of infantile hemangioma, Plast. Reconstr. Surg. 123 (2009) 195e–196e.

[18] F. Denoyelle, N. Leboulanger, O. Enjolras, R. Harris, G. Roger, E.N. Garabedian, Role of propranolol in the therapeutic strategy of infantile laryngotracheal hemangioma, Int. J. Pediatr. Otorhinolaryngol. 73 (2009) 1168–1173.

[19] E. Bonifazi, V. Colonna, F. Mazzotta, G. Balducci, N. Laforgia, Propranolol in rapidly growing hemangiomas, Eur. J. Pediatr. Dermatol. 18 (2008) 185–192.

[20] R. Sánchez Pérez, P. Cortes Mora, J.D. González Rodrígues, F. Rodríguez Sánchez, J. De la Peña de Torres, Treatment of infantile hemangioma with propranolol, Ann. Pediatr. (Barc.) (July) (2009) (Epub ahead of print).
[21] B. Eivazi, A. Teymoortash, S. Stiller, H.J. Cremer, J.A. Werner, Betablockers—new perspektives for infantile hemangiomas of the head and neck, Laryngorhinootologie (2009) (Epub ahead of print).
[22] L.P. Lawley, M.D. Siegfried, J.L. Todd, Propranolol treatment for haemangioma of infancy: risks and recommendations, Pediatr. Dermatol. 26 (2009) 610–614.
[23] V. Sans, E. Dumas de la Roque, J. Berge, N. Grenier, F. Boralevi, J. Mazereeuw-Hautier, et al., Propranolol for severe infantile hemangiomas: follow-up report, Pediatrics 124 (3) (2009).