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Review article

Propranolol therapy for infantile haemangiomas: Review of the literature

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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.

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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

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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-