Title: Side effects of propranolol used for the treatment of hemangiomas of infancy

The recent report of propranolol treatment for life threatening infantile hemangiomas (LTIH) is already a major milestone in this field (1). We started to use a protocol of treatment for LTIH that were refractory to other treatment options used as first line (2), after informed consent from patients' parents. Due to the excellent initial results we obtained even with low doses, we offered the choice of it for the patients that were on conventional therapy, for newly diagnosed patients, for patients with lesions not life threatening but with other indication for pharmacological treatment and for patients off treatment but with large residual lesions. All patients whose parents gave informed consent were initiated on therapy.

Siegfried *et al* (3) proposed a cautious initial approach to this treatment. Published data show that beta-blocker agents have been widely and safely used in children to prevent acute hypoxemia or supraventricular tachycardia, or to treat systemic hypertension, and they are well tolerated. Discontinuation of them because of low blood pressure is rarely required (4). Because of this, we used a simplified management. We started with 0.5mg/kg/day in a single dose and increased with one week intervals to 1mg/kg and finally 2mg/kg as final dose. We followed the children as outpatients, monitoring basic cardiovascular signs (pulse, cardiac frequency, arterial pressure) and had a concise but thorough clinical history every visit.

The objective of this brief report is not presenting results, as they are in the data acquisition stage. However, we confirm the previous report of good initial results and the sequence they observed: an almost immediate (less then 24h) change of color from red to pale purple (or pinkish in some of our cases) and softening of lesion to palpation, sometimes with a wrinkly appearance, followed in a matter of days by flattening. This sequence occurred in all the patients we are treating, without exception, even in those with previously treated large residual lesions. In this latter case, the change in color was only modestly apparent, once the lesions were not intense red anymore before treatment.

We want to report the first observed side effects of propranolol treatment for hemangiomas of infancy. We are treating 14 patients so far, all of them have more than a month of treatment. No one has less than 3 months of age and the oldest has 5 years. No one had signs of cardiac compromise before treatment initiation. No patient had pulse changing, bradycardia or hypotension after propranolol initial and final doses.

A couple of identical twins aged 14 months with never treated diffuse hemangiomatosis restricted to skin (round to oval elevated lesions ranging from 2 to 10 cm all over the body) had a history of wheezing and early mechanical ventilation due to prematurity. Both had rapid breathing (respiratory rate 45-55 breaths per minute) without other clinical symptoms, after taking 0.5mg/kg/day propranolol. The drug was discontinued, respiratory rate was back to normal and then propranolol was resumed with prednisone 1mg/kg/day, without any further changing in respiratory rate. Propranolol dose was increased to 2 mg/kg/day and the children experienced rapid breathing again, without clinical compromise. The dose was tapered back to 1mg/kg/day with respiratory rate normalization. A transient skin rash, erythematous, resembling urticaria but non-pruriginous developed right after that and subsidized spontaneously. The children are tolerating well this dose until now, with continued tumor response.

A 1 year old child with a “beard like” hemangioma with airway compromise had a partial response after 18 doses of weekly 0.05 mg/kg vincristine. Although the child was free of respiratory symptons and not in life danger anymore, there remained a large residual lesion which prompted us to offer the option of propranolol to the parents. The result of propranolol treatment was apparent in the first week with only 0.5 mg/kg propranolol and the dose was increased. When we had just begun 2 mg/kg/day, the child manifested important anorexia lasting 24-48h and remained with less appetite for 2 weeks. The child had normal blood glucose. Treatment was continued, once the child had no more alterations in food intake. The residual lesion is shrinking swiftly.

Our preliminary data show a very low incidence of side effects in the initial phase of propranolol treatment of infantile patients with hemangiomas. The side effects were transitory and no patient had to discontinue medication. This is in sharp contrast to the high morbidity of the conventional pharmacological treatment of hemangiomas of infancy, based in high doses of prednisone, interferon or vincristine, with great potential for side effects (2). This shows that propranolol, even before the results of clinical trials, can be an acceptable option for first line therapy of infants with hemangiomas, especially those with LTIH, but also with aesthetically disfiguring lesions without risk of death.

However, we are concerned about the use of propranolol (and potentially other beta-blockers) in patients with large hemangiomas with cardiac compromise. This subgroup of patients have high risk lesions with arteriovenous shunting or with arterialized vessels that give rise to high intralesional blood flow and to high output cardiac failure (5,6). Although most of the infantile hemangioma patients with cardiac failure have hepatic lesions, it can occur with large lesions in other sites (6). High output cardiac failure is associated with reduced systemic vascular resistance as its underlying primary physiological problem (7). Arteriovenous shunting can lead to a fall in systemic arterial blood pressure and neurohormonal activation leading to overt clinical heart failure. In contrast to low output heart failure, clinical trial data in this area are lacking. The use of conventional therapies for heart failure, such as beta-blockers with vasodilatory properties, is likely to further reduce systemic vascular resistance resulting in deterioration (7). Associated with this potential problem, there is the fact that to date no study has proved a consistent beneficial effect of beta-blockers in heart failure of the pediatric population, specially in those patients that do not have classical systemic left ventricles (4,8). Léauté-Labrèze *et al* have mentioned that the second patient in their series developed high output cardiac failure, but they did not give details about the management and cardiac symptomatology of this particular patient. We would recommend a careful approach to patients with this profile, given their high risk of mortality (5) and the uncertainties involved in the use of beta-blockers in them.

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