Hemangiol® in infantile haemangioma: A paediatric post-marketing surveillance drug study

Floriane Socchi[1], Michele Bigorre[1], Marion Normandin[1], Guillaume Captier[1], Didier Bessis[1], Michel Mondain[1], Catherine Blanchet[1], Mohamed Akkari[1], Pascal Amedro[1], and GAVOTTO Arthur[1]

[1]University Hospital Centre Montpellier

April 27, 2020

Abstract

Aim: Infantile haemangioma (IH) is the most common benign tumour in children. Since 2014, propranolol has become the first-choice therapy and currently Hemangiol® is the only approved drug for complicated haemangioma. This post-marketing study reported the use of Hemangiol® for IH in paediatric practice. Method and Results: From January 2014 to November 2018, 94 children (median age 4 [0;21] months; 75% female) treated with Hemangiol® for proliferative IH were enrolled in the study. The systematic paediatric cardiology consultation never contraindicated beta-blockers. Two Hemangiol® initiation protocols were used: a conventional ambulatory 3-week titration phase protocol (N=76, 80.9%), and a rapid initiation protocol with a 48-hour dose escalation in conventional hospitalization for severe proliferative IH (N=18, 19.1%). In both protocols, the haemodynamic tolerance was good. The mean maintenance dose of Hemangiol® was 2.7±0.8 mg/kg/day, with a median treatment duration of 7 [1.5;19] months. Adverse events (AEs) have been found in 25 (26,6%) patients including 8 (8.5%) patients with serious AEs (uncontrolled bronchial hyperreactivity, N=5; serious hypoglycaemia, N=3). Some patients had one or more AEs, a total of 24 non-serious AEs was reported in 19 patients (sleep disturbances, N=9; respiratory disorders, N=5; digestive disorders, N=6). No cardiac adverse event was reported. Conclusion: This post-marketing surveillance drug study supports the good tolerance of Hemangiol® in children with IH. A rapid initiation protocol is of interest when treatment is urgent. The pre-therapeutic paediatric cardiology consultation should not be systematic but only indicated on specific patients. ClinicalTrials.gov: NCT 04105517.

Introduction

Originally described by Mulliken and Glowacki[1], infantile haemangioma (IH) is the most common benign tumour in children[2,3]. IH belongs to the group of vascular tumours in the ISSVA (international society for the study of vascular anomalies) classification[4]. Usually, IH will appear at birth or within the first few weeks after birth, and up to 3 months of age for subcutaneous haemangioma[5]. IH is characterized by its natural course divided into three phases, a proliferative phase characterized by a rapid growth of the tumour (up to 6 to 12 months of life), a stabilization phase (from 12 to 36 months of life), and an involution phase marked by the regression of the lesion[6]. This regression is complete in 90% of cases by the age of 4, but without treatment we can observe up to 70% residual lesions, such as fibrofatty tissue, telangiectasia, skin laxity and scars[7]. The proliferative phase may be marked by severe complications, such as necrosis, ulceration, bleeding or infection. Obstruction and functional impairment such as amblyopia, upper respiratory obstruction, obstruction of the nostrils or auditory channel, sphincter dysfunction, or feeding disorders can be caused by periorificial locations of IH (e.g. perioral and periorbital skin). Moreover, the aesthetic impact is not trivial, especially when IHs located in the centrofacial area are a source of disfigurement[8,9]. Large segmental facial IHs may be part of the PHACES syndrome (posterior fossa anomalies, haemangioma, arterial lesions, cardiac abnormalities, eye anomalies, sternal defects)[10,11] and segmental IHs of the lower body may be part of the LUMBAR syndrome

(lower body haemangioma, urogenital, myelopathy, bony, anorectal and arterial, renal anomalies)[12]. Finally, liver haemangioma and haemangiomatosis are high-risk complicated IHs as they may lead to cardiac failure[13].

Initially, medical treatment of severe IH was based on systemic corticosteroid therapy[14,15]. In 2008, Leaute-Labreze et al. fortuitously discovered the anti-proliferative effect of propranolol, when using this non-selective beta-blocker for a hypertrophic obstructive cardiomyopathy, in a child with a nasal IH treated by corticosteroids[16]. The efficacy of oral propranolol in IH was demonstrated by two randomized controlled trials[17,18]. In 2014 Pierre Fabre dermo-cosmetics laboratory (Paris, France) obtained EMA (European Medicines Agency) and FDA (Food and Drug Administration) marketing authorization for Hemangiol®, the first and only drug currently approved for the treatment of proliferating IH. Hemangiol® is indicated to treat IH in children aged 5 weeks to 5 months, in case of life or functional risk, painful ulcerated lesions, or risk of permanent scarring or facial damage.

In this paediatric post-marketing surveillance drug study, we aimed to report the use of Hemangiol® in our institution from 2014 to 2018.

Methods

Study design and population

This retrospective study was carried out from January 2014 to November 2018 in Montpellier University Hospital, France. In this tertiary care institution, all children with an IH requiring a medical treatment with a beta-blocker are systematically hospitalized for treatment initiation. In this study, the hospital discharge database (PMSI, Programme de Medicalisation des Systemes d'Information) was used for patients screening. The PMSI is a mandatory national database linked to the social security, in which all hospitalizations are automatically and prospectively registered. This database uses a standardized diagnosis coding from the 10th revision of the International Classification of Diseases (ICD-10). The code associated to the term "haemangioma" (D13) was used to screen patients and finally only children <2 years old treated with Hemangiol® were included in the final analysis.

Initiation and use of Hemangiol®

Immediately after the marketing authorisation published by the EMA in April 2014 (EU/1/14/919/001), our group of experts in proliferative IH, involving plastic surgeons, dermatologists, ear nose and throat (ENT) physicians, and paediatric cardiologists, drafted a single and common institutional protocol on initiation and use of Hemangiol® for IH, adapted from the summary of product characteristics (SPC). This protocol included five consecutive stages:

1) The initial consultation with an expert in the diagnosis, treatment and management of IH (paediatric dermatologist, paediatric plastic surgeon, paediatric ENT physician, or paediatric cardiologist) determined whether Hemangiol® was indicated or not.

2) The paediatric cardiology consultation with clinical examination, electrocardiogram and echocardiography, assessed the absence of contraindications for beta-blocker use: premature infants for whom the corrected age of 5 weeks has not been reached, breastfed infants in mothers treated with medicinal products contraindicated with propranolol, hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC, asthma or history of bronchospasm, second- or third-degree atrioventricular blocks, disease of the sinus node (including sinoatrial block), bradycardia (heart rates <100 beats per minute (bpm) in infants 0-3 months old, <90 bpm in infants 3-6 months old, and <80 bpm in infants 6-12 months old), low blood pressure (<65/45 mmHg in infants 0-3 months old, <70/50 mmHg in infants 3-6 months old, and <80/55 mmHg in infants 6-12 months old), cardiogenic shock, heart failure not controlled by treatment, severe peripheral arterial circulatory disturbances, infants prone to hypoglycaemia, and pheochromocytoma.

3) To initiate Hemangiol® treatment, we defined a "conventional" initiation protocol and a "rapid" initiation protocol.

The conventional initiation protocol included a 3-week titration phase, as reported in the SPC: starting dose of 1 mg/kg/day (0.5 mg/kg b.i.d.) of propranolol base for 1 week, then 2 mg/kg/day (1 mg/kg b.i.d.) for 1 week, and finally 3 mg/kg/day (1.5 mg/kg b.i.d.) as a maintenance therapeutic dose. During the titration phase, the child was hospitalised in our ambulatory paediatric day care facility at day 1 (initiation), day 7 (week 1) and day 14 (week 2) with close clinical monitoring for 3 hours after treatment's administration (hourly monitoring of vital constants, and assessment of side effects). Bradycardia was defined as heart rates <100 bpm in infants 0-3 months old, <90 bpm in infants 3-6 months old, and <80 bpm in infants 6-12 months old. Hypotension was defined as tensions <65/45 mmHg in infants 0-3 months old, <70/50 mmHg in infants 3-6 months old, and <80/55 mmHg in infants 6-12 months old.

Parental education was provided by a specialist nurse, focusing on the three following key messages: i) Hemangiol® is to be given during or right after feeding to avoid the risk of hypoglycaemia, with one dose in the morning and one dose in late afternoon, respecting a time interval of at least 9 hours between two intakes. ii) If the child is not eating or is vomiting it is recommended to skip the dose. iii) In case the child spits up a dose or does not take the entire medicinal product, no other dose should be given before the next scheduled dose. The information booklet provided by the pharmaceutical company (Pierre Fabre) was systematically given to parents, as well as our emergency paediatric cardiology 24/7 phone number.

The rapid initiation protocol was used for severe proliferative IH involving any vital risk, uncontrolled bleeding, ulceration, pain, or infectious risk. Such severe forms were managed in conventional hospitalisation in the paediatric cardiology unit, using a rapid dose escalation scheme: Hemangiol® initiation dose of 0.5 mg/kg (stage 1), then 1 mg/kg 12 hours later (stage 2), then 1.5mg/kg 12 hours later (stage 3), in order to reach the maintenance therapeutic dose of 3 mg/kg/day in two daily intakes at day 2. Analgesics, antibiotics and local skin care were provided when required, upon IH specialist's recommendation. Continuous clinical monitoring was provided (hourly monitoring of vital constants, cardiac telemetry and assessment of side effects), as well as parental education (cf. previous section). In the absence of adverse effects or need for IH care, patient was discharged after day 2 (rapid initiation protocol in supplementary Figure).

4) The children underwent follow-up examination with the IH specialist 4 to 8 weeks after Hemangiol® initiation in non-severe IH, and 2 weeks after Hemangiol® initiation in severe cases. The IH specialist determined the frequency of the following consultations, as well as the overall treatment duration.

5) The child underwent a paediatric cardiology consultation 3 months after Hemangiol® initiation, or at any time if required by the IH specialist, the patient's family practitioner, or after any family emergency phone call.

Outcome measures

The data collection included the population and IH characteristics and the indication of treatment during the initial consultation. Patient follow-up included treatment initiation until the end of treatment.

We collected all data from patient monitoring (cardiac examination, echocardiogram, ECG, cardiac monitoring) before, during (at each titration stage for both conventional and rapid protocols), and after Hemangiol® initiation.

Parents of children under Hemangiol® were asked to call the paediatric cardiology 24-hour hotline for any clinical symptom. Therefore, we recorded all adverse events (AEs), defined as any undesirable experience possibly associated with the use of Hemangiol® from drug initiation and throughout the follow-up. Serious adverse events (SAEs) were defined as life-threatening events or adverse events leading to death, hospitalization, disability or permanent damage, intervention to prevent permanent impairment, or any important medical event as defined by the drug agencies. SAEs were reported to pharmacovigilance and causality was established using the standard method derived from Bégaud et al[19]. This algorithm is based on an intrinsic score including chronological and semiological criteria ranging from 0 to 6 (from absence to strong relationship between drug and the occurrence of adverse event; scores [?]2 indicating possible relation to treatment) and an extrinsic score based on bibliography[20].

Formal aspects

The study was conducted in compliance with the Good Clinical Practices and Declaration of Helsinki principles. The study was approved by Montpellier University Hospital's institutional review board (2019_IRB-MTP_09-07). The study was registered on ClinicalTrials.gov (NCT 04105517).

Statistical analyses

The study population was described using means and standard deviations (SD) for quantitative variables with normal distribution or medians and minimal/maximal values [min; max] otherwise. Frequencies and their associated percentage were used for qualitative variables. The normal distribution of continuous variables was explored graphically. Quantitative variables were compared using Student's t-test when the distribution was Gaussian, or the Mann-Whitney test otherwise. For qualitative variables, groups were compared using the chi-squared test or Fisher's exact test. The statistical significance was set at 0.05 and analyses were performed using Excel(r) software.

Results

Population

During the 5-year study period, 189 children <2 years old were hospitalized in our institution with a main diagnosis of "haemangioma" identified from the hospital PMSI database. From this cohort, 95 patients were not included in the study: 43 (22.8%) cases were included in a concomitant randomised controlled trial comparing acebutolol versus propranolol in IH (NCT01743885), 24 (12.7%) cases were treated with another drug than Hemangiol(r) (atenolol, N=2; corticoids, N=2; other form of oral propranolol, N=9; surgery, N=11), 20 (10.6%) cases received no drug to treat their IH, and 8 (4.2%) cases had significant missing data (lost to follow-up). Therefore, a total of 94 children (75% female) with IH treated with Hemangiol(r) were included in this study. All parents or legal guardians gave their informed consent.

The most common IH localisation was the head (59.6%), especially the periocular (N=23) and nasal (N=11) regions. Rare cases of syndromic (PHACES syndrome, N=2; LUMBAR syndrome, N=2), hepatic haemangioma (N=2), and miliary IH (N=1) were identified.

Hemangiol(r) was initiated at a median age of 4 [0; 21] months, including 2 children <5 weeks and 29 children >5 months old. The main indication for IH treatment with Hemangiol(r) was functional threat (N=36; 38.3%) and mainly concerned facial IH, predominantly for periocular (N=19) and nasal (N=6) localisations. Ulcerated IH were treated with Hemangiol(r) in 29 (30.9%) children, especially in perineal localisations (N=7). Life-threatening forms of IH required treatment with Hemangiol(r) for 5 children (hepatic haemangioma, N=2; miliary, N=1; subglottic haemangioma, N=2). Patients' clinical characteristics were reported in Table 1.

Paediatric cardiology consultation

The systematic paediatric cardiology consultation diagnosed a cardiac murmur in 8 (8.5%) subjects, of which four innocent murmurs and four congenital heart diseases: one case of minimal pulmonary valve stenosis, one case of coarctation of the aorta in a 4-month-old child with PHACES syndrome, one case of atrial septal defect, and one case of ventricular septal defect. Systematic echocardiography reported increased cardiac output for the two subjects with hepatic haemangiomas and 2 cases of patent ductus arteriosus (PDA) in a neonate with IH and non-sustained ventricular tachycardia (spontaneous PDA closure), and in a six-month-old infant born at 30 weeks gestation with PIK3CA mutation and subglottic haemangioma, who underwent percutaneous PDA closure.

The systematic echocardiography performed in the 86 remaining patients without any cardiac symptom or neonatal condition found 19 cases of non-significant cardiac features: patent foramen ovale (N=16), moderate flow acceleration in the pulmonary artery branches (N=1), small aorto-pulmonary collateral (N=1), and trivial pulmonary regurgitation (N=1). No further follow-up was indicated by the paediatric cardiologist in those 19 children.

The systematic ECG was normal in 93 (98.9%) cases and diagnosed Wolff-Parkinson-White syndrome in one patient with no family history.

Overall, none of the findings observed during the paediatric cardiology consultation resulted in any contraindication for Hemangiol(r).

Hemangiol(r) initiation protocol

The conventional Hemangiol(r) initiation protocol was the most commonly used (N=76; 80.9%). The rapid Hemangiol(r) initiation protocol concerned children with ulcerated IH (N=11), life-threatening IH (N=4), as well as the neonate with non-sustained ventricular tachycardia associated with IH of the cheek, the case of coarctation of aorta associated with IH of the arm and PHACES syndrome and a two month old child with parotid IH with a risk of compression. In children with ulcerated IH, the rapid Hemangiol(r) protocol included the prescription of strong analgesics and local treatment during hospitalisation.

Hospital monitoring at the initiation of the treatment showed a significant decrease in heart rate one hour after treatment initiation, especially in stage 1 (from mean 140.3+-18.1 bpm to mean 127.1+-16.1 bpm, P<0.01). Then the heart rate remained stable during the monitoring. In stage 2, one hour after treatment increase, a less marked than in stage 1 but significant heart rate decrease was observed (from mean 128.1+-19.0 bpm to mean 121.7+-17.0 bpm, P=0.02). No significant decrease in heart rate was observed in stage 3. Overall, no significant bradycardia was observed. We found a significant but non-symptomatic decrease in diastolic blood pressure at stage 2 and stage 3, without requiring any drug discontinuation. No change was observed in the systolic blood pressure (Table 2).

We found no significant difference in terms of heart rate and blood pressure change, between the two conventional and rapid initiation protocols.

Follow-up of children under Hemangiol(r)

The maintenance therapeutic dose of Hemangiol(r) was 2.7+-0.8 mg/kg/day. The first follow-up consultation with an IH expert occurred at 1 [0.5;6] month, and the second one at 6 [2;13] months after Hemangiol(r) initiation.

The first follow-up cardiology consultation occurred at 3 [1;7] months.

The median overall treatment duration was 7 [1.5;19] months.

Adverse events (AEs)

No AE was observed during the initiation of treatment, in both conventional and rapid protocols.

We did not find any significant change in the ECG before the initiation and 3 months after the initiation of Hemangiol(r) with a PR interval at 115.3+-17.6 ms vs. 110.3+-19.6 ms (P=0.1), QRS interval at 69.6+-11.5 ms vs. 68.8 ms+-12.1 ms (P=0.68), corrected QT interval at 378+-20 ms vs. 381+-26 ms (P=0.37). No case of atrioventricular block or any other cardiac adverse event was reported.

During the follow-up, after the initiation period, 25 (26.6%) patients experienced one or more adverse events. Among these patients, 8 (8.5%) children presented a SAE: 5 cases of uncontrolled bronchial hyperreactivity (one associated with pneumopathy and diarrhoea) and 3 cases of serious hypoglycaemia. SAEs led to permanent treatment discontinuation in 6 cases, temporary discontinuation in one case, and dose reduction in one case. For all SAEs, causality scores ranged from 2 to 5 out of 6, suggesting possible to strong association between SAEs and propranolol (Table 3). As recommended by drug agencies, all cases of SAEs were reported to the national pharmacovigilance centre.

A total of 24 non-serious AEs were reported in 19 (20.2%) patients (including 2 patients with SAEs and a non-serious AE, and 5 patients with 2 non-serious AEs): sleep disturbances (N=9), primarily nightmares; respiratory disorders, especially acute bronchiolitis with temporally discontinuation of treatment (N=5); and digestive disorders (N=6) with benign diarrhoea, constipation, vomiting and anorexia. We also found one

suspected case of hypoglycaemia, one case of asthenia, one skin rash, and one case of repeated disabling sneezing. No non-serious AE required hospitalization or prolonged drug discontinuation.

Discussion

This study investigated the current use of Hemangiol(r) in 94 children with proliferating IH. It provided new tolerance data on this treatment and the value of systematic cardiac screening before treatment. Moreover, the safety of a rapid initiation protocol was evaluated.

Overall, the population treated with Hemangiol(r) in this study is similar to previous reports[8] and our cohort is representative of the usually described population of IH, with a predominant female representation[21]. However, more subjects with preterm birth and low birth weight were present in our cohort, considering they were previously described as risk factors for IH[2,22]. The cases with PHACES or LUMBAR syndromes included in the study underwent screening evaluation of clinical and radiological associated anomalies, as recommended in children with large segmental haemangiomas of the upper and lower body[10,12]. The main indications for treatment of our cohort were IH with a functional threat, ulcerated haemangiomas and IH with an aesthetic prognosis, as recommended in the current guidelines[13]. Children of our study were treated for an average of 7 months, which is moderately longer than in the initial trial (e.g. 6 months)[18]. However, recent studies have suggested treatment for 6 to 12 months due to a greater IH rebound growth in shorter treatment duration[23,24]. Indeed, treatment duration is mostly dependent on clinical complete lesion regression[25]. Off-label use of Hemangiol(r) was rare in this study. Two neonates <5 weeks of age were treated with a good tolerance during initiation and no reported adverse event during follow-up, which confirms a previous study on the safety of oral propranolol for IH in the neonatal period [26]. Late Hemangiol(r) initiations >5 months of age concerned 29 subjects in our study. Usually, late treatment initiations are related to a delayed referral to the specialist, especially for superficial IH[27].

The safety analysis found AEs in 26.6% patients, which is consistent with previous studies on oral propranolol, which reported AEs rates from 19.6%[28] to 38.2%[29]. Sleep disturbances, wheezing and digestive side effects were the most frequently reported AEs in our cohort, as described in the previous studies, however peripheral coldness was not reported in our cohort[28,29]. SAEs were found in 8.5% patients, exclusively severe hypoglycaemia and uncontrolled bronchial hyperreactivity, which is higher than previous reported SAEs rates, ranging from 2.6%[30] to 4.8%[29]. Cardiac SAEs, such as atrioventricular block, bradycardia and symptomatic hypotension, were not found in our cohort, as opposed to previous studies[29,30] and despite a systematic paediatric cardiology pretherapeutic and follow-up assessment. Nevertheless, the causality of propranolol for cardiovascular SAEs in the literature remains unclear and suggests pre-existing conditions or incidental discovery[29,31]. Of note, SAEs occurred in two prematurely born children, who may be more prone to hypoglycaemia and bronchial hyperreactivity as previously reported[32]. Therefore, low dose of Hemangiol(r) (2mg/kg/day) could be of interest in such high-risk children[23,28], however the dosage of 3mg/kg/day has been more investigated in pharmacokinetics and pharmacodynamics studies[33,34] based on the manufacturer's clinical trial[18].

For all SAEs, causality scores concluded to possible to strong relation to Hemangiol(r). As severe hypoglycaemia and uncontrolled bronchial hyperreactivity are well known SAEs, variability of causality scores came from intrinsic causation with variable chronological criteria (time to onset after taking the treatment, or evolution after lowering the dosage or stopping treatment) and the presence of confounding factors (i.e. infectious for bronchospasms). As a result, SAEs with high causality scores (4 or 5) in our study were patients with complete description of the event, compatible time to onset, regression of AE after stopping treatment, and no confounding factor. Previous studies did not provide any details on the causality between such SAEs and treatment with Hemangiol(r).

From a general perceptive, those findings emphasize the importance of parental therapeutic education about these potential risks and how to manage them. During the treatment initiation period, oral information supported by an educational pack should be provided to parents, in order to identify symptoms potentially related to SAEs[35]. For example, parents should be fully aware that Hemangiol(r) needs to be temporarily

suspended in case of food intolerance or limited food intake in their child, in order to avoid hypoglycaemia[36]. Similarly, bronchial hyperreactivity reactions were often related to respiratory tract infections and therefore require appropriate parental supervision[29,37].

Overall, the cardiac tolerance was good. No AE, serious or not, was reported during drug initiation at the hospital, whatever the protocol used, as well as during the follow-up. No significant decrease in systolic blood pressure was observed, and the initial decrease in heart rate and diastolic blood pressure was moderate and not clinically relevant, as in the literature[38–40]. Similarly, previous studies have reported the safety of oral propranolol for the treatment of IH[41] and suggested not to extend cardiac monitoring beyond initiation period except for heart rate during following consultations[42]. In light of these results, an outpatient Hemangiol(r) initiation protocol could be considered in selected and non-at risk patients, as suggested by Puttgen and al.[43].

This study supports the absence of relevance for a systematic pre-therapeutic paediatric cardiology consultation. Indeed, all cardiac findings observed in this cohort were mostly non-significant and did not result in any contraindication for betablockers. Therefore, a simple physical examination made by the IH expert seems sufficient to identify patients at risk. Based on our cohort, children with IH requiring cardiological assessment are those with clinical symptoms (cardiac murmur), abnormal blood pressure or heart rate, syndromic forms (PHACES), high risk of heart failure (hepatic, military haemangiomas), or off-label use (preterm birth, neonate period). These results are consistent with previous studies reporting that systematic echocardiography[44,45] or ECG[40,46]before propranolol initiation are not relevant in terms of contraindication assessment and correlation with SAE occurrence[47].

Most patients (81%) underwent a conventional initiation protocol with a 3-week titration phase in day care hospital. This protocol seems safe and adapted to most children with IH, as reported in cost-effectiveness studies[48]. Nevertheless, a 3-week delay to reach the maintenance dose of 3 mg/kg/day may not be appropriate in a therapeutic emergency situation, such as in IH involving any vital risk, uncontrolled bleeding, ulceration, pain or infectious risk. In our study, nearly 20% of patients with severe proliferative IH underwent a rapid initiation protocol, with a 48-hour dose escalation in conventional hospitalization in paediatric cardiology. This rapid protocol was well tolerated and facilitated the prescription of strong analgesics and local treatment, as in ulcerated IH. In both conventional and rapid protocols, Hemangiol(r) was well tolerated in terms of blood pressure and heart rate adaptation.

Study limitation

Despite the collection of AEs during patients' follow-up at the hospital, as well as through parent's call to the 24-hour hotline, the existence of missing data may be inherent to the retrospective design of the study. Moreover, 54 children with IH and treated with other forms of betablockers (acebutolol, propranolol) during the study period were not included in the analysis.

Conclusion

In children treated with Hemangiol(r) for proliferative IH, this post-marketing surveillance drug study reported an AE incidence rate of 26.6%, of which 8.5% non-fatal SAEs, supporting the importance of parental therapeutic education. The pre-therapeutic paediatric cardiology consultation should not be systematic but only indicated on selected at-risk patients. In addition to the conventional initiation protocol with a 3-week titration phase in day care hospital, we suggest using a rapid initiation protocol with a 48-hours dose escalation in conventional hospitalization when treatment is urgent.

Acknowledgement

We thank our patients for their participation.

Declarations of interest: the authors have no competing interests to declare.

Financial support: This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Data availability statement : the data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Mulliken JB, Glowacki J. Hemangiomas and Vascular Malformations in Infants and Children: A Classification Based on Endothelial Characteristics. *Plast Reconstr Surg* . 1982;69(3):412-420. doi:10.1097/00006534-198203000-00002

2. Anderson KR, Schoch JJ, Lohse CM, Hand JL, Davis DM, Tollefson MM. Increasing Incidence of Infantile Hemangiomas over the Past 35-years: Correlation with Decreasing Gestational Age at Birth and Birth Weight.*J Am Acad Dermatol* . 2016;74(1):120-126. doi:10.1016/j.jaad.2015.08.024

3. Kilcline C, Frieden IJ. Infantile Hemangiomas: How Common Are They? A Systematic Review of the Medical Literature. *Pediatr Dermatol* . 2008;25(2):168-173. doi:10.1111/j.1525-1470.2008.00626.x

4. Wassef M, Blei F, Adams D, et al. Vascular Anomalies Classification: Recommendations From the International Society for the Study of Vascular Anomalies. *Pediatrics* . 2015;136(1):e203-e214. doi:10.1542/peds.2014-3673

5. Tollefson MM, Frieden IJ. Early Growth of Infantile Hemangiomas: What Parents' Photographs Tell Us. *Pediatrics* . 2012;130(2):e314-e320. doi:10.1542/peds.2011-3683

6. Chang LC, Haggstrom AN, Drolet BA, et al. Growth Characteristics of Infantile Hemangiomas: Implications for Management. *PEDIATRICS* . 2008;122(2):360-367. doi:10.1542/peds.2007-2767

7. Bauland CG, Luning TH, Smit JM, Zeebregts CJ, Spauwen PHM. Untreated Hemangiomas: Growth Pattern and Residual Lesions. *Plast Reconstr Surg* . 2011;127(4):1643-1648. doi:10.1097/PRS.0b013e318208d2ac

8. Leaute-Labreze C, Harper JI, Hoeger PH. Infantile haemangioma. *The Lancet* . 2017;390(10089):85-94. doi:10.1016/S0140-6736(16)00645-0

9. Cheng CE, Friedlander SF. Infantile hemangiomas, complications and treatments. *Semin Cutan Med Surg* . 2016;35(3):108-116. doi:10.12788/j.sder.2016.050

10. Garzon MC, Epstein LG, Heyer GL, et al. PHACE Syndrome: Consensus-Derived Diagnosis and Care Recommendations. *J Pediatr* . 2016;178:24-33.e2. doi:10.1016/j.jpeds.2016.07.054

11. Rotter A, Samorano LP, Rivitti-Machado MC, Oliveira ZNP, Gontijo B. PHACE syndrome: clinical manifestations, diagnostic criteria, and management. *An Bras Dermatol* . 2018;93(3):405-411. doi:10.1590/abd1806-4841.20187693

12. Iacobas I, Burrows PE, Frieden IJ, et al. LUMBAR: Association between Cutaneous Infantile Hemangiomas of the Lower Body and Regional Congenital Anomalies. *J Pediatr* . 2010;157(5):795-801.e7. doi:10.1016/j.jpeds.2010.05.027

13. Krowchuk DP, Frieden IJ, Mancini AJ, et al. Clinical Practice Guideline for the Management of Infantile Hemangiomas.*Pediatrics* . 2019;143(1). doi:10.1542/peds.2018-3475

14. Bennett ML, Fleischer AB, Chamlin SL, Frieden IJ. Oral corticosteroid use is effective for cutaneous hemangiomas: an evidence-based evaluation. *Arch Dermatol* . 2001;137(9):1208-1213. doi:10.1001/archderm.137.9.1208

15. Janmohamed SR, Madern GC, de Laat PCJ, Oranje AP. Educational paper: therapy of infantile haemangioma—history and current state (part II).*Eur J Pediatr* . 2015;174(2):259-266. doi:10.1007/s00431-014-2404-5

16. Leaute-Labreze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo J-B, Taieb A. Propranolol for severe hemangiomas of infancy. *N Engl J Med* . 2008;358(24):2649-2651. doi:10.1056/NEJMc0708819

17. Leaute-Labreze C, Roque ED de la, Nacka F, et al. Double-blind randomized pilot trial evaluating the efficacy of oral propranolol on infantile haemangiomas in infants < 4 months of age. *Br J Dermatol* . 2013;169(1):181-183. doi:10.1111/bjd.12217

18. 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(8):735-746. doi:10.1056/NEJMoa1404710

19. Begaud B, Evreux JC, Jouglard J, Lagier G. [Imputation of the unexpected or toxic effects of drugs. Actualization of the method used in France]. *Therapie* . 1985;40(2):111-118.

20. Arimone Y, Bidault I, Dutertre J-P, et al. Reactualisation de la methode francaise d'imputabilite des effets indesirables des medicaments. *Therapie* . 2011;66(6):517-525. doi:10.2515/therapie/2011073

21. Haggstrom AN, Drolet BA, Baselga E, et al. Prospective Study of Infantile Hemangiomas: Demographic, Prenatal, and Perinatal Characteristics. *J Pediatr* . 2007;150(3):291-294. doi:10.1016/j.jpeds.2006.12.003

22. Munden A, Butschek R, Tom WL, et al. Prospective study of infantile haemangiomas: incidence, clinical characteristics and association with placental anomalies. *Br J Dermatol* . 2014;170(4):907-913. doi:10.1111/bjd.12804

23. Yang H, Hu D-L, Shu Q, Guo X-D. Efficacy and adverse effects of oral propranolol in infantile hemangioma: a meta-analysis of comparative studies. *World J Pediatr* . 2019;15(6):546-558. doi:10.1007/s12519-019-00285-9

24. Baselga E, Dembowska-Baginska B, Przewratil P, et al. Efficacy of Propranolol Between 6 and 12 Months of Age in High-Risk Infantile Hemangioma. *Pediatrics* . 2018;142(3):e20173866. doi:10.1542/peds.2017-3866

25. Chang L, Gu Y, Yu Z, et al. When to stop propranolol for infantile hemangioma. *Sci Rep* . 2017;7:43292. doi:10.1038/srep43292

26. Ji Y, Chen S, Xiang B, Yang Y, Qiu L. Safety and tolerance of propranolol in neonates with severe infantile hemangiomas: a prospective study. *Sci Rep* . 2017;7(1):1-8. doi:10.1038/s41598-017-01321-2

27. Onnis G, Dreyfus I, Mazereeuw-Hautier J. Factors associated with delayed referral for infantile hemangioma necessitating propranolol. *J Eur Acad Dermatol Venereol JEADV* . 2018;32(9):1584-1588. doi:10.1111/jdv.14842

28. Wedgeworth E, Glover M, Irvine AD, et al. Propranolol in the treatment of infantile haemangiomas: lessons from the European Propranolol In the Treatment of Complicated Haemangiomas (PITCH) Taskforce survey. *Br J Dermatol* . 2016;174(3):594-601. doi:10.1111/bjd.14233

29. Leaute-Labreze C, Boccara O, Degrugillier-Chopinet C, et al. Safety of Oral Propranolol for the Treatment of Infantile Hemangioma: A Systematic Review. *PEDIATRICS* . 2016;138(4):e20160353-e20160353. doi:10.1542/peds.2016-0353

30. Prey S, Voisard J-J, Delarue A, et al. Safety of Propranolol Therapy for Severe Infantile Hemangioma. *JAMA* . 2016;315(4):413-415. doi:10.1001/jama.2015.13969

31. Droitcourt C, Kerbrat S, Rault C, et al. Safety of Oral Propranolol for Infantile Hemangioma. *Pediatrics* . 2018;141(6). doi:10.1542/peds.2017-3783

32. Ji Y, Chen S, Wang Q, et al. Intolerable side effects during propranolol therapy for infantile hemangioma: frequency, risk factors and management. *Sci Rep* . 2018;8(1):1-7. doi:10.1038/s41598-018-22787-8

33. Frari LD, Leaute-Labreze C, Guibaud L, et al. Propranolol pharmacokinetics in infants treated for Infantile Hemangiomas requiring systemic therapy: Modeling and dosing regimen recommendations. *Pharmacol Res Perspect* . 2018;6(3):e00399. doi:10.1002/prp2.399

34. Takechi T, Kumokawa T, Kato R, Higuchi T, Kaneko T, Ieiri I. Population Pharmacokinetics and Pharmacodynamics of Oral Propranolol in Pediatric Patients With Infantile Hemangioma. *J Clin Pharmacol* . 2018;58(10):1361-1370. doi:10.1002/jcph.1149

35. Martin K, Bleib F, Chamlin SL, et al. Propranolol Treatment of Infantile Hemangiomas: Anticipatory Guidance for Parents and Caretakers.*Pediatr Dermatol* . 2013;30(1):155-159. doi:10.1111/pde.12022

36. Holland KE, Frieden IJ, Frommelt PC, Mancini AJ, Wyatt D, Drolet BA. Hypoglycemia in Children Taking Propranolol for the Treatment of Infantile Hemangioma. *Arch Dermatol* . 2010;146(7):775-778. doi:10.1001/archdermatol.2010.158

37. Shepherd D, Adams S, Wargon O, Jaffe A. Childhood wheeze while taking propranolol for treatment of infantile hemangiomas. *Pediatr Pulmonol* . 2012;47(7):713-715. doi:10.1002/ppul.21603

38. Petrovic J, Trifunovic B, Vukomanovic G, Topalovic M, Trajkovic G, Parezanović V. Oral propranolol for infantile hemangiomas: a prospective study on the role of 48-hour Holter monitoring in additional safety assessment. *J Dermatol Treat* . 2017;28(6):554-558. doi:10.1080/09546634.2016.1277177

39. Hengst M, Oelert M, Hoeger PH. Blood Pressure Monitoring During the Induction and Maintenance Period of Propranolol Therapy for Complicated Infantile Hemangiomas: A Prospective Study of 109 Infants. *Pediatr Dermatol* . 2015;32(6):802-807. doi:10.1111/pde.12681

40. Raphael MF, Breugem CC, Vlasveld FAE, et al. Is cardiovascular evaluation necessary prior to and during beta-blocker therapy for infantile hemangiomas? *J Am Acad Dermatol* . 2015;72(3):465-472. doi:10.1016/j.jaad.2014.12.019

41. Xu D-P, Cao R-Y, Xue L, Sun N-N, Tong S, Wang X-K. Treatment of Severe Infantile Hemangiomas With Propranolol: An Evaluation of the Efficacy and Effects of Cardiovascular Parameters in 25 Consecutive Patients. *J Oral Maxillofac Surg* . 2015;73(3):430-436. doi:10.1016/j.joms.2014.09.010

42. Hoeger P, Harper J, Baselga E, et al. Treatment of infantile haemangiomas: recommendations of a European expert group. *Eur J Pediatr* . 2015;174. doi:10.1007/s00431-015-2570-0

43. Puttgen KB, Summerer B, Schneider J, Cohen BA, Boss EF, Bauman NM. Cardiovascular and blood glucose parameters in infants during propranolol initiation for treatment of symptomatic infantile hemangiomas. *Ann Otol Rhinol Laryngol* . 2013;122(9):550-554. doi:10.1177/000348941312200903

44. Frongia G, Byeon J-O, Arnold R, Mehrabi A, Günther P. Cardiac diagnostics before oral propranolol therapy in infantile hemangioma: retrospective evaluation of 234 infants. *World J Pediatr* . 2018;14(3):254-258. doi:10.1007/s12519-018-0137-7

45. Erdoğan I. Cardiac evaluation in children with hemangiomas. *Turk Kardiyol Dernegi Arsivi-Arch Turk Soc Cardiol* . January 2016. doi:10.5543/tkda.2016.65171

46. Yarbrough KB, Tollefson MM, Krol AL, Leitenberger SL, Mann JA, MacArthur CJ. Is Routine Electrocardiography Necessary Before Initiation of Propranolol for Treatment of Infantile Hemangiomas? *Pediatr Dermatol* . 2016;33(6):615-620. doi:10.1111/pde.12972

47. Tang LY, Hing JW, Tang JY, et al. Predicting complications with pretreatment testing in infantile haemangioma treated with oral propranolol. *Br J Ophthalmol* . 2016;100(7):902-906. doi:10.1136/bjophthalmol-2015-307284

48. Chaturvedi K, Steinberg JS, Snyder CS. Cost-effectiveness of treating infantile haemangioma with propranolol in an outpatient setting. *Cardiol Young* . 2018;28(10):1105-1108. doi:10.1017/S1047951118000987

Table 1. Patient clinical presentation at Hemangiol® initiation

Patients included (n)		94
Gender	Girls	70 (74.5)
	Boys	24 (25.5)
Age (median [min;max]); months		4 [0; 21]

Patients included (n)		94
Height (median [min;max]); cm		63.8 [45.5; 84]
Weight (median [min;max]); Kg		6.5 [3.6; 11]
Medical history	None (n,%)	82 (87.2)
	Preterm birth (n,%)	5 (5.3)
	Birth weight <2500 g (n, %)	1 (1.1)
	Congenital abnormalities	4 (4.3)
	Other	2 (2.1)
Type of IH	Superficial (n, %)	35 (37.2)
	Deep (n,%)	8 (8.5)
	Mixt (n,%)	51 (54.3)
Multifocal IH (n, %)		23 (24.5)
Location of IH	Head (n, %)	56 (59.6)
	Periocular (n, %)	*23 (24.5)*
	Nose (n,%)	*11 (11.7)*
	Lips (n,%)	*5 (5.3)*
	Parotid (n,%)	*5 (5.3)*
	Other (n,%)	*12 (12.8)*
	Cervical (n,%)	5 (5.3)
	Cutaneous (n,%)	*3 (3.2)*
	Subglottic (n,%)	*2 (2.1)*
	Thoracic and dorsal (n,%)	12 (12.8)
	Abdomen and pelvis (n,%)	12 (12.8)
	Hepatic (n,%)	*2 (2.1)*
	Perineal (n,%)	*7 (7.4)*
	Other (n,%)	*3 (3.2)*
	Limbs (n,%)	8 (8.5)
	Miliary (n,%)	1 (1.1)
Syndromic association	PHACES syndrome (n,%)	2 (2.1)
	LUMBAR syndrome (n,%)	2 (2.1)
Indication for treatment	Functional (n,%)	36 (38.3)
	Ulceration (n,%)	29 (30.9)
	Aesthetic (n,%)	24 (25.5)
	Life threatening (n,%)	5 (5.3)

Legends: IH, infantile haemangioma; PHACES, posterior fossa anomalies, haemangioma, arterial lesions, cardiac abnormalities, eye anomalies, sternal defects; LUMBAR, lower body haemangioma, urogenital, myelopathy, bones, anorectal/arterial, and renal anomalies.

Table 2. Patient cardiac monitoring during Hemangiol® initiation

Dose		Monitoring time	Monitoring time	Monitoring time	Monitoring time
	Cardiac monitoring	H0	H1	H2	H3
0.5mg/kg	SBP (mean ± SD)	94.8 ± 12.5	93.3 ± 12.7	90.8 ± 14.4	91.0 ± 13.3
	DBP (mean ± SD)	57.5 ± 14.2	54.8 ± 13.4	54.2 ± 14.0	53.7 ± 12.7
	BPM (mean ± SD)	140.3 ± 18.1	127.1 ± 16.1*	129.3 ± 15.0*	125.8 ± 16.4*
1 mg/kg	SBP (mean ± SD)	91.8 ± 13.0	90.8 ± 15.2	88.2 ± 12.9	91.0 ± 12.2
	DBP (mean ± SD)	59.7 ± 15.6	54.3 ± 15.1*	48.9 ± 14.3*	54.6 ± 13.7*

Dose		Monitoring time	Monitoring time	Monitoring time	Monitoring time
1.5 mg/kg	BPM (mean ± SD)	128.1 ± 19.0**	121.7 ± 17.0*	119.6 ± 15.7*	120.3 ± 14.2*
	SBP (mean ± SD)	91.3 ± 14.7	88.9 ± 15.3	89.0 ± 15.0	90.7 ± 12.2
	DBP (mean ± SD)	58.1 ± 13.5	52.6 ± 15.4*	51.7 ± 13.6*	52.8 ± 11.1*
	BPM (mean ± SD)	125.9 ± 20.1**	123.4 ± 15.8	120.7 ± 14.8	118.7 ± 14.5*

Legends: H0, before Hemangiol® initiation; H1, one hour after Hemangiol® initiation; H2, two hours after Hemangiol® initiation; H3 three hours after Hemangiol® initiation; SBP, systolic blood pressure; DBP, diastolic blood pressure; BPM, beats per minute (heart rate); SD, standard deviation.

* Significant statistical difference between H0 and H1 or H2 or H3 during the same hospitalization (P-value <0.05); ** Significant statistical difference between H0 at 0.5mg/kg initiation and H0 at 1mg/kg or 1.5mg/kg initiations (P-value <0.05).

Table 3. Serious adverse events

Case	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
SAE	Uncontrolled bronchial hyper reactivity	Hypoglycaemia without risk factor	Hypoglycaemia without risk factor	Hypoglycaemia after limited food intake	Uncontrolled bronchial hyper reactivity	Uncontrolled bronchial hyper reactivity	Uncontrolled bronchial hyper reactivity	Uncontr bronchi hyper reactivi
medical history	0	0	0	Preterm 35 WA	0	0	Preterm 34 WA	0
age at initiation (months)	6 months	5 months	2 months	3 months	4 months	11 months	7 months	5 months
Hemangiol® dosage during SAE	3 mg/kg/day	3 mg/kg/day	3 mg/kg/day	2 mg/kg/day	3 mg/kg/day	3 mg/kg/day	3 mg/kg/day	3 mg/kg/
Time between SAE and Hemangiol® initiation	1.5 months	7 months	5 months	4 months	8 months	4 months	5 months	11 months
Decision after SAE	Treatment suspended	Treatment suspended	Treatment suspended	Dose reduced under 2 mg/kg/day	Treatment suspended	Treatment reinitiated 3 months later	Treatment suspended	Treatme suspend
IH outcome after decision	Rebound growth Surgery	Involution	Involution	Rebound growth	Involution	Rebound growth	Involution	Involuti
Causality score	2/6	5/6	3/6	2/6	2/6	5/6	2/6	4/6

Legends: SAE, serious adverse event; WA, weeks of amenorrhea.

Figure legends

Supplementary Figure. Rapid initiation protocol