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

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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 reports 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 or ulcerated 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 nonserious 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 pretherapeutic paediatric cardiology consultation should not be systematic but only indicated for specific patients.

ClinicalTrials.gov: NCT 04105517.

KEYWORDS

Hemangiol, infantile haemangioma, oral propranolol, safety

Pascal Amedro and Arthur Gavotto contributed equally to this study.

The authors confirm that the PI for this study was Dr. Arthur Gavotto (MD) and that he had direct clinical responsibility for patients.

1 | INTRODUCTION

Originally classified in the vascular anomalies 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 International Society for the Study of Vascular Anomalies (ISSVA) classification.⁴ Usually, IH will appear the first few days or weeks after birth.⁵ IH is characterized by its natural course being divided into three phases: a proliferative phase characterized by a rapid growth of the tumour (up to 4-12 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 (eg, perioral and periorbital skin). Moreover, the aesthetic impact is not trivial, especially when IHs located in the centropacial 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 also initially referred as PELVIS syndrome by our group.¹³ Finally, liver haemangioma and haemangiomatosis are high-risk complicated IHs as they may lead to cardiac failure.¹⁴

Initially, medical treatment of severe IH was based on systemic corticosteroid therapy.^{15,16} In 2008, Leaute-Labreze et al fortuitously discovered the antiproliferative effect of propranolol when using this nonselective beta-blocker for a hypertrophic obstructive cardiomyopathy in a child with a facial IH treated by corticosteroids.¹⁷ The efficacy of oral propranolol in IH was demonstrated by two randomized controlled trials.^{18,19} In 2014 the Pierre Fabre dermo-cosmetics laboratory (Paris, France) obtained European Medicines Agency (EMA) and US Food and Drug Administration marketing authorization for Hemangirol, the first and only drug currently approved for the treatment of proliferating IH. Hemangirol 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 report the use of Hemangirol in our institution from 2014 to 2018.

2 | METHODS

2.1 | 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

What is already known about this subject

- Infantile haemangioma is the most common benign vascular tumour in children.
- Oral propranolol has become the first-choice therapy for complicated infantile haemangioma.
- Since 2014 Hemangirol has been the only approved drug.

What this study adds

- This postmarketing surveillance drug study supports the safety of Hemangirol and the importance of parental therapeutic education.
- This study supports the safety of a rapid initiation protocol when treatment is urgent.
- The pretherapeutic paediatric cardiology consultation should not be systematic but only indicated for selected at-risk patients.

for patient screening. The PMSI is a mandatory national database linked to the social security system, 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 with the term 'haemangioma' (D13) was used to screen patients and only children <2 years old treated with Hemangirol were included in the final analysis.

2.2 | Initiation and use of Hemangirol

Hemangirol (ligand: **propranolol**) is a nonselective beta-adrenoceptor antagonist.²⁰ 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 Hemangirol for IH, adapted from the summary of product characteristics (SmPC). This protocol includes 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 Hemangirol 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 SmPC, asthma or history of bronchospasm, second- or third-degree atrioventricular blocks, disease of the sinus node (including sinoatrial block), bradycardia (heart rate <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 (as described in the SmPC) and a 'rapid' initiation protocol (defined by our group of experts, and not described in the SmPC).

- The conventional initiation protocol included a 3-week titration phase, as reported in the SmPC: 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 daycare facility at day 1 (initiation), day 7 (week 1) and day 14 (week 2) with close clinical monitoring for 3 hours after treatment administration (hourly monitoring of vital constants and assessment of side effects). Bradycardia was defined as heart rate <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 tension <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 three 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 the two intakes; (ii) if the child is not eating or is vomiting it is recommended that the dose should be skipped; (iii) if 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.

- As urgent situations requiring propranolol initiation were not included in the original pharmaceutical drug trial, the SmPC only described the 3-week Hemangiol initiation protocol. Therefore, our group of IH experts designed a rapid initiation protocol dedicated to severe proliferative IH involving any vital risk or ulcerated IH with uncontrolled bleeding, 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 1.5 mg/kg 12 hours later (stage 3) to reach the maintenance therapeutic dose of 3 mg/kg/day in two daily intakes at day 2. Analgesics, local 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, the patient was discharged after day 2 (rapid initiation protocol in Supporting Information Figure S1).

- The children underwent follow-up examination with the IH specialist 4–8 weeks after Hemangiol initiation in nonsevere IH and 1–2 weeks after Hemangiol initiation in severe cases. The IH specialist determined the frequency of the following consultations, as well as the overall treatment duration.
- 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.

2.3 | 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. No clinical events directly related to the disease were observed. Adverse events (AEs) and serious adverse events (SAEs) were collected, therefore we recorded all AEs, defined as any undesirable experience possibly associated with the use of Hemangiol from drug initiation and throughout the follow-up. SAEs were defined as life-threatening events or adverse events leading to death, hospitalisation, 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.²¹ 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 an AE; scores ≥2 indicate possible relation to treatment) and an extrinsic score based on bibliography.²²

2.4 | 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).

2.5 | 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 percentages 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 software.

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

3.1 | Population

During the 5-year study period, 154 children <2 years old were hospitalized in our institution with a main diagnosis of 'haemangioma' identified from the hospital PMSI database. From this cohort, 60 patients were not included in the study: 25 (16.2%) cases were included in a concomitant randomised controlled trial comparing acebutolol versus propranolol in IH (NCT01743885), 17 (11%) cases received no drug to treat their IH, 10 (6.5%) cases had only surgical management, six (3.9%) cases were treated with oral capsule of propranolol, and two (1.3%) cases had significant missing data (lost to follow-up). In the group of patients not eligible for the study, children enrolled in the RCT or receiving oral capsule of propranolol had similar clinical characteristics as those receiving Hemangioli. Therefore, a total of 94 children (75% female) with IH treated with Hemangioli were included in this study (Figure 1). 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.

Hemangioli was initiated at a median age of 4 [0; 21] months, including two children <5 weeks and 29 children >5 months old. The main indication for IH treatment with Hemangioli was functional

FIGURE 1 The flowchart showed the excluded children for this study. IH, infantile haemangioma; RCT, randomized controlled trial

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 Hemangioli in 29 (30.9%) children, especially in peri-neal localisations (n = 7). Life-threatening forms of IH required treatment with Hemangioli for five children (hepatic haemangioma, n = 2; miliary, n = 1; subglottic haemangioma, n = 2). Patients' clinical characteristics were reported in Table 1.

3.2 | Paediatric cardiology consultation

The systematic paediatric cardiology consultation diagnosed a cardiac murmur in eight (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 two cases of patent ductus arteriosus (PDA) in a neonate with IH and nonsustained ventricular tachycardia (spontaneous PDA closure), and in a 6-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 nonsignificant 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.

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]
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)
	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)

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

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.

3.3 | Hemangiol initiation protocol

The conventional Hemangiol initiation protocol was the most commonly used (n = 76; 80.9%). The rapid Hemangiol initiation protocol concerned children with ulcerated IH (n = 11), life-threatening IH (n = 4), as well as the neonate with nonsustained 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 2-month-old child with parotid IH with a risk of compression. In children with ulcerated IH, the rapid Hemangiol 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 1 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, 1 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 nonsymptomatic 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.

3.4 | Follow-up of children under Hemangiol

The maintenance therapeutic dose of Hemangiol 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 initiation.

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

The median overall treatment duration was 7 [1.5; 19] months with a large majority of patients treated for 4 to 12 months (n = 60).

3.5 | Adverse events

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

TABLE 2 Patient cardiac monitoring during Hemangioli initiation

Dose	Monitoring time				
	Cardiac monitoring	H0	H1	H2	H3
0.5 mg/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*
	BPM (mean ± SD)	128.1 ± 19.0**	121.7 ± 17.0*	119.6 ± 15.7*	120.3 ± 14.2*
1.5 mg/kg	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*

Abbreviations: H0, before Hemangioli initiation; H1, 1 hour after Hemangioli initiation; H2, 2 hours after Hemangioli initiation; H3 3 hours after Hemangioli 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* < 0.05). **Significant statistical difference between H0 at 0.5 mg/kg initiation and H0 at 1 mg/kg or 1.5 mg/kg initiations (*P* < 0.05).

We did not find any significant change in the ECG before the initiation and 3 months after the initiation of Hemangioli 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, eight (8.5%) children presented a SAE: five cases of uncontrolled bronchial hyperreactivity (one associated with pneumonia and diarrhoea) and three cases of serious hypoglycaemia. SAEs led to permanent treatment discontinuation in six 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 nonserious AEs were reported in 19 (20.2%) patients (including two patients with SAEs and a nonserious AE, and five patients with two nonserious 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 nonserious AE required hospitalization or prolonged drug discontinuation.

4 | DISCUSSION

This study investigated the current use of Hemangioli 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 Hemangioli in this study is similar to previous reports⁸ and our cohort is representative of the usually described population of IH, with a predominant female representation.²³ 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 24} 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.¹⁴ Children of our study were treated for an average of 7 months, which is moderately longer than in the initial trial (eg, 6 months).¹⁹ However, recent studies have suggested treatment for 6 to 12 months due to a greater IH rebound growth in shorter treatment duration.^{25,26} Indeed, treatment duration is mostly dependent on clinical complete lesion regression.²⁷ Off-label use of Hemangioli 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.²⁸ Late Hemangioli 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.²⁹

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%³⁰ to 38.2%.³¹ 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.^{30,31} SAEs were found in 8.5% patients, exclusively severe hypoglycaemia and uncontrolled bronchial hyperreactivity, which is higher than previous reported SAEs rates,

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	Uncontrolled bronchial hyper reactivity
Medical history	0	0	0	Preterm 35 WA	0	0	Preterm 34 WA	0
Age at initiation, months	6	5	2	3	4	11	7	5
Hemangiol dosage during SAE, mg/kg/day	3	3	3	2	3	3	3	3
Time between SAE and Hemangiol initiation, months	1.5	7	5	4	8	4	5	11
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	Treatment suspended
IH outcome after decision	Rebound growth surgery	Involution	Involution	Rebound growth	Involution	Rebound growth	Involution	Involution
Causality score	2/6	5/6	3/6	2/6	2/6	5/6	2/6	4/6

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

ranging from 2.6%³² to 4.8%.³¹ Cardiac SAEs, such as atrioventricular block, bradycardia and symptomatic hypotension, were not found in our cohort, as opposed to previous studies^{31,32} 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.^{31,33} Of note, SAEs occurred in two prematurely born children, who may be more prone to hypoglycaemia and bronchial hyperreactivity as previously reported.³⁴ Therefore, low dose of Hemangiol (2 mg/kg/day) could be of interest in such high-risk children,^{25,30} but the dosage of 3 mg/kg/day has been more investigated in pharmacokinetics and pharmacodynamics studies^{35,36} based on the manufacturer's clinical trial.¹⁹

For all SAEs, causality scores concluded to possible to strong relation to Hemangiol. 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 (ie, 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.

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.³⁷ For example, parents should be fully aware that Hemangiol needs to be temporarily suspended in case of food intolerance or limited food intake in their child to avoid hypoglycaemia.³⁸ Similarly, bronchial hyperreactivity reactions were

FIGURE 2 Steps for a safe use of Hemangiol®. IH, infantile haemangioma; PHACES syndrome, posterior fossa anomalies, haemangioma, arterial lesions, cardiac abnormalities, eye anomalies and sternal defects

often related to respiratory tract infections and therefore require appropriate parental supervision.^{31,39}

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.^{40–42} Similarly, previous studies have reported the safety of oral propranolol for the treatment of IH⁴³ and suggested not extending cardiac monitoring beyond the initiation period except for heart rate during following consultations.⁴⁴ In light of these results, an outpatient Hemangirol initiation protocol could be considered in selected and not at-risk patients, as suggested by Puttgen et al.⁴⁵

This study supports the absence of relevance for a systematic pretherapeutic paediatric cardiology consultation. From a general perspective, cardiological tests are time-consuming and costly, and may cause a delay in the initiation of betablockers. Indeed, all cardiac findings observed in this cohort were mostly nonsignificant 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 for which a cardiological assessment would be necessary. 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, miliary haemangiomas or very large superficial IH) or off-label use (preterm birth, neonate period). These results are consistent with previous studies reporting that systematic echocardiography^{46,47} or ECG^{42,48} before propranolol initiation are not relevant in terms of contraindication assessment and correlation with SAE occurrence.⁴⁹

Most patients (81%) underwent a conventional initiation protocol with a 3-week titration phase in daycare hospital. This protocol seems safe and adapted to most children with IH, as reported in cost-effectiveness studies.⁵⁰ 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, 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, Hemangirol was well tolerated in terms of blood pressure and heart rate adaptation. We have drafted a diagram for safe use of Hemangirol, which is shown in Figure 2.

4.1 | Study limitation

Despite the collection of AEs during patients' follow-up at the hospital, as well as through parent calls 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.

5 | CONCLUSION

In children treated with Hemangirol for proliferative IH, this post-marketing surveillance drug study reported an AE incidence rate of 26.6%, of which 8.5% is nonfatal SAEs, supporting the importance of parental therapeutic education. The pretherapeutic 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 daycare hospital, the use of a rapid initiation protocol with a 48-hour dose escalation in conventional hospitalisation appears to address clinical management needs when treatment is urgent. Further evaluation in prospective studies is required to corroborate the effectiveness of this protocol in patients with severe proliferative IH involving any vital risk or ulcerated IH with uncontrolled bleeding, pain or infectious risk.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

Study concept and design: F.S., A.G. and P.A. Drafting of the manuscript: all. Critical revision of the manuscript for important intellectual content: all. Administrative, technical, or material support: P.A. Study supervision: A.G. and P.A.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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