Safety of Oral Propranolol for Infantile Hemangioma

Catherine Droitcourt, MD,[a,b,c,d] Sandrine Kerbrat, MS,[d] Caroline Rault, PharmD,[d] Marie-Anne Botrel, DVM,[d] André Happe, PhD,[d] Ronan Garlantezec, MD, PhD,[a,e,f] Bernard Guillot, MD, PhD,[g] Jean-Marc Schleich, MD, PhD,[h] Emmanuel Oger, MD, PhD,[a,d,i] Alain Dupuy, MD, PhD[a,b,d]

abstract

OBJECTIVES: The safety of oral propranolol for infantile hemangioma has not yet been studied at population level since the pediatric use marketing authorization was obtained in Europe.

METHODS: A survey of a nationwide, claim-based observational cohort of children <3 years old, with at least 1 delivery of oral propranolol between July 2014 and June 2016, was performed by using the database of the French National Health Insurance system. Standardized morbidity ratios (SMRs) were calculated by using, from the same database, a representative random sample of nonexposed subjects. The main outcomes were hospitalizations for cardiovascular (conduction disorders, bradycardia, and hypotension), respiratory (bronchial hyperactivity and bronchospasm), or metabolic events (hypoglycemia and hyperkalaemia), identified through the hospitalization diagnostic codes of the *International Classification of Diseases, 10th Revision*. The main analysis was conducted separately on "healthy" children (*N* = 1484), that is, free from of any prespecified underlying disease and on children with 1 of these underlying diseases (*N* = 269).

RESULTS: In all, 1753 patients <3 years of age had at least 2 deliveries of oral propranolol. In the healthy population, we observed 2 cardiovascular events (SMR = 2.8 [0–6.7]), 51 respiratory events (SMR = 1.7 [1.2–2.1]), and 3 metabolic events (SMR = 5.1 [0–10.9]). In the population with an underlying disease (mainly congenital heart disease), we observed 11 cardiovascular events leading to an SMR of 6.0 (2.5–9.6). SMRs were not significantly raised for respiratory or metabolic events in this "nonhealthy" population.

CONCLUSIONS: In this study on a large continuous nationwide claims database, we confirm the safety profile of oral propranolol in healthy children to be good.

FREE

[a]University of Rennes, Rennes, France; Departments of [b]Dermatology, [e]Public Health, [h]Cardiology, and [i]Centre of Pharmacovigilance, Centre Hospitalier Universitaire de Rennes, Rennes, France; [c]Institut National de la Santé et de la Recherche Médicale, Centre d'Investigation Clinique 1414, Rennes, France; [d]University of Rennes, EA 7449 REPERES Pharmacoepidemiology and Health Services Research, Rennes, France; [f]Institut de Recherche en Santé, Environnement et Travail, Unité Mixte de Recherche 1085, Rennes, France; and [g]Department of Dermatology, Centre Hospitalier Universitaire de Montpellier, Montpellier, France

WHAT'S KNOWN ON THIS SUBJECT: Oral propranolol was approved for the treatment of "proliferating infantile hemangioma requiring systemic treatment." A risk management plan was implemented, and the following serious risks were identified: cardiovascular, respiratory, and metabolic disorders. Further data on safety from postmarketing clinical trials experience are needed.

WHAT THIS STUDY ADDS: This is the first study at population level in which the safety of oral propranolol on a large nationwide claims database (covering of 98.8% of the 66 million of the French population) is described and its safety in healthy children is confirmed to be good.

ARTICLE

Infantile hemangioma (IH) is the most common soft tissue tumor in infants. Although the exact prevalence of IH remains unclear, it is estimated to affect 4% to 5% of white infants.[1] IH classically runs a well-recognized natural course, including 3 successive clinical phases. IH is not present at birth and begins to grow within days or weeks of birth; the growth phase is generally achieved within the first 6 months and is followed by a phase of stabilization from 12 to 18 months of age; then, a slow phase of involution is observed. Regression is complete for >80% of cases of IH at 4 years of age.[2] Although IH has a spontaneous course toward involution, treatment can be necessary to avoid or treat complications, which include painful, persistent ulcerations; compromised organ function; and disfiguring or life-threatening risks.[2,3]

Before 2008, the strategy for IH requiring treatment relied on systemic glucocorticosteroids as a first line; vincristine and interferon α were used for refractory IH. These treatments had limited success and raised a number of safety concerns.[4–6] In 2008, some French authors reported cases of IH with complications, treated with oral propranolol, a nonselective β-adrenergic receptor–blocking agent.[7,8] A multicenter, randomized, double-blind, phase 2 to 3 trial on 460 infants confirmed the efficacy and safety of an oral propranolol solution specific to pediatric use at 3 mg/kg in infants with IH.

After April 2010, children with IH requiring systemic therapy could receive oral propranolol under a compassionate use protocol (CUP) under the authorization of the French Drug Regulatory Agency (Agence Nationale de Sécurité du Médicament [ANSM]). Hemangiol (oral propranolol) was approved for the treatment of "proliferating IH requiring systemic treatment" and was given authorization from the European Commission and the Food

and Drug Administration. Hemangiol was granted pediatric use marketing authorization (PUMA) by the European Medicines Agency after April 2014.[9]

A risk management plan was implemented alongside the PUMA, and the following serious risks were identified: cardiovascular disorders including atrioventricular block, bradycardia, and hypotension; respiratory disorders including bronchospasm and/or bronchial hyperactivity; metabolic disorders including hypoglycemia or related seizure; and hyperkalemia for ulcerative IH. Furthermore, the risk of transient ischemic arterial stroke has been discussed in patients with IH as well as anomalies in the context of the posterior fossa brain malformations, hemangioma, arterial abnormalities of the blood vessels in the neck or head, cardiac abnormalities, eye abnormalities, and sternal anomalies (PHACES) syndrome; Online Mendelian Inheritance in Man 606 519) when treated with propranolol.[10–12] The Food and Drug Administration issued the same warnings and precautions, except for the risk of hyperkalemia. A recent comprehensive literature review on Hemangiol safety, including original data from the CUP, has recently been published.[13,14] However, the dosage of propranolol in the CUP (2 mg/kg) and in the case series is different from the dosage in the PUMA (3 mg/kg), and further data on safety from postmarketing clinical trials experience are needed.

Our objective was to assess the use of Hemangiol (oral propranolol) and its safety in real-life settings after the PUMA was granted, using observational data from the French national medico-administrative exhaustive database.

METHODS

Data Sources

The source was the Système National Inter-Regime de l'Assurance

Maladie (SNIIRAM) database,[15–17] the French national medico-administrative exhaustive database linked to the French hospital discharge database (Programme de Médicalisation des Systèmes d'information), covering of 98.8% of the 66 million people in the French population. Insurance and hospital databases are unambiguously linked (SNIIRAM database) through a single anonymous civil registration. The study protocol was authorized and approved by the ANSM (decision 2014S0121, October 18, 2016) by the National Institutional Review Board (Institut des Données de Santé) and by the Commission Nationale de l'Informatique et des Libertés (French data protection authority). The SNIIRAM database contains anonymous and individual data on demographic characteristics (sex, date of birth, and date of death) and all medical reimbursements, including drugs and their date of delivery and their quantity dispensed by month, laboratory tests, outpatient medical care and consultations, and hospitalizations (public hospital and private clinic), with primary, related, and associated diagnoses based on the *International Classification of Diseases, 10th Revision* (ICD-10) code. There is no information on the results of clinical examination, the results of laboratory tests and radiology, the diagnoses not linked to a hospitalization, or the drug daily doses. We selected a sample for the reference population, unexposed to Hemangiol, from a fraction of the complete database named Echantillon Généraliste des Bénéficiaires (EGB). This fraction is a 1/97th random and dynamic representative sample of the SNIIRAM database, has the same structure, and contains the same variables as the mother database.

Participants and Selection Criteria

The selection criteria for the patients exposed to Hemangiol included the

following: all infants <3 years of age covered by the French National Health Insurance, with at least 1 delivery of Hemangiol between July 28, 2014, and June 30, 2016, and identified through the SNIIRAM database. We focused on pediatric use at the age of IH according to the PUMA and on patients who had received propranolol after the July 28, 2014, date of the availability of Hemangiol in French hospital pharmacies after the PUMA was obtained. The CUP period was not considered and the patients with a switch to Hemangiol propranolol under CUP were excluded ($n = 192$).

The selection criteria for the unexposed patients (reference population) included the following: all infants <3 years old; covered by the French National Health Insurance; identified through the EGB database; born after January 1, 2010, and before September 30, 2015; and free of any delivery of Hemangiol.

Study Design and Population Analysis

We performed a nationwide, reimbursement-based observational study conducted on preexisting data. Because some underlying diseases could be a risk factor associated with the outcomes screened for or an indication for receiving Hemangiol in patients without IH, we analyzed 2 populations: a population of "healthy" children without any of the prespecified underlying diseases, and a population of "nonhealthy" children (ie, children with 1 of the prespecified underlying diseases). Underlying cardiovascular, respiratory, and metabolic diseases were defined through primary or linked hospitalization or associated diagnosis ICD-10 codes during the study period and are presented in Supplemental Tables 4 through 9.

Included patients had their data collected from birth to September 30, 2016. The date of the first delivery of Hemangiol (propranolol) was considered to be the beginning of exposure.

Hemangiol Exposure

Hemangiol (propranolol 3.75 mg/mL [vial of 120 mL]) deliveries were identified by using the anatomic, therapeutics, and chemical classification code C07AA05 between July 28, 2014, and June 30, 2016. A Hemangiol course was defined as consecutive deliveries interspaced by <3 months. A new course of Hemangiol was assumed if the time between 2 deliveries was >3 months. Exposure to Hemangiol was considered from the first delivery of Hemangiol course up to 3 months after the last Hemangiol delivery in the same course.

Outcomes

For each distinct, identified risk (cardiovascular, respiratory, and metabolic risks), we defined 3 composite cardiovascular, respiratory, and metabolic outcomes.

The cardiovascular composite outcome was any hospitalization with an ICD-10 diagnostic code from a prespecified list aimed at identifying conduction disorders, bradycardia, hypotension, and cardiac arrest; the respiratory composite outcome was any hospitalization with an ICD-10 diagnostic code from a prespecified list aimed at identifying bronchitis, bronchiolitis, and bronchospasm; and the metabolic composite outcome was any hospitalization with an ICD-10 diagnostic code from a prespecified list aimed at identifying hypoglycemia or related seizure and hyperkalemia. The date of admission was used as the date of the event. ICD-10 codes are presented in Supplemental Tables 4 through 9.

For cerebrovascular outcomes, any hospitalization with an ICD-10 diagnostic code from a prespecified list aimed at identifying cerebrovascular diseases and episodic and paroxysmal cerebrovascular disorders during the exposure period was analyzed separately.

Statistical Analysis

All hospitalizations for cardiovascular, respiratory, or metabolic events were taken into account for the descriptive analysis, and patients could have several hospitalizations linked to the same or different events. In the description of the population, all outcomes occurring under Hemangiol were considered. Premature children (ICD-10 code P07) defined 1 stratum.

In the comparative analysis for each of the cardiovascular, respiratory, and metabolic outcomes, only the first event during the first course of Hemangiol was considered. The numbers of events in the exposed and unexposed reference populations were compared by using indirect standardization. For each event (cardiovascular, respiratory, or metabolic), the ratio between the number of observed events and the number of expected events was calculated within the strata defined by sex, age (3-month periods), and prematurity. "Observed over expected" ratios (standardized morbidity ratios [SMRs]) were calculated with their 95% confidence interval (CI). P values < .05 were considered to be statistically significant. The duration of follow-up is presented in person-months in Supplemental Table 10.

RESULTS

Patients and Treatment Characteristics

In all, 1934 children <3 years of age had at least 1 delivery of Hemangiol between July 28, 2014, and June 30, 2016. Among these 1934 children, 181 have had a single delivery of Hemangiol (Fig 1). Among the 1753 exposed patients (>1 delivery of Hemangiol; 14 523 person-months), 420 patients (23.9%) had a history of

premature birth. Before Hemangiol introduction, 109 (6.2%) patients have had at least 1 delivery of timolol ophthalmic solution, and 284 (16%) have had at least 1 delivery of systemic corticosteroids. No patient had a delivery of vincristine or interferon α 2a. The mean age of patients at Hemangiol introduction was 5.7 months (±5; range: 0–35) and the median age was 4 months (interquartile range [IQR]: 3–7). Most patients received 1 course of Hemangiol, 198 (11%) patients received at least 2 courses, 15 (0.8%) patients received at least 3 courses, and 1 patient (0.06%) received 4 courses. The median duration of first course was 5.4 months (IQR: 3.2–7.5; range: 1–21.4 [Table 1]). The distribution of Hemangiol initiations according to age in months and per calendar month are given in Figs 2 and 3.

Outcomes

Because of the risk of confounding by the presence of an underlying disease (ie, a disease that could influence both the outcome and the probability of prescribing Hemangiol), we isolated a healthy population of 1484 children and conducted a distinct analysis for the same outcomes in a nonhealthy population of 269 children with an underlying cardiovascular, respiratory, or metabolic disease (Fig 1).

Healthy Children

The cohort of healthy children exposed to Hemangiol was composed of 1484 individuals, representing a total of 12 320 person-months. SMRs were used to compare incidences of various outcomes within this cohort with incidences in a population of matched healthy children who had never been exposed to Hemangiol.

Cardiovascular Outcomes

During the exposure period, 2 healthy children had cardiovascular events. No observed risk for cardiovascular outcomes was identified in healthy children exposed to Hemangiol (SMR = 2.8; 95% CI: 0–6.7; Table 2). One patient had hypotension 1 day after Hemangiol initiation and Hemangiol treatment was continued for 3 months without any further cardiovascular, respiratory, or metabolic events. One

TABLE 1 Characteristics of 1753 Children With at Least 2 Deliveries of Hemangiol and Hemangiol Courses (*N* = 1753)

|	*n* (%)
Sex	
Male	487 (27.8)
Female	1266 (72.2)
History of prematurity	420 (23.9)
Age at Hemangiol course initiation, median (Q1–Q3), mo	5 (3–7)
No. Hemangiol courses per patient	
At least 1 course	1753 (100)
At least 2	198 (11)
At least 3	16 (0.9)
Duration of Hemangiol course, median (Q1–Q3), mo	
First course	5.4 (3.2–7.5)
All courses	5.1 (2.8–7.3)
Time-lapse between 2 courses of Hemangiol (if at least 2 courses), mean (minimum–maximum), mo	7.1 (3–12.9)
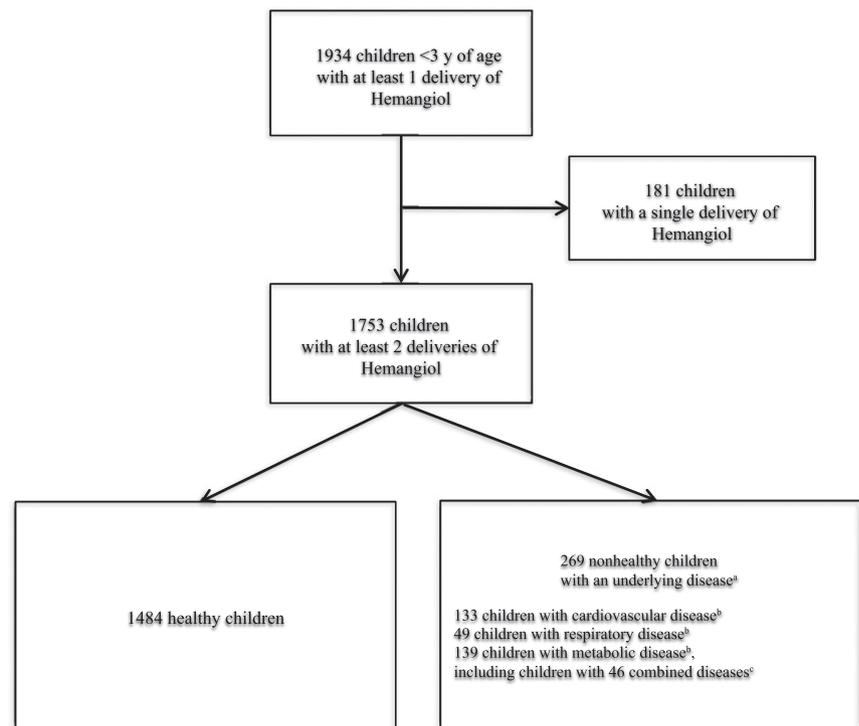
FIGURE 1

Flowchart. [a] Not mutually exclusive. [b] From a predefined list: cardiovascular diseases: I42 cardiomyopathy, P29 cardiovascular disorders originating in the perinatal period, Q20 to Q28 congenital malformations of cardiac chambers and connections, Q87.4 Marfan syndrome; respiratory diseases: J44 other chronic obstructive pulmonary disease, P27 chronic respiratory disease originating in the perinatal period, Q30 to Q34 congenital malformations of the respiratory system; metabolic diseases: E84 cystic fibrosis, E10 insulin-dependent diabetes mellitus, P70 Transitory disorders of carbohydrate metabolism specific to the fetus and newborn infant. [c] Among the 46 children with combined diseases: 6 children had cardiovascular, respiratory, and metabolic diseases; 13 children had cardiovascular and respiratory diseases; 23 children had cardiovascular and metabolic diseases; and 4 children had respiratory and metabolic diseases[b].
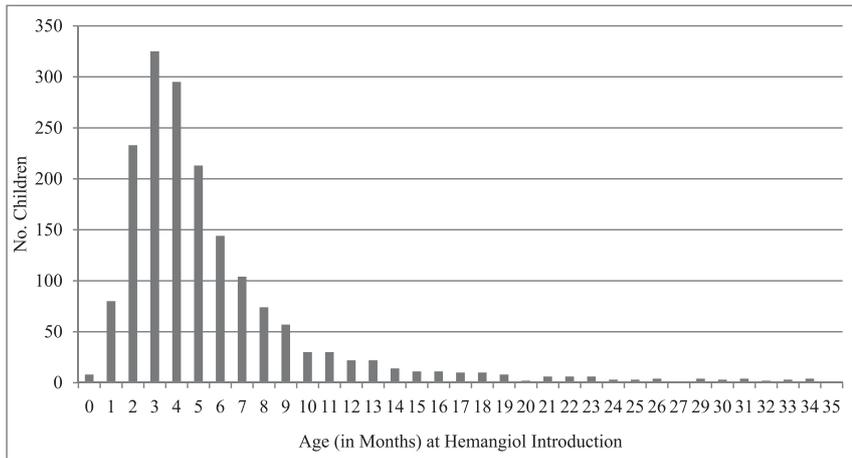
FIGURE 2
Age at initiation of Hemangiol in months.

patient with a history of premature birth developed bradycardia 38 days after Hemangiol introduction, and Hemangiol treatment was continued for 7 months without any further cardiovascular, respiratory, or metabolic events (Supplemental Table 11).

Respiratory Outcomes

In all, we observed 51 acute respiratory events, which was more than the number to be expected (SMR = 1.7; 95%CI: 1.2–2.1; Table 2). More specifically, a significant risk for hospitalized bronchiolitis was observed in healthy children (*n* = 38) treated with Hemangiol (SMR = 1.6; 95% CI: 1.1–2.1). In a sensitivity analysis, we took account of the epidemic period and the results were similar (Supplemental Table 12). No observed risk was observed for bronchospasm and acute bronchitis, but the number of events was much smaller (*n* = 2 for each of them). Respiratory events occurred after a median time of 67 days (IQR: 40–137) after Hemangiol initiation (Supplemental Table 11).

Metabolic Outcomes

Only 3 metabolic events (hypoglycemia) were observed in the healthy children exposed

to Hemangiol, with no identified related risk (SMR = 5.1; 95% CI: 0–10.9; Table 2). Metabolic events occurred after a median time of 141 days (IQR: 62–212). None had an intercurrent illness during these hospitalizations.

Nonhealthy Children: Children With an Underlying Cardiovascular, Respiratory, or Metabolic Disease

The cohort of nonhealthy children was composed of 269 individuals, representing a total of 2203 person-months (Table 3).

Cardiovascular Outcomes

Underlying cardiovascular diseases were identified in 133 children. In this population, 11 cardiovascular

events for 1025 person-months were observed during Hemangiol treatment (including 9 conduction disturbances; details given in the Supplemental Information) in a median time after exposure of 104 days (IQR: 53–308), compared with 1.8 expected in the reference population (51 events for 18 563 person-months), giving an SMR of 6 (95% CI: 2.5–9.6; Table 2 and Supplemental Table 10). The risk of conduction disturbances, including blocks, was significantly higher among children exposed to Hemangiol (SMR = 19; 95% CI: 6.6–31.5; Table 2). No observed risk for the cardiovascular outcomes (hypotension and bradycardia) was identified. No patient was hospitalized for a cerebrovascular event.

Respiratory Outcomes

Underlying respiratory diseases were identified in 49 children. In this population, 11 respiratory events for 366 person-months were observed during Hemangiol treatment in a median time after exposure of 72 days (IQR: 39–141; details given in the Supplemental Information), compared with 1.1 expected in the reference population (86 events for 3186 person-months), giving an SMR of 1.1 (95% CI: 0.5–1.8; Table 2 and Supplemental Table 10).
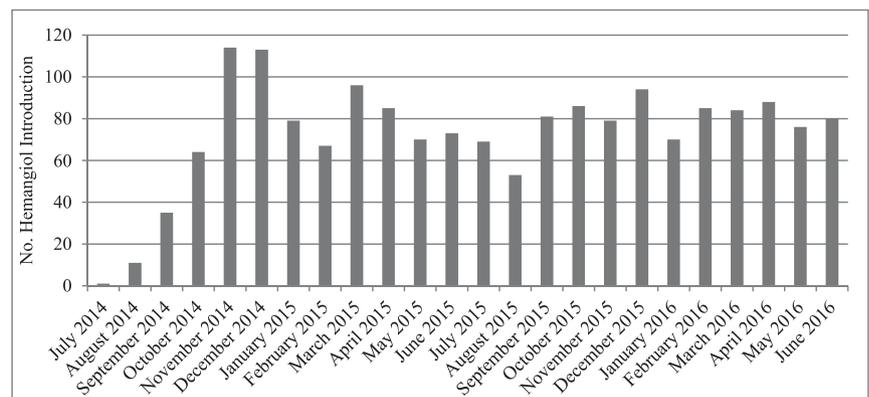

FIGURE 3
Numbers of Hemangiol introduction by calendar month.

TABLE 2 SMRs for Each Type of Outcome in Healthy Children

Category of Events	Healthy Children			
	Observed	Expected	SMR[a]	CI 95%
Cardiovascular events	2	0.7	2.8	(0–6.7)
Conduction disturbances	0	0.2	0	—
Bradycardia	1	0.2	4.2	(0–14)
Hypotension	1	0.4	4.7	(0–7.9)
Cardiac arrest	0	0.3	0	—
Respiratory events	51	30.5	1.7	(1.2–2.1)
Acute bronchitis	2	2.7	0.7	(0–1.7)
Chronic bronchitis	0	0.03	0	—
Bronchiolitis	38	23.9	1.6	(1.1–2.1)
Bronchospasm	2	6.9	0.3	(0–0.7)
Others	10	3.0	3.3	(1.3–5.4)
Metabolic events	3	0.6	5.1	(0–10.9)
Death	0	0.7	0	—

Only the first events are taken into account. —, not applicable.

[a] Indirect standardization on sex, age, and premature birth.

Metabolic Outcomes

During the exposure period, we did not observe any patients with an underlying metabolic disease experience a metabolic event.

Children With a Single Delivery of Hemangiol

A population of 181 children with a single delivery of Hemangiol was analyzed separately because the reason for discontinuation was unknown. It could be related to failure to take the treatment or conversely to early intolerance. We observed 3 patients with a cardiovascular event in a mean time after exposure of 49 days (±49) and all of them had an underlying cardiovascular disease. There were 12 patients with a respiratory event (7 patients with bronchiolitis, 4 patients with bronchospasm, and 1 patient with bronchitis) with a mean time after exposure of 47 days (±30), and none of them had an underlying respiratory disease. No child was hospitalized for metabolic or cerebrovascular events. The population with a single issue of Hemangiol is detailed in Supplemental Table 13.

DISCUSSION

Key Results

This nationwide claim-based cohort study of 1934 patients treated with Hemangiol (propranolol) is the first analysis conducted

TABLE 3 SMRs for Each Type of Outcome in Children With an Underlying Disease

Category of Events	With Cardiovascular, Respiratory, or Metabolic Disease[a]			
	Observed	Expected	SMR[b]	CI 95%
With cardiovascular disease				
Cardiovascular events	11	1.8	6.0	(2.5–9.6)
Conduction disturbances	9	0.5	19.0	(6.6–31.5)
Bradycardia	0	0.2	0	—
Hypotension	2	0.8	2.6	(0–6.3)
Cardiac arrest	1	0.3	3.4	(0–10.1)
With respiratory disease				
Respiratory events	11	9.6	1.1	(0.5–1.8)
Acute bronchitis	1	1.1	0.9	(0–2.8)
Chronic bronchitis	0	0.2	0	—
Bronchiolitis	5	5.3	0.9	(0.1–1.8)
Bronchospasm	2	3.3	0.6	(0–1.5)
Others	4	1.9	2.1	(0–4.1)
With metabolic disease				
Metabolic events	0	0.5	0	—
With cardiovascular disease				
Death	1	1.4	0.7	(0–2.2)

Only the first events are taken into account. —, not applicable.

[a] Population with cardiovascular disease was used to calculate the ratio between the number of observed and the number of expected cardiovascular events and death. Population with respiratory disease was used to calculate the ratio between the number of observed and the number of expected respiratory events. Population with metabolic disease was used to calculate the ratio between the number of observed and the number of expected metabolic events.

[b] Indirect standardization on sex, age, and premature birth.

DROITCOURT et al

at the population level since the PUMA was granted. Compared with the general population, the risks under Hemangiol were contrasted according to the type of outcome and the absence or presence of an underlying disease. In healthy children, we observed no association between Hemangiol and cardiovascular events, but a higher risk for bronchiolitis under Hemangiol was identified. In children with an underlying cardiovascular disease (mainly represented by congenital heart diseases), we observed a higher risk of conduction disturbances under Hemangiol. The number of initiations was stable over the study period from mid-2014 to mid-2016.

Interpretation

Our main objective was to assess the safety among children who were given Hemangiol for their IH. Although IH accounts for the vast majority of indications for oral propranolol, other indications have emerged in recent years. For instance, it is well known that oral propranolol has been given to patients with a tetralogy of Fallot because it was the only pediatric-specific oral propranolol solution available, even before the ANSM issued a recommendation for a temporary use in such patients in February of 2017. Although conduction disturbances are not a direct manifestation of tetralogy of Fallot, the context points to complex interactions between comorbid diseases, side effects of multiple drugs, and the outcomes screened for here. In the absence of information about the precise indication of Hemangiol, a global analysis would have been prone to both confounding by an underlying disease (which could influence the probability of prescribing Hemangiol and the occurrence of outcomes) and to misclassification (Hemangiol given for indications other than IH).

The absence of risk for cardiovascular outcomes in the healthy population is reassuring. However, much concern has been raised about cardiovascular effects and, more precisely, conduction disturbances, bradycardia, and hypotension. In a recent literature review including data on >5000 children treated with Hemangiol for IH, no case of conduction disturbances was reported. Only 2 cases of conduction disturbances were identified in the CUP and the manufacturer's clinical trials: 1 patient with second-degree Mobitz type 1 atrioventricular block followed by the identification of an underlying cardiovascular disease and 1 patient with type third-degree atrioventricular block occurring during sclerotherapy of esophageal varicose veins due to biliary atresia.[13] An excess of cardiovascular events (conduction disturbances) under Hemangiol seems restricted to the population with an underlying cardiovascular disease. In our study, in the population of children with underlying cardiovascular diseases, the risk of conduction disturbances was higher in children with an underlying cardiovascular disease and under Hemangiol than in the general population with an underlying cardiovascular disease. The context of cardiovascular disease (tetralogy of Fallot) is likely to have been be the indication for the treatment with Hemangiol. Hemangiol had a recommendation for a temporary use for the treatment of pediatric patients with high blood pressure, heart failure and cardiomyopathy, cardiac rhythm disorders, tetralogy of Fallot, congenital long QT syndrome, and Marfan syndrome, which justify a treatment with β-blockers; however, we cannot exclude the case of patients treated with Hemangiol for IH that also have a cardiovascular disease. In our study, 1 healthy child was hospitalized for a primary diagnosis of bradycardia 38 days

after Hemangiol introduction without treatment, discontinuation, or new hospitalization for a cardiovascular event. During the CUP and the manufacturer's clinical trials, 3 and 2 cases, respectively, of bradycardia were observed; in our recent literature review on the safety of propranolol given for IH, we identified 53 children with bradycardia. This event was considered nonserious, transient, and manageable. In our study, 1 healthy child had a hypotension 1 day after Hemangiol introduction without discontinuation. Among the identified cardiovascular risks, hypotension was the most frequent, including 7 patients in the manufacturer's clinical trials, 4 patients during the CUP, and 118 patients in the literature; the majority of them were asymptomatic. Lastly, no hospitalization for a stroke was observed under Hemangiol. The question of risk of arterial ischemic stroke under propranolol and in case of PHACES syndrome is still in debate.[11,12] We cannot know whether Hemangiol was given to patients with PHACES syndrome. The researchers of a large, prospective study initiated by the Hemangioma Investigator Group found that among 1096 children with hemangiomas, 25 had extracutaneous anomalies associated with PHACES syndrome.[10] We can hypothesize that among the patients exposed, some of them had PHACES syndrome.

The higher risk of acute respiratory disease, mainly bronchiolitis, in healthy children is worthy of note. This is a well-identified risk in children who are given propranolol because it increases airway resistance. Because this is a well-monitored risk, we cannot exclude the possibility that the higher rate of hospitalization for bronchiolitis in children under Hemangiol is related to better monitoring and parental education on this risk and that hospitalization

is more a consequence of better monitoring than an indication of more severe disease. The absence of risk for acute respiratory disease identified in children with an underlying respiratory disease seems paradoxical. However, indications for Hemangiol were carefully weighted in this population, and it is probable that people with more severe diseases are negatively selected.

Regarding the risk of hospitalization for metabolic events, 4 healthy patients had hypoglycemia under Hemangiol, with treatment discontinuation for 3 children. During the CUP and the manufacturer's clinical trials, 2 and 9 cases, respectively, of hypoglycemia were observed, and in the recent literature review on the safety of propranolol given for IH, 26 children with hypoglycemia were identified, but details on these events are not complete. For the cases in the CUP and the manufacturer's clinical trials, hypoglycemia occurred during concomitant infection and reduced nutritional intake and could be minimized with appropriate education on the administration of Hemangiol.

Strengths and Limitations

Our study has several strengths. First, the study was based on 1 of the largest continuous nationwide health reimbursement databases, with a size comparable to the Sentinel in the United States or the Canadian Network for Observational Drug Effect Studies, providing comprehensive data and covering 98.8% of the French population, which is >66 million patients.[15,17,18] This database provides exhaustive information on the medical prescription of Hemangiol in France, with virtually no selection bias toward the population included and no attrition bias. Secondly, this is the

first safety study on Hemangiol in a pharmacoepidemiological approach on a large claims database since the PUMA was obtained in which patients are less closely monitored than in the CUP and the manufacturer's clinical trials, providing useful information for prescribers. Third, the comparative study included an appropriate control group drawn as a random sample of the general population of children <3 years old from the SNIIRAM database, without any exposure to Hemangiol, and with the same definitions for cardiovascular, respiratory, and metabolic events and underlying diseases.

Some limitations should be discussed. First, cardiovascular, respiratory, metabolic, and cerebrovascular events were based on information encoded in the Programme de Médicalisation des Systèmes d'information, and some misclassifications may have occurred. Second, we had access to the deliveries of drugs, but we cannot ascertain that the treatment was actually taken. This limitation is of special importance for children who had a single issue, and results from this subgroup are presented separately. However, repeated issues can confidently be assumed to reflect actual drug consumption. Third, we had no access to clinical events not linked to hospitalization, and this is a bias toward more severe side effects. Without clinical data from the patients' health records, it was not possible to analyze precisely the indications for treatment nor to monitor the side effects in an exhaustive manner. Fourth, although we examined the totality of deliveries at a nationwide level, a lack of power is a limitation for rare events.

CONCLUSIONS

In this study on a large continuous nationwide database based on

health reimbursements, we provide data on the safety and use of Hemangiol after the PUMA was granted. The data confirm the overall good safety profile of oral propranolol in children with IH, in particular for serious side effects with hospitalization, and the data show a stability of prescription levels for oral propranolol in children since the PUMA was granted. Our results do not support a reinforcement of Hemangiol monitoring in infants. It is currently limited to a clinical monitoring, and avoidance is advised in case of lower respiratory infection or low food intake; during the titration phase, a cardiovascular monitoring based on clinical parameters is recommended.

ABBREVIATIONS

ANSM: Agence Nationale de Sécurité du Médicament
CI: confidence interval
CUP: compassionate use protocol
EGB: Echantillon Généraliste des Bénéficiaires
ICD-10: *International Classification of Diseases, 10th Revision*
IH: infantile hemangioma
IQR: interquartile range
PHACES: posterior fossa brain malformations, hemangioma, arterial abnormalities of the blood vessels in the neck or head, cardiac abnormalities, eye abnormalities, and sternal anomalies
PUMA: pediatric use marketing authorization
SMR: standardized morbidity ratio
SNIIRAM: Système National Inter-Régime de l'Assurance Maladie

DROITCOURT et al

REFERENCES

1. 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

2. Léauté-Labrèze C, Harper JI, Hoeger PH. Infantile haemangioma. *Lancet*. 2017;390(10089):85–94

3. Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. *Pediatrics*. 2013;131(1):128–140

4. Sadan N, Wolach B. Treatment of hemangiomas of infants with high doses of prednisone. *J Pediatr*. 1996;128(1):141–146

5. Barlow CF, Priebe CJ, Mulliken JB, et al. Spastic diplegia as a complication of interferon Alfa-2a treatment of hemangiomas of infancy. *J Pediatr*. 1998;132(3 pt 1):527–530

6. Kim KH, Choi TH, Choi Y, et al. Comparison of efficacy and safety between propranolol and steroid for infantile hemangioma: a randomized clinical trial. *JAMA Dermatol*. 2017;153(6):529–536

7. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taïeb A. Propranolol for severe hemangiomas of infancy. *N Engl J Med*. 2008;358(24):2649–2651

8. Sans V, de la Roque ED, Berge J, et al. Propranolol for severe infantile hemangiomas: follow-up report. *Pediatrics*. 2009;124(3). Available at: www.pediatrics.org/cgi/content/full/124/3/e423

9. Léauté-Labrèze 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

10. Metry D, Heyer G, Hess C, et al; PHACE Syndrome Research Conference. Consensus statement on diagnostic criteria for PHACE syndrome. *Pediatrics*. 2009;124(5):1447–1456

11. Siegel DH, Tefft KA, Kelly T, et al. Stroke in children with posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities (PHACE) syndrome: a systematic review of the literature. *Stroke*. 2012;43(6):1672–1674

12. Metry D, Frieden IJ, Hess C, et al. Propranolol use in PHACE syndrome with cervical and intracranial arterial anomalies: collective experience in 32 infants. *Pediatr Dermatol*. 2013;30(1):71–89

13. Léaute-Labrèze 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

14. Prey S, Voisard JJ, Delarue A, et al. Safety of propranolol therapy for severe infantile hemangioma. *JAMA*. 2016;315(4):413–415

15. Bezin J, Duong M, Lassalle R, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: powerful tools for pharmacoepidemiology. *Pharmacoepidemiol Drug Saf*. 2017;26(8):954–962

16. Palmaro A, Moulis G, Despas F, Dupouy J, Lapeyre-Mestre M. Overview of drug data within French health insurance databases and implications for pharmacoepidemiological studies. *Fundam Clin Pharmacol*. 2016;30(6):616–624

17. Tuppin P, Rudant J, Constantinou P, et al. Value of a national administrative database to guide public decisions: from the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. *Rev Epidemiol Sante Publique*. 2017;65(suppl 4):S149–S167

18. Suissa S, Henry D, Caetano P, et al; Canadian Network for Observational Drug Effect Studies. CNODES: the Canadian network for observational drug effect studies. *Open Med*. 2012;6(4):e134–e140

Updated Information & **Services**	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/141/6/e20173783
References	This article cites 18 articles, 5 of which you can access for free at: http://pediatrics.aappublications.org/content/141/6/e20173783#BIBL
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Dermatology** http://www.aappublications.org/cgi/collection/dermatology_sub **Administration/Practice Management** http://www.aappublications.org/cgi/collection/administration:practice _management_sub **Safety** http://www.aappublications.org/cgi/collection/safety_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Safety of Oral Propranolol for Infantile Hemangioma

Catherine Droitcourt, Sandrine Kerbrat, Caroline Rault, Marie-Anne Botrel, André Happe, Ronan Garlantezec, Bernard Guillot, Jean-Marc Schleich, Emmanuel Oger and Alain Dupuy

The online version of this article, along with updated information and services, is
located on the World Wide Web at:
http://pediatrics.aappublications.org/content/141/6/e20173783

Data Supplement at:
http://pediatrics.aappublications.org/content/suppl/2018/05/24/peds.2017-3783.DCSupplemental

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®