Safety of Oral Propranolol for the Treatment of Infantile Hemangioma: A Systematic Review

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abstract

BACKGROUND AND OBJECTIVES: Given the widespread use of propranolol in infantile hemangioma (IH) it was considered essential to perform a systematic review of its safety. The objectives of this review were to evaluate the safety profile of oral propranolol in the treatment of IH.

METHODS: We searched Embase and Medline databases (2007–July 2014) and unpublished data from the manufacturer of Hemangiol/Hemangeol (marketed pediatric formulation of oral propranolol; Pierre Fabre Dermatologie, Lavaur, France). Selected studies included ≥10 patients treated with oral propranolol for IH and that either reported ≥1 adverse event or effect (AE) or planned to capture AEs. Data capture was standardized and extracted study design, demographic characteristics, IH characteristics, intervention, and safety outcomes. AEs were assigned a system organ class and preferred term.

RESULTS: A total of 83 of 398 identified literature records met the inclusion criteria, covering 3766 propranolol-treated patients. The manufacturer's data for 3 pooled clinical trials (435 propranolol-treated patients) and 1 Compassionate Use Program (1661 patients) were included. AE data were reported for 1945 of 5862 propranolol-treated patients. The most frequently reported AEs included a range of sleep disturbances, peripheral coldness, and agitation. The most serious AEs (atrioventricular block, bradycardia, hypotension, bronchospasm/bronchial hyperreactivity, and hypoglycemia-related seizures) were managed by decreasing doses or temporary/permanent discontinuation of propranolol. Limitations included the variety of included study designs; monitoring, collection, and reporting of AE data; small sample sizes for some articles; and the wide scope of review.

CONCLUSIONS: Oral propranolol is well tolerated if appropriate pretreatment assessments and within-treatment monitoring are performed to exclude patients with contraindications and to minimize serious side effects during treatment.

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Dr Léauté-Labrèze conceptualized and designed the manufacturer's pivotal clinical study and was the coordinating investigator, reviewed and interpreted the data, and was an investigator for the manufacturer's Compassionate Use Program (CUP); Dr Prey was an investigator for the manufacturer's pivotal clinical study and CUP and was involved in the review and interpretation of the CUP data; Drs Boccara and Mazereeuw-Hautier were investigators for the manufacturer's pivotal clinical study and CUP; Dr Degrugillier-Chopinet was an investigator for the manufacturer's CUP; Dr Lebbé was involved in data review and interpretation of the manufacturer's pivotal clinical study and data collection and interpretation of the manufacturer's CUP; Ms Gautier provided the statistical analysis data

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The treatment of infantile hemangioma (IH), the most common childhood vascular tumor with an incidence of 3% to 10%,[1–4] has undergone a revolution since the observation in 2008 of dramatic regression of IH with oral propranolol, a nonselective β-adrenergic receptor–blocking agent.[5,6] Although most IHs resolve naturally without treatment, ~10% to 15% cause complications requiring referral to a specialist for intervention, ideally early in the proliferative phase of growth.[7] Severe cases requiring therapy include those that, due to location or distribution, are life-threatening (subglottic, multifocal with visceral involvement), function-threatening (periorificial), or cause severe ulceration and bleeding (lumbosacral, genital) or risk of permanent disfigurement (central facial, breast).

Propranolol is now considered first-line therapy for IH requiring systemic therapy.[8–10] Several systematic reviews of efficacy published since the widespread adoption of oral propranolol reported its superiority overall (response rate of up to 98%)[11,12] and compared with other therapies, such as corticosteroids.[13–15] Consensus conferences have made recommendations regarding the indication for propranolol treatment and its target dose, frequency, initiation, and monitoring.[7,10] A pediatric-specific formulation has shown efficacy[16] and has been available internationally for the treatment of IH requiring systemic therapy since 2014.[16–18]

Although propranolol has been in use since the 1960s (largely for cardiovascular indications) and has a well-established safety profile, its profile in infants is less well known. Serious risks that have been identified in the treatment of IH are hypoglycemia or related seizure, bradycardia, hypotension, prolonged atrioventricular conduction or intensification of atrioventricular block, and bronchospasm/bronchial hyperreactivity.[7,16,19–21] Other common, nonserious events related to propranolol are sleep disturbances, diarrhea, constipation, and cold extremities.[7,20,21] Given the widespread use of propranolol in IH and the accumulation of safety data, we considered it essential to perform a systematic review of the safety of oral propranolol in this indication to inform current usage.

METHODS

A protocol for this systematic review is presented in Supplemental Appendix 1.

Data Sources

To identify suitable studies for this systematic review, Embase and Medline were searched between January 2007 and July 2014. The search strategy covered terms for infantile hemangioma/hemangioma; newborn, infant, infancy, or child; propranolol (excluding topical); and various terms concerning safety and adverse events or effects (AEs). An example Medline strategy is presented in Supplemental Appendix 1. The manufacturer of Hemangiol[17]/Hemangeol[18] (Pierre Fabre Dermatologie, Lavaur, France) holds extensive, currently unpublished safety data on the use of oral propranolol in IH. This review therefore presents the manufacturer's clinical data for Hemangiol/Hemangeol that meet the study selection criteria described below; these data are collectively referred to as "manufacturer's" data.

Study Selection

All citations retrieved by database searches were screened by 2 reviewers to assess eligibility for inclusion according to the selection criteria. Eligible studies included patients with IH (no age limit) treated with oral propranolol; no comparator was specified. Included studies had to present either the reporting of ≥1 AE (adverse "event" and "effect" were used interchangeably, according to data source) or the plan to capture AEs. Due to the paucity of randomized controlled trials in the field, study type was not limited other than by the exclusion of those including <0 patients, abstracts, posters, conference reports, and responses to editors. English language limits were imposed for logistical reasons.

Data Extraction

Data were extracted independently by 2 reviewers (M.L. and A.M.) by using a standardized data capture form. Details on study design, population, IH characteristics, intervention, and safety outcomes including AE term, action, and resolution were extracted. Data extraction was checked independently. Discrepancies were resolved by consensus through discussion.

Data Synthesis

AEs reported in the selected publications were assigned a system organ class and preferred term by the Pierre Fabre Clinical Department with the use of the Medical Dictionary for Regulatory Activities (MedDRA, version 18.0). Due to the expected heterogeneity of study designs and reporting of safety findings, the severity, seriousness, and relationship to treatment were not assigned and safety data collected were summarized descriptively (number and percentage of patients) in tables, accompanied by narrative synthesis. Protocol-defined subgroup analyses were carried out only if clinically appropriate.

RESULTS

Study Selection

A total of 398 records were identified through database searching (after

duplicates were removed), of which 83 articles met the inclusion criteria. Two unpublished records were identified from the manufacturer's database: pooled data for 3 clinical trials and a Compassionate Use Program (CUP) conducted for patients not meeting clinical trial selection criteria. The selection process is presented in Fig 1.

Study Characteristics

In the 83 articles selected (Tables 1 and 2), 3766 patients were treated with oral propranolol. The majority of studies were retrospective (n = 44) or prospective (n = 35), noncontrolled (n = 78), and nonrandomized (n = 79), including a majority of case series or cohort studies as well as 1 open-label study versus a historical control.[22] Four studies were comparative randomized controlled trials of propranolol versus (1) placebo (Hogeling et al[23]; 19 vs 20 patients), (2) corticosteroids (Bauman et al[24]; 10 vs 8 patients; Malik et al[25]; 10 patients receiving propranolol alone, 10 patients on propranolol and corticosteroids, and 10 patients on corticosteroids alone), or (3) other β-blockers (Ábarzúa-Araya et al[26]; 10 vs 13 patients). Due to this low amount of data, comparator safety data were not captured. Four studies investigated safety in >100 patients: Luo et al[27] (635 patients), Phillips et al[28] (188 patients), Hermans et al[29] (174 patients), and Gan et al[30] (109 patients).The majority (55 articles) studied 20 to 99 propranolol-treated patients.

Pooled manufacturer's clinical trial data (detailed in Table 3 and Supplemental Appendix 2) comprised the following:

- Study 102: open-label, 3-month repeated-dose pharmacokinetics trial of propranolol in 23 infants with proliferating IH
- Study 201: pivotal, adaptive phase II/III, randomized placebo-controlled trial to select the best of 4 propranolol regimens and to show efficacy against placebo after 6 months of treatment; 456 patients received treatment (401 propranolol and 55 placebo); patients were followed up for 18 months after the end of study treatment[16]
- Study 301: open-label trial of propranolol in 11 infants with proliferating IH requiring systemic therapy, allowing the continued use of propranolol in patients who had participated in studies 102 or 201

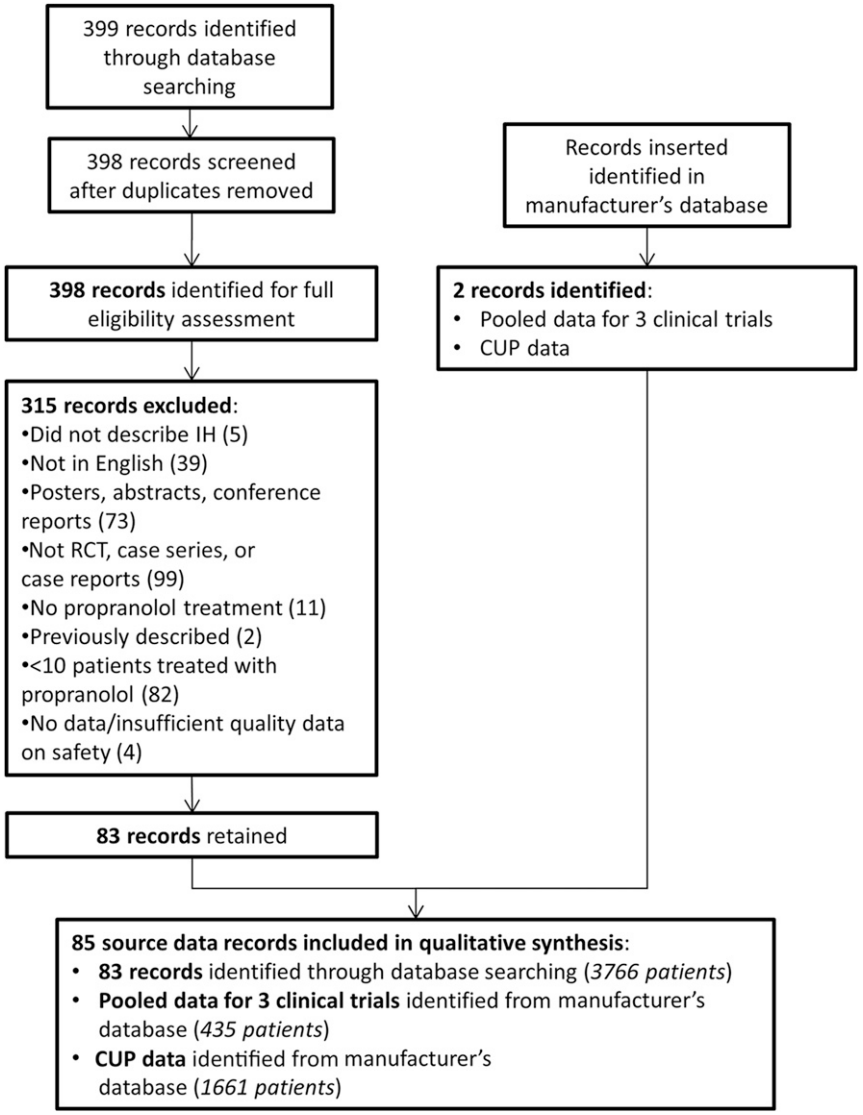

FIGURE 1
Flowchart of selection of articles and other identified data for inclusion in the systematic review (number of propranolol-treated patients assessed are shown in parentheses in the bottom box). RCT, randomized controlled trial.

In addition, a CUP was completed in France (detailed in Table 3 and Supplemental Appendix 3) allowing the use of Hemangiol before marketing authorization in 1661 infants with high-risk IH unable to be included in the ongoing clinical trials. Data reporting was the responsibility of the treating physician. A summary of the results for 906 propranolol-treated CUP patients has been published[101]; this systematic review

TABLE 1 List of Studies Identified and Selected Through Database Searches

First Author and Reference	Study Type	Patients Treated With Propranolol, *n*	Sex, *n*		Age at Treatment Initiation, mo				Type or Localization of IH
			Female	Male	Mean	Median	Min	Max	
Ábarzúa-Araya[26]	RCT, noninferiority of propranolol versus atenolol	10							"Problematic" IH; various loc
Al Dhaybi[31]	Retrospective	18	13	4		3.7	1	31	Periocular IH incl PHACES
Albuquerque[32]	Retrospective	69	46	23	31.0	8	1	228	Various loc incl PHACES
Andersen[33]	Retrospective	37	28	9			0.1	22	Complicated IH; various loc
Bagazgoitia[34]	Retrospective	71	56	15	5.8		1	45	"Problematic" IH; various loc excl PHACES
Balma-Mena[35]	Retrospective	44	32	12	7.8				Various loc
Bauman[24]	RCT, propranolol versus prednisolone	10 (+1 patient withdrawn before treatment)	8	3	2.5		1.7	3.4	Symptomatic IH; various loc incl PHACES
Ben-Amitaï[36]	Retrospective	10	6	4	6.3		2	22	Isolated nasal tip IH
Bernabeu-Wittel[37]	Prospective	28					1.4	32.7	Severe IH; various loc incl PHACES
Bertrand[38]	Retrospective	35	31	4		3.5	1	120	Problematic IH; various loc incl PHACES
Betlloch-Mas[39]	Prospective	20	17	3	5.2		2	19	Complicated IH; various loc excl PHACES
Blatt[40]	Retrospective	54				4	0.1	26	Various loc incl PHACES
Buckmiller[41]	Retrospective	41	27	5	7.1		1.5	30	Problematic IH; various loc
Celik[42]	Prospective	67	31	36	7.0		1	24	Problematic IH; various loc
Chai[43]	Prospective	27	21	6	4.1		0.7	7	"Problematic" IH; various loc excl PHACES
Cheng[44]	Retrospective	10	7	3	7.8		1	23	Periorbital IH
Chik[45]	Retrospective	12	10	2	7		2	22	"Problematic" IH; various loc
Claerhout[46]	Prospective	10			6.8		2	19	Periocular IH
Corapcioğlu[47]	Prospective	12	9	3		4.5			"Problematic" IH (with resistance to corticotherapy); various loc
Cushing[48]	Retrospective	44	35	9	5.8		0.7	49.2	"Problematic" IH; various loc
Dyme[49]	Retrospective	15				3.8	1.8	8.4	"Problematic" IH; various loc
El Ezzi[50]	Retrospective	29	21	8		3.5	1.5	12	Complicated and problematic IH; various loc
El-Essawy[51]	Prospective	15	11	4	8.1				Periorbital or orbital IH
Erbay[52]	Prospective	16	13	3		3.6	−1.1	25.2	Complicated IH; various loc
Fuchsmann[53]	Retrospective	39	27	12	4.1		1	11	"Problematic" head and neck IH
Gan[30]	Retrospective	109	67	42					Various loc
Georgountzou[54]	Prospective	28	20	8		5.95	2	16	Problematic IH; various loc
Giachetti[55]	Retrospective	30					0.5	14	"Problematic" IH; various loc
de Graaf[19]	Prospective	28	21	7	8.8		2	43	"Problematic" IH; various loc incl PHACES
Haider[56]	Retrospective	17					0.7	12	Periocular IH
Harper[57]	Prospective	30	27	3	5.8				Complicated IH; various loc
Hasan[58]	Prospective	36	26	10	25.75		0.7	120	"Problematic" IH; various loc
Hassan[59]	Prospective	30	21	9	3.7		2	12	Complicated (or huge); various loc
Hermans[60]	Retrospective	20	15	5	3.5				Ulcerating IH; various loc
Hermans[29]	Prospective	174	123	51	4.8		0.9	2.9	Complicated IH; various loc
Hogeling[23]	RCT, propranolol versus placebo	19	14	5	15.5		2.1	60	"Problematic" IH; various loc
Holmes[61]	Prospective	31	23	8	3.9		1.2	9.7	Problematic IH; various loc
Hong[62]	Retrospective	45	27	18	3.5		0.5	5.5	Severe IH; head and neck IH
Hsu[63]	Retrospective	13	10	3		4	1	11	"Problematic" IH; various loc
Javia[64]	Retrospective	12	9	3	3		1	7	Laryngotracheal IH (incl PHACES)
Jian[65]	Retrospective	97	65	32	7.2		3	18	Cavernous or mixed IH
Kagami[66]	Prospective	15	12	3		2.6	1.2	3.9	Various loc
Katona[67]	Retrospective	22	17	5	3.7		1	8	Head and neck IH
Küpeli[68]	Retrospective	14	9	5		4	0.15	36	"Problematic" IH; various loc
Laforgia[69]	Prospective	23	15	8	4.0		1	13	Severe IH; various loc (incl PHACES)
Leboulanger[70]	Retrospective	14	13	1	5.2		0.7	16	Laryngotracheal (incl PHACES)
Liu[71]	Retrospective	31	22	9	4.6		0.5	21	Problematic IH
Luo[27]	Retrospective	635	431	204			0.5	36	Various loc
Lv[72]	Retrospective	37	27	10	2.8		1.5	8	Problematic head and neck IH
Lynch[73]	Prospective	44	34	10	4.3		0.9	10.8	Complicated IH; various loc (incl PHACES)
Ma[74]	Prospective	89	52	37	3.6		1	12	Various loc

TABLE 1 Continued

First Author and Reference	Study Type	Patients Treated With Propranolol, *n*	Sex, *n*		Age at Treatment Initiation, mo				Type or Localization of IH
			Female	Male	Mean	Median	Min	Max	
Mahadevan[75]	Prospective	10	7	3	2.7		2	4	Subglottic IH
Malik[25]	RCT, propranolol versus prednisolone versus propranolol+prednisolone	20	8	12	4.7		1	8	Problematic IH; various loc
Manunza[76]	Prospective	30	27	3	5.8		1.2	13.5	Complicated IH; various loc (incl PHACES)
McGee[77]	Retrospective	24	19	5		2.8	1.8	17	"Problematic" IH; various loc (incl PHACES)
McSwiney[78]	Prospective	20	15	5		5.5	1.8	50	Various loc (excl PHACES)
Meng[79]	Prospective	22	13	9	5.5		1.5	15	Facial IH
Metry[80]	Retrospective	32			4.8		0.2	24	PHACES with cervical and intracranial arterial anomalies
Missoi[81]	Retrospective	17	12	5		4.5	2.2	5.6	Periocular IH (incl PHACES)
Ozyörük[82]	Retrospective	14	9	5		4	1	16	Complicated IH; various loc
Park[83]	Retrospective	83	60	23	5.4		1	41	Problematic IH; various loc
Phillips[28]	Retrospective	188	143	45	4.0		0.2	84	"Problematic" IH; various loc (incl PHACES)
Price[9]	Retrospective	68			4.9				Various loc
Puttgen[84]	Retrospective	50	39	11	4.0		0.8	12	Symptomatic IH; various loc
Rössler[85]	Retrospective	30	21	9	4.4				"Problematic" IH; various loc
Sadykov[86]	Prospective	71	56	15	5.8		1	45	Problematic maxillofacial IH (excl PHACES)
Sagi[87]	Retrospective	99	80	19	9.4		2	54	"Problematic" IH; various loc
Saint-Jean[88]	Retrospective	33	23	10	5.2		2	16	Ulcerated IH; various loc
Sans[6]	Prospective	32	21	11	4.2				"Problematic" (severe) IH; various loc
Schiestl[89]	Retrospective	25	16	9		3.6	1.5	9.1	Problematic IH; various loc
Schupp[90]	Prospective	55	40	15	6.4		1.2	35.5	(Severe) IH; various loc
Snir[91]	Retrospective	30	22	8	5.0		1	17	Periocular IH
Sondhi[22]	OCT versus historical control	31	22	9		5	1	108	"Problematic"; various loc (excl PHACES)
Szychta[92]	Prospective	60			4.9				"Problematic"; various loc (excl PHACES)
Tan[93]	Prospective	15			2.5		0.7	8.5	Problematic IH; various loc
Vassallo[94]	Prospective	14	7	7	20.9		2	96	"Problematic" eyelid IH
Vercellino[95]	Prospective	68	49	19					Complicated IH (incl PHACES)
Weiss[96]	Retrospective	11							Parotid IH
Xiao[21]	Prospective	64	51	13		3.6	0.5	9.1	"Problematic" IH; various loc
Yuan[97]	Prospective	35	23	12	6.0		2	12	Various loc
Zaher[98]	Prospective	30	21	9	6.0		2	12	Problematic IH; various loc
Zegpi-Trueba[99]	Prospective	57	46	11	9.7		2	79	"Problematic" IH; various loc
Zvulunov[100]	Retrospective	42	37	5	28.0		7	120	IH beyond proliferation phase

excl, excluding; incl, including; loc, localizations; Max, Maximum; Min, minimum; OCT, open clinical trial; PHACES, posterior fossa brain anomalies, hemangiomas, arterial anomalies, and cardiac defects and coarctation of the aorta, eye abnormalities, and sternal abnormalities or ventral developmental defects; "Problematic" when set in quotation marks is not used in the original article and has been chosen as generic qualifier of IH type when appropriate; RCT, randomized controlled trial.

covers the full CUP population (1661 infants).

The overall population across data source types (Table 4) represents that expected of a pediatric population with IH requiring systemic therapy; the majority were females (72%–75%) presenting with severe or complicated IH (except for study 201). Treatment was initiated at a mean age of 3.4 to 7.0 months (higher in the literature due to the inclusion of patients with IH beyond the proliferative phase). The average target dose in the literature was 2.1 mg/kg per day and mean treatment duration was 7.7 months (Table 5).

The manufacturer's clinical trial patients received propranolol of 1, 2, or 3 mg/kg per day or placebo; overall, the mean propranolol treatment duration was 3.9 months (due to the assignment in study 201 of patients to 3-month or 6-month regimens[16]), representing a total exposure of 1704 patient-months (Table 5). The average dose for CUP patients was 2 mg/kg per day; mean treatment duration was 8.6 months (Table 5).

Safety Monitoring

For the manufacturer's clinical trials and the CUP, the following specific precautions were taken to monitor and minimize known risks:

- initial administration and first administration at each uptitration were carried out on-site;
- temperature, heart rate (HR), blood pressure (BP), respiratory rate, and pulmonary auscultation were measured before first administration then every hour for 4 hours after the first administration;
- glycemia was measured by pin-prick and electrocardiogram (ECG) was performed before the first administration and at 120 and 240

TABLE 2 List of Studies Identified and Selected Through Database Searches

First Author and Reference	Target Dose of Propranolol		Planned Initiation (Uptitration) Dose(s)		End of Treatment Tapering Details	Treatment Duration in Completers, mo			
	mg/kg per day	Regimen	mg/kg per day	Uptitration Regimen; Duration		*n*[a]	Mean	Median	Min	Max
Ábarzúa-Araya[26]	2	TID		—		10	6			
Al Dhaybi[31]	2–3	TID	0.5, 1, 1.5	TID; incremental increases by 0.5 mg/kg per day every 4 d		17				
Albuquerque[32]	2–4	BID/TID	0.5+	BID/TID; 0.5 mg/kg per day (D1–D7) then weekly increases		37	11		1	27
Andersen[33]	1–2	BID/TID	1	—	2 wk (half dose)	16		6.75	1.5	12
Bagazgoitia[34]	2	BID		—		71	4.7			
Balma-Mena[35]	2–3	TID	0.3, 0.6, 1.2	TID; doubled every 3 d for 2 wk		16	7.2			
Bauman[24]	2	TID		—		9	10.6			
Ben-Amitai[36]	2	BID	0.5+	TID; uptitrated over 3 d		10	9.7		5	13
Bernabeu-Wittel[37]	2	BID	0.5, 1.0, 1.5	BID; increase of 0.5 every 3 d		28	8.7		2	16
Bertrand[38]	2–3	TID	0.5, 1.0, 1.5	TID; increase of 0.5 every 4 d		35	8.9		1	13
Betlloch-Mas[39]	2	TID	—	—	1 mg/kg per day for 2 wk and 0.5 mg/kg per day for 2 wk	20	—	—	3	14
Blatt[40]	1–4	BID/TID	0.25–1	BID/TID	Yes	54				
Buckmiller[41]	2	TID	—	No uptitration	Half dose for 1 to 2 wk	32	5.5		2	10
Celik[42]	2	BID	—	—	Half dose for 2 wk	49	8.3		3	18
Chai[43]	2		0.5, 1.0	TID: 0.5 mg/kg per day then doubled every day over 3 d	Over 2 wk	27	3.83		2.75	5.75
Cheng[44]	2	BID/TID	—	No uptitration		3	7.5		2.8	9.8
Chik[45]	2	TID	0.5, 1.0	TID; doubled every day over 3 d		12			2	6
Claerhout[46]	2	BID	1	BID; to D10–D14		10	7.6		7.6	
Corapcioğlu[47]	2	TID	—	No uptitration		12		5	4	9
Cushing[48]	2–3	TID	0.5–0.7	First dose; follow-up for 3 h after first dose		44				
Dyme[49]	3	TID	—	No uptitration		15	2.8		0.2	10
El Ezzi[50]	2	TID	1, 2	TID; D1, D2		29		7.1	4	16
El-Essawy[51]	1–2	TID	0.48+	TID; gradually increased over 2 wk	Yes	15	7.67		6	12
Erbay[52]	2–3	TID	1	TID; for patients <3 kg		16			1.5	6.5
Fuchsmann[53]	2–3	TID	0.5, 1,	TID; for 2 d for each dose, then increased by 1 mg/kg per day every 2 d until final dose		39	8.5			
Gan[30]	2		0.5, 1, 1.5	1-wk uptitration starting at 0.5 mg/kg per day on D1, at 1 mg/kg per day on D2, at 1.5 mg/kg per day on D3, then target dose if no AE		109			6	12
Georgountzou[54]	2	BID	—	No uptitration		24	7.56		2.5	16
Giachetti[55]	1.5–2 (4 in 2 premature twins)	TID	1	TID; D1–D7		30			3	13
de Graaf[19]	1.8–4	BID/TID	—	BID/TID; 1 mg/kg per day increased to 2 mg/kg per day after 5 doses, to 4 mg/kg per day if inadequate response		6	8.5		4.5	17
Haider[56]	2	TID	0.5, 1, 1.5	TID; increase by 0.5 mg/kg per day every 3 d	Over 2-wk period	17				
Harper[57]	2	TID	1	TID; for 1 wk	Half-dose twice every 2 wk	30				
Hasan[58]	3	TID	—	—		36	3.36		2	7

TABLE 2 Continued

First Author and Reference	Target Dose of Propranolol		Planned Initiation (Uptitration) Dose(s)		End of Treatment Tapering Details	Treatment Duration in Completers, mo				
	mg/kg per day	Regimen	mg/kg per day	Uptitration Regimen; Duration		*n*[a]	Mean	Median	Min	Max
Hassan[59]	3	BID	1	BID; for 1 wk then increased to full dosage	Over 4 wk	30	9.4		6	14
Hermans[60]	2.0–2.5	TID	0.7–1.0	TID, increased over 3 d to target dose		20	9.1			
Hermans[29]	2.0–3.0	TID	0.7–1.0	TID, gradually increased to target dose	BID for 2 wk then QD for 1 wk	174	10.7			
Hogeling[23]	2	TID	1	TID; for 1 wk	For 2 wk (half-dose every week)	19	6.3			
Holmes[61]	3	TID	0.5, 1	TID; 0.5 mg/kg if tolerated, then 1 mg/kg, then target dose		31	2.92		0.23	13.5
Hong[62]	2	TID	0.5+	TID; uptitration of 1–2 wk		45	6.5		3	11
Hsu[63]	2–3	BID/TID	0.5, 1	BID or TID; if tolerated, dose doubled at every weekly visit		13		5.5	3	14
Javia[64]	2	TID	0.5, 1	TID; 0.5 mg/kg per day on D1, 1 mg/kg per day on D2		12	9.6		4.5	13
Jian[65]	2		1-2	At initial dose		97			6	12
Kagami[66]	2		1	TID; D1–D7	1 mg/kg per day × 2 wk, 0.5 mg/kg per day × 2 wk	15				
Katona[67]	2	TID	—	No uptitration		22			6	14
Küpeli[68]	2	BID	—	—		14			6	
Laforgia[69]	2	BID/TID		No uptitration	Over 2 mo	11	8		4	12
Leboulanger[70]	2–3	—	—	—		14			6	
Liu[71]	2	TID	—	No uptitration		31				
Luo[27]	2	BID	—	—		635	18.6		5	32
Lv[72]	2	QD	—	—		37		3	3	6
Lynch[73]	2	TID	0.5, 1	TID; 0.5 mg/kg per day (D1), 1 mg/kg per day (D2)		44	10.7		0.7	24.5
Ma[74]	0.75–1	BID	—	—		89	13.6		5	16
Mahadevan[75]	1–2	BID	—	—		10	7.7		4	11
Malik[25]	1–3	BID	—	1 mg/kg per day BID (D1), 2 mg/kg per day at D2 if well tolerated, 3 mg/kg per day if not improved at 1 mo	Over the last month	7	9.8		3	16
Manunza[76]	2	TID	1	TID; for 1 wk		30			3.5	15
McGee[77]	1–2	TID	0.5, 1	TID; 1 wk of uptitration from 1 mg/kg per day (23 infants) or 0.5 mg/kg per day (1 infant/PHACES)		24		10.5	3.5	14
McSwiney[78]	2	BID; from D4	0.5, 1	BID; 0.5 mg/kg per day (if normal exam), if no side effect discharge at 1 mg/kg per day BID for 3 d		20				
Meng[79]	1–1.5	QD	—	—		22				5
Metry[80]	1.8	BID/TID	—	—		32	12.3			
Missoi[81]	2	TID	0.5, 1	TID; 0.5 mg/kg per day for 1 wk then 1 mg/kg per day for 1 wk	For 4 wk	17		6.8	4.1	7.2
Ozyörük[82]	2	BID		No uptitration		14		6	3	12
Park[83]	2	TID	0.5, 1	TID; 1 mg/kg per day at D2, 2 mg/kg per day at D3		83	8.7		2.5	28
Phillips[28]	2	BID	1	BID; for 3 d		188	8		10	30
Price[9]	2	BID/TID	0.5, 1	BID or TID; for 3 d each	For 2 wk	68	7.9		3.5	14
Puttgen[84]	2	TID	1	TID; on D1		50				
Rössler[85]	2	BID	1	BID; on D1		30	6.5		0.6	9.8
Sadykov[86]	2	TID	1	TID; on D1		71	4.7			
Sagi[87]	2	TID	0.5	TID; D1 and D2		99	8.5		2	15
Saint Jean[88]	2–3	BID/TID	—	—		33	5.9			

TABLE 2 Continued

First Author and Reference	Target Dose of Propranolol		Planned Initiation (Uptitration) Dose(s)		End of Treatment Tapering Details	Treatment Duration in Completers, mo				
	mg/kg per day	Regimen	mg/kg per day	Uptitration Regimen; Duration		*n*[a]	Mean	Median	Min	Max
Sans[6]	2–3	BID/TID	—	No uptitration		32	6.1			
Schiestl[89]	2	TID	1	TID; on D1	1 mg for last 4 wk	25	10.5		7.5	16
Schupp[90]	2	TID	1	TID; on D1; if well tolerated, increased to target dose		55	5.8			
Snir[91]	2	BID	—	—		30	7.3		1.5	15
Sondhi[22]	2	BID	—	—	Half the dose twice at 2-wk interval	31	7		2.8	11.7
Szychta[92]	2	TID	1	TID; on D1 for age <2 y		60	10.5			
Tan[93]	1.5–2		0.5, 1	BID; 0.5 mg/kg per day on D1 then 1 mg/kg per day, then increased by 0.5 mg/kg per day until response or 2 mg/kg per day		15				
Vassallo[94]	2			—		14	2.5		1	4
Vercellino[95]	2	TID	1	TID; 1 mg/kg per day to lowest effective dose		68	6			
Weiss[96]	2	BID	—	—		11				
Xiao[21]	2	TID	—	No uptitration		64		8.5	4.5	14
Yuan[97]	1.5	QD	1	QD; for 3 mo		35			4	8
Zaher[98]	2	TID	—	—		30	6		2	14
Zegpi-Trueba[99]	2	BID	—	No uptitration		57	7.3		1	24
Zvulunov[100]	—	—	—	—		42	3.6		1	8

BID, twice daily; D, day; Max, Maximum; Min, minimum; PHACES, posterior fossa brain anomalies, hemangiomas, arterial anomalies, and cardiac defects and coarctation of the aorta, eye abnormalities, and sternal abnormalities or ventral developmental defects; QD, once per day; TID, 3 times per day; —, not specified in the original article.
[a] Number of patients used to calculate duration of treatment (if available); otherwise, total number of patients treated is presented.

min after the first administration; and

- parents were informed on safety monitoring and advised on the potential risk of and actions to be taken for hypoglycemia and bronchospasm.

For the literature, planned safety monitoring (Supplemental Appendix 4) varied and included outpatient treatment initiation[29,41,48,49,55] or hospitalization for up to 2 weeks,[27,28,45,51,65,74,79,87] especially in premature or at-risk patients. The majority included a pretreatment examination for contraindications and close follow-up monitoring. One of the 4 studies treating >100 patients presented pretreatment and monitoring details[29] and included ECG and echocardiography in the first 75 patients and later only in those with a cardiac pathology; treatment initiation at the clinic, later initiating at home if no contraindications; HR and BP monitoring 3 times/day for days 1 to 3 and after dose uptitration; fasting plasma glucose if patient <3 months old; and parent education.

Synthesis of Results

Summary of AEs

Due to differences in safety reporting for each data source type, AE percentages for the manufacturer's pooled clinical trial data (solicited reporting) cannot be easily compared with percentages for the manufacturer's CUP data (spontaneous reporting based on the known safety profile) or for literature data (a mixture of solicited and spontaneous reporting). All events are referred to as AEs (ie, adverse event or effect, according to data source and reporting methods).

In the manufacturer's clinical trials, a higher percentage of propranolol-treated patients experienced AEs (88.5%), related AEs (38.2%), and serious AEs (4.8%) compared with placebo-treated patients (67.8%, 15.3%, and 2.5%, respectively) (Table 6). There were fewer AEs leading to definitive discontinuation (including IH worsening) in propranolol-treated patients (2.5%) than in patients who received a placebo (4.2%). The CUP and literature data reflected a similar pattern in a lower percentage of patients (10%–15% experiencing what might be considered "known"/"related" AEs with propranolol and 2.4%–2.6% with events leading to propranolol discontinuation). Five of the 5862 patients in this review died (Table 6): 3 (0.2%) in the CUP, none of which were considered treatment-related (atrioventricular block and cardiac failure during sclerotherapy for esophageal varices [see below], choking on food long

TABLE 3 List of Manufacturer's Pooled Clinical Studies and CUP

Study ID and Enrollment	Design Control Type	Test (and Reference) Treatment	Study Objectives	Diagnosis Inclusion Criteria	Number of Patients by Arm	Sex and Median Age (Range)	Safety Endpoint(s)
102							
Twenty patients planned to be included (10 in each stratification group); 23 patients included (10 in group 1, 13 in group 2)	An open-label, multicenter,[4] repeated-dose study;stratified by age: group 1, aged 35–90 d inclusive at inclusion; group 2, aged 91–150 d inclusive at inclusion	Test: propranolol oral solution (Hemangiol), 3.75 mg/mL, 3 mg/kg per day at the end of titration; BID (morning and late afternoon) for 12 wk	To characterize PK of Hemangiol and propranolol metabolite (4-OH-propranolol) at steady-state in patients during treatment; to assess efficacy of Hemangiol on evolution of IH over 12 wk and to assess safety profile	Age 35–150 d; proliferating IH requiring systemic therapy; function-threatening, in certain anatomic locations that often leave permanent scars or deformity, large facial IH, smaller IH in exposed areas, severe ulceration, pedunculated IH	Entered: 23 patients (10 in group 1, 13 in group 2); completed: 22 patients (10 in group 1, 12 in group 2)	Group 1: 3 males, 7 females, 69.7 d (50–89 d); group 2: 3 males, 10 females, 128.2 d (91–152 d)	Endpoints based on the following evaluations: AEs, height, weight, head circumference, temperature, HR, BP, respiratory rate, pulmonary auscultation, liver palpation, global physical examinations, ECGs, laboratory examinations
201							
Approximately 450 patients planned to be randomized overall (100:50 per Hemangiol arm:placebo arm); 460 patients randomized overall (55:99:103:101:102; placebo:Hemangiol; 1 mg/kg per day for 3 mo, 1 mg/kg per day for 6 mo, 3 mg/kg per day for 3 mo, 3 mg/kg per day for 6 mo)	Multidose, 2-stage, adaptive, seamless phase II/III design with regimen selection at end of the first stage. Stage 1: randomized, 4 Hemangiol arms and placebo[a]; stage 2: randomized, placebo, and best regimen of Hemangiol from stage 1; primary analysis at week 24	Test: propranolol oral solution (Hemangiol) 1 or 3 mg/kg per day BID for 3 or 6 mo. Reference: placebo oral solution BID for 3 or 6 mo; total treatment duration was 6 mo	To identify appropriate dose and duration of Hemangiol treatment, demonstrate superiority over placebo on the basis of resolution of target IH at week 24. Safety profile of Hemangiol. Long-term follow-up of patients for 72 wk after study treatment discontinuation.	Aged 35–150 d, inclusive; presence of proliferating IH (target hemangioma) requiring systemic therapy present anywhere on body except diaper area; largest diameter at least 1.5 cm	Randomized and treated: 456 patients (55 in placebo group; 98, 102, 100, 101 in Hemangiol regimens 1, 2, 3, and 4). Completed (24 wk): 323 patients (19 in placebo group; 63, 88, 65, 88 in Hemangiol regimens 1, 2, 3, and 4)	131 males, 325 females, 103.9 d (35–152 d); 167 patients in 35- to 90-d group; 289 patients in >90-d group	Endpoints based on the following evaluations: AEs, height, weight, head circumference, temperature, HR, BP, respiratory rate, pulmonary auscultation, liver palpation, global physical examination, ECG measurements, laboratory examinations, two-dimensional cardiac ultrasounds, and neurodevelopment assessments
301							
Eleven patients enrolled	Open-label uncontrolled study at French centers	Test: propranolol oral solution (Hemangiol) 2 or 3 g/kg per day BID for 6 mo	Allow the use of propranolol in infants still requiring this systemic treatment after participation in study 102 or 201 (French centers); safety profile and effect on resolution of IH	Received treatment in study 102 or 201 and completed end of study visit within ≥6 mo; proliferating IH requiring systemic therapy with propranolol in investigator's opinion	*N* = 11; 2 mg/kg per day: 4 patients; 3 mg/kg per day: 7 patients	10 females, 1 male; aged 101–397 d	Endpoints based on the following evaluations: AEs, height, weight, head circumference, temperature, HR, BP, respiratory rate, pulmonary auscultation, liver palpation, global physical examination, ECG measurements, neurodevelopment evaluation
CUP							
1661	Compassionate use; open-label, noncontrolled	Hemangiol; planned doses in protocol: 1–3 mg/kg per day; median: 2.0 mg/kg per day	Allow compassionate use	Infants with proliferating IH that was life-threatening or gave rise to a functional risk, and ulcerative IH not responding to simple treatment and who could not be included in the ongoing clinical studies	NA	1227 females, 401 males (of 1628); 3.8 mo (1 d to 6.4 y)	Collection of safety data; reporting was the responsibility of the treating physician

BID, twice daily; NA, not applicable; PK, pharmacokinetics.

[a] Regimen 1: 3 mo, 1 mg/kg per day followed by 3 mo of placebo; regimen 2: 6 mo, 1 mg/kg per day; regimen 3: 3 mo, 3 mg/kg per day followed by 3 mo of placebo; regimen 4: 6 mo, 3 mg/kg per day; placebo group: 6 mo of placebo. Stratified by age (35–90 d, 91–150 d) and IH localization (facial, nonfacial).

TABLE 4 Summary of Study and Population Characteristics

	Manufacturer's Pooled Clinical Trial Data (Safety Set)[a]					
	Propranolol				Propranolol	
	1 mg/kg per day (*n* = 200)	3 mg/kg per day (*n* = 235)	All (*N* = 435)	Placebo (*N* = 55)	Literature Data (*N* = 3766)	CUP (*N* = 1661)
Number of study types included	3				83	1
RCT	1 pivotal RCT				4	
Prospective	2 open-label studies				35	Yes
Retrospective	—				44	—
Patients treated, *n*	200	235	435	55	3766	1661
Age at initiation of treatment, mo						*N* = 1628
Mean (SD)	3.39 (1.04)	3.57 (1.33)	3.49 (1.21)	3.41 (1.02)	7.0 (*n* = 56)[b]	5.6
Range	1.2–5.1	1.1–13.0	1.1–13.0	1.2–5.0	−1.1[c] to 228 (*n* = 70)	1 d–6.4 y
Sex, *n* (%)					*N* = 3407	*N* = 1628
Male	62 (31.0)	59 (25.1)	121 (27.8)	17 (30.9)	971 (28.5)	401 (24.6)
Female	138 (69.0)	176 (74.9)	314 (72.2)	38 (69.1)	2436 (71.5)	1227 (75.4)
IH characteristics	Non–high risk (studies 102, 201, 301) and high risk[100]				Various	High risk[d]

RCT, randomized controlled trial.

[a] Manufacturer's pooled clinical trial data are presented by dose of propranolol or placebo (whatever the assigned regimen) and for all patients treated with propranolol whatever the dose. Therefore, for those patients assigned to one of the two 3-mo propranolol regimens (followed by 3 mo taking placebo) data are presented within both the propranolol and placebo groups according to the period during which the event occurred. Patients in study 301 who received 2 mg/kg per day of propranolol were analyzed with the 3-mg/kg-per-day group for data described by dose and in the "all propranolol" column describing all patients treated with propranolol whatever the dose.

[b] Estimated mean age for articles presenting mean-age data (*n* = 56).

[c] Age corrected for prematurity.

[d] Seventy-two percent functional impairment, 40% severe ulceration, 16% at vital risk.

TABLE 5 Summary of Propranolol Exposure

	Manufacturer's Pooled Clinical Trial Data (Safety Set)[a]					
	Propranolol				Propranolol	
	1 mg/kg per day (*n* = 200)	3 mg/kg per day (*n* = 235)	All (*N* = 435)	Placebo (*N* = 55)	Literature Data (*N* = 3766)	CUP (*N* = 1661)
Propranolol dose, mg/kg per day						*N* = 1587
Descriptive data	Not applicable; specified dose received according to assigned treatment				Target dose	Average received
Mean	—				2.1 (*n* = 82)	2.0
Median	—				—	2.0
Range	—				0.75-4.0	0.4–4.0
Treatment duration, mo				*N* = 236 (Placebo)		*N* = 657 (CUP)
Descriptive data	Actual extent of exposure by dose of propranolol or placebo whatever regimen, and taking all propranolol[b]				Mean of mean/median (in completers)	
Mean (SD)	3.95 (1.62)	3.91 (1.45)	3.93 (1.53)	2.39 (1.30)	7.7 (*n* = 51)[c]	8.6
Median	2.90	2.90	2.90	2.75	—	7.3
Range	0.0–7.2	0.2–6.2	0.0–7.2	0.2–5.8	0.2–32.0 (*n* = 56)	0.1–36.8
Actual extent of exposure, patient-months	787.1	917.2	1704.3	562.3	—	—

[a] Manufacturer's pooled clinical trial data are presented by dose of propranolol or placebo (whatever the assigned regimen) and for all patients treated with propranolol whatever the dose. Therefore, for those patients assigned to one of the two 3-mo propranolol regimens (followed by 3 mo taking placebo), data are presented within both the propranolol and placebo groups according to the period during which the event occurred. Patients in study 301 who received 2 mg/kg per day of propranolol were analyzed with the 3-mg/kg-per-day group for data described by dose and in the "all propranolol" column describing all patients treated with propranolol whatever the dose.

[b] Note that mean exposure for the manufacturer's data for 1 and 3 mg/kg per day pooled by dose, both the 1- and 3- mg/kg-per-day doses included patients assigned to the 3- and 6-mo regimens, which is therefore reflected in the mean dose. Refer to the study for further details.[16]

[c] Estimated mean duration for articles presenting mean duration data (*n* = 51).

after treatment discontinuation, and drug ineffective in a patient with a final diagnosis of multifocal lymphangioendotheliomatosis [relationship not assessable]), and 2 (0.1%) in the literature (acute renal failure after diarrhea[58] and worsened peripheral arteriopathy with digital infarcts and severe sleep disturbance in a patient with PHACES [posterior fossa brain anomalies, hemangiomas, arterial anomalies and cardiac defects and coarctation of the aorta, eye abnormalities and sternal abnormalities or ventral developmental defects][80]; Supplemental Appendices 3 and 4).

TABLE 6 Summary of Treatment-Emergent AEs Across Selected Data Sources

	Manufacturer's Pooled Data[a]											
	Propranolol								Propranolol			
	1 mg/kg per day (*n* = 200)		3 mg/kg per day (*n* = 235)		All (*N* = 435)		Placebo (*N* = 236)		CUP[b] (*N* = 1661)		Literature Data (*N* = 3766)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Patients with at least 1 AE	173	86.5	212	90.2	385	88.5	160	67.8	161	9.7	578[c]	15.3
Patients with at least 1 related AE[d]	82	41.0	84	35.7	166	38.2	36	15.3	—	—	—	—
Patients with at least 1 AE leading to definitive study drug discontinuation	4	2.0	7	3.0	11	2.5	10	4.2	43	2.6	89	2.4
Patients with at least 1 serious AE[e]	7	3.5	14	6.0	21	4.8	6	2.5	40	2.4	—	—
Deaths	—	—	—	—	—	—	—	—	3	0.2	2	0.1

[a] Manufacturer's pooled clinical trial data: AEs in the 3-mg/kg-per-day arm included those that occurred during the uptitration period; "related" indicates events with a relationship to the study drug other than "Not Suspected"; patients in study 301 who received 2 mg/kg per day of propranolol were analyzed with the 3-mg/kg-per-day group for data described by dose and in the "all propranolol" column describing all patients treated with propranolol whatever the dose. All AEs presented are treatment-emergent AEs. Data are presented by dose of propranolol or placebo (whatever the assigned regimen) and for all patients treated with propranolol whatever the dose. Therefore, for those patients assigned to one of the two 3-mo propranolol regimens (followed by 3 mo taking placebo), data are presented within both the propranolol and placebo groups according to the period during which the event occurred.
[b] CUP data were reported by case; 1 patient could present ≥1 case. For the purpose of this review, the worst-case scenario has been taken (ie, 1 case = 1 patient).
[c] A total of 578 patients reported to have experienced at least 1 AE and 1399 patients reported to have experienced individual AEs by preferred term (see Supplemental Appendices 4 and 5).
[d] Not determined for CUP or literature data.
[e] Not determined for literature data.

In the manufacturer's clinical trials, the most frequently reported AEs in propranolol-treated patients (≥2%; Table 7) that were reported in at least a threefold higher percentage than placebo were either known nonserious side effects of propranolol (diarrhea, peripheral coldness, sleep disorder, moderate insomnia, somnolence, hypersomnia, and agitation) or nonspecific events frequently occurring in young infants (including constipation, vaccination complication, conjunctivitis, gastroenteritis, diaper dermatitis, infantile colic, flatulence, and influenza). The most common AEs considered related to treatment were peripheral coldness, diarrhea, moderate insomnia, sleep disorder, and nightmares. AEs reported in <2% of patients are presented in Supplemental Appendix 5. In the CUP, 1 AE was reported in ≥2% of patients (bronchiolitis [2.3%], followed by nightmares (1.1%), sleep disorder (0.8%), agitation (0.5%), and decreased appetite (0.5%) (AEs reported in <2% of patients are presented in Supplemental Appendix 5). In the literature, the most frequently reported AEs (≥2%) were decreased HR (4.4%) and BP (4.1%, of which 54% were reported in a single article[74]), hypotension (3.1%, of which 42% were reported in a single article[84]), sleep disorder (2.9%), and peripheral coldness (2.7%; AEs reported in <2% of patients are presented in Supplemental Appendix 5).

AEs of Interest: Cardiovascular Disorders

During the manufacturer's clinical trials and the CUP, 2 cases of atrioventricular block were reported (both serious; 1 with fatal acute heart failure) (Table 8). In 1 clinical trial patient, second-degree Mobitz-type 1 atrioventricular block occurred 240 minutes after the first dose (0.5 mg/kg), which resolved spontaneously after stopping treatment. Further investigation showed a probable preexisting cardiologic disease (intermittent atrioventricular block). In one 5-month-old CUP patient treated at 2 mg/kg per day (after uptitration) for 13 days, third-degree atrioventricular block and fatal acute cardiac failure occurred during sclerotherapy of esophageal varices due to biliary atresia, after the last injection of lauromacrogol 400, 2% diluted. There were no reports of atrioventricular block in the literature.

During the manufacturer's clinical trials, 2 cases of bradycardia were reported. One 3-month-old premature patient, with several comorbidities, had an HR of 105 beats per minute in the context of enterocolitis on day 6 of treatment at 1 mg/kg per day, which resolved with corrective treatment. The other patient had mild nonsymptomatic bradycardia (99 beats per minute) after 24 weeks of treatment at 3 mg/kg per day.

During the CUP, 3 cases of bradycardia were reported. A 4-month-old patient treated with 2 mg/kg per day (after uptitration) experienced asymptomatic bradycardia and sinus arrest discovered during ECG and Holter monitoring on day 7, which resolved after stopping treatment. In a 9-month-old patient, 6 months after initiation of treatment, severe bradycardia related to hypoglycemia

TABLE 7 Manufacturer's Pooled Clinical Trial Data: Summary of AEs by Preferred Term Reported in ≥2% of Patients in Any Propranolol Group

	Propranolol[a,b]							
	1 mg/kg per day (*n* = 200)		3 mg/kg per day (*n* = 235)		All (*N* = 435)		Placebo[b] (*N* = 236)	
	n	%	*n*	%	*n*	%	*n*	%
Patients with at least 1 AE	173	86.5	212	90.2	385	88.5	160	67.8
Preferred term								
Nasopharyngitis	41	20.5	69	29.4	110	25.3	37	15.7
Pyrexia	44	22.0	53	22.6	97	22.3	19	8.1
Diarrhea	29	14.5	53	22.6	82	18.9	9	3.8
Teething	36	18.0	32	13.6	68	15.6	24	10.2
Cough	28	14.0	28	11.9	56	12.9	17	7.2
Vomiting	24	12.0	26	11.1	50	11.5	10	4.2
URTI	17	8.5	28	11.9	45	10.3	19	8.1
Bronchitis	11	5.5	30	12.8	41	9.4	10	4.2
Peripheral coldness	18	9.0	15	6.4	33	7.6	1	0.4
Rhinitis	21	10.5	11	4.7	32	7.4	11	4.7
Vaccination complication	16	8.0	16	6.8	32	7.4	2	0.8
Constipation	14	7.0	15	6.4	29	6.7	3	1.3
Bronchiolitis	11	5.5	16	6.8	27	6.2	10	4.2
Toothache	6	3.0	21	8.9	27	6.2	7	3.0
Conjunctivitis	11	5.5	15	6.4	26	6.0	3	1.3
Sleep disorder	17	8.5	9	3.8	26	6.0	3	1.3
Gastroenteritis	7	3.5	18	7.7	25	5.7	4	1.7
Middle insomnia	10	5.0	14	6.0	24	5.5	4	1.7
Diaper dermatitis	9	4.5	12	5.1	21	4.8	3	1.3
Nightmare	5	2.5	15	6.4	20	4.6	5	2.1
Ear infection	10	5.0	9	3.8	19	4.4	8	3.4
Decreased appetite	8	4.0	9	3.8	17	3.9	2	0.8
Eczema	10	5.0	5	2.1	15	3.4	3	1.3
Nasal congestion	8	4.0	7	3.0	15	3.4	3	1.3
Irritability	11	5.5	3	1.3	14	3.2	3	1.3
Infantile colic	6	3.0	8	3.4	14	3.2	1	0.4
Rhinorrhea	5	2.5	8	3.4	13	3.0	9	3.8
Flatulence	8	4.0	5	2.1	13	3.0	2	0.8
Rash	5	2.5	7	3.0	12	2.8	4	1.7
Somnolence	10	5.0	2	0.9	12	2.8	1	0.4
Restlessness	8	4.0	3	1.3	11	2.5	3	1.3
Influenza	4	2.0	7	3.0	11	2.5	2	0.8
GERD	4	2.0	7	3.0	11	2.5	1	0.4
Hypersomnia	6	3.0	5	2.1	11	2.5	1	0.4
Abdominal pain	5	2.5	5	2.1	10	2.3	1	0.4
Agitation	7	3.5	3	1.3	10	2.3		—
Insomnia	3	1.5	6	2.6	9	2.1	5	2.1
Gingival pain	2	1.0	7	3.0	9	2.1	4	1.7
Pharyngitis	5	2.5	4	1.7	9	2.1	4	1.7
Viral URTI	5	2.5	4	1.7	9	2.1	2	0.8
Viral infection	5	2.5	4	1.7	9	2.1		—
Frequent bowel movements	3	1.5	5	2.1	8	1.8	2	0.8
Erythema	3	1.5	5	2.1	8	1.8	1	0.4
Regurgitation	5	2.5	1	0.4	6	1.4	5	2.1
Crying	4	2.0	2	0.9	6	1.4		—
Viral respiratory tract infection	4	2.0	1	0.4	5	1.1	2	0.8

AEs are presented by frequency in the overall propranolol group. GERD, gastroesophageal reflux disease; URTI, upper respiratory tract infection.

[a] AEs in the 3-mg/kg-per-day arm included those that occurred during the uptitration period; patients in study 301 who received 2 mg/kg per day of propranolol were analyzed with the 3-mg/kg-per-day group for data described by dose and in the "all propranolol" column describing all patients treated with propranolol whatever the dose. All AEs presented are treatment-emergent AEs.

[b] Data are presented by dose of propranolol or placebo (whatever the assigned regimen) and for all patients treated with propranolol whatever the dose. Therefore, for those patients assigned to one of the two 3-mo propranolol regimens (followed by 3 mo taking placebo), data are presented within both the propranolol and placebo groups according to the period during which the event occurred.

occurred during a period of fasting; treatment was discontinued. Finally, a premature 1-month-old (corrected age) patient treated with 2 mg/kg per day experienced bradycardia with malaise on day 2, which resolved after temporarily stopping treatment for 1 day.

In the literature, 53 patients experienced bradycardia. Where time to event was presented, this was largely within <1 week of

TABLE 8 Summary of Treatment-Emergent AEs or Adverse Drug Reactions Identified as Risks With Propranolol, by Data Source and Preferred Term

	Manufacturer's Pooled Data[a]											
	Propranolol								Propranolol			
	1 mg/kg per day (*n* = 200)		3 mg/kg per day (*n* = 235)		All (*N* = 435)		Placebo (*N* = 236)		CUP (*N* = 1661)		Literature Data (*N* = 3766)	
Cardiovascular disorders												
Hypotension	3	1.5	3	1.3	6	1.4	1	0.4	4	0.2	118	3.1
Bradycardia	1	0.5	1	0.4	2	0.5	—	—	3	0.2	53	1.4
Bundle branch block, right	1	0.5	1	0.4	2	0.5	—	—	—	—	—	—
Atrioventricular block	1[b]	0.5	—	—	1	0.2	—	—	1[c]	0.1	—	—
Cardiac failure	—	—	—	—	—	—	—	—	1	0.1	—	—
Sinus arrest	—	—	—	—	—	—	—	—	1	0.1	—	—
Investigations												
BP decreased	—	—	—	—	—	—	—	—	—	—	156	4.1
HR decreased	—	—	—	—	—	—	—	—	—	—	166	4.4[d]
Respiratory disorders												
Bronchiolitis	11	5.5	16	6.8	27	6.2	10	4.2	38	2.3	10	0.3
Bronchitis	11	5.5	30	12.8	41	9.4	10	4.2	7	0.4	8	0.2
Bronchospasm	—	—	2	0.9	2	0.5	2	0.8	6	0.4	11	0.3
Bronchial hyperreactivity	—	—	1	0.4	1	0.2	—	—	—	—	8	0.2
Metabolic and nutritional disorders												
Hypoglycemia	1	0.5	1	0.4	2	0.5	—	—	7	0.4	24	0.6
Hypoglycemic seizure	—	—	—	—	—	—	—	—	2	0.1	2	0.1

[a] Manufacturer's pooled clinical trial data: AEs in the 3-mg/kg-per-day arm included those that occurred during the uptitration period; patients in study 301 who received 2 mg/kg per day of propranolol were analyzed with the 3-mg/kg-per-day group for data described by dose and in the "all propranolol" column describing all patients treated with propranolol whatever the dose. All AEs presented are treatment-emergent AEs. Data are presented by dose of propranolol or placebo (whatever the assigned regimen) and for all patients treated with propranolol whatever the dose. Therefore, for those patients assigned to one of the two 3-mo propranolol regimens (followed by 3 mo taking placebo), data are presented within both the propranolol and placebo groups according to the period during which the event occurred.

[b] Second-degree atrioventricular block.

[c] Full atrioventricular block.

[d] Vital sign events not reported as an AE/adverse drug reaction by the authors of literature data (eg, BP decreased) were captured as AEs as a conservative approach for the purpose of this review (see Supplemental Appendix 1).

treatment initiation. Of the 32 events with outcome details, all resolved; 1 specified resolution was after no change in treatment, 8 after dose adjustments/temporary discontinuation (the majority were retitrated to the planned dose), and 12 after early discontinuation of treatment.[27] Bradycardia was reported in ≥5% of patients per article in 7 articles[47,49,50,71,81,84,89]; all 33 events were considered mild/not clinically significant, transient, or asymptomatic. Dyme et al[49] observed a significant reduction in HR within 1 hour of propranolol administration (nonsignificant variation observed up to 5 hours). In some cases, dose titration or in-patient observation was prolonged.[83,89]

During the manufacturer's clinical trials, asymptomatic hypotension was reported in 7 patients (4 during uptitration, 3 after uptitration; 1 with placebo, 3 at 1 mg/kg per day, and 3 at 3 mg/kg per day). All were reported within 12 weeks of treatment initiation and resolved without change in treatment.

During the CUP, hypotension was reported in 4 patients. In 2 cases, an asymptomatic decrease in BP occurred at titration to 2 mg/kg per day, leading to temporary discontinuation of propranolol or a dose decrease, which was later successfully restarted/increased. The 2 remaining cases, both nonserious and reported at 2 mg/kg per day, concerned 2 patients who experienced pallor, hypotonia, and/or vomiting; the propranolol dose was decreased to 1 mg/kg per day in 1 patient. All 4 CUP events resolved or were resolving.

In the literature, 118 patients experienced hypotension; the majority were asymptomatic. Where time to event was presented, this ranged from soon after the first dose to within 2 months of initiation. Of the 29 events with outcome details, 28 resolved (1 improved); of the 103 events with action details, 75 required no change in treatment, 25 led to dose adjustment or temporary discontinuation of propranolol, and 3 led to permanent discontinuation.[37,94] Hypotension was reported in ≥5% of patients per article in 14 articles[19,31,37,38,45,50,54,57,71,73,84,89,93,94]; 104 of 107 events were considered transient or asymptomatic. Of the remaining 3 events, 1 was symptomatic with cold extremities for which the dose was maintained at <2 mg/kg per day[19] and 1 event was significant persistent hypotension on day 1 of treatment in a premature child and propranolol was temporarily discontinued[31]; details were not specified for the other case, although treatment was definitively

discontinued after 2 months.[94] In addition, there were a further 3 symptomatic cases,[29,37,40] one of which was considered life-threatening by the authors but resolved after temporary discontinuation followed by dose reduction.[40]

Respiratory Disorders

During the manufacturer's clinical trials, there were 4 cases of bronchospasm. One case was during the first few weeks (with 2 mg/kg per day, during uptitration), which resolved with corrective treatment and no change in dose; 1 case was >2 months after treatment initiation (with 3 mg/kg per day), which resolved after temporary discontinuation of propranolol and corrective treatment. The other 2 cases were with placebo. There was 1 case of bronchial hyperreactivity.

During the CUP, 6 cases of bronchospasm were reported. All 6 cases were serious; where dates were available, none occurred at treatment initiation, 4 led to permanent discontinuation of propranolol, and 2 led to temporary discontinuation. In addition, there were 12 serious cases of bronchiolitis considered as "bronchial hyperreactivity reactions," including 4 associated with respiratory distress, 1 with circulatory shock and respiratory arrest (propranolol not discontinued at start of bronchiolitis episode, 3 weeks earlier), and 1 with asthma.

In the literature, there were 11 cases of bronchospasm and 8 cases of bronchial hyperreactivity. All 8 bronchial hyperreactivity reactions occurred soon after the first dose and approximately half of all cases were associated with respiratory infection. Of the 12 cases with resolution details, all resolved. Nine cases (6 bronchial hyperreactivity) led to permanent discontinuation of treatment[19,46,65,69]; in 3 cases, propranolol was temporarily discontinued; and in 4 cases, no measures were taken regarding propranolol dosing (only concomitant treatment or symptomatic management). Bronchospasm or bronchial hyperreactivity was reported in ≥5% of patients per article in 6 articles.[19,46,55,65,68,82] The 3 cases of bronchial hyperreactivity in de Graaf et al[19] were all associated with a viral infection and resolved after discontinuation of propranolol, which was restarted in 2 patients; the 5 cases in Jian et al[65] had no evidence of viral infection; symptoms resolved spontaneously within 3 to 5 minutes without treatment and propranolol was discontinued. Five of the 8 cases of bronchospasm were detailed as occurring in the context of a viral infection.[46,55,68]

Metabolic and Nutritional Disorders

During the manufacturer's clinical trials, there were 2 cases of hypoglycemia. Two patients had asymptomatic hypoglycemia during uptitration (one had concurrent gastroenteritis with vomiting, diarrhea, and poor feeding). Both recovered within 1 day without a change in dose.

During the CUP, there were 7 cases of hypoglycemia and 2 cases of hypoglycemic seizure. Four serious cases (including 2 hypoglycemic seizures) occurred when propranolol had not been administered according to protocol (not temporarily discontinued during an infectious episode [diarrhea/vomiting] or low food intake and/or fasting); in 1 case, the parents gave the dose twice by mistake. Two of these serious cases led to definitive discontinuation of propranolol (one with bradycardia [treatment had not been discontinued during fasting] and one not related to infection or fasting).

In the literature there were 24 cases of hypoglycemia and 2 cases of hypoglycemic seizure. Where time to event was presented (16 events), this time ranged from soon after the first dose to several months after initiation. Of the 14 events with resolution details, all resolved, and of the 16 events with action details, 1 led to permanent discontinuation of treatment[73] and 9 events led to dose adjustment or temporary discontinuation of treatment. Hypoglycemia was reported in ≥5% of patients per article in 4 articles[19,24,25,73]; 5 of the 7 cases concerned were considered asymptomatic or mild and the 2 reported by de Graaf et al[19] were symptomatic (reduced/unresponsiveness and nausea), leading to a temporary dose reduction and intake of cornstarch yogurt at bedtime in 1 case. One case of hypoglycemic seizure was related to overdose[40] and the other was associated with reduced oral intake due to infection.[62]

Subgroup Analysis

Subgroup analyses were not performed due to the variability in data collection and presentation and the difficulties associated with comparing data from the 3 different source types.

DISCUSSION

As far as we are aware, this is the largest systematic review of the safety of oral propranolol in IH, covering 5862 patients with IH requiring systemic therapy. An assessment of the incidence of side effects in the literature presents a challenge. By far the largest and most coherent set of data are presented in the clinical trials and CUP conducted by the manufacturer of the pediatric oral formulation (2096 patients). Combined with data on 3766 patients in the literature, the safety profile in this sample of nearly 6000 patients confirms that the use of oral propranolol in the treatment of IH has a similar profile to that observed in cardiologic indications in the pediatric population. The most common propranolol-related events (eg, sleep disorders, diarrhea, peripheral coldness, agitation)

are nonserious, transient, and manageable; serious risks in certain cases can be avoided with appropriate screening and exclusion and in others can be minimized and managed with appropriate monitoring, caregiver education, and discontinuation of propranolol when necessary.

Consensus recommendations for pretreatment screening include collection of cardiovascular and pulmonary history and clinical examination to identify patients at risk of heart block, arrhythmia, or pulmonary abnormalities/reactive airway diseases.[7,10] Routine echocardiography and ECG are not considered necessary unless there are abnormal clinical findings.[10,78,84,102–104] In the manufactuer's pivotal study, a mild increase in PR interval was observed and there was no clinically significant QTc prolongation.[16] As expected, a mean decrease in HR occurred, with a maximum mean decrease of approximately −7 beats per minute 1 hour after propranolol administration at each titration step.[16] Of ∼1200 monitoring sessions during the 4 hours postdose in the manufacturer's clinical trials, only 2 confirmed cases of bradycardia were reported. During the CUP there were 3 events of bradycardia. The majority of bradycardia events reported in the literature were mild, transient, and not clinically significant and resolved after dose adjustment or temporary discontinuation. Most hypotension events were transient or asymptomatic and did not require a change in propranolol dose; some required adjustment of propranolol dose or temporary discontinuation, but few required permanent discontinuation. The higher occurrence of decreased HR and/or BP and hypotension in the literature is probably due to the conservative AE coding methods used in this review. It is currently considered sufficient to monitor BP and HR (without ECG) at least hourly for at least 2 hours after the first dose and at each dose increase,[7,10,17,18] which is also justified by propranolol's pharmacokinetic characteristics in this population (T_{max} of 2 hours; Supplemental Appendix 2, study 102 synopsis). In the manufacturer's clinical trials, blood glucose monitoring on dose initiation days and dose increase did not give cause for concern. Hypoglycemia events often occurred during concurrent infection and/or fasting and can therefore be minimized with education of caregivers on the importance of administering propranolol during or right after a feeding and temporary withdrawal of treatment during fasting or vomiting. Bronchospasm and bronchial hyperreactivity reactions, often related to respiratory tract infections, in many cases required either temporary or permanent discontinuation of propranolol. Due to the potential seriousness of the event, recommendations are to discontinue propranolol upon such signs.

One of the main limitations of this review is the wide range of methods used in the included literature data sources regarding both study design and the monitoring, collection, and reporting of safety data. This fact could, however, be considered beneficial in capturing as much safety information as possible.[105] Conversely, some articles presented low sample sizes and some safety data will not have been captured (studies of <10 patients and non-English articles). Confounding factors in the literature included previous and concomitant treatment, age at treatment initiation, variability across articles in classification of AEs, underreporting of AEs, and our conservative coding of vital sign information. This safety review will be indirectly affected by publication bias in favor of articles reporting positive efficacy results, and the most reliable sources (manufacturer's pooled clinical trial and CUP data) were both funded by the marketing authorization holder. On the other hand, long-term neurologic effects are still unclear and future updates of this safety database may allow the identification of possible delayed side effects.

CONCLUSIONS

No unexpected side effects were detected from this review. Oral propranolol treatment at a dose of up to 3 mg/kg per day, taken 2 or 3 times daily, for an average of 6 months (and up to 36 months) appears to be well tolerated, if appropriate pretreatment assessments and within-treatment monitoring are performed to exclude patients with contraindications and to minimize rare but potentially severe well-known side effects during treatment (bradycardia, hypotension, bronchospasm, hypoglycemia).

The results of this review provide extensive data on the safety of oral propranolol in pediatric patients with IH and will assist health care providers in understanding the pretreatment assessments required and within-treatment monitoring necessary when treating patients with IH. This review also contributes to the overall safety profile of oral propranolol in pediatric patients, which has previously been less well defined than for adults.

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ABBREVIATIONS

AE: adverse event or effect
BP: blood pressure
CUP: Compassionate Use Program
ECG: electrocardiogram
HR: heart rate
IH: infantile hemangioma

of the manufacturer's pivotal clinical study and pooled clinical data, Ms Ortis was involved in study management and data monitoring and collection and review of the manufacturer's CUP; Drs Montagne and Lafon supervised writing of the review protocol, designed the data collection form, coded the adverse events reported in the literature, performed the safety literature review for this article, and supervised the data interpretation and report writing for the manufacturer's pivotal clinical study; Dr Delarue conceptualized this review, conceptualized and designed the manufacturer's pivotal clinical study, performed medical study management and data review and interpretation of the manufacturer's pivotal clinical study, and performed data review and interpretation of the manufacturer's CUP; Dr Voisard conceptualized and designed and participated in data interpretation for the manufacturer's pivotal clinical study and designed the manufacturer's CUP; and all authors reviewed and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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