

Title: Knowledge of community pharmacists on infantile hemangioma: gaps and lack confidence to deliver propranolol still need to be filled

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ABSTRACT (199 words)

Aim: To evaluate the knowledge, practices and self-confidence of community pharmacists, pharmacy technicians and pharmacy students about infantile haemangioma (IH) and propranolol treatment.

Method: A national survey was conducted in France from May 2022 to October 2022. A 42-item online questionnaire was used to assess pharmacists' knowledge of the epidemiology, clinical features and management of IH and propranolol treatment.

Results: The survey included 255 participants. The mean age was 34.9 years (± 9.0); 225 (88%) were women. In all, 193 (76%) practiced in urban pharmacies. Altogether, 83 participants (33%) had delivered oral propranolol solution for IH in the last six months. Participants' median score for self-confidence regarding propranolol dispensing was five (interquartile range, 2.5-6) on a scale of 1 to 10. Overall, 96 (38%) had more than 50% correct answers on the questionnaire. Multinomial regression models showed high scores on the questionnaire associated with high self-confidence when delivering oral propranolol solution, low number of years since graduation and having already delivered propranolol treatment.

Conclusion: This study highlights a lack of knowledge of IH and modalities of propranolol treatment by community pharmacists and slight self-confidence when delivering propranolol. Greater cooperation between healthcare professionals could improve the proper use of medicine.

Keywords: community pharmacists, infantile haemangioma, knowledge, propranolol, survey

KEY RESULTS (70 words)

- Propranolol, used for managing complicated IH, is delivered by community pharmacies.
- This survey found that community pharmacists, pharmacy technicians and pharmacy students lack knowledge of IH and modalities of propranolol and have only slight self-confidence when delivering propranolol.
- Beyond continued education and information dedicated to pharmacists that could be proposed, there is a need for greater cooperation between healthcare professionals to improve the proper use of medicine.

INTRODUCTION

Infantile haemangioma (IH) is the most common non-malignant vascular tumour of infancy and affects 2-10% of infants under 1 year of age.^{1,2} It is more common in girls than boys and premature than term babies.² IH is usually not present at birth and is characterised by a rapid proliferation of endothelial cells and vascular channels in the first days or first weeks of life. A precursor lesion such as telangiectatic erythema or anaemic skin may be visible at birth.³ The diagnosis is usually made during the clinical examination. It can be classified according to the depth of skin involvement, such as superficial, deep or mixed, and the morphologic aspect, such as focal, multifocal or segmental.¹ Rarely visceral locations may be associated.⁴ Most of patients are asymptomatic, except with ulceration, which is the most common complication.^{3,5} Other complications can occur and include amblyopia for peri-orbital IH, cosmetic disfigurement for facial IH or airway obstruction for perioral or laryngeal IH.⁴ IH is a benign lesion with a slow involution over years and therefore, in most cases, does not require treatment.⁶ Early interventions are required for complicated IHs, with a functional or vital risk.⁴ Oral propranolol in the form of a dedicated specialty for the paediatric population. It has been approved since 2014 by the US Food and Drug Administration and the European Medicines Agency, under the Paediatric Use Marketing Authorisations. is widely used as first-line treatment for complicated IHs.^{6,7} Treatment is usually well tolerated. Adverse events are rare and can include hypoglycaemia, hypotension, peripheral cyanosis and bronchospasm.⁸

Practices in prescribing oral propranolol were heterogeneous, linked to personal experience with the treatment and heterogeneity of care organisation depending on the country.⁹ However, the delivery of propranolol for IH is similar across countries in Europe and the United States and is delivered by a community pharmacy, including community pharmacists, pharmacy technicians

or pharmacy students, after the first administration in the hospital. Therefore, pharmacists have a key role in the care pathway for children receiving propranolol for IH. They analyse by analysing the prescription, such as checking for the absence of contraindications, and giving give information to parents for its use, such as explaining the dosage, modalities and time of administration, potential adverse events and how to manage them. Pharmacists can contribute to better parent adherence with the treatment. Thus, we need a basic understanding of the disease and its management by these health professionals.

The aim of this study was to assess the level of knowledge of community pharmacists regarding IH and propranolol treatment.

METHODS

Study design and setting

This was a prospective, questionnaire-based observational study performed from 23 May 2022 to 22 October 2022.

Participants and survey administration

The study population was professionals delivering treatment in community pharmacies and included pharmacists, pharmacy technicians and pharmacy students, who are allowed to dispense medication from the third year of study in community pharmacies. The questionnaire was disseminated by fax to a sample of 200 French community pharmacies in about 20 000 pharmacies,¹⁰ and on a social media platform via pharmacist associations with more than two reminders sent.

Questionnaire

The questionnaire was developed by a panel of six experts: two paediatric, three pharmacists and one methodologist/statistician. It was tested with three community pharmacists. The questionnaire contained four parts and 42 items. Part one included questions on demographic data such as age, sex, occupation, year of graduation, rural area - less than 2000 residents vs urban area - greater than or equal to 2000 residents,¹¹ and questions about the number of times the respondent had delivered propranolol for IH in the last six months and the respondent's confidence when delivering propranolol for IH. Part two included 12 closed questions (yes/no/I don't know) on the epidemiology and clinical aspects of IH. Part three included three clinical vignettes and 14 closed questions on the indications, modalities of prescription and administration of propranolol for IH. Finally, part four included 12 closed questions on adverse events of propranolol and their management at the pharmacy. Closed questions included correct and incorrect statements. The questionnaire was completed online by using Google Forms and was anonymous. Answers were mandatory for all questions and therefore no data were missing. Before answering the questionnaire, participants were asked to not use resources so that we could evaluate their knowledge and not their ability to find the information among available resources.

Endpoints

The binary endpoint of the study, defined before analysing the data, was the proportion of participants with more than 50% correct answers to the questionnaire. Each correct answer equalled 1 point and a wrong answer, or I don't know answer equalled 0. The total score was 42. The score was classified in quartiles labelled very poor knowledge, poor knowledge, good knowledge and very good knowledge. Characteristics of participants associated with the score

quartile were assessed. Finally, we estimated the self-assessment of pharmacists' confidence when delivering propranolol for IH to assess association between participants self-rated confidence and scores obtained from the questionnaire.¹²

Statistical analysis

Continuous variables are described with mean and standard deviation (SD) or median and interquartile range (IQR) for quantitative variables with skewed distribution. Categorical variables are summarised with number and percentages. We used multinomial regression to calculate odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) for the association between characteristics of participants and the score quartile, that is, the quartile of correct answers to the questionnaire. The reference category was the group with the lowest proportion of correct answers to the questionnaire: very poor knowledge. We aimed to describe the association between the score quartile and the following characteristics of participants: sex, number of years since graduation, occupation - pharmacist/pharmacy technician/pharmacy student, location of the pharmacy - rural/urban, and already delivered treatment - yes/no. Other endpoints included self-assessment of participants' confidence when delivering propranolol for IH on a visual analog scale from 0 to 10, with 0 being not confident at all and 10 very confident. All statistical analyses were performed with R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided $p < 0.05$ was considered statistically significant. The geographic map was created using the online open-source Khartis software (SciencesPo, Atelier de Cartographie, Paris, France).

RESULTS

Characteristics of the study participants

A total of 255 (88.2% female) participants were included from 79 counties in France (Figure 1, Table 1). Their mean age was 34.9 years (± 9.0). Overall, 177 (69.4%) were pharmacists, 65 (25.5%) pharmacy technicians and 13 (5.1%) pharmacy students. Mostly urban pharmacies were included (193 participants, 75.7%). No duplicate responses were identified in the sociodemographic data summarised in Table 1.

Self-confidence in delivering propranolol for IH

A total of 83 participants (32.5%) had already dispensed propranolol for IH in the last six months with a median of one time (range 0-20). The median confidence score regarding delivering propranolol for IH was 5.0 (IQR 2.5-6.0) on a 10-point scale.

Participants with more than 50% correct answers to the questionnaire

Altogether, 96 participants (37.6%) had more than 50% correct answers (Table 2). The median score was 18 (IQR 11-25). The proportion of correct answers was lower for indications, modalities of prescription and administration of propranolol for IH.

The findings for the association of pharmacist characteristics and questionnaire score are in Tables 3 and 4. A high score on the questionnaire was associated with a low number of years since graduation (OR 0.94, 95% CI 0.89-0.99) for very good knowledge as compared with very poor knowledge. A high score was associated with high self-confidence when delivering this treatment for IH. The odds of a high score increased with increasing self-confidence in delivering treatment (OR 1.51, 95% CI 1.25-1.82) for very good knowledge as compared with very poor knowledge. Similarly, a high score was associated with having already delivered the treatment (OR 4.02, 95% CI 1.63-9.88; OR 7.98, 95% CI 3.03-21.03) for good knowledge and

very good knowledge, respectively, as compared with very poor knowledge. When excluding pharmacy technicians and pharmacy students (post-hoc analysis) and analysing data for only pharmacists (n=177), results were similar (Tables S1 and S2).

Knowledge of epidemiology and clinical aspects of IH (Table S3)

For Part 2, only 112 participants (43.9%) answered that IH is not a rare condition. Regarding the pathophysiology of IH, most participants answered “I don’t know” to “IH is a genetic disease”, “IH is secondary to a treatment received by the mother during pregnancy” and “IH is secondary to a maternal viral infection during pregnancy”.

Knowledge of modalities of propranolol for IH

One hundred and twenty-three participants (48.2%) correctly indicated that propranolol was the first-line treatment for complicated infantile haemangiomas. However, 113 participants (44.3%) indicated that the propranolol is indicated for all infantile haemangiomas, which is incorrect, propranolol is indicated only for complicated IH. Duration and modalities of propranolol administration were poorly known by participants (Table S3): 44 (17.3%) correctly answered that treatment is given once a day. For 20% (n=54) of participants, they thought that the treatment is given before a meal. Finally, 61% (n=155) indicated that they did not know if propranolol could be mixed with a small amount of fruit juice or milk to facilitate administration.

Knowledge of adverse events

Regarding potential adverse events 112 (43.9%), 120 (47.1%), 90 (35.3%) and 177 (69.4%) of the participants reported hypoglycaemia, sleep disturbances, diarrhoea and hypotension, respectively (43.9%, 47.1%, 35.3% and 69.4%, respectively). For 28 (11.0%) participants, skin infections are a potential adverse event of propranolol, which is incorrect, and 172 (67.5%) participants answered that they did not know. A total of 139 (54.5%), 167 (65.5%) and 193

(75.7%) participants reported an interruption of the treatment and rapid physician appointment in case of bronchiolitis, repeated vomiting and loss of consciousness, respectively.

DISCUSSION

This study is the first to evaluate by questionnaire the knowledge community pharmacists have of IH and its management. Overall, 37.6% had more than half correct answers on the questionnaire, which was consistent with the slight self-confidence reported when delivering propranolol as treatment. Indeed, we highlighted a mistrust about IH and its pathophysiology and about the administration of oral propranolol and management of adverse events. In our study, scores for questions regarding the administration and management of adverse events with oral propranolol were low, despite this being the core professional practice of pharmacists and that propranolol is delivered for other conditions. Factors associated with better knowledge were having already delivered the treatment and increased self-confidence when delivering the treatment as well as recent graduation. No differences were found between pharmacists, pharmacy technicians and pharmacy students.

Community pharmacists have multiple roles in the care of patients and these could be complementary to the roles of primary care doctors who can refer patients with IH for management and monitor/renew the prescription of oral propranolol. First, they are at the forefront of healthcare and are easily accessible to patients and therefore are often solicited for advice on skin conditions.^{13,14} In dermatology, pharmacists agree that they play an important role in managing skin problems,¹³ and are confident in advising patients with dermatological complaints.^{15,16} For IH, a physician rapid appointment is required, and community pharmacists could be solicited by parents. Although IH is a common skin disease in infants, knowledge about

this condition is necessary to properly refer parents to a specialist healthcare professional, such as a primary care doctor, paediatrician or dermatologist,¹⁷ but we found this knowledge limited. However, we highlighted better scores for recent graduates. Indeed, common skin diseases are included in pharmacy studies, which could explain these better scores. Thus, continuing education programs focused on common dermatoses could be offered to practicing pharmacists.

Second, community pharmacists are responsible for dispensing and reviewing physicians' prescriptions, advising patients on the use and adverse events of medications, and reinforcing the information provided by prescribers. In the paediatric population, most of the adverse events are due to poor adherence, inadequate administration, dosage and unsuitable formulations.^{18,19} Pharmacist interventions have been associated with increased medication adherence, alleviation of chronic disease and reduced drug-related problems.²⁰⁻²² In an observational prospective study of 63 patients with IH treated with propranolol, 30 experienced problems during treatment administration, mainly an inadequate dose, non-adherence to treatment, adverse events and wrong administration. An intervention by a pharmacist increased adherence to treatment and reduced the incidence of adverse events.²¹ However, for advising and informing patients, a basic knowledge of this condition and its management is required to advise parents of children experiencing adverse events with oral propranolol. Although parents are informed by the prescriber and when the treatment is first administered at the hospital, complete information by the community pharmacist could limit the incidence of adverse events. Scores obtained for questions on tolerance were higher (60.0% of participants with at least 50% of correct answers for this part) than scores obtained for questions on epidemiology and modalities of treatment. We hypothesised that pharmacists' answers are linked to their knowledge of beta-blockers rather than

oral propranolol solution because the adverse events are similar. However, we expected higher scores because beta-blockers are used for many conditions.

Finally, the professional caregiver's mistrust can increase phobia among parents, especially for paediatric medications, such as corticophobia in atopic dermatitis.²³

Strengths and limitations

The main strength of our work is that we included a large sample of participants of community pharmacists in France with homogenous distribution in the country, that is, both rural and urban community pharmacists with a proportion similar to the French demographic situation: 18% of community pharmacists were in rural areas in 2022.²⁴ However, several limitations should be mentioned. The main limitation is linked to the study design as an online survey. We may have selected participants with an interest in this disease and then obtained a higher score than in the general population of pharmacists. Moreover, characteristics of our population differ from those of the general population of pharmacists with higher proportion of female pharmacists and lower mean age.²⁴ Also, we limited the recruitment to participants in France, where oral propranolol is delivered by community pharmacists. Therefore, the generalisability of the results is uncertain and depends on regulatory frameworks in other countries.

CONCLUSION

According to our survey, there is a need to improve the knowledge of pharmacists about IH and its management. Continued education of pharmacists should be proposed, and information, already available for practitioners and parents, should be developed and disseminated to pharmacists. Mobile applications for both parents and pharmacists could be developed. Moreover, there is a need for greater cooperation between healthcare professionals to improve the proper use of medicine.

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ABBREVIATIONS

IH, infantile haemangioma

REQUIRED STATEMENTS

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Conflict of interest: None declared

TABLES

Table 1. Sociodemographic characteristics of pharmacist respondents (n=255)

Characteristics	
Age, years, median (IQR)	34.0 (27-41)
Sex, n (%)	
Male	30 (11.8)
Female	225 (88.2)
Already delivered treatment, n (%)	
No	172 (67.5)
Yes	83 (32.5)
Self-confidence in delivering treatment, median (IQR)	5.0 (2.5-6.0)
Number of years since graduation (n=242), median (IQR)	10.0 (3.0-17.0)
Occupation, n (%)	
Pharmacists	177 (69.4)
Pharmacy technicians	65 (25.5)
Pharmacy students	13 (5.1)
Location of the pharmacy	
Rural (<2000 people)	62 (24.3)
Urban (≥2000 people)	193 (75.7)

IQR, interquartile range

Table 2. General characteristics of responses obtained at the 42 questions (n=255)

General characteristics of responses	
Score obtained (/42), median (IQR)	18 (11-25)
Number of participants with > 21/42 score, n (%)	96 (37.6)
Notes obtained for part 2 on epidemiology and clinical aspects of IH (/12), median (IQR)	6 (2-8)
Number of participants with > 6/12 score, n (%)	133 (52.2)
Notes obtained for part 3 on indications, modalities of prescription and administration of propranolol for IH (/18), median (IQR)	5 (2-9)

Number of participants with > 9/18 score, n (%)	66 (25.9)
Notes obtained for part 4 on adverse events of propranolol and management (/12), median (IQR)	7 (4-9)
Number of participants with > 6/12 score, n (%)	153 (60.0)

IQR, interquartile range; IH, infantile hemangioma

Table 3. Characteristics of participants in terms of questionnaire score stratified by quintiles (n=255)

	Score (0-11) <i>Very poor knowledge</i>	Score (12-18) <i>Poor knowledge</i>	Score (19-25) <i>Good knowledge</i>	Score (26-42) <i>Very good knowledge</i>
Already delivered treatment, n (%)				
No	65 (86.7)	45 (77.6)	41 (61.2)	21 (38.2)
Yes	10 (13.3)	13 (22.4)	26 (38.8)	34 (61.8)
Self-confidence in delivering treatment, median (IQR)	3.0 (1.5-5.0)	4.0 (2.0-5.0)	4.0 (2.0-6.0)	7.0 (5.0-7.5)
Sex, n (%)				
Male	9 (12.0)	7 (12.1)	6 (9)	8 (14.5)
Female	66 (88.0)	51 (87.9)	61 (91)	47 (85.5)
Number of years since graduation, median (IQR)	11.0 (3.0-17.0)	7.0 (2.25-15.0)	10.0 (4.0-18.0)	10.0 (4.0-13.5)
Role, n (%)				
Pharmacists	46 (61.3)	44 (75.9)	49 (73.1)	38 (69.1)
Pharmacy technicians	24 (32.0)	11 (19.0)	17 (25.4)	13 (23.6)
Pharmacy students	5 (6.7)	3 (5.2)	1 (1.5)	4 (7.3)
Location of the pharmacy, n (%)				
Rural	19 (25.3)	14 (24.1)	18 (26.9)	11 (20.0)
Urban	56 (74.7)	44 (75.9)	49 (73.1)	44 (80.0)

IQR, interquartile range

Table 4. Multinomial logistic regression analysis of questionnaire score stratified by quintiles (n=255)

	Score (12-18) <i>Poor knowledge</i>	Score (19-25) <i>Good knowledge</i>	Score (26-42) <i>Very good knowledge</i>
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Already delivered treatment			
No	Reference	Reference	Reference
Yes	2.03 (0.76-5.43)	4.02 (1.63-9.88)	7.98 (3.03-21.03)
Self-confidence in delivering treatment	1.11 (0.94-1.31)	1.15 (0.98-1.36)	1.51 (1.25-1.82)
Sex			
Male	Reference	Reference	Reference
Female	1.52 (0.49-4.74)	2.21 (0.65-7.44)	2.11 (0.60-7.38)
Number of years since graduation*	0.97 (0.93-1.01)	0.98 (0.94-1.02)	0.94 (0.89-0.99)
Role			
Pharmacists	Reference	Reference	Reference
Pharmacy technicians	0.45 (0.19-1.07)	0.53 (0.24-1.19)	0.58 (0.22-1.51)
Pharmacy students	0.54 (0.11-2.60)	0.23 (0.02-2.17)	0.85 (0.15-4.75)
Location of the pharmacy			
Rural	Reference	Reference	Reference
Urban	1.11 (0.49-2.52)	1.03 (0.46-2.27)	1.58 (0.59-4.20)

Bold font indicates significant data

The reference category was the group with the lowest proportion of correct answers to the questionnaire "very poor knowledge."

**For pharmacy students, number of years since graduation was imputed with 0*

OR, odds ratio; CI, confidence interval; IH, infantile hemangioma

FIGURE LEGEND

Figure 1. Geographical distribution of pharmacy participants in France.

SUPPLEMENTAL FILE

Table S1. Characteristics of pharmacists (excluding pharmacy technicians and pharmacy students) in terms of questionnaire score stratified by quintiles (n=177)

Table S2. Multinomial logistic regression analysis of questionnaire score stratified by quintiles for pharmacists (excluding pharmacy technicians and pharmacy students) (n=177)

Table S3. Proportion of correct answers to the questionnaire (n=255)