
CLINICAL ASPECTS OF DIFFERENT PHARMACEUTICAL FORMULATIONS OF PROPRANOLOL IN THE TREATMENT OF INFANTILE HEMANGIOMA

Jasmina Ristov

Lek, Sandoz, Skopje, University Goce Delchev, Faculty of Medical Sciences, Stip,
Republic of North Macedonia, jasmina.276s@student.ugd.edu.mk

Emilija Janevik-Ivanovska

University Goce Delchev, Faculty of Medical Sciences, Stip, Republic of North Macedonia,
emilija.janevik@ugd.edu.mk

Abstract: Infantile hemangiomas are one of the most common benign vascular tumors in infants and children. Because hemangiomas can resolve spontaneously, they usually do not require specific treatment unless the proliferation interferes with normal function or causes interference with the function of essential vital organs. There are several types of therapy, but in recent decades the use of propranolol has become more common due to its excellent effectiveness.

The purpose of this paper is to analyze different pharmaceutical formulations of propranolol in the treatment of infantile hemangioma, including technological differences of the oral and topical pharmaceutical dosage forms of propranolol. The European Medicines Agency (EMA) has approved the commercially available oral propranolol therapy in the countries of the European Union, but this is not yet happened in our country. Recommendations to follow and use the protocols for the oral application of propranolol in the treatment of this disease are difficult due to the fact that this drug formulation is not registered in our country and patients are forced to obtain it from countries where it is registered.

The use of syrup as an oral form of therapy has been clinically proven and has a high percentage of efficiency in infantile hemangioma, but side effects such as sleep disturbance, bronchospasm, hypoglycemia, hypotension.

The goal of this publication is to propose the most appropriate topical formulation of propranolol for external use in infantile hemangioma through a review of relevant published data on the use of various pharmaceutical formulations of propranolol in clinical studies and documents from the European Medicines Agency,

In this paper, we used compilation and comparison methods, as most useful for a high-quality critical evaluation of the literature regarding problematic topics, in our case the pharmaceutical formulation of propranolol, the effect of clinical treatment and the required legislation, and which have the potential to promote clearer, shared understandings and accelerate advances in the research.

Our results were focused on obtained and published data related to pharmaceutical-technological aspects of production of topical formulations and the effect of clinical application, especially when it is necessary to define exactly the amount of the released active compound from the topical form (cream, ointment or gel) and its absorption through the skin.

Topical form of propranolol avoids the side effects of oral administrated propranolol, can help maintain a high level of active ingredient in a local or focal region, and has an easy way of administration.

The obtained research data showed that the topical application and penetration of propranolol through the skin is good and has a lower and controlled systemic absorption. To achieve this, the choice of the formulation and the excipients used are particularly important. Lipophilic formulations have limited release and penetration of propranolol. The best results are achieved by using a hydrophilic cream.

After the research done, we can conclude that the production of topical formulations containing specific active components with a strong systemic effect, such as propranolol, can be carried out in galenic laboratories or hospital pharmacies. For this, already existing validated equipment and excipients that are readily available can be used.

We believe that the use of topical pharmaceutical forms for local application, even in children such as the case of propranolol in infantile hemangioma, is justified, especially to the fact that so far no side effects have been registered even after long-term therapy.

Keywords: infantile hemangioma, propranolol, pharmaceutical formulations, topical formulation, oral formulation

1. INTRODUCTION

Infantile hemangiomas are non-cancerous growth of blood vessels, occurring in 4% to 10% of children under 1 year of age, common in girls and premature infants. Some of the studies suggested that infantile hemangiomas, with the most common benign skin tumors in infants and young children. It is accepted that an average of 4.5% of children

under 1 year of age have some form of infantile hemangioma, while the frequency in premature children weighing under 1.5 kg reaches 30%. It occurs up to 3 times more often in girls. This is literally a mass illness and regardless of the size of the formation, it has a great psycho-logical and social impact on the parents (Brankov,2017). They appear usually in first weeks of life, growth rapid for 3 to 6 months and may go on for 24 months, then a period of stabilization followed by spontaneous involution usually occurring in several years. Because of spontaneous involution usually does not require specific treatment unless the proliferation interferes with normal function or causes interference with the function of essential vital organs.

Infantile hemangiomas may be classified according to their depth: superficial, located in the upper dermis (and therefore visible on the skin), deep, extending to subcutaneous fascia or mixed. (Khattab, 2021) They can occur anywhere on the body but are most commonly found on the head and neck. In that position they can have adversely affect in the appearance and mentality of infants.

The major complications that can occurs, in patients referred to tertiary center is ulceration, with incidence of up to 16%. Visual disturbance, and airway obstruction are also often complications. (Price,2018)

Therapeutic interventions typically performed include surgical interventions, laser therapy, oral administration, or local injections of steroids. However, surgical intervention and laser therapy are highly invasive. Oral administration and local injections of steroids are associated with a high incidence of adverse drug reactions. The administration of steroid therapy requires caution.

Oral administration of propranolol, a b- adrenergic antagonist was discovered incidentally in 2008. In French patient with hypertrophic obstructive cardiomyopathy complicated by infantile hemangioma was treated with propranolol, which ameliorated the hemangioma (L'èaut,2008)

Pharmacological effect of propranolol in proliferating infantile hemangioma described potential mechanisms of action of propranolol in proliferating infantile hemangioma described in the literature could include various mechanisms (EMA,2014)

Recommendations to follow and use the protocols for the oral application of propranolol in the treatment of this disease are difficult due to the fact that this drug formulation is not registered in our country and patients are forced to obtain it from countries where it is registered. Oral form of therapy has been clinically proven and has a high percentage of efficiency in infantile hemangioma, but has side effects such as sleep disturbance, bronchospasm, hypoglycemia, hypotension. (Price,2018)

Topical skin application can help the maintain high drug concentration at local or focal sites, is easy method of administration, can directly delivery to the diseased area and is avoiding first-pass metabolism. Topical form of propranolol avoids the side effects of oral administrated propranolol and can help maintain a high level of active ingredient in a local or focal region, also has an easy way of administration. It has been suggested that topical propranolol acts to suppress hemangioma proliferations by reducing the levels of vascular endothelial growth factor. The optimal preparation, dosage and duration of topical propranolol treatment are currently unknown.(Nagata, 2022) The aim of this systematic review was to obtained and published data related to pharmaceutical-technological aspects of production of topical formulations and the effect of clinical application, especially when it is necessary to define exactly the amount of the released active compound from the topical form (cream, ointment or gel) and its absorption through the skin.

2. MATERIAL AND METHODS

Materials needed for this paper were obtained from EMA and FDA. In addition to this, as materials in the research, and in the direction of fulfilling the goals of this paper, primary and secondary sources were used, that is, a review of literature from research and studies that are on the same or similar topic. In this way, and through the use of certain studies, an appropriate comparison of the obtained data and analysis of their results could be made in the direction of what is needed for this paper.

3. RESULTS

By analyzing the literature review and the EMA and FDA databases, it can be said that a large number of studies, older and more current, are concerned with the research and analysis of the impact of formulas containing propranolol, which were used for the treatment of infantile hemangioma.

Therefore, the analysis conducted by EMA (2014) in infants (aged 5 weeks to 5 months at the start of treatment) with proliferative infantile hemangioma that requiring systemic therapy shows the clinical effects of the oral formulation of propranolol syrup as a commercially available form. That has been demonstrated in a pivotal randomized, controlled, multicenter, multidose, adaptive phase II/III study comparing four regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo (double blind). (EMA, 2019)

The treatment was carried out on 456 subjects (401 propranolol at a dose of 1 or 3 mg/kg/day for 3 or 6 months; 55 Placebo), including a titration phase over 3 weeks. Patients (71.3% female; 37% aged 35-90 days and 63% aged 91-150 days) presented head hemangioma in 70% and the majority of infantile hemangiomas were localized (89%).

Treatment success was evaluated by blinded centralized independent assessments made on photographs at week 24 and was defined as complete or near-complete resolution of the entire hemangioma, which was, in the absence of premature discontinuation of treatment.

After 5 weeks of treatment with propranolol improvement of the hemangioma was observed at in 88% of patients, 11.4% of patients had to be re-treated after treatment termination.

Demonstration of efficacy was not established in patients with a high risk of hemangioma, for ethical reasons related to the use of placebo. In the literature and in a specific compassionate use program are available the evidence of efficacy on propranolol in patients with high-risk hemangioma.

Based on a retrospective study, conducted by EMA (2014) a minority of patients (12%) required re-initiation of systemic treatment. When treatment was restarted, a satisfactory response was observed in a large majority of patients.

EMA clinically prove the use of syrup as an oral form of therapy with high percentage of efficiency in infantile hemangioma, but also shows side effects such as sleep disturbance, bronchospasm, hypoglycemia, hypotension.

In several countries, including countries from the European Union, where the syrup is commercially available, due to the financial benefit, syrup and topical forms are made in galenic laboratories in hospitals and pharmacies. It is made with safe and easily available auxiliary substances.

Based on the retrospective study of Horak (2013) liquid formulation of propranolol requires the use of a pH3 buffer to obtain optimal stability and masking of the simplex syrup taste. Stability has been proven by keeping the temperature at 2-8 degrees and using the HPLC method. The effectiveness of the antimicrobial presence was proven by the European Pharmacopoeia (Ph. Eur.5.1.3).

Infantile hemangiomas are most often found in the region from the upper dermis to the subcutaneous fat and therefore propranolol, which is the active component of topical formulations, should be absorbed into the dermis. To achieve a therapeutic indication, the active component has to pass through the epidermis and reach the dermis. Permeation studies are therefore performed to estimate the therapeutic concentration of propranolol.

The production of topical forms is without predetermined standard protocols. Composition and production of topical forms are simple and affordable and do not require additional preparation and can be produced in galenic laboratories in hospitals and pharmacies.

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The experiments of the studies (Padula,2017) were done on pig ear skin, where the basic tests are to prove the permeability of propranolol in different topical formulations. The data indicated that propranolol hydrochloride can penetrate the human dermis, and its absorption is directly dependent on the composition of the semisolid formulation substrate. The release and action of propranolol hydrochloride from lipophilic substrates are limited depending on their composition. The best results are obtained with hydrophilic creams. Propranolol retention studies indicate that the epidermis acts as a reservoir, releasing propranolol after application. Permeability through the epidermis, the upper layer of the skin, is a particularly important factor for achieving a local effect of propranolol. It has been tested for hydrophobic creams, where in addition to the permeability of the epidermis, the permeability through the dermis, the lower layer of the skin where the capillaries are located, is additionally tested. Depending on the fatty phase, the hydrophobic fat, i.e., olive oil, has high retention performance and low skin penetration, with a recommended application time of 4 hours. Thanks to the fat composition and the use of propranolol hydrochloride, it can be said that propranolol is not completely soluble in lipophilic formulations, that is, the concentration of dissolved propranolol is lower than necessary. Penetration of propranolol in creams showed satisfactory permeability compared to ointment and gel. The difference in the permeability of the creams has been demonstrated by replacing the olive oil with Glyceryl monooleate, a less lipophilic component that indicates faster penetration through the skin.

Lipophilic formulations, especially lipophilic cream containing olive oil, have high retention performance and low skin penetration, with a recommended application time of 4 hours. Changing olive oil to a less lipophilic component such as glyceryl monooleate significantly reduces skin retention. Hydrophilic formulations such as gels have limited skin retention.

The total permeability of propranolol over 24 hours in the hydrophilic cream compared to the three gel forms indicated the highest permeability of the gel formulation with gelatin, followed by the hydrophilic cream.

(Kashiwagura,2022). And the permeability compared to the hydrophilic cream with different concentration of propranolol hydrochloride increases proportionally.

Therefore, the analysis of studies (Padula,2018) shows test that are made by drilling to determine the relevant permeability parameters. Isolated epidermis is used for these experiments because it better simulates the situation in vivo, in fact in vivo systemic absorption takes place at the level of the upper dermis, where the capillaries are located, and the epidermis is the barrier for permeability of propranolol. The use of lipophilic components leads to difficulty in the permeability of 6-7 hours and retention of propranolol. Ointment creams and gels have been taken in clinical studies.

The dosage is usually 2-3 times a day with 1% propranolol. Side effects have not occurred in patients treated with topical formulations.

In the study of Nagata (2022) suggest that 5% propranolol topical cream can be first-line treatment for small and superficial infantile hemangioma in cosmetically problematic areas. In clinical study, they measured plasma concentration of propranolol and showed that the drug had little systemic effect and was locally effective. This study suggest that 5% propranolol topical cream is safe, with no serious side effects such as hypotension, bradycardia, or hypoglycemia.

4. DISCUSSION

The interpretation of the studies was aimed at distinguishing between pharmaceutical formulations, primarily oral versus topical formulations but also differences between topical formulations. The production can be done in galenic laboratories in combination with hospitals and pharmacies because it does not require special equipment, it is prepared with auxiliary substances that are easily available. The oral formulation in the form of syrup proves its effectiveness in clinical studies, as well as the risk/benefit advantage for the pediatric population, but side effects caused by its use have also been mentioned. Unlike syrup, which is commercially available and has data on it, topical formulations are still in the research phase.

Since the target site of infantile hemangioma is in the region of the upper dermis, the goal is for the drug to reach the dermis as well as pass through it. Therefore, skin permeation studies were analyzed, and corresponding permeation profiles of gelatin gum gel and hydrophilic cream were obtained. Comparisons of a hydrophobic cream and a lipophilic ointment with a hydrophilic cream were made and the hydrophobic formulations showed greater skin retention and lower permeability, requiring 4-hourly application.

The pH value is also an important point. In the syrup, it has been proven that propranolol is most stable at pH3, and in the analyzed topical formulations the pH value is 4.1 – 5.8. However, within 3 months there is no change in appearance, separation of phases, and reduction of content.

In terms of storage, solutions with propranolol should be stored in well-closed containers at pH 3 and dissolve quickly in an alkaline environment. Thus, it is recommended to keep the syrup at a temperature of 2-8 degrees, and the creams at a room temperature of 25 degrees. After 12 months, although the result is satisfactory from 90% preservation of active component. Propranolol is unstable to light. It should be protected from light and stored at room temperature. I would put the manufactured creams in a package protected from light, as is done with the commercially available syrup form, and is indicated for the active component.

The size of the hemangioma treated with the topical formulations is reduced, but in some cases, it is not completely gone. Side effects have not been reported, so I would increase propranolol percentages after intermittently used formulation. The treatment, both with the oral and the topical formulation, should take place in stages. Since oral therapy is defined as treatment at the beginning with 1 mg/kg/day, then 2-3 mg/kg/day in topical therapy, this has not yet been proven. Usually 1% is used, rarely 3% and the dosage is 2 or 3 times a day. Dosage of 1% topical cream with propranolol should be at the beginning of therapy. Depending on the age and weight of the infant, it should be gradually titrated with 2%, then with 3%, and if necessary with 5% propranolol. The goal is to obtain a better therapeutic response, in patients who have not shown side effects but do not have a complete response to the hemangioma. Regarding the age of the child, the effectiveness of the cream would be greater if it were started at a younger age. Although the syrup shows its greatest effectiveness from the 5th week, the results would not be different obtained with the topical use.

5. CONCLUSION

Preliminary evidence of topical propranolol suggests that it is effective and safe and can be alternative option for treatment of infantile hemangioma. Topical application and penetration of propranolol through the skin is good and has a lower and controlled systemic absorption. Choice of the formulation and the excipients showed that hydrophilic cream has best results. Lipophilic formulations have limited release and penetration of propranolol.

According to permeability research, for better results with topical application of propranolol, a hydrophilic cream is the choice.

In our further research we will focus on ensuring the propranolol concentration by offering several different concentrations. Only in this way the most appropriate therapeutic effect, frequency of dosage and length of treatment can be proven.

Apart from choosing a pharmaceutical formulation with the best permeability, to achieve the goal of increasing the success of therapy without side effects, the treatment may need to be based on the age and weight of the infant.

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