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Access to medications in pediatric patient with hereditary angioedema: the role of the pharmacist

Abstract

A request for icatibant 30 mg/3ml, a high-cost drug, was made to the pharmacy at the Hospital in San Francisco (Córdoba, Argentina). This medication was not available at the institution (off-formulary), and its active ingredient is only marketed by two laboratories in the country. The cost ranges between 3,500 and 4,500 USD per ampoule, depending on the brand.

The medication was requested for a 9-year-old female pediatric patient diagnosed with hereditary angioedema, confirmed by laboratory tests, and prescribed a dose of 15 mg via the subcutaneous route. It was indicated for treating acute episodes, such as facial and/or laryngeal edema, and for administration prior to surgery, such as a dental extraction. The cost of the medication was unaffordable for a family without private health insurance. Additionally, the family lived far from the health center, so it was requested that at least two doses be made available for her.

This case highlights the significant challenges in accessing high-cost, life-saving medications for a young patient with hereditary angioedema in a low-resource setting. The situation emphasizes the critical role of pharmacists in navigating these challenges to ensure that patients receive the necessary treatment despite financial and logistical barriers.

The pharmacist plays a pivotal role in overcoming these difficulties by addressing the five dimensions of access to medication: availability, affordability, accessibility, acceptability, and quality.

In this case, the pharmacist's role extends far beyond dispensing medications. It involves active participation in the management of rare and complex conditions, advocating for patient access to necessary treatments, and ensuring that the care provided is both effective and sustainable.

Keywords: angioedema, hereditary, pediatrics, icatibant, patient-centered care, pharmacist

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Abbreviation: HAE, hereditary angioedema

Introduction

Background

In September 2022, a request for icatibant 30 mg/3ml, a high-cost drug, was made to the pharmacist at the Hospital in San Francisco (Córdoba, Argentina). This medication was not available at the institution (off-formulary), and its active ingredient is only marketed by two laboratories in the country. The cost ranges between 3,500 and 4,500 USD per ampoule, depending on the brand.[1]

The medication was requested for a 9-year-old female pediatric patient diagnosed with hereditary angioedema, confirmed by laboratory tests, and prescribed a dose of 15 mg via the subcutaneous route. It was indicated for treating acute episodes, such as facial and/or laryngeal edema, and for administration prior to surgery, such as a dental extraction. The cost of the medication was unaffordable for a low-income family without private health insurance. Additionally, the family lived far from the health center, so it was requested that at least two doses be made available for her.

Introduction to Hereditary Angioedema (HAE)

Hereditary angioedema is a rare disease with an estimated prevalence of 1 case per 10,000 to 50,000 people, characterized by unpredictable episodes of edema that can last several days. The most common forms are caused by the deficiency or malfunction of the plasma protein called C1 esterase inhibitor (C1-INH), a glycoprotein synthesized in hepatocytes. From a pathophysiological perspective, the disease is characterized by an increase in the production of bradykinin (BK), which binds to the type 2 BK receptor (RB2). This rare genetic condition causes a biochemical imbalance, leading to increased vascular permeability.[2] In our patient, this enzyme was below the quantification limit, and the determination of its functional activity was 34% (VR >70%), indicating a "deficiency."

Mucosal and submucosal edemas (crises) can affect the face, larynx, extremities, genitals, etc. In children under 10 years of age, intestinal colic and limb edema are the most common manifestations. The frequency and severity of crises vary greatly between individuals, families, and even within the same family (clinical polymorphism). Our patient was the only member in the family with this condition. Attacks usually develop within the first 24 hours and spontaneously disappear within 48 to 96 hours. In some cases, the crises can have potentially fatal consequences if they affect the larynx, posing a challenge for healthcare personnel.[2,3] Mortality associated with this disease is primarily due to asphyxia secondary to laryngeal edema, and before specific treatments were available, the mortality rate of HAE ranged between 25% and 50%.[3]

Possible triggers for this condition include trauma, dental and medical procedures such as endoscopy, surgery, anesthesia intubation, fatigue, stress, infections, and hormonal imbalances. These recurrent

non-itchy edema attacks, which can affect any part of the body, do not respond to treatment with antihistamines and corticosteroids. There are other therapeutic options for acute attacks as well as for short- and long-term prophylaxis.[4]

About the HAE pharmacotherapy

Current therapeutic options for HAE consist of long-term prophylaxis, short-term prophylaxis before triggering events, and acute treatment of attacks. Each HAE patient should have a well-defined treatment plan, personalized according to their specific clinical features, preferences, and available resources.[3] For both acute episodes and short-term prophylaxis, the plasma-derived C1 inhibitor concentrate is indicated and approved for use in the pediatric age group. It is administered intravenously at a dose of 20 IU/kg, with a maximum dose of 1,000 to 1,500 IU per administration.[4] This on-demand (acute) treatment must be administered upon HAE attacks. The drugs used in on-demand treatment aim to relieve angioedema as quickly as possible, avoiding complications.[3] Antifibrinolytics and androgens are no longer recommended as first-line treatment owing to their unfavorable side effect profiles.[5]

In Argentina, for acute episodes, the use of the bradykinin receptor inhibitor icatibant was authorized for children over 2 years of age and weighing more than 12 kg. The guidelines recommend that, in the absence of medication, fresh plasma can be used as an exception (considering that this treatment may exacerbate symptoms in some patients).[4]

Icatibant is a 10-amino acid synthetic peptide that acts as a competitive antagonist of the RB2, which mediates the vasoactive effects of bradykinin. It has been available in Europe since 2008 and in the United States since 2011. The efficacy of icatibant was demonstrated in clinical trials and in real-world settings. A study showed that icatibant was used earlier from symptom onset in the real-world compared to clinical trials, which shortened the time to symptom resolution and attack duration. The safety and tolerability of icatibant demonstrated being good, with the most common side effects being transient local injection site reactions, headache, fever, and gastrointestinal discomfort.[3,6,7]

Problems in HAE patient care

Patients and caregivers face important challenges related to the symptoms and management of HAE, and the burden of chronic disease management. Previous studies have shown that patients' health-related quality of life is significantly diminished during an HAE attack, and that HAE imposes a considerable socioeconomic burden due to medical costs and lost productivity.[8,9]

Caregivers are often unpaid family members or friends who provide care to individuals with chronic medical conditions and immediate needs. These informal caregivers can experience various psychosocial impacts related to caregiving, including anxiety, depression, feelings of guilt, and social isolation.[8]

In a survey, caregivers reported engaging in several treatment-related tasks to assist HAE patients, stating that they often "perform medical- or nursing-related tasks for their care recipients." They also described various psychosocial burdens associated with caregiving for patients with rare diseases, such as missing work or school, dealing with uncomfortable or inconvenient infusions or injections, and witnessing a loved one suffer.[8,9] However, such data is not currently available for patients or caregivers in Argentina.

Pharmacist's role in HAE patient care

Given the high cost of the medication and its unavailability at the institution, this work explores the role of the pharmacist in accessing the required pharmacotherapy for the patient and her family.

Access to medication has five dimensions: availability, affordability, accessibility, acceptability, and quality. The dimensions of availability and affordability are crucial for access, ensuring that the medicine is available when the patient need it. Availability depends largely on manufacturing, authorization, distribution, and marketing. Accessibility to medication is related to the dispensing process, as it is essential that the patient (and caregivers) can access pharmaceutical services to request their medications. Acceptability promotes the rational use of medicines during the prescribing and administration/use processes. The therapeutic chain also includes the evaluation of therapeutic outcomes, allowing for the improvement of the rational use of medications. Quality is transversal to all dimensions and ensures compliance with the specifications of each process to guarantee patient safety and the best health outcomes.[10]

Pharmacists' activities can be divided into two main aspects: one focused on the management necessary to obtain the medication. This implies that the pediatrician writes an order and the pharmacist requests authorization from the Ministry of Health, as an exception, to purchase only two ampoules. Afterward, it is necessary to manage the medication's arrival at the institution, ensure proper storage, and dispense it appropriately. Considering that the city of San Francisco is located 210 kilometers from Córdoba (the main city in the province), the availability of the drug is a challenge to overcome.

The aspect related to acceptability involves dispensing and the correct use of the medication, which allows the patient to achieve the therapeutic goal. A very important intervention is patient education, regarding disease triggers and potential risks, and on how to manage an acute attack. Trigger awareness and, when possible, avoidance is a critical aspect of HAE management. Among the most relevant attack triggers are physical trauma, infections, emotional stress, hormonal changes, and medications (e.g., estrogen-containing medications, tamoxifen, angiotensin-converting enzyme inhibitors, and dipeptidyl peptidase 4 inhibitors).[3]

Also, patient training on self-administered therapy should be made available and is recommended by current guidelines.[4] Related to follow-up, the pharmacist must consider long-term prophylaxis. Most patients should be taught to conduct serial assessments to ensure that morbidity is minimal, and therapy is effective.[11]

Related to our patient, parents have records about all the acute attacks in the last two years along with the drug administration. The patient is provided with one ampoule of icatibant per month, and the cost is covered by the local government through the Ministry of Health. However, the girl is approaching puberty, and the associated hormonal changes are triggers, so a new drug for long-term prophylaxis is under evaluation.

Effective and sustainable HAE treatment

Long-term prophylaxis administered on a regular basis is intended to reduce future attack frequency and severity, with the ultimate goal of achieving complete disease control (i.e., complete prevention of attacks). There is no absolute consensus on whom and when to start this prophylaxis remaining as a matter of debate among experts.[3,5]

The healthcare team is assessing the possibility of changing therapy to the human monoclonal antibody lanadelumab. In Argentina, this drug is available in solution in a prefilled single-dose syringe of 300

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mg in 2 mL and the cost exceeds 25,000 dollars.[1] The recommended dose for adults and children above the age of 12 years is 300 mg subcutaneously every 2 or 4 weeks meanwhile the dose for children between 2 and 12 years of age is 150 mg subcutaneously every 2 or 4 weeks. Common adverse events include injection site reactions, hypersensitivity, nasopharyngitis, headache, rash, diarrhea, myalgia, and dizziness. Potentially serious but uncommon adverse events include severe hypersensitivity reactions.[12]

Lanadelumab is more expensive than Icatibant. The rising costs of innovative drugs and therapeutics create challenges in resource allocation for healthcare institutions. Razvi et al,[13] mentions that there is limited evidence to guide priority-setting for institutional funding of high-cost drugs. Institutions are increasingly faced with requests to fund high-cost inpatient-administered drugs that are not included on hospital formularies, either due to their novelty or to an absence of well-established indications.[13]

With the change of therapy, the pharmacist faces new challenges participating in the selection of drugs, the evaluation of evidence-based information, the analysis of economic studies, and developing a recommendation that favors the patient and the institution.[14]

According to Karakolias, patient expectations have shifted from simply dispensing prescriptions to a comprehensive care model. More specifically, patients were found to expect more with respect to overall health recommendations, encouragement to achieve their treatment goals, and dedication to improving their health.[15]

Conclusion

In this case, the pharmacist's role extends far beyond dispensing medications. It involves active participation in the management of rare and complex conditions, advocating for patient access to necessary treatments, and ensuring that the care provided is both effective and sustainable.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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