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CASE SERIES

Effectiveness of the antihistamine and anti-PAF effects of rupatadine in allergic diseases: off-label use in a case series study

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Abstract

Rupatadine is a modern, long-acting, non-sedating antihistamine that targets the H_1 receptor and exhibits additional strong antagonist activity toward platelet-activating factor (PAF) receptors as well as exerting other anti-inflammatory effects. All these properties have positioned rupatadine as a remarkable treatment option for adults and children with various allergic and skin disorders, including allergic rhinitis and urticaria of different causes. This case series shows the real-world effectiveness and safety of off-label rupatadine use in paediatric patients with clinically relevant complex allergy-related and dermatology-related conditions, whose underlying pathogenetic mechanisms were successfully addressed by the pharmacological profile of rupatadine.

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Introduction

Rupatadine is an oral long-acting second-generation antihistamine (inverse agonist of H_1 receptor) that, in addition to being a strong H_1 receptor antagonist, is also a potent platelet-activating factor (PAF) inhibitor.[1] The drug also exhibits other anti-inflammatory effects, including the inhibition of mast cell degranulation and eosinophil chemotaxis.[1–3] Approved indications of the use of rupatadine (as fumarate) include symptomatic treatment of allergic rhinitis and urticaria in adults and adolescents over 12 years of age in the form of tablets (10 mg), and in children aged 2–11 years in the form of oral solution (1 mg/mL). There is a large body of literature supporting the efficacy and safety of rupatadine for the management of adult and paediatric patients with these disorders.[2,4–8]

In addition to being a powerful antihistamine and PAF antagonist, rupatadine also inhibits other inflammatory mediators and effector cells involved in the underlying pathophysiological mechanisms of allergic disorders.[9] PAF, mainly synthesized by human endothelial cells, is an inflammatory lipid mediator and a potent attractor and activator of granulocytes and monocytes, thereby exacerbating allergic inflammation. It is involved in various allergic conditions, including anaphylaxis, asthma, allergic rhinitis and urticaria.[9,10] In allergic rhinitis, PAF increases vascular permeability, thereby exacerbating rhinorrhoea and nasal congestion. In chronic spontaneous urticaria, PAF-associated effects, such as increased permeability, development of oedema and release of inflammatory mediators, contribute to the persistence of inflammation.[10] Additionally, elevated PAF levels appear to maintain increased disease activity and resistance to treatment

with antihistamines.[10] Therefore, inhibition of PAF has been proposed as a novel approach in the treatment of allergic rhinitis and chronic urticaria as part of a global strategy directed at blocking as many relevant inflammatory mediators as possible.[10,11] The off-label use of rupatadine in other clinical settings takes advantage of the dual antihistamine and PAF-antagonist profile of the drug. A recent review has shown that off-label prescription of rupatadine was associated with remarkable success in a variety of clinical scenarios, including improvement of oral immunotherapy tolerance in food allergy, conjunctival allergies, mast cell activation disorders, skin diseases-related pruritus or cutaneous allergy after mosquito bites.[12]

However, real-world clinical experiences on the off-label use of rupatadine are still scant. The present study adds evidence of the off-label use of rupatadine in five demonstrative paediatric clinical cases, contributing to a broader understanding of its effectiveness and safety for the management of complex allergic and cutaneous conditions in real-life practice.

Patients and methods

The authors retrospectively reviewed and described clinical cases of patients in the adolescent age group and children, one of them an infant as young as 6 months old, with various challenging allergic or skin conditions treated with different doses of rupatadine and a variable duration of treatment. Diagnostic and treatment-related difficulties and challenges in each case are interesting aspects of the present report.

Case studies

A summary of the main characteristics of the five clinical cases is shown in Table 1.

Case 1: a paediatric case of severe cold urticaria

A 9-year-old boy presented with a 4-year history of reproducible urticaria triggered by cold exposure. The first symptoms were localized wheals on the hands and face, which appeared after playing with snow at the age of 5. The reactions were self-limited and resolved in about 15 minutes. At the age of 8 and whilst swimming in the ocean, he developed generalized urticaria with dyspnoea, perioral cyanosis, dizziness and transient syncope, which was suggestive of an anaphylactic reaction. Personal history included mild atopic dermatitis and allergic rhinoconjunctivitis, but the family history was unrevealing. At the time of physical examination, the child appeared healthy and asymptomatic. Results of laboratory tests, including blood cell count, biochemical profile, complement levels, cryoglobulins and infectious serologies, were within normal limits. Serum total IgE level was elevated at 850 IU/mL. Skin prick testing was positive for *Dermatophagoides pteronyssinus* and cat dander. A cold stimulation test with an ice cube (5 min exposure and 10 min rewarming) elicited a 3 × 4 cm wheal, confirming acute cold urticaria. A symptom threshold temperature test was not performed due to prior anaphylaxis.

Treatment with rupatadine oral solution (5 mg/day) and montelukast (5 mg/day) was indicated; however, due to the severity of symptoms and history of anaphylaxis, the dose of rupatadine was increased to 10 mg, administered twice daily at 5 mg each. No breakthrough symptoms occurred during the first 2 months of treatment, and the dose was then de-escalated to 5 mg/day. An epinephrine auto-injector (0.15 mg) was prescribed with instructions for use. Educational sessions were provided for the patient, caregivers and school personnel. Strict avoidance of cold exposure was emphasized, including the use of thermal clothing and exclusion from aquatic activities. After 1 month of treatment, the patient remained asymptomatic. A second cold stimulation test was negative, and no further episodes occurred during 6 months of follow-up. He returned to daily activities with restrictions on swimming and ice contact.

Case 2: food allergy in a 6-month-old infant

The patient was a 6-month-old male infant who presented for evaluation due to a possible allergic reaction to egg. The first symptom after egg ingestion was delayed moderate eczema, which was treated with 2.5% hydrocortisone ointment. However, upon the second egg ingestion, the patient developed a hive-like rash around the mouth. No treatment was instituted, though egg products were strictly avoided. The family was also very concerned about the risk of peanut allergy and its prevention. There was a positive maternal history of eczema. Skin prick testing to egg white elicited an 8-mm wheal. No other diagnostic studies were performed. After a shared decision-making discussion, the family decided to introduce peanut in-office without prior testing at the age of 7 months. The body weight was 10 kg. At a cumulative peanut protein dose of 43 mg, the patient developed several perioral and abdominal urticaria lesions. The off-label use of 2.5 mg of rupatadine orally resulted in complete resolution of symptoms in 45 minutes.

At 18 months of age, the patient was tolerating baked egg in muffins and waffles. Skin prick testing to egg white and peanut extract showed 5 mm and 9 mm wheals, respectively. Specific IgE serum levels were 4 KU/L for egg

Table 1. Main clinical characteristics of patients treated with rupatadine.

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	Male	Male	Male	Male	Female
Age	9 years	6 months	6 years	12 years	2 years
Personal history	Atopic dermatitis, allergic rhinoconjunctivitis, cold-elicited urticaria	Moderate eczema	Atopic dermatitis, bronchitis/laryngitis, watery rhinitis	Large local allergic reactions, allergic rhinoconjunctivitis	Atopic dermatitis (index case and mother)
Family history	Unrevealing	Eczema (mother)	Allergic rhinitis and heavy smoker (father) Atopic dermatitis/asthma (brother)	Unrevealing	Atopic dermatitis (mother)
Presenting complaints	Generalized urticaria, dyspnoea, perioral cyanosis, dizziness, transient syncope whilst swimming in the ocean	Hive-like rash around the mouth after egg ingestion and mild peanut-related allergic reactions	Diagnostic workup for recurrent respiratory infections, cough, dyspnoea, allergy symptoms	Large local allergic reaction	Intense pruritus, painful blisters due to insect bites
Diagnosis	Idiopathic acquired cold urticaria and documented cold-induced anaphylaxis	Food allergy (white egg), perioral/abdominal urticaria after in-office peanut introduction	Asthma, allergic rhinitis, atopic dermatitis, oral allergy syndrome	Large local allergic reaction by wasp sting, allergic rhinoconjunctivitis due to grass/rye pollen allergy	Insect prurigo
Rupatadine	Initial: 5 mg twice daily (10 mg/day) for 2 months After clinical stability: 5 mg/day	2.5 mg single dose	2.5 mg/day for 3 days	Initial: 20 mg/day followed by 10 mg/day (May to mid-August) or 20 mg/day in case of exacerbations of allergic rhinoconjunctivitis symptoms; 20 mg/day for 3 days after a sting	5 mg/day for 15 days
Other treatment/measures	Avoidance of cold exposure, montelukast 5 mg/day	Oral immunotherapy	Montelukast 5 mg/day, inhaled budesonide and β2 adrenergic receptor agonist, topical treatment for atopic dermatitis	Topical glucocorticoid ointment	Zinc oxide-based drying paste
Outcome	Symptom resolution	Symptom resolution	Symptom resolution	Symptom resolution	Symptom resolution

white, 8 KU/L for peanut and 3.5 KU/L for Ara h 2 protein. In view of possible oral immunotherapy, an oral food challenge test was performed to confirm the diagnosis. At a cumulative dose of 143 mg of peanut protein, the patient developed several hives and a single episode of vomiting, which was treated with 2.5 mg rupatadine with full resolution of symptoms. The family decided to proceed with peanut oral allergen immunotherapy. After 2 years of treatment, mild reactions at 21 and 30 months of age were noted, both of which were successfully treated with 2.5 mg of rupatadine. In a final oral challenge test at 3.5 years of age, the patient was tolerant to 4000 mg of peanut protein, and the family reported a substantial improvement in their quality of life.

With regards to egg allergy, because tolerance to baked egg within a wheat matrix increases the likelihood of spontaneous resolution, formal oral tolerance induction was not initiated, and the persisting peanut allergy was prioritized for this child's long-term safety and quality of life.

Case 3: atopic march in a child with complex clinical course and management

A 6-year-old boy was admitted to the paediatric department due to a severe attack of breathlessness with expiratory whistling, intense dry cough and chest pain that occurred the night before admission after walking in the park. He was diagnosed with atopic dermatitis at 6 months of age. The father was a heavy smoker and had allergic rhinitis, and his 8-year-old brother also had atopic dermatitis and asthma. The patient reported a long-standing history of recurrent bronchitis and laryngitis, up to 10 episodes a year, since the beginning of kindergarten. He had been treated with antibiotic courses, inhaled budesonide and prednisone due to laryngitis. The previous spring and summer, watery rhinitis with itching and redness of the conjunctiva appeared, with dry cough in the afternoon and night or after physical exertion. Additionally, itching in the lips, mouth and pharynx appeared when eating apples. Regular medications included emollients and first-generation antihistamines for his atopic dermatitis.

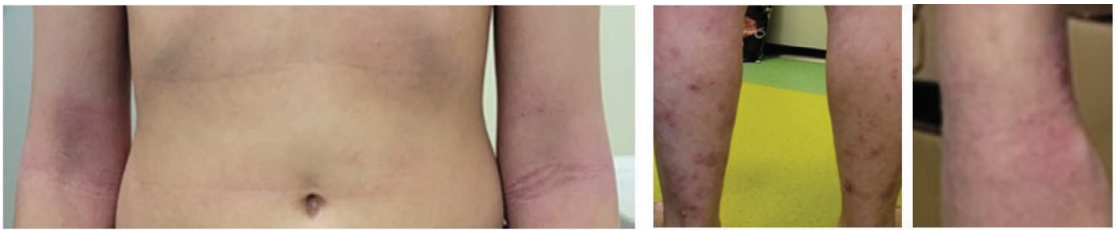
Physical examination showed a dry, erythematous, scaly and itchy skin, with eczematous lesions mainly located in the flexion surfaces of the limbs. The throat mucosa was red and congested, and rhinoscopy revealed congestion of the mucous membrane, scabs and scratches on the septum of the nose. Cytological examination of the mucous membranes demonstrated an abundance of eosinophils and neutrophils. The blood eosinophil count was 6300 cells/μL (11.9%) (normal range <500 eosinophil cells/μL or <5%). Microbiological examination of cutaneous and nasal tissue showed growth of *Staphylococcus aureus*. Allergic sensitization was confirmed by specific IgE test results, showing class 5 for birch and class 4 for grass. Pulmonary function test showed a forced expiratory volume in one second (FEV_1) of 1.07 L (63.5% of predicted), Tiffeneau index of 86.3% and positive reversibility after inhaling a short-acting β2 agonist. The fractional exhaled nitric oxide (FeNO) was 41.2 ppb (normal value <20 ppb). The final diagnosis was atopic dermatitis (Figure 1), allergic rhinitis, asthma and oral allergy syndrome.

After 3 days of treatment in hospital with inhaled budesonide (400 μg/day) using a powder inhaler and a β2 adrenergic receptor agonist delivered via inhalation chamber, rupatadine 2.5 mg/day, montelukast 5 mg/day, and topical 0.1% methylprednisolone cream and emollients, respiratory symptoms and skin lesions disappeared. Recommended treatment at discharge included regular use of inhaled corticosteroids (budesonide dry powder inhaler), antileukotriene and antihistamines, with intranasal fluticasone for exacerbation of rhinorrhoea, and an inhaled β2 adrenergic receptor agonist for episodes of severe cough, shortness of breath or wheezing. After 2 months of being discharged from the hospital, a follow-up visit showed that asthma and allergic rhinitis were well controlled but atopic dermatitis persisted. Topical steroids and antibiotics daily, followed by pimecrolimus cream 1% twice a week, combined with emollients, were recommended.

Case 4: severe allergic rhinoconjunctivitis and LLAR due to wasp sting

A 12-year-old boy presented with a large local allergic reaction (LLAR) of the left foot after being stung by a

Figure 1. Visible lesions in the upper extremity flexures and lower limbs are characteristic of atopic dermatitis.



wasp whilst walking barefoot on grass. He reported four previous LLARs when walking in uncovered shoes, and though the stings were confined to the foot, they caused pain and limited walking for several days. Treatment with first-generation and second-generation antihistamines during these episodes was partially effective, and occasional treatment with systemic oral steroids (1 mg/kg) was poorly tolerated and increased blood pressure. There was a positive family history of severe arterial hypertension. He also reported a 2-year history of moderate to severe allergic rhinoconjunctivitis during the grass pollen season, with a tendency to nasal bleeding in high pollen season and exacerbation of bleeding after administration of nasal glucocorticoids.

Physical examination showed erythema and large swelling of the entire left foot and ankle (about 30 cm in diameter), nasal congestion, oedema of the nasal turbinates, watery nasal discharge, epiphora and conjunctival hyperaemia. Other symptoms were occasional cough, itching of the nose and palate, and paroxysmal sneezing. Skin prick testing with a panel of aeroallergens was positive to grass, rye and *Alternaria* allergens. Venom allergy tests performed elsewhere showed positive specific IgE for wasp venom extract (class 4, 25 kU/L) and negative for bee venom extract. The final diagnosis was LLAR due to wasp sting and moderate-to-severe allergic rhinoconjunctivitis due to grass/rye pollen allergy.

Treatment included 20 mg/day of rupatadine and topical glucocorticoids with complete resolution of symptoms. Given the high grass pollen season, the patient was advised to take rupatadine regularly, 10 mg daily from May to mid-August, up to two tablets per day (20 mg) in case of exacerbations of allergic rhinoconjunctivitis symptoms. During the summer months, telephone follow-up visits revealed that he had been stung twice (once by wasp, once by bee), with a normal reaction, which did not impair his activities and quality of life. As he was regularly taking one tablet of rupatadine at the moment of the sting, he took one more tablet for three consecutive days and applied mometasone ointment beneath a dressing for 12 hours at the site of the lesion. He also reported clinically relevant improvement of allergic rhinoconjunctivitis when taking one tablet of 10 mg rupatadine daily and the second one on demand (usually two to three times per week).

Case 5: insect prurigo of the blistering variety

A 2-year-old girl presented with an approximately 10-day history of intense pruritus and painful blisters in the lower extremities associated with insect bites. The patient had been diagnosed with atopic dermatitis, and she also had a mother's history of atopic dermatitis. On physical examination, the child was uncooperative and restless, with normal vital signs. In the skin, a single polymorphous dermatosis, predominantly affecting the lower limbs, was observed. It was characterized by the presence of welt lesions with blisters on the surface, and subacute oedema (Figure 2). A diagnosis of insect prurigo of the blistering variety was established. Treatment included rupatadine, 5 mg/day, for 15 days, together with general skincare measures with a zinc oxide-based drying paste and insect repellent. After 1 day of treatment with rupatadine, there was a marked decrease in the severity of pruritus. A follow-up appointment at the end of treatment showed total disappearance of lesions.

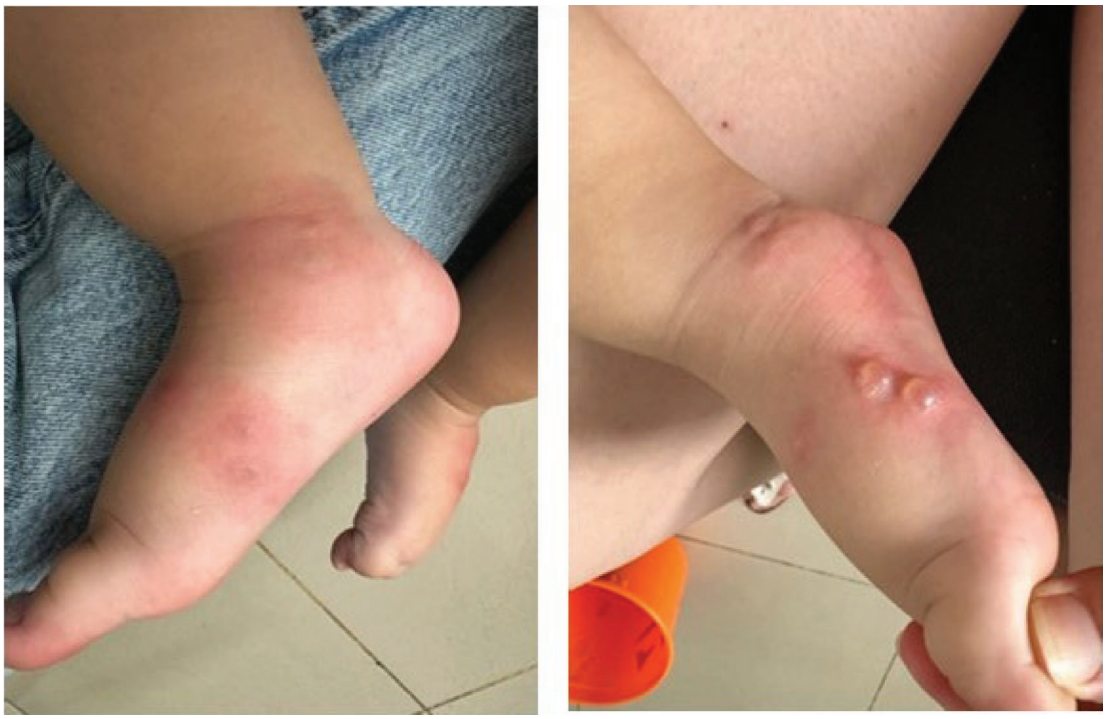
Discussion

This collection of clinical experiences in four children and one adolescent in the real-world practice adds data on the efficacy and safety of the off-label administration of rupatadine in managing allergic conditions. The present case histories align with a previous clinical review focused on the off-label prescription of the drug, confirming its advantageous pharmacological profile as a potent, non-sedating dual-action antihistamine and PAF inhibitor.[12]

Cold urticaria is characterized by mast cell degranulation upon cold exposure, with histamine and PAF playing key roles in the pathogenesis. In adults with cold urticaria, rupatadine 20 mg/day and 40 mg/day has been shown to be highly effective compared with placebo in reducing critical temperature thresholds,[13–15] but cold urticaria has been rarely observed in children, particularly as a potentially life-threatening condition when associated with systemic reactions, as the case here reported. Current EAACI/GA²LEN/EuroGuiDerm/APAAACI guidelines[16] recommend second-generation antihistamines as first-line treatment, with dose escalation based on the clinical response. A systematic review and meta-analysis also demonstrated that greater dosages of non-sedating antihistamines are more effective than standard dosages in controlling severe cold urticaria symptoms.[17] In our case, an initial up-dosing approach (10 mg twice a day) was used to ensure full control of symptoms, and the ability to later taper to a standard once-daily regimen of 5 mg/day without recurrence supports the value of flexible, individualized treatment strategies. This rare case of idiopathic acquired cold urticaria with cold-induced anaphylaxis in a child highlights the potential usefulness of rupatadine in achieving the therapeutic goals, including symptom suppression and prevention of systemic reactions.

Food allergy management has evolved from complete allergen avoidance to a more proactive approach

Figure 2. Welt-like lesions (left) and blisters on lower extremities (right).



involving the introduction of allergenic foods. Early introduction of peanut has been demonstrated to substantially reduce the risk of developing peanut allergy in at-risk individuals (e.g. early-onset severe atopic dermatitis).[18] However, many barriers hinder the successful implementation of early peanut introduction on both personal and societal levels.[19] A variety of guidelines have suggested different approaches, but in general, screening is not recommended.[20] Generally, index reactions to peanut in infants are typically relatively mild, though they may be bothersome to patients and parents.[18,21] Mild reactions are usually managed with antihistamines, though no second-generation antihistamine has been approved for this use in infants. The first-generation diphenhydramine is not recommended due to safety and effectiveness concerns.[21] In the present case of a 6-month-old baby, the antihistaminergic and anti-PAF properties of rupatadine were considered when selecting the appropriate medication for in-office and at-home reactions. A 2.5 mg dose of rupatadine achieved complete resolution of peanut-induced urticaria after early food introduction, as well as following an oral food challenge test to confirm the diagnosis. It has been described that many younger patients may not be allergic to peanuts despite positive skin testing and that confirmation of diagnosis is important before starting oral immunotherapy.[22,23] Despite these reactions, the family felt confident to move ahead with a long-term proactive immunotherapy and managing allergic reactions moving forward. Subsequently, mild reactions that occurred during oral immunotherapy over 2 years were also promptly resolved with 2.5 mg of rupatadine. In a prior case series study of five cases, rupatadine was useful in the treatment or mitigation of local allergic reactions due to sublingual immunotherapy tablets in allergic rhinitis.[24] The burden of oral immunotherapy on families is significant and they are expected to take on considerable responsibility in the active management of the disease with a daily therapy that can result in reactions. Careful preparation of families outlining allergic reactions and management of anaphylaxis before considering immunotherapy for food allergy enhances parental awareness and improves outcome.[25]

The progression from atopic dermatitis to allergic rhinitis and asthma, known as the atopic march, is dependent on individual factors, particularly the time of onset and the severity of atopic dermatitis.[26] In our patient, there was a long-standing history of atopic dermatitis and recurrent episodes of dry, non-productive cough that occurred at night outside periods of infection, shortness of breath with wheezing, pain or feeling of tightness in the chest, and worsening of symptoms after exposure to the allergen. In the presence of suggestive asthma symptoms, the diagnosis of asthma was confirmed by limitation of expiratory flow (FEV_1/FVC ratio was reduced to <0.90) and a positive reversibility test in spirometry.[27] Measurement of FeNO is not required for diagnosis, but elevated FeNO levels are an indicative parameter of the presence of an inflammatory process in the airways.[28] Two controller drugs were

used (budesonide and montelukast) due to high exposure to allergens and passive smoking. In addition, our patient presented common symptoms of an oral allergy syndrome, including itching or swelling of the mouth, face, lip, tongue and throat, which usually appear immediately after eating raw fruits or vegetables in people allergic to birch and grass pollen. Although there is no specific treatment for oral allergy syndrome other than avoidance, taking antihistamine, such as rupatadine in that case, might help stop a reaction or keep it from getting worse.

For the control of allergic rhinitis, rupatadine (2.5 mg/day), intranasal fluticasone and montelukast, in combination with allergen avoidance, are recommended. In a randomized double-blind, placebo-controlled study in patients aged between 6 and 11 years with persistent allergic rhinitis, the use of rupatadine oral solution (1 mg/mL) over 6 weeks was associated with a significant reduction of the total nasal symptoms score as compared with placebo, both at 4 and 6 weeks of treatment.[29] Additionally, in an open prospective study of 2–5-year-old children with allergic rhinitis treated with rupatadine 1 mg/mL oral solution, there was a reduction of the total five-symptoms score of 26.6% and 37.4% as compared with baseline after 14 and 28 days of treatment, respectively.[30] The case of a 6-year-old boy treated with 2.5 mg/day of rupatadine here reported enlarges the available information of the effectiveness of the drug in young paediatric patients, for which there is a general paucity of evidence, especially in complex clinical settings such as co-occurrence of atopic dermatitis, asthma and allergic rhinitis.

Stings from Hymenoptera insects, in the case of large local reactions, despite not meeting the criteria for anaphylaxis, can impair quality of life and, in exceptional circumstances (local swelling when stung in the mouth or throat), can be life-threatening. Acute management includes antihistamines (with a rapid onset of action and at high dose) for the treatment of skin symptoms, topical corticosteroids and, if necessary, systemic steroids.[31,32] Atopic eczema and allergic rhinitis are risk factors for systemic reactions to insect sting in children.[32] Because the large local reaction did not meet the criteria for anaphylaxis, specific venom immunotherapy is not recommended and the risk of progression to systemic reactions is low (2–7%).[33] Allergic rhinoconjunctivitis was a distinct feature in the clinical spectrum of the patient, with a tendency to nasal bleeding in high pollen season and after nasal corticosteroid administration. Intranasal corticosteroids are generally safe to use in the paediatric population but are not recommended in cases of nosebleeds.[34] In the present case with severe oedematous skin reactions subsequent to insect stings and allergic rhinoconjunctivitis, the combination of the dual antihistamine and anti-PAF action of rupatadine was particularly advantageous.[12]

Off-label use of rupatadine included a high initial dose of 20 mg/day followed by the recommendation of 10 mg/day for 3 days after a sting. Moreover, regular use of rupatadine 10 mg/day during the high pollen allergenic season was recommended due to his history of allergic rhinoconjunctivitis, doubling the dose in case of exacerbations of symptoms. This therapeutic strategy was very effective for the long-term control of allergic rhinitis complaints. These results are consistent with a pooled analysis of data from seven randomized, double-blind, placebo-controlled seasonal allergic rhinitis studies, in which rupatadine promoted higher proportions of responders in a dose-dependent manner, with faster and higher response rates in the 20 mg group *versus* the 10 mg group, with both doses being more effective than placebo.[35]

Insect prurigo is a hypersensitivity reaction to antigens in the saliva of insects, primarily mosquitoes, characterized by skin lesions such as hives, welts, vesicles, and in some cases, blisters. Additionally, it can produce severe and exaggerated anaphylactic reactions.[36] The case here presented showed a painful blistering skin eruption and subacute oedema in the lower extremities caused by insect bites. An intense pruritus was also a relevant presenting complaint. She was successfully treated with rupatadine at 5 mg/day for 15 days with total resolution of lesions.

The interaction of histamine with its receptors, located on sensory nerve endings, is responsible for the reflex erythema and pruritus associated with several diseases, including insect prurigo.[12] Some substances delivered to the dermis are pruritic, e.g. biogenic amines, neuropeptides, proteinases, cytokines, acetylcholine, opioids, PAF-like lipids and prostaglandins.[12] A 52-week, multicentre, open-label clinical trial conducted in Japanese adult and adolescent patients demonstrated the short-term and long-term benefits of up-dosing of rupatadine to 20 mg for the treatment of pruritic diseases and the safety of treatment on a long-term basis.[37] In a placebo-controlled study of 26 mosquito-bite-sensitive adults, administration of rupatadine 10 mg prophylactically for 4 days before receiving *Aedes aegypti* mosquito bites on the forearm was associated with a significant decrease in the size of the bite reaction and the intensity of the accompanying pruritus at 15 minutes after the mosquito bite.[38] The favourable clinical response of our patient treated with rupatadine supports its use in insect prurigo with intense pruritus and in the presence of an allergic blistering skin reaction.

Conclusion

This collection of five clinical cases in four children, including a 6-month-old infant and one adolescent, illustrates that the off-label use of rupatadine was associated

with successful outcomes in the treatment of complex allergy-related conditions and provides additional evidence of the beneficial dual antihistaminic and anti-PAF effects of the drug. Nevertheless, the cases here reported are isolated and involve specific clinical observations and physicians should be aware that any off-label use of rupatadine should always be based on a careful and individualized medical evaluation.

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