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Rupatadine – a panacea for allergies? A literature review

Rupatadyna – panaceum na choroby alergiczne? Przegląd literatury

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Abstract

Allergic diseases are one of the most common chronic diseases. The incidence of allergies is constantly increasing, and it is currently estimated that around 40% of the population suffers from at least one allergy. Current guidelines for the treatment of allergic rhinoconjunctivitis and urticaria recommend modern second-generation antihistamines. Rupatadine is the first hybrid molecule with high affinity for the H₁ receptor resulting from remarkably strong binding to this receptor. It exhibits significant H₁ receptor binding selectivity, greater in the lungs than in the cerebellum. It has antihistamine effect that is about 25 and 75 times stronger than that of cetirizine and loratadine, respectively. The second mechanism of its action is a strong antagonism of the platelet-activating factor (PAF) receptor. Rupatadine is rapidly absorbed, which correlates with the onset of anti-H₁ and anti-PAF activity. Rupatadine is approximately 99% bound to plasma proteins, but at the same time it is very well distributed to other tissues. It undergoes metabolism in the liver through oxidative processes and glucuronide conjugation. Many studies indicate that rupatadine (10 mg) was at least as effective as desloratadine, cetirizine, loratadine and ebastine in reducing allergic symptoms in allergic rhinitis and urticaria. It has also been confirmed to be effective in relieving the symptoms of insect bite response. Rupatadine has a positive effect on the daily functioning of patients with allergic rhinitis and urticaria, and improves the quality of life of these people. At the same time, many cross-sectional studies have shown that rupatadine has a good safety and tolerability profile in adults and children and has not shown adverse cardiovascular effects.

Keywords: rupatadine, allergic rhinitis, urticaria, treatment

Streszczenie

Choroby alergiczne należą do najczęstszych chorób przewlekłych. Częstość ich występowania stale wzrasta i obecnie szacuje się, że około 40% populacji cierpi na przynajmniej jedną z chorób alergicznych. Aktualne wytyczne dotyczące leczenia alergicznego zapalenia błony śluzowej nosa i spojówek oraz pokrzywki zalecają nowoczesne leki przeciwhistaminowe II generacji. Rupatadyna jest pierwszą cząsteczką hybrydową o wysokim powinowactwie do receptora H₁, wynikającym z wybitnie silnego wiązania z tym receptorem. Wykazuje ona znaczną selektywność wiązania receptorów H₁, większą w płucach niż w mózgu. Cechuje się około 25 razy silniejszym działaniem przeciwhistaminowym w porównaniu z cetytryzyną i 75 razy w porównaniu z loratadyną. Drugi mechanizm działania rupatadyny polega na silnym wpływie antagonistycznym w stosunku do receptora dla czynnika aktywującego płytki (PAF). Rupatadyna jest szybko wchłaniana, co koreluje z początkiem aktywności anti-H₁ i anti-PAF, ocenianej przez hamowanie nasilenia zaczerwienienia i bąbla pokrzywkowego. Z białkami osocza jest wiązana w około 99%, ale równocześnie jest bardzo dobrze rozprowadzana do innych tkanek i nie jest zatrzymywana we krwi obwodowej. Ulega metabolizmowi w wątrobie poprzez procesy utleniające i sprzęganie z glukuronidem. Wiele badań wskazuje, że rupatadyna w dawce 10 mg jest co najmniej tak samo skuteczna jak desloratadyna, cetytryzyna, loratadyna i ebastyna w zmniejszaniu objawów alergicznych w przebiegu alergicznego nieżytu nosa i pokrzywki. Potwierdzono również jej skuteczność w łagodzeniu reakcji po ukąszeniu owadów. Rupatadyna wpływa korzystnie na codzienne funkcjonowanie pacjentów z alergicznym nieżytem nosa i pokrzywką oraz poprawia jakość ich życia. Jednocześnie w wielu przekrojowych badaniach udowodniono, że rupatadyna ma dobry profil bezpieczeństwa i tolerancji u dorosłych i u dzieci oraz nie powoduje niekorzystnych skutków sercowo-naczyniowych.

Słowa kluczowe: rupatadyna, alergiczny nieżyt nosa, pokrzywka, leczenie

Allergic diseases are one of the most common chronic diseases diagnosed by general practitioners. At the same time, they are often underdiagnosed and undertreated. Additionally, the incidence of these conditions increases continuously. It is currently estimated that about 40% of the population suffer from one of allergic diseases. Children, young adults and urban residents seem to be affected the most^(1–5). This phenomenon has a negative impact on the quality of life, lifestyle (including sport and recreation), school or work performance and, importantly, it generates huge costs^(6,7). Two of the most common allergic diseases, i.e. allergic rhinitis (AR) and urticaria, are particularly troublesome as their symptoms can interfere with sleep, affect behaviour and daily activities, impair cognitive functions and performance at school or work. Epidemiological studies in Poland showed that AR affects 22.54% of the population⁽⁸⁾, and that 11.2% of people experienced at least one episode of urticaria in their lifetime⁽⁹⁾. Is it possible to effectively treat these diseases? Is there a panacea (a remedy that supposedly would cure all diseases) for AR and urticaria?

Since histamine plays a key role in the pathophysiology of these diseases, H₁-antihistamines are the first-line treatment for AR and urticaria^(10–12). In addition to histamine, there are many other inflammatory mediators involved in the inflammatory cascade, which play a leading role in response to allergens. In recent years, increasing attention has been paid to the platelet-activating factor (PAF) as a potential target for improved symptom control in allergic diseases^(13–15). Current guidelines for the treatment of allergic rhinoconjunctivitis and urticaria recommend modern second-generation H₁-antihistamines. They replaced first-generation antihistamines due to higher efficacy and a broader safety profile^(16,17).

RUPATADINE – THE FIRST HYBRID MOLECULE WITH HIGH AFFINITY TO H₁ RECEPTOR

Rupatadine, the first hybrid molecule, is likely to become a new quality and a fulfilment of hopes for effective treatment in children and adults⁽¹⁸⁾. It combines two functionally separate pharmacological subunits. It is a second-generation antihistamine with strong effects on the H₁ receptor due to its very high affinity to this receptor (about 7 times stronger compared to levocetirizine and 29 times stronger than fexofenadine). At the same time, rupatadine shows a significant selectivity for the H₁-histamine receptor, which is greater in the lungs than in the cerebellum (70% for receptor occupancy <10%). This drug is about 25 times more potent than cetirizine and 75 times more potent than loratadine^(19,20). The second mechanism of action of rupatadine involves strong antagonistic activity on the PAF receptor – a pro-inflammatory, endogenous lipid

mediator. Effects attributed to PAF include platelet aggregation, mast cell degranulation, macrophage and neutrophil activation as well as eosinophil chemotaxis and activation. It activates two different signalling and effector pathways linked to the monomeric or dimeric receptors for this factor on the cell membrane. Depending on which G protein is activated, PAF may induce eosinophil chemotaxis or degranulation. It is one of the strongest mediators of eosinophil chemotaxis in the airways. Through these mechanisms, PAF causes symptoms typical of the inflammatory process: bronchial smooth muscle contraction and an increase in the permeability of blood vessels (oedema). Provoked in healthy individuals, it induces symptoms of rhinitis (nasal blockage, itch, sneezing and watery discharge), which indicates significant contribution of this mechanism in allergic inflammation⁽¹⁵⁾. As a PAF inhibitor, rupatadine inhibits PAF-induced mast cell degranulation (there are no such effects for other second-generation antihistamines). Although it was demonstrated that PAF induces histamine release from mast cells in the human lungs and peripheral blood, it has no degranulating effects on cutaneous mast cells⁽²¹⁾. A study in healthy volunteers using microdialysis showed that 80% of wheal responses to intradermal injection of PAF were mediated by PAF itself, with no significant increase in histamine levels, which indicates that PAF mediates skin reaction via mechanisms independent of mast cell degranulation⁽²²⁾. Subcutaneous injection of PAF causes pain, extreme itch, and urticarial wheals. All the confirmed mechanisms of action of rupatadine are shown in Tab. 1.

PHARMACOKINETICS OF RUPATADINE

Rupatadine has a well-documented pharmacokinetic profile. The drug is rapidly absorbed following a single dose in an adult ($T_{\max}$ = 0.75–1 hour). Its rapid absorption is correlated with the onset of anti-H₁ and anti-PAF activity, assessed based on reduced flushing and urticarial wheals. Clinical trials showed the onset of action and symptom reduction already 12 hours after administration. Rupatadine is highly bound to plasma proteins (98.5–99%), but at the same time it is well distributed to other tissues and is not retained in the peripheral blood. The compound is metabolised in the liver through oxidative processes and glucuronide conjugation. It is metabolised mainly by the cytochrome P450 3A4 enzyme (CYP3A4), and some of its active metabolites retain antihistamine activity (though not against PAF), contributing to its long-term action^(13,23,24). Rupatadine has several active metabolites, such as desloratadine, 3-hydroxydesloratadine, 6-hydroxydesloratadine and 5-hydroxydesloratadine. Its half-life ($T_{1/2}$) is 5.8 hours, which allows for administering doses once daily both in children and adults^(18,25).

1	It is a potent and selective inverse agonist of the histamine H ₁ receptor, which also causes specific inhibition of PAF receptors
2	It has a high affinity for histamine H ₁ receptors and shows a strong binding selectivity for peripheral H ₁ receptors in the lungs compared to the brain (cerebellar) receptors
3	It inhibits other inflammatory processes/mediators (except for mast cell degranulation): eosinophil and neutrophil chemotaxis, secretion of pro-inflammatory cytokines (interleukins IL-5, IL-6, IL-8, GM-CSF and TNF- α), as well as production and expression of adhesion molecules (CD11b and CD18)
GM-CSF – granulocyte-macrophage colony-stimulating factor; PAF – platelet-activating factor; TNF- α – tumour necrosis factor α .	

Tab. 1. The mechanisms of action of rupatadine

THE CLINICAL USE OF RUPATADINE – EFFICACY

The presented observations led to the inclusion of rupatadine in the treatment standards for AR and urticaria. Currently, the drug in the form of tablets is recommended for the symptomatic treatment of AR and urticaria in adults and adolescents ≥ 12 years of age; the recommended dose is 10 mg once daily. Rupatadine 1 mg/mL oral solution is approved for the treatment of AR and urticaria in children 2–11 years of age^(26–28).

Rupatadine in the treatment of AR

A 2013 meta-analysis assessed the efficacy of rupatadine in allergic rhinitis by collecting data on symptom reduction from 10 randomised, double-blind, placebo-controlled studies in a total of 2,573 patients⁽²⁹⁾. Rupatadine was superior in reducing rhinitis, sneezing, nasal itching, nasal congestion as well as itchy and watery eyes compared to placebo in all these studies. It has been shown to have a rapid onset of action and long-term action after administering doses at 24-h intervals. Comparative studies have shown that the effect of rupatadine is similar to that of other antihistamines (cetirizine, desloratadine, ebastine and loratadine) in both seasonal and chronic AR^(30–37). A multicentre study in 360 AR children aged 6–11 years showed statistically significant symptom reduction compared to placebo, both after 4 and 6 weeks of treatment (Total Nasal Symptoms Score, T4SS). The study also confirmed excellent efficacy of the drug in relieving nasal congestion in children with chronic AR. This unique activity may significantly alleviate disease symptoms. This was reflected by the observed improvement in the quality of life (measured with the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire, PRQLQ) for all investigated aspects. Rupatadine was significantly superior in improving the quality of life compared to placebo. The same group of researchers obtained similar results for children with chronic AR and body weight >25 kg⁽³⁸⁾. A similar methodology yielded results suggesting that adult patients with chronic AR on continuous 12-week treatment with

rupatadine attained better symptom control than those receiving a single dose⁽³⁹⁾. These findings suggest that the population of patients with chronic AR is likely to benefit from long-term, continuous treatment with rupatadine. Despite proven efficacy of rupatadine in the treatment of AR and its position in the recommendations, new studies assessing this drug are underway. Several very interesting reports were published in 2019. Okubo et al. assessed the efficacy of rupatadine administered for 52 weeks in adult and adolescent patients aged 12–18 years for chronic AR. The study demonstrated that long-term treatment with 10 and 20 mg rupatadine is effective and safe in the treatment of chronic AR. At the same time, it was shown that a dose increased to 20 mg is a justified option for patients with chronic AR whose symptoms are ineffectively controlled with the 10 mg dose. Rupatadine significantly improved the quality of life in patients with chronic AR⁽⁴⁰⁾. The same team of researchers demonstrated that rupatadine used at 10 mg once daily for 2 weeks showed better efficacy vs. placebo in adults and adolescents with seasonal AR (SAR). The doses of rupatadine were well-tolerated. Considering the absence of evident differences in the efficacy, it may be assumed that the baseline dose should be 10 mg per day for most patients, whereas 20 mg may be an option for those with severe symptoms⁽⁴¹⁾. Similar conclusions were drawn by a team led by Professor Santamaría, who assessed safety and efficacy of rupatadine in children aged between 2 and 5 years. Oral solution of rupatadine administered once daily showed safety and correlated with significant improvement in AR symptoms in children (2–5 years). Additionally, the authors concluded that only a very small number of second-generation antihistamines ensure such symptom alleviation in such young patients, with low rates of adverse effects⁽⁴²⁾.

Another meta-analysis of seven randomised, double-blind, placebo-controlled trials assessing the proportion of patients responding to AR treatment with rupatadine (10 or 20 mg) or placebo (real life study) has been published recently. A team led by Professor Mullaol demonstrated superior efficacy of rupatadine vs. placebo in reducing SAR symptoms (Total 4 Nasal Symptom Score, T4NSS; Total 2 Ocular Symptom Score, T2OSS; Total 6 Symptom Score, T6SS) over 14 days of treatment. The improvement in the 20 mg rupatadine group was achieved within a shorter time compared to those on 10 mg and placebo. Patients treated with 20 mg rupatadine also accounted for a higher percentage of those who achieved complete or almost complete reduction of symptoms (both in T4NSS and T6SS)⁽⁴³⁾.

In conclusion, rupatadine 10 mg was at least as effective as desloratadine, cetirizine, loratadine and ebastine in reducing allergic symptoms in adults and adolescents with SAR or chronic AR. Rupatadine was more effective than levocetirizine in reducing nasal symptoms, especially oedema. These conclusions resulted in the drug being qualified for

the treatment of seasonal and chronic AR as category A (according to Global Alliance against Chronic Respiratory Diseases, GARD)⁽¹⁸⁾.

Rupatadine in the treatment of urticaria

Clinical studies have demonstrated the efficacy of rupatadine in chronic spontaneous urticaria and other urticarial conditions, and confirmed its rapid and sustained effect.

Significantly more patients with chronic spontaneous urticaria achieved $\geq 50\%$ or $\geq 75\%$ symptom improvement with 10 or 20 mg rupatadine compared to placebo. The 20 mg dose was significantly more effective than the 10 mg dose, as supported by the guidelines for the use of doses higher than standard doses of second-generation H_1 -antihistamines in the treatment of chronic spontaneous urticaria^(23,44). Comparative studies showed greater improvement in urticaria symptoms with rupatadine compared to cetirizine, desloratadine and levocetirizine^(24,45,46). A multi-centre, randomised, placebo-controlled double-blind study showed the efficacy of oral solution of rupatadine in alleviating the symptoms of chronic spontaneous urticaria in children aged 2–11 years. According to the current recommendations, rupatadine in the form of oral solution is an effective therapy for young children with chronic spontaneous urticaria^(47,48).

Based on the observations that itch, redness and swelling following intradermal injection of histamine and PAF are identical to those following a mosquito bite⁽¹³⁾, a double-blind, placebo-controlled study comparing 10 mg rupatadine with placebo in adults with increased cutaneous response to a mosquito bite was conducted⁽⁴⁹⁾. Fifteen minutes after a mosquito bite, the severity of skin reactions was 48% lower with rupatadine treatment than with placebo (55 vs. 106 mm²; $p = 0.0003$), and there was a 21% greater reduction in itch intensity. These findings suggest that rupatadine is an effective treatment for insect bites.

RUPATADINE IMPROVES THE QUALITY OF LIFE

Rupatadine has a positive effect on the daily functioning of patients with AR and urticaria, and improves their quality of life. Improvement in quality of life was observed throughout the long-term (12-month) treatment in patients with chronic AR⁽⁵⁰⁾ and for acute (4–6-week) use in the event of worsening SAR symptoms^(51,52). At the same time, it was shown that rupatadine had a greater positive effect on the quality of life (assessed with the health-related quality of life, HRQoL) compared to other second-generation H_1 -antihistamines (desloratadine, levocetirizine) in adult patients with chronic urticaria^(45,46).

Rupatadine was significantly superior to placebo in improving the quality of life in young children (2–11 years) with chronic spontaneous urticaria⁽⁴⁸⁾. It also significantly contributed to the quality of life in adult patients with mastocytosis⁽⁵³⁾.

SAFETY FIRST

Although rupatadine is biotransformed by cytochrome P450, no interactions were observed when rupatadine was co-administered with fluoxetine (a CYP2D6 substrate) or ethanol. Studies conducted with healthy volunteers showed no clinically significant interactions when rupatadine was administered concomitantly with azithromycin (a substrate of gastrointestinal P-glycoprotein). Furthermore, rupatadine did not potentiate the inhibitory effects of lorazepam on the central nervous system. After alcohol intake, the 10 mg dose of rupatadine had marginal effects in some psychomotor performance tests, which did not differ significantly from those induced by alcohol consumption alone. Co-administration of grapefruit juice caused a 3.5-fold increase in the systemic exposure to rupatadine; therefore it should not be ingested concomitantly with this drug⁽⁵⁴⁾.

Many cross-sectional studies have shown that rupatadine has a good safety and tolerability profile in adults and children with AR and urticaria. Higher doses (two or four times the standard doses) were not associated with a significant increase in adverse events. The oral solution was well tolerated in children with chronic AR or chronic spontaneous urticaria, showing a safety profile not significantly different from that of placebo. No unexpected adverse events have been reported during long-term use (1 year) of rupatadine, which confirms its good tolerability^(29,39,45,52).

Rupatadine caused no adverse cardiovascular effects in extensive clinical trials in adults and children. Doses of 10 and 100 mg per day used for 5 days in healthy adult volunteers had no statistically or clinically significant effects on cardiac repolarisation⁽⁵⁵⁾.

The safety of rupatadine used as a long-term (12 months) treatment for chronic urticaria has been confirmed in recently published studies^(56,57). Also, increased doses of the drug (recommended in the event of failure to treat chronic urticaria) did not cause significant adverse effects related to cardiac function⁽⁵⁸⁾.

CONCLUSIONS

Rupatadine is a well-studied, modern, second-generation antihistamine with an additional anti-PAF component. It is highly effective in many allergic disorders and is well tolerated even with long-term use (12–24 months). Its safety has been proven in adults, adolescents and children over 2 years of age. Importantly, there is real life evidence for rupatadine efficacy (real life studies). It is an innovative, effective and safe therapeutic option.

Conflict of interest

The author does not report any financial or personal connections with other persons or organisations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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