

# Rupatadine: a novel second-generation antihistamine

Iwona Grzelewska-Rzymowska, Paweł Górski

Department of Pneumonology and Allergology, Chair Internal Diseases, Medical University of Lodz, Poland  
Head: Prof. Paweł Górski MD, PhD

Post Dermatol Alergol 2011, XXVIII, 6: 480–488

## Abstract

Histamine is the primary mediator involved in the pathogenesis of allergic rhinitis and chronic idiopathic urticaria. Platelet-activating factor (PAF) is also a mediator which plays a key role in the allergic reaction. Rupatadine is a novel antihistamine of the second generation approved recently in Europe for the treatment of allergic rhinitis and chronic idiopathic urticaria in patients aged  $\geq 12$  years. Rupatadine shows both antihistamine and anti-PAF effects because it presents hybrid molecule. One unit of this molecule has high affinity to H1 receptor, and the second one blocks the receptor for PAF. Relative potency of rupatadine is much higher than that of other second generation antihistamines. Rupatadine also has anti-allergic and anti-inflammatory activity. The drug blocked the release of histamine from mast cells and other proinflammatory cytokines such as IL-5, IL-6, IL-8, TNF- $\alpha$  and GM-CSF from activating human lymphocytes. It also blocked in vitro chemotaxis of human eosinophils to eotaxin, and neutrophils to PAF and LTB<sub>4</sub>. Anti-allergic and anti-inflammatory activity of rupatadine results from blocking NF $\kappa$ B. Clinical trials have indicated that rupatadine is significantly more effective than placebo and equally effective as other antihistamines of the second generation. Rupatadine is well tolerated, and side effects are mild and moderate, the most common ones were headache and somnolence. The drug is safe, not cardiotoxic, does not impair psychomotor or cognitive activity.

**Key words:** histamine, H1-receptors, platelet-activating factor, antihistamines.

## Histamine and histamine receptors

Histamine is one of the earliest known mediators of allergic reactions. This mediator is stored mainly in mast cells and basophils [1]. The activation of mast cells and basophils in human body is primarily a result of an immune response mediated by immunoglobulin E. The synthesis of histamine, which is a biogenic amine with a molecular weight 112, takes place in Golgi apparatus from decarboxylation of L-histidine with the action of L-histidine decarboxylase enzyme. The metabolism of histamine is bidirectional. One way is related to the action of N-methyltransferase enzyme, which plays a major role in the respiratory track. A smaller portion of histamine is metabolized by diamine oxidase (DAO, histaminase).

Histamine causes clinical symptoms by acting on four types of histamine receptors, defined as the first, second, third and fourth type. Histamine receptors are protein structures. The symptoms of allergic diseases caused by histamine result from the action of this mediator on type 1 receptors (rH1). H1 receptor is composed of a single polypeptide chain, which seven times passes through the cell membrane leading to the formation of seven trans-

membrane domains. These domains are alternately connected with extracellular and cytoplasmic loops. rH1 chain consists of 487 amino acids, of which 205 form the intracellular loop, which includes spaces for protein kinase C (PKC). A short, carbon terminal end of the chain (COOH) is located in the cytoplasm, while amino terminal end (NH<sub>2</sub>) is situated in the extracytoplasmic space. The rH1 gene was cloned in 1993 [2]. In humans it is located on the short arm of chromosome 3p 14-17 or on chromosome 3p25 [3, 4]. In the promoter region of the rH1 gene, transcription factors can join, such as activating protein AP1 and AP2 and nuclear transcription factor  $\kappa$ B (NF $\kappa$ B), which determine the expression of rH1 as well as regulate the activity of genes for various inflammatory mediators.

The activation of the receptor by histamine leads to the activation of protein kinase C, which is in fact an element of G-protein, resulting in phosphorylation of cytoplasmic regulatory proteins (second-order carrier information) with the following molecular actions (see below).

Through transmembrane domains, H1 receptor binds the agonist, that is histamine, and antagonists, which are compounds with antihistamine activity. The amine part of histamine interacts with domain 3 (asparagine at position

---

**Address for correspondence:** Prof. Iwona Grzelewska-Rzymowska MD, PhD, Department of Pneumonology and Allergology, Chair Internal Diseases, Medical University of Lodz, 22 S. Kopcińskiego, 91-153 Lodz, Poland, e-mail: rzym@binar.pl

116), while imidazole ring with domain 5, which is amino acid lysine located at position 200 of the polypeptide chain receptor [5, 6]. Antagonists of rH1 are bound at sites located in domains 3, 4, and 6 [7]. Stimulation of rH1 in cells of target organs leads to an increase, even 3-fold, of calcium ion concentration, which is mobilized from its storage situated intracellularly and from external surface influx. Inositol 1,4,5-triphosphate and 1,2-diacylglycerol play a role of second-order carrier information and lead to the mobilization of stored calcium ions. To determine the distribution as well as biological and chemical properties of rH1, selective radioligands are used, which are binding substances to the receptor. Radioligands are usually marked with mepyramine, chlorpheniramine, and doxepin. These compounds readily penetrate the blood-cerebrospinal fluid, and thus they were applied to mark rH1 in human brain in studies using positron emission tomography (PET) [8].

Histamine, by stimulating the sensory receptors, causing itching of the nose and sneezing, and by dilatation of arteries and postcapillary veins within mucous membranes and skin, is responsible for their increased permeability and edema formation in the nasal mucosa and the occurrence of a watery runny nose. Histamine in skin is responsible for the appearance of urticarial wheals, swelling of the skin and subcutaneous tissue. This mediator has a great contribution in the pathogenesis of allergic diseases, mainly allergic rhinitis and urticaria and is responsible for many clinical symptoms observed in the early phase of allergic response. Histamine also increases the secretion of proinflammatory cytokines and cell adhesion phenomena, which is defined as non-histamine receptor-related anti-inflammatory property. It is responsible for the development of early (EAR) and late allergic reaction (LAR).

### Model studies on antihistamines

Antihistamines are used in all allergic diseases, especially those in which histamine is directly responsible for the observed acute symptoms. A study on antihistamines (AH) is a multi-stage one. At each stage of the research process, various, specific methods are applied.

Pharmacokinetic studies determine the fate of the drug in the body at the phase of absorption (bioavailability – AUC, maximum concentration in serum – C<sub>max</sub>, the time after administration of a drug when the maximum plasma concentration is reached – T<sub>max</sub>), distribution (volume of distribution – V<sub>d</sub>, degree of protein binding, time of appearance of a plateau level, or steady state), and in the elimination phase (the mean of drug elimination from the body, a half-life – T<sub>1/2</sub> and clearance) as well as drug-drug interactions.

The research on receptor activity includes *in vitro* research, which allows to specify binding affinity to rH1, half-time dissociation from rH1, the degree of selectivity towards another type receptors and degree of saturation of rH1.

*In vivo* pharmacodynamic studies are performed in humans in various organs (nose, throat, skin, eyes) to specify the size of blocking the histamine-induced reactions by antihistamines [9-11].

Non-histamine receptor-related activity. Non-histamine receptor-related activity of AH includes their anti-allergic and anti-inflammatory properties. Anti-allergic action is determined *in vitro* on isolated mast cells, basophils and other cells or lung tissue sections, which are subjected to immune and non-immune provocation, and then the secretion of mediators and varied cytokines is determined [12] as well as *in vivo* in humans, who are subjected to provocation tests with allergen using different models, such as a cutaneous one (skin window), nasal mucosa, bronchi, eye conjunctiva [13, 14]. An anti-inflammatory property is determined:

- *in vitro* using Boyden chamber, in which various inflammatory cells are exposed to chemotactic factors and this phenomenon is defined after application of antihistamines [15];
- *in vivo* using different organ models, from which the material is obtained and the inflammatory cells influx, secreted product concentration and the expression of adhesion molecules such as intercellular adhesion molecule (ICAM-1) or vascular cell adhesion molecule (VCAM-1) are detected on cells involved in inflammation and in some tissue cells [16].

### Antihistamines

Antihistamines were introduced in the 1940s for the treatment of allergic diseases and thanks to their clinical efficacy they were identified as “miraculous”. Over the years of using these drugs, it turned out that their action is not selective, meaning that they act on receptors other than rH1: dopaminergic, serotonergic and cholinergic ones. Hence, a number of side effects arose. But the most serious limitation on the use of these drugs was the fact that they penetrate the blood brain-barrier and block 70-100% of central rH1 located in frontal, temporal, hippocampus, and bridge regions. Blocking of rH1 in the brain is responsible for the sedative action of AH, and drugs of such properties are identified as the “first-generation AH” or “classic AH” [17, 18]. A risk of sedation is mainly observed in the elderly. The first-generation AH in adults cause sleepiness, impaired psychomotor reactions and lower cognitive abilities. They are responsible for traffic accidents and accidents when operating machinery. In children they impair learning ability, and in rare cases cause paradoxical agitation and impaired concentration. The most commonly used first-generation AH include hydroxyzine, chlorpheniramine, diphenhydramine and clemastine.

In the 1980s these drugs were replaced by more clinically effective (except for relief of the itch) and safer drugs called the “second-generation” drugs. The first second-generation drugs, terfenadine and astemizole, have been

withdrawn from the pharmaceutical market because of cardiotoxicity (the promotion of polymorphic tachycardia torsades de pointes). This action was proved to involve only these two drugs, rather than an entire class of the second-generation AH.

The second-generation antihistamines are characterized by:

- good absorption from the gastrointestinal tract and rapid onset of action;
- long duration of action, which allows for taking one dose per day;
- good penetration into tissues, absence of accumulation phenomenon;
- selective and potent action on H1 peripheral receptors;
- high efficiency during prolonged treatment;
- high degree of safety.

### Mechanism of action

Antihistamines compete (competitive antagonism) with histamine about rH1, they inhibit the binding of the mediator with these receptors in a reversible and concentration-dependent manner. Their receptor activity is defined as “inverse agonism” [19]. According to this concept, AH have an affinity to the inactive (constitutive) forms of H1 receptor and thus, as inverse agonists, they stabilize the receptor in the inactivated state. In this situation, the receptor cannot be excited despite the presence of the natural agonist, i.e. histamine.

### Metabolism

In intestinal absorption and distribution of antihistamines two main systems are involved: P-glycoprotein (P-GP) and carriers of the intestinal transport system (organic anion transporter polypeptide – OATP). Modulation of P-GP or OATP due to, for example the grapefruit juice, can alter drug absorption at the intestinal level.

P-glycoprotein, beside the degree of drug binding to proteins and the size of passive diffusion across the blood-brain barrier, determines the antihistamine penetration into the central nervous system (CNS) serving as a “goal-keeper”. This system limits the penetration of the drug into the CNS. If the drug is characterized by a high degree of binding with plasma proteins, lack or weak passive permeation through the blood-brain barrier, and at the same time it is substrate for P-GP, then its penetration into the CNS is much more difficult and the drug has no sedation effect. The problem of antihistamine penetration into the CNS is complex and depends on several factors and, therefore, even within the “second-generation” drugs there may be important differences in this respect. Although it is commonly assumed in a simplified manner though not quite correctly, that the “second-generation drugs are devoid of sedation”. In addition, concomitant diseases can change significantly the penetration of drugs into the CNS (meningitis, age, diabetes).

Most antihistamines are metabolized by liver involving cytochrome P-450 isoenzymes, primarily CYP3A4 and CYP2D6. Some antihistamines (terfenadine, loratadine, ebastine) during the “first pass” liver metabolism produce metabolites, which are the main active compounds. Such drugs generally have a slightly delayed onset of action, and their effectiveness depends on functional status of the liver and interactions with CYP3A4 inhibitors.

Cetirizine, a hepatic metabolite of hydroxyzine is not activated in liver. Fexofenadine and desloratadine behave similarly. Rupatadine is also a ready and very active substance blocking rH1 (and not only H1, see below), and additionally during its conversion desloratadine occurs, which may be responsible for the prolonged time of its action. The second generation drugs include cetirizine and loratadine, which were the earliest synthesized and incorporated into treatment, as well as azelastine, mizolastine, ebastine, levocabastine and rupatadine. Drugs referred to as “new AH” are terfenadine and loratadine hepatic metabolites, which are fexofenadine and desloratadine, respectively, while levocetirizine is more active L-enantiomer of cetirizine.

### Rupatadine

Rupatadine is a first hybrid molecule introduced into the therapeutics. It consists of two connected but functionally distinct pharmacological subunits: one with high-affinity to H1 receptor and the second one strongly blocking the receptor for PAF. This formula provides simultaneous blocking of both types of receptors within the same target tissues and creates a theoretical basis for the synergy of these two actions.

### Pharmacokinetics

Rupatadine is an N-alkyl piperidine derivative. The drug is well absorbed from the gastrointestinal tract, and food has a minimal effect on C<sub>max</sub>. The maximum blood concentration (C<sub>max</sub>) after single and multiple doses of 10 mg once a day is an average of 2.3 ng/ml after 0.75 to 1 h (T<sub>max</sub>) [20], Table 1. The half-life (T<sub>1/2</sub>) average value in healthy volunteers is 6.2 h (4.3-14.3 h). In the elderly, T<sub>1/2</sub> is prolonged to 8.7 h. The drug is in 98% bound to blood proteins. Its metabolism takes place mainly in the liver by oxidation, hydroxylation and conjugation with glucuronic acid, while CYP3A4 plays an important role. The drug is mainly excreted in bile, approximately 35% is excreted in the urine and 60% in the stool [20, 21]. One of the less active metabolites of precursor material rupatadine is desloratadine, which can co-decide of its prolonged action. Due to the participation of CYP3A4 in the metabolism of rupatadine, the drug should not be administered concomitantly with inhibitors of this enzyme, such as ketoconazole, erythromycin, and also grapefruit juice. Azithromycin, which is also a macrolide antibiotic, does not affect the pharmacokinetics of rupatadine.

### Rupatadine as an antihistamine

Rupatadine has a strong affinity to rH1. Research on this indicator was performed on different models, labeled with  $^3\text{H}$  mepyramine. Rupatadine showed similar affinity to rH1 as loratadine and terfenadine on the guinea pig cerebellum membranes [22], and on ovary cells of the Chinese hamster, the dissociation constant  $K_i$  was 1.4 nM for rupertadine and 1.6 nM for desloratadine, 9.4 nM for levocetirizine and 40.3 nM for fexofenadine [23]. This study indicates that rupatadine has a greater affinity to rH1 because its  $K_i$  value is the smallest in comparison to the other tested drugs. High affinity of the drug to rH1 means that in a comparable molar concentration (dose), the drug effectively ensures the maintenance of the histamine receptor in an inactive state (constitutive), with relatively higher concentrations of histamine in the environment. Rupatadine's high affinity to rH1 was confirmed *in vitro* using human umbilical vascular endothelial cells (HUVEC) [22]. In a study conducted in the guinea pig rupatadine showed a high selectivity for the peripherally located H1, occupying 70% of rH1 in the lungs, compared with those located in the cerebellum, where it took less than 10% of rH1 [24].

In *in vitro* studies on various models such as guinea pig histamine-induced intestine [22], isolated mast cells of animals provoked with an antigen, anti-IgE and non-immunological stimuli [25-28] rupatadine showed several times greater antihistamine activity than other AH of the first- and second-generation. If the relative potency of rupatadine blocking was taken as unity, then to induce this reaction, cetirizine required 23.7-fold higher concentration, while other AH require many times higher concentrations, that is they were all weaker antagonists of rH1 (Table 2) [22]. In *in vitro* studies on guinea pig intestine exposed to acetylcholine, serotonin and LTD4, it was found that rupatadine does not block intestine response to these substances. Rupatadine shows no anticholinergic, and antileukotriene and antisero-toninergic effect (although in other experiments, by secondary route, the drug may reduce production of LCT4). Blocking of the first two systems is related to the induction of adverse effects [22].

Antihistamine activity of rupatadine has been demonstrated on volunteers using two research models. Patients with seasonal allergic rhinitis (SAR) underwent allergen challenge in the Vienna chamber (Vienna Challenge Chamber) and the drug significantly blocked SAR symptoms showing rapid onset of action [29]. In healthy volunteers, rupatadine used in single doses ranging from 10 mg to 40 mg as well as in doses of 20 mg and 40 mg for 7 days significantly inhibited the wheal and erythema caused by intradermal injection of histamine [30]. In the skin test model, the equivalent doses that cause similar histamine-induced wheal blocking were 80 mg for rupatadine and 25 mg for hydroxyzine.

### Rupatadine as a platelet-activating factor inhibitor

Platelet-activating factor (PAF) belongs to the inflammatory mediators secreted by many cells such as eosinophils, mast cells, basophils, platelets, neutrophils and alveolar macrophages after activation of immune stimuli [31]. This mediator is involved in the pathogenesis of allergic diseases causing constriction and hyperactivity of bronchi, increased vascular permeability and eosinophils chemotaxis. It is detected in urticarial and

**Table 1.** Pharmacokinetics of rupatadine as an example of antihistamine used to eliminate short-term allergic symptoms and for chronic administration. On the basis of the Product Characteristics and [25]

Parameter	After a single dose (10 mg) administration	After repeated administration
$C_{\max}$ [ng/ml]	2.6	3.8
$T_{\max}$ [h]	0.8	0.75-1.0
AUC <sub>0-24 h</sub> [ng/ml]	7.6	8.4
Protein binding [%]	98.5-99.0	
The effect of the food intake	Minimal for drug and metabolites. Main active ingredient – an increase of AUC of 23%	
Metabolism	Considerable hepatic metabolism	
Elimination half-life $T_{1/2}$ [h]	4.6	5.9
$C_{\max}/\text{AUC}$	Linearity in the dose range 10-40 mg	
Route of elimination	60.9% in the feces, 34.6% in the urine	
The effect of age	Without clinical significance	

#### Abbreviations in the text

**Table 2.** The concentration of antihistamines expressed in nM causing 50% inhibition ( $\text{IC}_{50}$  – inhibition concentration) of guinea pig histamine-induced intestine contraction [22]

Antihistamine	$\text{IC}_{50}$ nM (95% CI)	Relative potency *
Rupatadine	3.8 (3.1-4.6)	1
Chlorpheniramine	6.1 (4.6-8.0)	1.6
Ketotifen	21 (12-38)	5.5
Cetirizine	90 (58-140)	23.7
Clemastine	231 (136-391)	60.8
Hydroxyzine	276 (199-382)	72.6
Loratadine	286 (170-480)	75.3
Diphenhydramine	321 (212-485)	84.5
Terfenadine	362 (258-508)	95.3

\*The concentration required to achieve an effect equivalent to the rupatadine action

psoriatic skin lesions, but it is not present in healthy skin. Platelet-activating factor administered intradermally produces a wheal/erythema [32]. This model is used to test anti-PAF activity of various chemical compounds. In studies using radioligand for PAF receptors performed on rabbit platelet membranes, rupatadine replaced selective strong antagonist WEB-2086 in the binding with this receptor. Rupatadine showed significant activity against PAF (as stated at concentrations corresponding to therapeutic concentrations), which is only slightly smaller than the model strong PAF receptor blockers, such as ginkgolide B [22]. In terms of anti-PAF action, rupatadine showed greater activity than loratadine, cetirizine and fexofenadine [22]. Rupatadine activity against PAF has been demonstrated in various research models, such as bronchoconstriction induced by PAF [22], or cutaneous wheal induced by PAF in dogs [33], in which rupatadine showed greater activity than loratadine, cetirizine and levocabastine. Using an animal model (dog), rupatadine demonstrated peak activity after 4 h, and this was maintained, depending on the dose used for 1 h to 48 h [33]. The skin model, equal to achieving erythema after administration of PAF, was used in healthy subjects. Rupatadine blocked erythema, while the dose of 80 mg worked much better than the 10 mg dose as regards the erythema blocked area and length of action [34]. Rupatadine activity against PAF was also studied in healthy volunteers *ex vivo* in the platelet aggregation test [34]. Oral single doses of 40 mg to 80 mg were subject to individual assessment. Also in this test, the maximal blocking activity of rupatadine was demonstrated after 4 h, and ceased after 24 h.

#### Anti-allergic and anti-inflammatory activity

Rupatadine, like all other second-generation AH, beside research relating to the assessment of antihistamine and anti-PAF activity, has been widely tested to determine its anti-inflammatory and anti-allergic action. The blocking of degranulation of mast cells isolated from the dog skin was determined to assess anti-allergic activity of rupatadine. The drug blocked the release of histamine from these cells, subject to immunological and non-immunological provocation [26-28]. Rupatadine, beside histamine, also blocked the release of other mediators such as leukotriene C4 (LTC<sub>4</sub>), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) from mast cells obtained from the rat peritoneal, dog skin and the line of human mast cell [28, 35].

The next phase of studies included an assessment of the impact of rupatadine on cells involved in allergic inflammation. The drug blocked *in vitro* chemotaxis of human eosinophils to eotaxin [36], neutrophils to PAF and LTB<sub>4</sub> [37]. The degree of rupatadine activity depended on the applied dose and was greater than the activity of cetirizine, fexofenadine, mizolastine and loratadine [38]. Rupatadine blocked secretion of several proinflammatory

cytokines such as IL-5, IL-6, IL-8, TNF- $\alpha$  and GM-CSF from activated human lymphocytes [39]. Rupatadine blocked release of cytokine IL-6 and IL-8 from the HUVEC activated by histamine [40]. The activity of rupatadine was greater than that of desloratadine, levocetirizine and fexofenadine [40]. Anti-inflammatory activity of rupatadine was also demonstrated in guinea pig ovalbumin-sensitized bronchi. The drug blocked the eosinophils influx in BAL fluid [41]. Nuclear factor  $\kappa\beta$ , which determines the production of proinflammatory cytokines, is involved in the inflammatory response. Rupatadine on HUVEC line and on human alveoli, which were exposed to histamine, blocked the increase of NF $\kappa\beta$  activity. The blocking of NF $\kappa\beta$  activity was associated with reduced production of proinflammatory cytokines IL-6 and IL-8 [40]. Based on these studies it can be stated that in addition to antihistaminic activity rupatadine also has anti-allergic and anti-inflammatory action that results from blocking NF $\kappa\beta$ . These characteristics may be responsible for clinical efficacy, particularly in relation to chronic allergy (urticaria, chronic rhinitis).

#### Clinical efficacy

Studies on pharmacokinetics, antihistamine activity, anti-PAF, as well as anti-inflammatory and anti-allergic action using different models *in vivo* and *in vitro* are an extremely important first phase of the study on the antihistamine drug. But the best method of assessing the drug is to perform a clinical double-blind, randomized, placebo-controlled trial. Based on clinical studies that evaluated the clinical efficacy of different doses of rupatadine, researcher and patient preferences as well as safety, it was found that the dose of 10 mg administered once daily should be considered as basic for adults [42, 43].

#### Allergic rhinitis

Rupatadine efficacy was assessed in seasonal and chronic allergic rhinitis (seasonal allergic rhinitis – SAR, chronic allergic rhinitis – CAR). It is estimated that at least 50% of the symptoms of allergic rhinitis (AR) result from the action of histamine. Efficacy of rupatadine was evaluated in comparison to placebo [43], cetirizine [44], loratadine [34, 45], ebastine [46], desloratadine [21] and levocetirizine [47]. All these drugs have clinical efficacy which was wellproven in large clinical trials [48]. Studies suggesting clinical efficacy are often experimental. Patients undergo nasal allergen challenge or provocation in the “Vienna chamber”. These studies have shown that rupatadine reduces allergen-induced resistance in the nose measured by acoustic rhinomanometry [49], and also reduces nasal and ocular symptoms induced by allergen provocation in the Vienna chamber [29]. In comparative clinical trials, rupatadine was applied for 2-4 weeks at a dose of 10 mg or 20 mg once daily in patients with SAR. Ten milligrams of rupatadine acted like 10 mg of ebastine [46],

10 mg of loratadine and 10 mg of cetirizine [34, 44, 45]. It was found that rupatadine should be administered at a dose of 10 mg and not 20 mg, and moreover 10 mg of rupatadine is a better choice than loratadine [45]. In a 2-week single-center parallel-group non placebo-controlled comparative study with 10 mg of rupatadine daily and 10 mg levocetirizine daily on 60 patients with SAR, it was found that the overall symptom severity improvement was significantly higher in the group receiving rupatadine [47]. The same was related to the quality of life estimated in a questionnaire (Rhinocconjunctivitis Quality of Life Questionnaire – RQLQ), and also only in case of rupatadine, a significant reduction of total immunoglobulin E level and the number of eosinophils in the blood was observed. In 2001, ARIA (Allergic Rhinitis and its Impact on Asthma) report was published, according to which there are two forms of AR: intermittent and persistent or chronic [50]. Following this classification, a study in which 543 patients with chronic rhinitis used placebo or rupatadine of 10 mg/day and cetirizine 10 mg/day for 12 weeks was performed [51]. Both drugs acted significantly better than placebo, but with greater efficacy of rupatadine than cetirizine. Similar results were obtained by other authors treating patients with CAR for 1 year [52]. Rupatadine proved to be an effective drug in improving the clinical course of AR and positively influencing patients' quality of life. The same results were obtained in studies conducted on Spanish patients with AR, whose severity was assessed according to the ARIA report [53].

### Urticaria

According to the recommendations presented in 2009 in the EAACI/GA<sup>2</sup>LEN/EDF report (European Academy Allergy and Clinical Immunology – EAACI, Global Allergy and Asthma European Network – GA<sup>2</sup>LEN, European Dermatology Forum – EDF), antihistamines are the first choice in the treatment of urticaria. The report recommends the use of second-generation drugs [54], which should lead to complete control of clinical symptoms. The same statement that AH which have hypnotic action are dangerous to patients, can be found in the GALEN report of 2010 [55].

Efficacy of rupatadine was determined in a number of studies involving several hundred patients with idiopathic urticaria. A study which evaluated the efficacy of doses of 5 mg, 10 mg and 20 mg showed that a dose of 5 mg does not decrease significantly the severity of urticaria, in comparison to placebo [56]. Rupatadine at doses of 10 mg and 20 mg used for 6 weeks significantly reduced the pruritus and severity of urticarial wheals. This effect appeared in the first week of treatment and persisted throughout the study. The quality of life assessed by the Dermatology Life Quality Index (DLQI) has also improved [56]. Rupatadine at a dose of 20 mg was more effective in controlling urticaria symptoms than

10 mg [56, 57]. What is more, rupatadine at a dose of 20 mg once daily also proved to be an effective drug for the treatment of acquired cold urticaria [58].

In all clinical trials performed on patients with idiopathic urticaria or AR, rupatadine turned out to be a drug rapidly disclosing its beneficial effects.

### Safety and tolerability

Antihistamines are usually administered for many weeks and even months, that is why their safety associated with their use is just as important as clinical effectiveness. Second-generation AH were thoroughly assessed using different research methods, especially in regard to their impact on the heart and CNS [48]. In clinical studies, tolerance of rupatadine was evaluated in comparison to placebo. In a large group consisting of 2025 patients treated with rupatadine compared to 1315 patients receiving placebo, it turned out that the drug was well tolerated, and side effects were mild and moderate, and included: somnolence (9.5% vs. 3.4% for placebo), headache (6.8% vs. 5.6%) and fatigue (3.3% vs. 2.0%), while general weakness, mouth dryness and dizziness occurred in 1.5%, 1.2%, 1.0% of patients treated with rupatadine, respectively, and in no-one from the placebo group [47]. Rupatadine was similarly well tolerated as other AH of the second generation, such as loratadine, ebastine and cetirizine [34, 44-46]. Safety of treatment with rupatadine over 1 year in EMEA (European Agency for the Evaluation of Medicinal Products) and ICH (International Conference on Requirements for Registration of Pharmaceuticals for Human Use) reports showed a good medium-term tolerability of this drug [52, 59, 60]. The most common, though rarely observed, side effects were headache and somnolence.

### Effects on the heart

Cardiotoxic action of terfenadine and astemizole presents as QT prolongation and arrhythmia in the form of the so-called "twisting of the points" (*torsades de pointes*) and ventricular fibrillation. Concomitant use of macrolide antibiotics, ketoconazole or fluoxetine especially easily led to this action. The arrhythmias were caused by blocking cardiac potassium channels (I<sub>Kr</sub>) [61]. Therefore, terfenadine and astemizole were withdrawn from treatment, and other AH underwent thorough research as regards their effects on potassium channels and ECG. It turned out that other AH in doses used and even many times higher did not block the I<sub>Kr</sub> channels [61]. Rupatadine was also subject to detailed studies on its effects on the heart. Studies performed in animals did not reveal that very high doses of 30 mg/kg administered intravenously and 100 mg/kg administered orally have changed ECG or physical activity [62]. *In vitro* studies showed that for blocking the gene (HERG, ether-a-go-go gene) responsible for human cloned potassium channel hKv1.5, con-

centration of rupatadine needed would be 2000 times greater than that achieved in human serum. In studies conducted on 6450 people, young and elderly of both sexes, who used rupatadine for 2-4 weeks at doses ranging from 2.5 mg to 80 mg, there was no significant effect on the QT interval, regardless of whether the subjects received the drug on an empty stomach or after a meal, with alcohol, with erythromycin or with ketoconazole [34]. In the cross-over study strictly scheduled in accordance with the ICH guidelines, conducted on 160 healthy volunteers who used rupatadine at doses of 10 mg and 100 mg (that is 10-fold greater than the standard dose), the heart rate-corrected QT interval has not changed significantly, stated as a dangerous extension [63], in contrast to the positive control group using a model substance.

#### *Effects on the central nervous system*

Consensus Group on New Generation Antihistamines (CONGA) recommends that the AH used in the treatment of allergic diseases be devoid of sedation [64]. The concept of "sedation" means a set of subjective symptoms, such as propensity to fall asleep, decreased psychomotor performance, which consists of reduced alertness and ability to concentrate, and also reduced ability to memorize. To evaluate the sedative effect of AH many different tests are used [48], including quality of life questionnaires. Rupatadine used in animals at doses up to 100 mg/kg administered orally had no effect on EEG and motor activity [22, 24]. In humans, doses of 10 mg and 20 mg did not worsen the psychomotor activity. In turn, the dose of 80 mg resulted in changes, such as 25 mg of hydroxyzine [65]. Rupatadine at a 10 mg dose had no negative impact on the drive test [66].

It may be stated that rupatadine is a second-generation antihistamine to be used once daily at a basic dose of 10 mg. The drug has highly predictable pharmacokinetics, and its bioavailability is not substantially affected by either food (though the concomitant consumption of grapefruit juice is not recommended) or other drugs metabolized in the liver, with the involvement of CYP3A4. Beside a strong antihistamine effect, the drug is additionally an effective PAF antagonist, what increases its anti-allergic activity and perhaps determines the anti-inflammatory action. The latter last activity measured by decline in the influx of inflammatory cells to the organ affected by allergic inflammation as well as a decrease of peripheral eosinophilia and the reduction in IgE levels deserves special attention and further in-depth studies. The drug very quickly controls periodic symptoms of allergic rhinitis and is highly effective in the long-term treatment of chronic rhinitis and urticaria. The drug is safe, not cardiotoxic, does not impair psychomotor or cognitive activity, and does not reduce the concentration. The drug in recommended doses is approved for use for drivers without restrictions.

#### **References**

- Riley JF, West DB. Histamine and tissue mast cells. *J Physiol* 1953; 120: 528-37.
- Chowdhury BA, Kaliner MA, Strader CM. Cloning of a gene encoding the human H1-receptor. *Soc Neurosci Abstr* 1993; 19: 84.
- Fukui H, Fujimoto K, Mizuguchi H, et al. Molecular cloning of the human histamine H1-receptor gene. *Biochem Biophys Res Commun* 1994; 201: 894-901.
- De Backer MD, Loonen I, Verhasselt P, et al. Structure of the human histamine H1-receptor gene. *Biochem J* 1998; 335: 663-70.
- Ter Laak AM, Timmerman H, Leurs R, et al. Modelling and mutation studies on the histamine H1-receptor agonist binding site reveal different binding modes for H1-agonists: Asp<sup>116</sup> (TM3) has a constitutive role in receptor stimulation. *J Comput Aided Mol Des* 1995; 9: 319-30.
- Leurs R, Smit MJ, Tensen CP, et al. Site-directed mutagenesis of the histamine H1-receptor reveals a selective interaction of asparagine207 with subclasses of H1-receptor agonists. *Biochem Biophys Res Commun* 1994; 201: 295-301.
- Wieland K, ter Laak AM, Smit MJ, et al. Mutational analysis of the antagonist-binding site of the histamine H1-receptor. *J Biol Chem* 1999; 274: 29994-30000.
- Yanai K, Watanabe T, Yokoyama H, et al. Histamine H1-receptors in human brain visualized in vivo by [<sup>11</sup>C] doxepin and positron emission tomography. *Neurosci Lett* 1992; 137: 145-8.
- Frossard N, Melac M, Benabdesselam O, et al. Consistency of the efficacy of cetirizine and ebastine on skin reactivity. *Ann Allergy Asthma Immunol* 1998; 80: 61-5.
- Larbig M, Stamm H, Casper A, et al. Twenty-four hour anti-H1 activity of levocetirizine measured by thermography is superior to fexofenadine. [abstract no. 248]. Abstract book of the XXIII EAACI Congress, Amsterdam 2004, p. 80.
- Grzelewska-Rzymowska I, Gondorowicz K, Cieśliewicz G, et al. Wpływ loratadyny, wybiórczego antagonisty receptorów histaminowych (H1) na skurcz oskrzeli wywołany wziewaniem histaminy. *Pneumonol Allergol Pol* 1992; 60: 16-21.
- Miadonna A, Milazzo N, Lorini M, et al. Inhibitory effect of the H1 antagonist loratadine on histamine release from human basophils. *Int Arch Allergy Immunol* 1994; 105: 12-7.
- Charlesworth EN, Kagey-Sobotka A, Norman PS, et al. Effect of cetirizine on mast cell-mediator release and cellular traffic during the cutaneous late-phase reaction. *J Allergy Clin Immunol* 1989; 83: 905-12.
- Stübner P, Zieglmayer R, Horak F. A direct comparison of the efficacy of antihistamines in SAR and PAR: randomised, placebo-controlled studies with levocetirizine and loratadine using an environmental exposure unit – the Vienna Challenge Chamber (VCC). *Curr Med Res Opin* 2004; 20: 891-902.
- Leprevost C, Capron M, De Vos C, et al. Inhibition of eosinophil chemotaxis by a new anti-allergic compound (cetirizine). *Int Arch Allergy Immunol* 1988; 87: 9-13.
- Ciprandi G, Buscaglia S, Pesce GP, et al. Cetirizine reduces inflammatory cell recruitment and ICAM-1 (or CD 54) expression on conjunctival epithelium in both early- and late-phase reactions after allergen-specific challenge. *J Allergy Clin Immunol* 1995; 95: 612-21.
- Meltzer EO. Performance effects of antihistamines. *J Allergy Clin Immunol* 1990; 86: 613.
- Yanai K, Watanabe T, Hatazawa J, et al. Mapping of histamine H1 receptors in human brain by positron emission tomography with [<sup>11</sup>C] pyrilamine. *J Neurochem* 1992; 59: 128-36.

19. Leurs R, Church MK, Taglialatela M. H1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. *Clin Exp Allergy* 2002; 32: 489-98.
20. Keam SJ, Plosker GL. Rupatadine: a review of its use in the management of allergic disorders. *Drugs* 2007; 67: 457-74.
21. Picado C. Rupatadine: pharmacological profile and its use in the treatment of allergic disorders. *Expert Opin Pharmacother* 2006; 7: 1989-2001.
22. Merlos M, Giral M, Balsa D, et al. Rupatadine, a new potent, orally active dual antagonist of histamine and platelet-activating factor (PAF). *J Pharmacol Exp Ther* 1997; 280: 114-21.
23. Barron S, Ramis I, Garcia-Rafanell J, Merlos M. Inhibitory activity of rupatadine on pro-inflammatory cytokine production, relationship with binding affinity. *Methods Find Exp Clin Pharmacol* 2005; 27 (Suppl. 2): 161-2.
24. Giral M, Balsa D, Ferrando R, et al. CNS activity profile of rupatadine fumarate, a new dual receptor antagonist of platelet-activating factor (PAF) and histamine. *Allergy* 1998; 53 (Suppl.): 131.
25. Izquierdo I, Merlos M, Garcia-Rafanell J. Rupatadine, a new selective histamine H1 receptor and platelet-activating factor (PAF) antagonist: a review of pharmacological profile and clinical management of allergic rhinitis. *Drugs Today (Barc)* 2003; 39: 451-68.
26. Queralt M, Merlos M, Giral M, Puigdemont A. Dual effect of a new compound, rupatadine, on edema induced by platelet-activating factor and histamine in dogs: comparison with antihistamines and PAF antagonists. *Drug Dev Res* 1996; 39: 12-8.
27. Queralt M, Brazis P, Merlos M, Puigdemont A. Inhibitory effects of rupatadine on mast cell histamine release and skin wheal development induced by *Ascaris suum* in hypersensitive dogs. *Drug Dev Res* 1998; 44: 49-55.
28. Queralt M, Brazis P, Merlos M, et al. In vitro inhibitory effect of rupatadine on histamine and TNF- $\alpha$  release from dispersed canine skin mast cells and the human mast cell line HMC-1. *Inflamm Res* 2000; 49: 355-60.
29. Stuebner P, Horak F, Ziegelmayer R, et al. Effects of rupatadine vs placebo on allergen-induced symptoms in patients exposed to aeroallergens in the Vienna Challenge Chamber. *Ann Allergy Asthma Immunol* 2006; 96: 37-44.
30. Izquierdo I, Nieto C, Ramis J, et al. Pharmacokinetics and dose linearity of rupatadine fumarate in healthy volunteers. *Methods Find Exp Clin Pharmacol* 1997; 19 (Suppl. A): 189-203.
31. Curtin ML. Current status of platelet activating factor antagonists. *Exp Opin Ther Patents* 1998; 8: 703-11.
32. Marques SA, Dy LC, Southall MD, et al. The platelet-activating factor receptor activates the extracellular signal-regulated kinase mitogen-activated protein kinase and induces proliferation of epidermal cells through an epidermal growth factor-receptor-dependent pathway. *J Pharmacol Exp Ther* 2002; 300: 1026-35.
33. Merlos M, Balsa D, Giral M, et al. Inhibition of rat peritoneal mast cell exocytosis by rupatadine fumarate: a study with different secretagogues. *Methods Find Exp Clin Pharmacol* 1997; 19 (Suppl. A): 148.
34. Izquierdo I, Merlos M, Garcia-Rafanell J. Rupatadine, a new selective histamine H1 receptor and platelet activating factor (PAF) antagonist: a review of pharmacological profile and clinical management of allergic rhinitis. *Drugs Today (Barc)* 2003; 39: 451-68.
35. Merlos M, Ramis I, Balsa D, et al. Inhibitory effect of rupatadine on TNF- $\alpha$  release from human monocytes and mast cell line HMC-1. *J Allergy Clin Immunol* 2000; 105 (Suppl. 1): S62.
36. Barron S, Ramis I, Merlos M. Rupatadine inhibits the inflammatory component of allergic response: cytokine release, adhesion molecule expression and inflammatory cell recruitment. 23<sup>rd</sup> EAACI Congress, 12-16 June 2004, Amsterdam.
37. Izquierdo I, Nieto C, Ramis J, et al. Pharmacokinetics and dose linearity of rupatadine fumarate in healthy volunteers. *Methods Find Exp Clin Pharmacol* 1997; 19 (Suppl. A): 189-203.
38. Ramis I, Giral M, Ferrando R, Merlos M. Inhibition of PAF- and LTB4-induced human neutrophil chemotaxis by rupatadine using a new fluorescent chemotaxis assay. *Allergy* 2000; 55 (Suppl. 63): 94-5.
39. Barron S, Ramis I, Merlos M. Effect of rupatadine on lymphocyte cytokine production. *Allergy Clin Immunol Int* 2005; 1 (Suppl. 1): 427.
40. Barron S, Roman J, Michelena P, et al. Rupatadine inhibits cytokine production and NF $\kappa$ B activity by histamine H1 receptor-dependent mechanism. *Rev Rinol* 2006; 6: 18.
41. Merlos M, Giral M, Balsa D, et al. Rupatadine inhibits the eosinophil recruitment in BAL fluid of ovalbumin-sensitized guinea pigs. *J Allergy Clin Immunol* 1998; 101 (Suppl. 1): S218.
42. Izquierdo I, Paredes I, Lurigados C, et al. A dose ranging study of rupatadine fumarate in patients with seasonal allergic rhinitis. *Allergy* 2000; 55 (Suppl. 63): 275.
43. Perez I, De la Cruz G, Villa M, Izquierdo I. Rupatadine in allergic rhinitis: pooled analysis of efficacy data. *Allergy* 2002; 57 (Suppl. 73): 245.
44. Martinez-Cocera C, De Molina M, Marti-Guadano E, et al. Rupatadine 10 mg and cetirizine 10 mg in seasonal allergic rhinitis: a randomised, double-blind parallel study. *J Investig Allergol Clin Immunol* 2005; 15: 22-9.
45. Saint-Martin F, Dumur JP, Perez I, Izquierdo I. A randomized, double-blind, parallel-group study, comparing the efficacy and safety of rupatadine (20 and 10 mg), a new PAF and H1 receptor specific histamine antagonist, to loratadine 10 mg in the treatment of seasonal allergic rhinitis. *J Investig Allergol Clin Immunol* 2004; 14: 34-40.
46. Guadano EM, Serra-Batlles J, Meseguer J, et al. Rupatadine 10 mg and ebastine 10 mg in seasonal allergic rhinitis: a comparison study. *Allergy* 2004; 59: 766-71.
47. Maiti R, Rahman J, Jaida J, et al. Rupatadine and levocetirizine for seasonal allergic rhinitis. A comparative study of efficacy and safety. *Arch Otolaryngol Head Neck Surg* 2010; 136: 796-800.
48. Polish Allergology Society – Consensus. Antihistamines in medicine practice. Ed. Sesja 2005 [in Polish].
49. Valero A, Bartra J, Serrano C, et al. Rupatadine reduces nasal obstruction in allergen-induced rhinitis. *Allergy* 2007; 62 (Suppl. 83): 137-8.
50. Bousquet J, Van Cauwenberge P, Khaltaev N; ARIA Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108 (5 Suppl): S147-53.
51. Fantin S, Maspero J, Bisbal C, et al. A 12-week placebo-controlled study of rupatadine 10 mg once daily comparative with cetirizine 10 mg once daily, in the treatment of persistent allergic rhinitis. *Allergy* 2008; 63: 924-31.
52. Valero A, de la Torre F, Castillo JA, et al. Safety of rupatadine administered over a period of 1 year in the treatment of persistent allergic rhinitis. A multicentre, open-label study in Spain. *Drug Safety* 2009; 32: 33-42.



53. Valero A, Izquierdo I, Giralt, et al. Rupatadine improves nasal symptoms, quality of life (ESPRINT-15) and severity in a sub-analysis of a cohort of spanish allergic rhinitis patients. *J Investig Allergol Clin Immunol* 2011; 21: 229-35.
54. Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA2LEN/EDF/WAO guideline: management of urticaria. *Allergy* 2009; 64: 1427-43.
55. Church MK, Maurer M, Simons FE, et al. Risk of first-generation H1-antihistamines: a GA2LEN position paper. *Allergy* 2010; 65: 459-66.
56. Dubertret L, Zalupca L, Cristodoulo T, et al. Once daily rupatadine improves the symptoms of chronic idiopathic urticaria: a randomised, double-blind, placebo-controlled study. *Eur J Dermatol* 2007; 17: 223-28.
57. Giménez-Arnau A, Izquierdo I, Maurer M. The use of a responder analyses to identify clinically meaningful differences in chronic urticaria patients following placebo-controlled treatment with rupatadine 10 and 20 mg. *J Eur Acad Dermatol Venerol* 2009; 23: 1088-91.
58. Krause K, Zuberbier T, Maurer M. Modern approaches to the diagnosis and treatment of cold contract urticaria. *Curr Allergy Asthma Rep* 2010; 10: 243-9.
59. European Agency for the Evaluation of Medicinal Products (EMA). Committee for Medicinal Products for Human Use: guideline on the clinical development of medicinal products for the treatment of allergic rhinoconjunctivitis. London: Committee for Medicinal Products from EMA.
60. International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Topic E1 A note for guidance: population exposure: the extent of population exposure to assess clinical safety. Geneva: ICH, 1995.
61. Grzelewska-Rzymowska I, et al. The cardiac effect of the second generation of antihistamines. *Pneumonol Alergol Pol* 2001; 69: 217-26.
62. Caballero R, Valenzuela C, Longobardo M, et al. Effects of rupatadine, a new dual antagonist of histamine and platelet-activating factor receptors, on human cardiac Kv1.5 channels. *Br J Pharmacol* 1999; 128: 1071-81.
63. Donado E, García O, Pérez I, Barbanoj M, et al. Cardiac safety of rupatadine according to the new ICH guideline: a „thorough QT/ QTc study” [Abstract no. 760 plus poster]. 25<sup>th</sup> EAACI Congress 10-14 June, 2006, Vienna.
64. Holgate ST, Canonica GW, Simons FER, et al. Consensus group on new-generation antihistamines (CONGA): present status and recommendations. *Clin Exp Allergy* 2003; 33: 1305-24.
65. Barbanoj MJ, Garcia-Gea C, Morte A, et al. Central and peripheral evaluation of rupatadine, a new antihistamine/platelet-activating factor antagonist, at different doses in healthy volunteers. *Neuropsychobiology* 2004; 50: 311-21.
66. Vuurman E, Theunissen E, van Oers A, et al. Lack of effects between rupatadine 10 mg and placebo on actual driving performance of healthy volunteers. *Human Psychopharmacol Clin Exp* 2007; 22: 289-97.