Rupatadine: efficacy and safety of a non-sedating antihistamine with PAF-antagonist effects

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Summary
Rupatadine is a modern non-sedating H1-antihistamine that also has additional antagonist effects on platelet-activating factor (PAF). Under the tradenames Rupafin® and Urtimed®, Rupatadine is approved in Germany for the treatment of allergic rhinitis and urticaria in adults and children aged over 12 years. In this review, the available literature available to date on the pharmacological profile and clinical application of Rupatadine is reviewed and compared to other conventional histamines. In conclusion, finally, the side effects, safety and interaction profile of Rupatadine are discussed. Due to CYP p450 metabolism, Rupatadine should not be given together with Erythromycin, Ketoconazole or grapefruit juice. Rupatadine has been found to be effective and safe in a variety of randomized clinical trials both in seasonal and perennial allergic rhinitis, as well as in chronic urticaria. Rupatadine has been found as effective and safe.

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Introduction
More than 45 H1 antihistamines (H1 histamine receptor antagonists), forming the largest class of drugs for the treatment of allergic diseases, are available worldwide [1]. Despite comparable efficacy in the treatment of allergic rhinoconjunctivitis, urticaria and other allergic diseases, approved preparations differ in terms of their chemical structure, clinical pharmacology and potential toxicity.

Rupatadine is a novel substance which, in addition to being an H1 antagonist, is also a potent platelet-activating factor (PAF) inhibitor. It belongs to the N-alkyl pyridine derivatives. Animal and human models [2] have shown rupatadine to have dual antihistamine and PAF-antagonist properties. It is commercially available in Spain as 10-mg tablets and has already been approved in several other European countries [3, 4]. Rupatadine has been available in Germany for the treatment of allergic rhinitis and chronic urticaria in adults and children aged over 12 years under the tradename Rupafin® since August 1, 2008, and under the tradename Urtimed® since 2010 [5]. The present article discusses the pharmacology, kinetics, anti-inflammatory effects, clinical efficacy as well as the side effects and interaction profile of this antihistamine.

Pharmacology and kinetics
Rupatadine (8-chloro-11-[1-[(5-methyl-3-pyridinyl)methyl] piperidin-4-ylidene]-6,11-dihydro-5H-benzocyclohepta[1,2-b]pyridine fumarate), a second-generation antihistamine, is a selective, long-acting histamine receptor antagonist with peripheral H1 receptor activity (Fig. 1) [2]. Desloratadine and its hydroxylated metabolites are some of the rupatadine metabolites that may contribute to the drug’s overall efficacy [5].

In vitro metabolism studies using human liver microsomes show that the cytochrome P450 CYP3A4 is the isoenzyme primarily responsible for the biotransformation of rupatadine [5, 6].

The time to maximum plasma concentration (Tmax) in adults is between 45 min and 1 h following oral intake (Tab. 1). The drug’s half-life is 5.9 h. Rupatadine undergoes significant presystemic metabolism when administered orally. The most important biotransformation pathways of rupatadine include oxidative processes, oxidation of the pyridine ring, and hydroxylation of the piperidine moiety.
idine-methyl group to carboxylic acid, N-dealkylation of piperidine nitrogen and hydroxylation of the 3-, 5- and 6-positions in the tricyclic ring system [7]. Only insignificant amounts of unaltered active substance were found in urine and feces [4, 5, 8, 9].

The pharmacokinetics of rupatadine are linear for doses between 10 mg and 40 mg [5, 8]. The binding rate of rupatadine to plasma protein is 98%–99%. Despite this high binding rate, it is well distributed and is able to reach target receptors [6].

Studies have shown that the active substance’s maximum plasma concentration is delayed by approximately 1 h when taken with food; despite this delay, the maximum concentration in blood remained unaltered by food intake [5, 8].

Anti-inflammatory and antihistaminergic effects of rupatadine

Rupatadine has a high affinity for the H1 receptor. This activity has been demonstrated in vitro and in a broad spectrum of pharmacological in vivo models in mice, rats, guinea pigs, rabbits, dogs and humans.

Rupatadine inhibits histamine-induced guinea pig ileum contraction at concentrations in the nanomolar range [2]. This ability has been compared in several studies with data on already established antihistamines such as loratadine or terfenadine [8]. The dissociation constant Ki for the three antihistamines was 102, 127 and 144 nM. The same model showed that rupatadine is better than loratadine and fexofenadine at suppressing 3H-mepyramin—a radioligand for the histochemical investigation of histamine receptors—from its H1 binding site (shown in Tab. 2 as the mean inhibitory concentration IC50) [2].
Rupatadine shows strong selectivity for binding to lung-tissue H1 receptors compared to brain (cerebellum) H1 receptors following oral administration of 0.16 mg/kg in guinea pigs. Similar findings have been reported for loratadine, whilst hydroxyzine showed no differentiation between lung and brain and diphenhydramine blocked lung receptors only weakly (< 10 %) [8].

Merlos and co-workers [2] were also able to show that rupatadine has a selective effect on histamine H1 receptors; however, no effects on acetylcholine, serotonin or leukotriene receptors were observed.

The intensity and duration of inhibition of wheal and erythema formation in the histamine skin prick model increases with dose escalation, reaching peak values of 69 %, 82 % and 93 % following doses of 10, 20 and 40 mg, respectively [9].

Rupatadine’s antihistamine activity has been investigated in a number of in vitro models (Tab. 2) [2].

**PAF antagonist activity**

PAF is an endogenous phospholipid mediator of inflammation made up of inflammatory cells such as alveolar macrophages, eosinophils, mast cells, basophils, platelets and neutrophils, which are released in response to allergic/inflammatory reactions. These reactions are associated with increased vascular permeability, eosinophil chemoattraction, bronchoconstriction and airway hyperresponsiveness, all of which are involved in the pathophysiology of rhinitis, asthma and anaphylaxis. Moreover, increased plasma levels of PAF have been reported in patients with urticaria and psoriasis compared with healthy controls [10, 11, 12].

Rupatadine demonstrates competitive PAF antagonistic activity in the submicromolar range in vitro, with IC50 values of 0.2 and 0.68 µM in models to evaluate thrombocyte aggregation in washed thrombocytes from rabbit or human platelet-rich plasma, respectively. In these models, rupatadine’s anti-PAF activity was lower than the specific PAF antagonists WEB-2086 and Ginkgolid B, but significantly higher than that of the antihistamines loratadine, ketotifen, mepyramine, cetirizine or terfenadine [8].

The dose-response relationship of rupatadine in the inhibition of PAF-induced wheals and erythema is shown in Tab. 3 [9]. The efficacy of rupatadine increases in a linear fashion at increasing doses up to 40 mg; beyond this dose, dose escalation is associated with a slower increase in efficacy [7].

Church [13] showed rupatadine to have long-lasting efficacy at four times the recommended dose over up to 72 h against PAF-induced dermal flares following skin prick testing.
Anticholinergic effects
In contrast to many other first-generation antihistamines, no anticholinergic effects were observed for single doses of rupatadine in the 10- to 80-mg dose range [7].

Other antiinflammatory/antiallergic effects
Several studies have confirmed that rupatadine exhibits inhibitory effects, e.g. on mast cell degranulation and eosinophil chemotaxis, in various type-1 hypersensitivity models.

Rupatadine blocks isolated mast cell degranulation in sensitized dogs. In this particular model, the effects of rupatadine were comparable to those of loratadine, although rupatadine tends to achieve a greater overall effect [4, 8, 14, 15, 16].

In addition to histamine, it was also possible to inhibit the release of LTC4 from peritoneal rat mast cells, as well as the release of tumor necrosis factor (TNF)-α from human mast cell lines. It has been suggested that this property may play a beneficial role in the late phase of allergic reactions [7, 17, 18, 19].

Barrón et al. [20] demonstrated that, at concentrations of between 10 and 100 nM, rupatadine inhibits human eotaxininduced eosinophil chemotaxis.

Rupatadine also inhibits PAF- and LTB4-induced human neutrophil chemotaxis. In Ramis et al.’s model, rupatadine was shown to be more effective than other antihistamines, such as cetirizine, fexofenadine, loratadine and mizolastine [21].

The inhibitory effects of a number of antihistamines (rupatadine, desloratadine, levocetirizine and fexofenadine) on proinflammatory cytokine (interleukin [IL-6] and IL-8) secretion were investigated in human umbilical venous endothelial cells (HUVEC) activated by histamine. Rupatadine showed the lowest IC50 value, followed by desloratadine, levocetirizine and fexofenadine [22].

Furthermore, several studies observed inhibition of: secretion of other lymphocyte cytokines (IL-5, IL-6, IL-8, granulocyte macrophage colony-stimulating factor [GM-CSF] and TNF-α), as well as expression of allergy-associated adhesion molecules (CD18 and CD11b) and various transcription factors (nuclear factor κ-light-chain-enhancer of activated B-cells, NF-κB) [8].

Clinical studies
Numerous randomized placebo-controlled double-blind studies on the efficacy of rupatadine in allergic rhinitis and chronic urticaria have been conducted. Comparative studies with various non-sedating H1 receptor antagonists have also been carried out.

The majority of available studies still subdivide allergic rhinitis according to the older system into seasonal (SAR) and perennial allergic rhinitis (PAR), whilst only a small number refer to the new ARIA (allergic rhinitis and its impact on asthma) criteria, which classify allergic rhinitis into intermittent or persistent allergic rhinitis [23, 24, 25].

Interestingly, many authors observed a fast onset of action in patients with SAR, PAR, persistent allergic rhinitis (PER) and chronic idiopathic urticaria in clinical studies on rupatadine. These observations are consistent with the drug’s pharmacokinetic profile [7, 8, 13].

Seasonal allergic rhinitis
Clinical studies on rupatadine in patients with moderate to severe SAR are summarized in Tab. 4. The
results of these studies confirm the efficacy of rupatadine to reduce mean daily total symptom scores (mDTSS). Covariate analysis found no age- or sex-specific differences.

All rupatadine doses investigated were more effective at reducing SAR symptoms in a dose-dependent manner than placebo. Two studies measured the objective efficacy of rupatadine 10 mg in the reduction of nasal obstruction following allergen provocation; here again, rupatadine was significantly superior to placebo [26, 27].

Overall, doses of 10 mg and 20 mg were the most effective compared to lower doses and, apart from a general trend towards faster symptom relief at 20 mg, significant differences following 1-week treatment were observed [7, 28].

Rupatadine 10 mg once daily was compared with ebastine 10 mg once daily and placebo [29]. After 2 weeks, mDTSS values in the rupatadine group were 33 % lower than placebo (p = 0.005). The total symptom score for rupatadine was 22 % lower compared with ebastine; however, this result did not reach statistical significance. Compared with placebo, rupatadine reduced all symptoms with a statistically significant reduction of sneezing, rhinorrhea, lacrimation and nasal itch. The greatest difference between active treatment and placebo was observed for rhinorrhea (rupatadine vs. placebo, p < 0.001; ebastine vs. placebo, p < 0.005).

The efficacy of rupatadine and levocetirizine was compared for 2 weeks in SAR patients [30]. A significantly greater reduction (p = 0.004) in immunoglobulin-E (IgE) levels and overall nasal symptom scores (p < 0.001) was observed in the rupatadine group compared with the levocetirizine group. There was an 18.08 % (p = 0.02) reduction in the score for the rhinoconjunctivitis quality of life questionnaire (RQLQ) in the rupatadine group, a significantly greater reduction than that seen in the levocetirizine group.

Several studies comparing the 10- and 20-mg doses of rupatadine with the approved daily doses of cetirizine and loratadine showed rupatadine to be beneficial [31, 32, 33].

In a newly published study, the efficacy of rupatadine and olopatadine was compared in SAR patients [34]. The olopatadine group showed a significantly greater reduction in serum IgE values (p = 0.01), total nasal symptoms scores (p < 0.001) and RQLQ scores (p = 0.015) compared to rupatadine.

**Perennial allergic rhinitis**

Rupatadine at doses of 10 or 20 mg once daily was significantly superior to placebo in the treatment of PAR [35].

Compared with other antihistamines, rupatadine proved to be at least as effective as cetirizine, ebastine and loratadine for the relief of nasal and ocular symptoms in patients with PAR [35, 36].

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**Table 4**

### Summary of efficacy of rupatadine in adults and adolescents (> 12 years) with seasonal allergic rhinitis (SAR)

| Study design | RU dose and comparative treatment | Treatment duration (weeks) | No. of patients | Efficacy (mDTSS) | Reference Author (year) |
|--------------|----------------------------------|---------------------------|-----------------|------------------|------------------------|
| R, DB, PC    | PL vs. RU 10 mg/20 mg             | 2                         | 50/54/45        | RU 10 vs. PL* RU 20 vs. PL* | [28] Izquierdo et al. (2000) |
| R, DB, PC    | PL vs. RU 2.5 mg/5 mg/10 mg/20 mg | 2                         | 392             | RU 2.5 vs. PL* RU 5 vs. PL* RU 10 vs. PL* RU 20 vs. PL* | [4] Izquierdo et al. (2003) |
| R, DB, PC    | PL vs. RU 10 mg vs. EBA 10 mg     | 2                         | 81/79/83        | RU 10 vs. PL* EBA vs. PL ns | [29] Guadano et al. (2004) |
| R, DB        | RU 10 mg vs. LCT 10 mg            | 2                         | 60              | RU vs. LCT*      | [30] Maiti et al. (2010) |
| R, DB        | RU 10 mg vs. CTZ 10 mg            | 2                         | 124/117         | RU vs. CTZ ns    | [31] Martinez-Cocera et al. (2005) |
| R, DB        | RU 10 mg/20 mg vs. LOR 10 mg      | 2                         | 339             | RU 10 vs. LOR ns RU 20 vs. LOR ns | [33] Saint-Martin et al. (2004) |
| R, DB        | RU 10 mg vs. OLP 10 mg            | 2                         | 70              | OLP 10 vs. RU 10 ns | [34] Maiti et al. (2011) |

R, randomized; DB, double-blind; PC, placebo-controlled; RU, rupatadine; PL, placebo; CTZ, cetirizine; LOR, loratadine; OLP, olopatadine; LCT, levocetirizine; mDTSS, mean daily total symptom score *p < 0.05.
Rupatadine also proved to be effective in the treatment of cold urticaria [44].

**Tolerability and safety**

Results from the clinical phase-III study carried out by Picado et al. [45] in a total of 3490 patients or healthy volunteers are summarized in Table 5.

In a multicenter phase-IV study, 120 PER patients were treated with rupatadine for 12 months to evaluate the substance’s long-term safety in accordance with guidelines of the European Medicines Agency (EMEA) [46, 47]. In particular, headache, drowsiness and dry mouth were the most commonly observed side effects. No clinically relevant changes in electrocardiogram (ECG) were observed. This study confirms rupatadine’s good long-term safety profile.

One case of fixed drug eruption was attributed to rupatadine and confirmed by oral provocation testing [48].

**Cardiac toxicity**

A number of older antihistamines, such as astemizole and later terfenadine, are known to cause prolongation of the QT interval by direct blockade of repolarizing potassium channels, thereby increasing the risk of torsades de pointes arrhythmias [49] [50]. However, these effects are not related to interaction with specific H1 receptors and, as such, are not histamine-specific [8, 51].

The cardiac safety of rupatadine has been extensively and repeatedly investigated in clinical studies [4, 45, 52].

Preclinical studies yielded the following results:

- Rupatadine doses 100 times that of the clinically recommended dose of 10 mg had no effect whatsoever on ECG parameters, blood pressure or pulse rate in rats, guinea pigs and dogs. No arrhythmias or other cardiovascular complications were observed [53].
- Concentrations of rupatadine and one of its most important metabolites in humans (3-hydroxydesloratadine) exceeding at least 2000-fold the Cmax values reached after the administration of a 10-mg dose in humans had no effect on the cardiac action potential in vitro isolated canine Purkinje fibers [5, 7, 8].
- In a study designed to investigate the effect on a cloned human ether-a-go-go-related gene (HERG) potassium channel, the channel was blocked by rupatadine at a concentration 1685 times greater than the Cmax value reached following administration of 10 mg rupatadine. Tissue distribution studies using radiolabeled rupatadine in rat tissue showed no accumulation of rupatadine in heart tissue [5, 7, 8].
- A QT/QTc study was carried out in line with the guideline recommendations of the EMEA and the
International Conference on Harmonisation (ICH) E14. In the positive control group, moxi-
floraxin demonstrated the expected changes in QTc interval. ECG data for rupatadine at 10 and
100 mg showed no effects. There were no sex-spe-
cific effects and no pharmacodynamic link be-
tween rupatadine and its main metabolites, thereby
confirming that rupatadine has no particular effect whatsoever on QTc interval. This study
demonstrated that rupatadine has no proarrrhyth-
mic side effects even at 10 times the therapeutic
dose [5, 7, 8].

Central nervous system toxicity
Rupatadine behaves like other second-generation
antihistamines and is non-sedating. Even doses as
high as 100 mg/kg in a series of tests in rats and
mice failed to produce changes in ECG or motor ac-
tivity [2, 54].

No psychomotor impairment could be detected
in humans at doses of up 20 mg. However, dose-
dependent impairments were seen at higher doses. Hydroxyzine 25 mg (p = 0.01) and rupatadine
80 mg (p = 0.02) produced significant impairment
of similar degree. The cognitive and psychomotor
impairment produced by a single 10-mg oral dose
of rupatadine in combination with ethanol was no
greater than the impairment produced by ethanol
alone, whilst a higher dose (20 mg) in combination
with ethanol caused cognitive and psychomotor
impairment comparable to that seen with hydroxyzine 25 mg and cetirizine even at therapeutic
doses [55, 56].

The effects of rupatadine on fitness to drive were
investigated in a study on healthy subjects: at the
recommended dose of 10 mg rupatadine, no diff-
erences could be seen compared to placebo [3, 57].

Drug interactions
Simultaneous administration of 20 mg rupatadine
and ketoconazole or erythromycin (or any other po-
tential CYP3A4 inhibitor) increases systemic rupa-
tadine exposure (as measured by the area under the
concentration time curve, AUC) by 10- and two-
to three-fold, respectively. These changes were not
associated with any effect on the QT interval or an in-
crease in side effects.

Rupatadine is well tolerated in combination with
azithromycin or fluoxetine and can be administered
in therapeutic doses without risk [5, 7, 8].

Simultaneous intake of grapefruit juice increased
rupatadine exposure 3.5-fold. When administering
a four times higher dose of rupatadine, as recom-
"
Efficacy and safety of rupatadine

Conflict of interest
The corresponding author states that there are no conflicts of interest.

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