Pharmacology of Desloratadine
Special Characteristics

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Abstract

Desloratadine is a new, non-sedating H1 receptor antagonist, which has been shown to have good tolerability and to be effective in the treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria. The pharmacological profile of desloratadine exhibits particular advantages compared with other antihistamines in terms of binding and occupancy of the human H1 receptor and its pharmacokinetics. This review describes aspects of these pharmacological properties, focusing on H1 receptor antagonism by desloratadine, its predictable pharmacokinetics when administered with food and common medications, and its lack of effect on important drug transport molecules, such as P-glycoprotein and organic anion transport polypeptide.

1. Introduction

Desloratadine is a new histamine H1 receptor antagonist that has been shown to be effective and well tolerated in placebo-controlled clinical trials in seasonal allergic rhinitis (SAR),[1] perennial allergic rhinitis (PAR)[2] and chronic idiopathic urticaria (CIU).[3] Desloratadine provides good control of nasal and non-nasal symptoms of SAR, such as sneezing and rhinorrhea. In addition, desloratadine treatment has been shown to produce moderate, but significant reductions in the symptoms of nasal congestion.[4-6] Desloratadine has full 24-hour efficacy, demonstrated by its significant relief of symptoms of SAR and PAR at trough concentrations 24 hours after administration, which is consistent with the long half-life and prolonged H1 receptor occupancy of desloratadine.[1,2] The onset of action of desloratadine in SAR has been shown to be as soon as 30 minutes after administration in a controlled allergen exposure model.[7] In the case of CIU, desloratadine treatment demonstrated early and sustained relief of symptoms and signs, such as pruritus, hive size and hive numbers.[8] These clinical improvements in CIU severity were accompanied by less sleep disturbance and improved ability to perform daily activities.

The antihistamine class of allergy drugs has seen the introduction of metabolites and chiral derivatives to supersede parent compounds on several occasions. In general this has been done in an effort to overcome safety problems encountered with the parent molecule. For instance, fexofenadine, the carboxylic acid metabolite of terfenadine, was introduced to avoid the significant cardiotoxicity encountered with elevated plasma concentrations of terfenadine. Levocetirizine, an enantiomer of the sedation-associated compound cetirizine, was introduced to avoid the significant cardiotoxicity encountered with elevated plasma concentrations of terfenadine. Levocetirizine, an enantiomer of the sedation-associated compound cetirizine, has recently become available in Europe.[9] The pharmacological activity of cetirizine is probably attributable largely to levocetirizine.[10] Therefore, as cetirizine is an equimolar racemic mixture of dextro- and levocetirizine, a 5mg tablet of levocetirizine provides the same amount of levocetirizine as 10mg of cetirizine.

In contrast to both terfenadine and cetirizine,
loratadine is both a noncardiotoxic and a nonsedating antihistamine. Desloratadine exhibits advantages over other antihistamines in terms of strong affinity for and slow dissociation from the H1 receptor. Also, the pharmacological profile of desloratadine is influenced little by coadministration with grapefruit juice, food and other medications. Furthermore, unlike fexofenadine, desloratadine does not rely on important drug transport molecules, such as P-glycoprotein (Pgp) and organic anion transport polypeptide (OATP), for its absorption and elimination following oral administration. The combination of these pharmacological factors with the in vitro inhibition by desloratadine of the elaboration of many allergic inflammatory mediators may help to explain the significant impact of desloratadine on symptoms of SAR, including nasal congestion, PAR and CIU. General aspects of the pharmacology of desloratadine, including its inhibitory effects on the allergic inflammatory cascade, have been reviewed comprehensively (see Table I for pharmacokinetic data). This review concentrates on the H1 receptor-binding and pharmacokinetic profiles of desloratadine, which differentiate it pharmacologically from other commonly used second-generation antihistamines.

2. Receptor Binding Characteristics

A full range of in vitro and in vivo H1 receptor dissociation and association studies has shown desloratadine to have the strongest affinity for the histamine H1 receptor and the most potent H1 receptor antagonism of all currently available antihistamines. The H1 receptor-binding characteristics of desloratadine were performed largely in cloned human H1 receptors, which provides a fuller picture of the antihistaminic activity of desloratadine at the human H1 receptor.

2.1 Animal Models

The H1 receptor-binding properties and in vivo antihistaminic activities of desloratadine have been studied in guinea-pig, mouse and monkey models. Compared with loratadine and terfenadine, desloratadine was 14 and 23 times more potent, respectively, in inhibiting [3H]mepyramine binding to guinea-pig lung H1 receptors. Desloratadine was 10 times more potent than loratadine and terfenadine at inhibiting histamine-induced guinea-pig ileal contraction. In vivo studies, wherein mice were dosed orally with desloratadine or loratadine, demonstrated that desloratadine was 4 times more potent than loratadine in inhibiting histamine-induced paw oedema. Furthermore, in vivo studies of guinea-pigs showed that oral desloratadine was 2.5 times more potent than oral loratadine in protecting against death due to a lethal injected dose of histamine. Desloratadine reduced allergic cough to a significantly greater degree than loratadine in an ovalbumin-sensitised guinea-pig model. Histamine-induced nasal microvascular permeability in guinea-pigs was also inhibited by topically applied desloratadine to a greater extent than by topically applied loratadine: the concentration of desloratadine was 10-fold less than the concentration of loratadine required to antagonise histamine-induced nasal secretion in guinea-pigs. In cynomolgus monkeys sensitised to ascaris, desloratadine significantly reduced ascaris-induced and histamine-induced bronchospasm and lessened the allergen-induced increase in airway resistance and reduction in lung compliance compared with placebo.

Desloratadine is selective for H1 receptors and has no significant effects on other systems, including cholinergic muscarinic receptors, when studied at concentrations consistent with recommended therapeutic dosages. Kreutner et al. studied the receptor selectivity of desloratadine in a wide range of biochemical, in vitro and in vivo assays. In vitro biochemical studies showed that

| Table I. Pharmacokinetic parameters of desloratadine following a 5mg single oral dose |
|---------------------------------|----------------------------------|
| Maximum concentration 3.3 μg/L | Area under the plasma concentration-time curve 77.5 μg • h/L |
| Clearance (apparent total) 114 L/h | Half-life (elimination) 27h |

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desloratadine had no effect on dopamine, mono-
amine oxidase, GABA and other receptor and en-
zyme systems, even at doses as high as 10 μmol/L. Desloratadine exhibited 62 times greater affinity for H1 receptors than H2 receptors. With respect to muscarinic receptors, the in vitro affinity of desloratadine for recombinant human M1, M2, M4 and M5 receptors was approximately 8 to 50 times less than its affinity for H1 receptors. The relevant Ki (inhibition constant) values were 5.7 nmol/L for H1 receptors and 50, 47, 104 and 320 nmol/L for M1, M2, M4 and M5 muscarinic receptors, respectively. Similarly, desloratadine did not affect pilo-
carpine-induced salivation across a clinically rele-
vant dose range in a mouse model, 70 times the dosage required for H1 receptor antagonism being required to antagonise pilocarpine-induced salivation. Other animal studies have confirmed that desloratadine has no functional antimuscarinic activity when administered within clinically relevant dosage ranges. At high doses up to 300 mg/kg, desloratadine did not protect mice against cholin-
ergic agonist (physostigmine)-induced death.

2.2 Human H1 Receptors

Occupancy of the H1 receptor by desloratadine is a function of its binding affinity and its resis-
tance to spontaneous or competitive displacement by other compounds. Both of these parameters have been studied specifically in human H1 recep-
tors in vitro.

Lippert et al.[12] studied the associative binding of desloratadine in human H1 receptors in vitro. Desloratadine bound to H1 receptors with high affinity and was saturable [Kd (dissociation constant) = 1.1 ± 0.2 nmol/L]. The binding of desloratadine to human H1 receptors was rapid and reached steady state within 60 minutes (figure 1). The affinity of desloratadine for human H1 recep-
tors was compared with that of other antihista-
mines. H1 receptor affinity was assessed by inhibi-
tion of [3H]pyrilamine (2 nmol/L) binding and inhibition of Ca2+ flux, the latter of which is nor-
ma lly associated with activation of the H1 receptor by histamine.[18] Desloratadine had a markedly higher H1 receptor affinity than other compounds; in particular, desloratadine had 200 times the affinity of fexofenadine and more than 150 times the affinity of loratadine (table II).[18] Desloratadine also inhibited histamine-induced Ca2+ flux in hu-
man H1 receptor-expressing cells to a greater ex-
tent than fexofenadine, cetirizine and loratadine. The Kd (base ionisation constant) for desloratadine was 0.2 nmol/L, compared with 18.6 nmol/L for cetirizine, 23 nmol/L for fexofenadine and 16 nmol/L for loratadine.[18]
chial smooth muscle cells that express H₁ receptors constitutively, desloratadine inhibited histamine-induced Ca²⁺ flux with greater potency than all other second-generation antihistamines. The inhibition of histamine-induced Ca²⁺ flux by desloratadine in models, such as H₁ receptors cloned in Chinese hamster ovary cells or on endogenous H₁ receptors expressed on human bronchial smooth muscle cells, demonstrated desloratadine to be 50 to 100 times more effective in blocking the function of H₁ receptors than either fexofenadine or cetirizine.

Lippert and colleagues also recently reported human H₁ receptor dissociation experiments with desloratadine and pyrilamine. Cell membranes expressing human H₁ receptors were incubated with either [³H]desloratadine or [³H]pyrilamine in the presence or absence of chlorpheniramine. The dissociation kinetics of desloratadine showed prolonged H₁ receptor occupancy, with 63% of desloratadine still bound after 6 hours (figure 2). This was much greater than pyrilamine, which had a short H₁ receptor-binding time (t₁/₂ = 3.8 minutes). In summary, these multiple in vitro studies show that desloratadine binds to the human H₁ receptor with much greater affinity than other antihistamines. Also, once bound to the human H₁ receptor, desloratadine displays prolonged receptor occupancy, as it dissociates very slowly from the receptor. This combination of high affinity for and slow dissociation from the human H₁ receptor represents ideal H₁ receptor dynamics for an antihistaminic drug.

### 3. Cytochrome P450 Drug Metabolism

Desloratadine is one of approximately 12 active metabolites of loratadine. Approximately 70% of loratadine is converted eventually to desloratadine by hepatic cytochrome P450 (CYP) metabolism – primarily via the CYP3A4 and CYP2D6 isoenzymes – after oral administration. The conversion of loratadine to desloratadine is relatively rapid, with peak plasma concentrations of desloratadine occurring 1.3 to 3.7 hours after oral loratadine administration. When given as a loratadine tablet, the unchanged loratadine has a much shorter elimination half-life (t₁/₂β) than that of desloratadine generated in vivo (7.8 to 11 vs 17.3 to 24 hours). Patients receiving oral loratadine have greater exposure to desloratadine than to loratadine, as measured by the area under the concentration-time curve (AUC). Hence, a proportion of the clinical activity of loratadine can probably be attributed to desloratadine derived from metabolism of loratadine. The delivery to the H₁ receptor of desloratadine derived from metabolised loratadine is dependent on the absorption of loratadine and the rate of conversion of loratadine to desloratadine. Alterations in the rate of forma-

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**Table II.** Binding affinity constants for desloratadine and other antihistamines at human H₁ receptors expressed on Chinese hamster ovary cell membranes, based on tritiated pyrilamine binding. (Adapted from Anthes et al.[18])

<table>
<thead>
<tr>
<th>Compound</th>
<th>Kᵢ (nmol/L) ± SEM</th>
<th>Relative potencyᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desloratadine</td>
<td>0.87 ± 0.1</td>
<td>201</td>
</tr>
<tr>
<td>Pyrilamine</td>
<td>1.7 ± 0.1</td>
<td>103</td>
</tr>
<tr>
<td>Mizolastine</td>
<td>22 ± 6</td>
<td>8.0</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>40 ± 4.6</td>
<td>4.4</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>47.2 ± 10</td>
<td>3.7</td>
</tr>
<tr>
<td>Ebastine</td>
<td>51.7 ± 6.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Loratadine</td>
<td>138 ± 23</td>
<td>1.2</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>175 ± 68</td>
<td>1.0</td>
</tr>
</tbody>
</table>

ᵃ Relative potency with fexofenadine expressed as 1.0.

Kᵢ = inhibition constant; SEM = standard error of the mean.

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**Fig. 2.** Dissociation of tritiated pyrilamine and tritiated desloratadine from human H₁ receptors expressed on Chinese hamster ovary cell membranes. (Adapted from Geha & Meltzer[16])
tion of desloratadine from loratadine can occur at the level of the gut and the liver. After oral administration, loratadine must be absorbed by the gut before being metabolised to desloratadine by hepatic CYP isoenzymes. The time to peak plasma concentration (t\text{max}) of loratadine and desloratadine is delayed by 1 hour when loratadine is consumed with food, and longer in the case of the Claritin® Reditab® formulation of loratadine. Also, coadministration of loratadine with CYP3A4 inhibitors, such as ketoconazole and erythromycin can alter the metabolism of loratadine, leading to increased loratadine AUC. While the AUC of desloratadine generated from loratadine is substantially increased following coadministration of loratadine with erythromycin (40% increase in desloratadine AUC), a much smaller effect occurs when a desloratadine tablet is coadministered with erythromycin (14% rise in desloratadine AUC). Hence, for desloratadine derived from hepatic CYP metabolism of loratadine to bind to human H\textsubscript{1} receptors, it must overcome potential pharmacological obstacles in terms of absorption and metabolism. The CYP conversion of loratadine to desloratadine can be inhibited by other medications, such as ketoconazole, erythromycin and cimetidine.

The bioavailability of orally administered desloratadine is not affected by food (unlike loratadine) and it is absorbed rapidly from the gut into the bloodstream. The t\text{1/2} of desloratadine is long (~27 hours). It is available immediately in its most active form and does not require metabolism to maximise its pharmacological activity. The major active metabolite of desloratadine, 3-OH-desloratadine, exhibits less H\textsubscript{1} receptor antagonism than desloratadine. The precise rate of metabolic conversion of desloratadine to 3-OH-desloratadine is not yet known. Approximately 6% of the general population and 20% of African Americans are slow metabolisers of desloratadine, defined as <10% conversion rate of desloratadine to 3-OH-desloratadine, which results in up to a 6-fold increase in the desloratadine AUC. However, as both desloratadine and 3-OH-desloratadine are active, this shift in the balance to more desloratadine and less 3-OH-desloratadine is unlikely to affect the efficacy and adverse-event profiles of desloratadine in this slow metaboliser subgroup.

Metabolic biotransformation plays an important role in the activity and safety of many antihistamines. As outlined above, a proportion of the clinical activity of loratadine is attributable to desloratadine formed by hepatic CYP3A4 and/or CYP2D6. Induction or inhibition of CYP subtypes can influence the rate of formation of desloratadine from loratadine. As both desloratadine and loratadine have good safety profiles and are not associated with cardiotoxicity, increased exposure (i.e. elevated AUC) to either compound may not represent a hazard for the patient. Inhibition of CYP isoenzymes has been shown to affect the metabolism and safety of other antihistamines, such as terfenadine. This phenomenon of increased QTc interval has been reported with other antihistamines such as astemizole and ebastine.

Desloratadine is metabolised to hydroxylated active metabolites, including its main metabolite, 3-OH-desloratadine, and minor metabolites, including 5-OH-, 6-OH- and dihydroxy-desloratadine. These hydroxylated metabolites are subsequently glucuronidated to form inactive compounds. Barecki et al. recently studied the effect of desloratadine on the function of CYP subtypes using pooled human microsomes. Desloratadine caused no significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 isoenzymes at concentrations many multiples of normal plasma levels in humans. Therefore, coadministration of desloratadine with drugs that utilise the above CYP isoenzymes would be unlikely to cause significant accumulation of coadministered drugs.

The profile of desloratadine has been studied extensively in humans in coadministration studies with CYP3A4 and CYP2D6 inhibitors (table III).
When desloratadine 7.5mg once daily (50% greater than the clinical dose) was given in combination with erythromycin 500mg every 8 hours for 10 days, only minor changes in desloratadine pharmacokinetics were seen. The AUC and peak plasma concentration (C$_{\text{max}}$) for desloratadine increased by 14% and 24%, respectively, while no clinically relevant changes in electrocardiographic data occurred. The AUC for loratadine after 10 days of coadministration with erythromycin (500mg every 8 hours) rose by 40%. When desloratadine 7.5mg once daily was combined with ketoconazole 200mg every 12 hours for 10 days, the AUC and C$_{\text{max}}$ values for desloratadine rose by 39% and 45%, respectively. In contrast, the AUC for loratadine rose by 307% during coadministration with ketoconazole. Again, no clinically relevant QTc interval effects were seen during ketoconazole-desloratadine coadministration. The pharmacokinetics and electrocardiographic safety profile of desloratadine 5mg once daily have also been studied in combination with the commonly prescribed drugs azithromycin, a macrolide antibiotic, and fluoxetine, an antidepressant metabolised predominantly by CYP2D6. Following coadministration with azithromycin, the AUC and C$_{\text{max}}$ of desloratadine rose by 5% and 15%, respectively. The AUC and C$_{\text{max}}$ values for fexofenadine 60mg twice daily, on the other hand, rose 67% and 69%, respectively, when fexofenadine was coadministered with azithromycin. Fluoxetine 20mg once daily had no effect on the AUC of desloratadine, while the C$_{\text{max}}$ of desloratadine showed a small increase of 15%. No significant electrocardiographic changes were seen when desloratadine was coadministered with either azithromycin or fluoxetine. Coadministration of desloratadine 5mg and cimetidine 600mg twice daily in 36 healthy volunteers had little effect on the pharmacokinetics of desloratadine, with minor increases in AUC and C$_{\text{max}}$ of 19% and 12%, respectively. The results of these studies demonstrate that desloratadine does not interact significantly with individual inhibitors of CYP subtypes.

### 4. Drug Transport Proteins

Recently it has become clear that drug disposition and metabolism cannot be explained solely in terms of hepatic biotransformation by CYP isoenzymes and subsequent excretion. A large number of membrane proteins have been identified that are responsible for active and passive transport of common cardiac, antimicrobial, anticancer and antihistaminic drugs. The best described of these systems is Pgp, a 170kD protein with 12 membrane-spanning domains which transports a wide range of substrates out of cells. The multidrug resistance gene, MDR1, codes for Pgp and it was originally described as being overexpressed in multidrug-resistant tumours. Pgp is heavily expressed on the luminal surfaces of cells in the small intestine, proximal renal tubules and biliary canaliculi, in addition to cells of the blood-brain barrier and in placental trophoblasts. The role of Pgp is thought to be protective against exogenous toxins or xenobiotics. In humans, however, many drugs are substrates, inhibitors or inducers of Pgp, and drug-drug interactions have been attributed to interference with Pgp function. Such interactions are most significant when they involve drugs that rely heavily on Pgp for their excretion, such as digoxin and fexofenadine. Desloratadine is neither a significant inhibitor nor a substrate of Pgp and is thus unlikely to cause

<table>
<thead>
<tr>
<th>Antihistamine</th>
<th>Coadministered drug</th>
<th>Coadministered drug</th>
<th>Coadministered drug</th>
<th>Coadministered drug</th>
<th>Coadministered drug</th>
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<tbody>
<tr>
<td>Desloratadine</td>
<td>AUC 14%↑</td>
<td>AUC 39%↑</td>
<td>AUC 5%↑</td>
<td>AUC 19%↑</td>
<td>AUC unchanged</td>
</tr>
<tr>
<td>Loratadine</td>
<td>AUC 40%↑</td>
<td>AUC 307%↑</td>
<td>NA</td>
<td>AUC 103%↑</td>
<td>NA</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>AUC 109%↑</td>
<td>AUC 164%↑</td>
<td>AUC 69%↑</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

AUC = area under the plasma concentration-time curve; NA = not available; ↑ indicates increase.

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significant drug interactions via this transporter. Loratadine does inhibit MDR1 function (daunorubicin transport) more readily than desloratadine, although this is unlikely to be clinically relevant, as the $K_i$ of loratadine for MDR1 was 300 times the $C_{max}$ normally achieved in patients taking loratadine 10mg, whereas the $K_i$ for desloratadine is 1500 times the $C_{max}$ of desloratadine. It should be noted that the inhibition of MDR1 function by loratadine was much less than that of ketoconazole, which is a potent inhibitor of Pgp. In contrast to desloratadine, fexofenadine relies heavily on Pgp for its excretion. Fexofenadine, being an organic acid/anion (originally terfenadine carboxylate), appears to be dependent on another transporter, OATP, for its absorption. An international panel recently adopted fexofenadine as the recommended research probe for Pgp drug disposition studies. In most tissues Pgp is an outward transporter of substrates such as fexofenadine. OATP is often expressed on the basal surface of cells and may be involved in cellular uptake of fexofenadine from the bloodstream and absorption of fexofenadine by enterocytes. It has been suggested that Pgp and OATP act cooperatively to transport fexofenadine from hepatic sinusoids into hepatocytes (via OATP), after which it is excreted into bile (via Pgp). The role of Pgp and OATP in the absorption and excretion of fexofenadine has been studied extensively in cell lines, genetically engineered ('knockout') mice and humans. Cvetkovic et al. showed fexofenadine to be a Pgp substrate in cell culture. Knockout mice deficient in Pgp (mdr1a --/) had significantly elevated brain and plasma concentrations of fexofenadine after oral and intravenous administration, indicating that Pgp functions to restrict the penetration of the blood-brain barrier by fexofenadine. Others have found that induction of Pgp in the human intestine occurs with rifampicin treatment, which in turn increases intestinal fexofenadine efflux, causing a 2.5-fold increase in the clearance of fexofenadine. St. John’s wort, a herbal remedy, acts as an inhibitor of Pgp after acute administration, thereby increasing the $C_{max}$ of fexofenadine, whereas with long-term administration, St. John’s wort induces Pgp and reduces the AUC of fexofenadine by up to 50%. Genetic variations in Pgp substrate transport dynamics have been reported in humans. A recent investigation demonstrated that expression of the main genetic variant form of Pgp resulted in up to 40% reduction in bioavailability of fexofenadine. Variant forms of Pgp are seen in up to 62% of European Americans and up to 13% of African Americans. Furthermore, a recent report suggests that polymorphisms in the MDR1 gene and Pgp structure can influence the efficacy of fexofenadine in inhibiting the histamine-induced cutaneous wheal and flare that healthy Korean volunteers manifest.

The transporter protein OATP relies on concentration gradients rather than energy to transport substrates across membranes and is usually involved in absorption of substrates from the bloodstream and the gut. OATP attaches substrates such as fexofenadine via ionic bonds, and it is likely that these bonds can be disrupted by a diet rich in highly charged molecules, such as flavinoids. OATP and Pgp share many similar substrate specificities. Cvetkovic et al. showed fexofenadine is a substrate for OATP, the uptake of which can be inhibited by various drugs in cell culture (e.g. verapamil, quinidine and ketoconazole).

Grapefruit juice is well recognised to interfere with the metabolism of many drugs via inhibition of CYP3A4 by components such as flavinoids and bergamottin. Recently, grapefruit and other juices have also been noted to influence the function of OATP. This is demonstrated by studies that have shown that the pharmacokinetics of fexofenadine are altered significantly when it is administered in combination with fruit juices. Banfield et al. compared the bioavailabilities of single doses of desloratadine 5mg and fexofenadine 60mg with or without grapefruit juice 8oz (220ml) 3 times a day for 2 days in 24 healthy volunteers. The $C_{max}$ and AUC for desloratadine were virtually unchanged (7% and 9% increased, respectively,
over control level). Both C\text{max} and AUC for fexofenadine were decreased by 30%. Dresser et al.\cite{60} studied the effect of various fruit juices on the pharmacokinetics of fexofenadine and reported that administration of fruit juices reduced significantly (p < 0.05) the AUC and C\text{max} of fexofenadine compared with water. The percentage reductions in fexofenadine AUC∞ were 23% with 25% strength grapefruit juice, 63% with normal strength grapefruit juice, 69% with orange juice and 73% with apple juice, each administered as a 1200ml volume of juice (total volume consumed over 3 hours). Concomitantly, statistically significant reductions (68 to 69%) in 24-hour urinary fexofenadine excretion were seen when fexofenadine was administered with 100% strength grapefruit, orange and apple juices (p < 0.05). As urinary clearance of fexofenadine and 24-hour urinary volume were unaffected, the authors concluded that the decrease in urinary fexofenadine excretion was due to inhibition of drug absorption from the gut by fruit juices in a fruit juice dose-dependent manner. This study is interesting, as it extends the previously reported effects of grapefruit juice on fexofenadine pharmacokinetics to other citrus and non-citrus juices. The authors also performed a series of in vitro experiments, which demonstrated that oatp3 (rat OATP analogue) was highly sensitive to citrus juices and purified citrus fruit extracts at concentrations 2- to 150-fold less than those found in fresh fruit.\cite{60,61}

Taken together, these recent investigations indicate that the bioavailability of fexofenadine may be reduced via induction of Pgp, or inhibition of OATP, or both, by constituents of fruit juices. The possible effect of these findings on the clinical profile of fexofenadine is yet to be determined. Desloratadine, unlike fexofenadine, is not a substrate for Pgp and its pharmacokinetic profile is essentially unaffected by coadministration with grapefruit juice.

5. Other Effects on Intestinal Absorption

Interestingly, it has been noted recently that a high-salt diet can affect the bioavailability of drugs such as verapamil that are substrates of transport proteins.\cite{62,63} In the case of fexofenadine, a high-salt diet (400 mEq/day) reduced the bioavailability of fexofenadine compared with a low-salt diet (10 mEq/day).\cite{64} The AUC of fexofenadine was 1605 ± 167 on a low-salt diet and 1087 ± 142 on a high-salt diet, while C\text{max} values were 362 ± 40 and 241 ± 34 on low- and high-salt diets, respectively. Dietary salt at a level of about 15 g/day can reduce the bioavailability of fexofenadine by approximately 40%, which may be due to modulation of transport protein function in the gut. Most likely, this is due to perturbation of OATP-mediated gut fexofenadine absorption by dietary components with a high anionic content.

Other dietary constituents such as fat and over-the-counter treatments such as aluminium- and magnesium-based antacids can also interfere significantly with fexofenadine absorption. A high-fat diet has been shown to reduce the AUC of fexofenadine by 17% when the drug is administered as a capsule and 24% when it is administered as a tablet;\cite{65} this rises to a 40% reduction in the case of the fexofenadine/pseudoephedrine (Allegra-D®) preparation of fexofenadine.\cite{66} The effect of fat on fexofenadine absorption is probably related to fexofenadine being an organic acid, which is poorly miscible in lipids. The opposite is true of loratadine, for which a high-fat diet increases bioavailability by 40%; this rises to 80 to 125% in the case of loratadine-pseudoephedrine combination tablets, consequent to the poor water solubility and relatively greater fat miscibility of loratadine. Desloratadine, having at least 7-fold greater water solubility than loratadine and more than 500-fold less lipophilicity than loratadine, has no significant change in AUC when taken with or without a high-fat meal. Fexofenadine, the anionic carboxylic acid metabolite of terfenadine, combines with poorly absorbable magnesium- and aluminium-containing antacids (e.g. Maalox®) to form a salt, which alters the pharmacokinetics of fexofenadine. Up to 28% binding of fexofenadine to these antacids occurs when they are coadministered within 15 minutes, resulting in a reduc-
tion in bioavailability of a single dose of fexofenadine 120mg by 41% and C<sub>max</sub> by 43%.[67]

6. Conclusion

Clinical trials of desloratadine in SAR, PAR and CIU have demonstrated excellent efficacy and tolerability in terms of symptom control, with rapid onset, extended duration of action and an adverse-event profile not different from that of placebo.[1,2,8] These clinical effects are supported by extensive in vitro pharmacological studies that have shown desloratadine to be the most potent H<sub>1</sub> receptor antagonist currently available, being rapidly absorbed and having both <sup>1</sup><sub>t<sub>β</sub> and prolonged H<sub>1</sub> receptor occupancy consistent with a full 24-hour duration of action. Preclinical pharmacodynamic studies demonstrate that desloratadine has inhibitory effects on allergic inflammatory cells and on the elaboration of mediators, such as cytokines, chemokines and adhesion molecules, that are responsible for orchestrating the systemic allergic inflammatory response to allergen exposure.[15]

This review has focused on specific pharmacological features that differentiate desloratadine from other available antihistamines, such as fexofenadine and loratadine. Fexofenadine is not metabolised to a significant extent in the liver (<4% of total dose) and the evidence to date suggests that fexofenadine is dependent to a significant extent on Pgp and OATP transporters for its gut absorption and elimination in bile and urine.[49,50,66] Up-regulation of intestinal Pgp can increase elimination of fexofenadine,[52-54] thereby reducing overall bioavailability. Gut absorption of fexofenadine is also altered by food,[65] fruit juices,[60] dietary salt[64] and magnesium- and aluminium-containing antacids.[66,67] In contrast, desloratadine is readily absorbed from the gut and is unaffected by coadministration with fatty food,[26] antacids[27] or grapefruit juice.[59] Desloratadine is not a significant substrate of Pgp[48] and it is reliably and predictably absorbed after oral administration.[113,16] In vitro binding studies have shown that desloratadine binds with higher affinity to H<sub>1</sub> receptors than other antihistamines and has a long receptor occupancy time.[12,17,18] The combination of prolonged selective H<sub>1</sub> receptor antagonism, broad inhibition of the allergic cascade, and a low risk of clinically significant drug-drug and drug-food interactions helps to underpin the efficacy and safety profile of desloratadine in clinical studies of SAR, PAR and CIU.

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