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Second-generation antihistamines in the treatment of allergies on the example of loratadine

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Summary:

This paper discusses the use of loratadine as a second-generation histamine H1 receptor antagonist in the treatment of allergic diseases. Pharmacokinetics, metabolism and physicochemical parameters of loratadine are reviewed. Commercial Loratadine-containing products are presented.

Key words: allergy, antihistamine drugs, loratadine.

Allergic diseases are a serious social and medical problem, considered by the experts to be the epidemics of the 21st century. The number of individuals suffering from allergies has doubled every 10 years since the 1950s [1,2]. The problem pertains to all age groups from infants to the elderly and is manifested as atopic dermatitis, bronchial asthma, allergic rhinitis and conjunctivitis in the form of hives and angioedema as well as gastrointestinal allergies [3,4]. Newer and newer factors may become allergens, including not only pollens or insect venoms, but also animal fur, mites, foods (e.g. milk, fruit), as well as medicines, cosmetics, chemicals [4]. The International Study of Asthma and Allergy in Childhood showed that allergies are less prevalent in less-developed countries, which is in line with the hygienic theory of allergy development [5]. Studies conducted in 2006 showed that the number of patients with allergies in Poland had increased, the suspected cause being the change in living conditions and lifestyles, increased exposure to pollutants and chemicals used in households, agriculture and industry [6,7]. A conclusion may be drawn that excessively polluted environment, as well as excessively hygienic lifestyle may impact the development of allergies, as evidenced for instance by children's homes in Łódź, where a lower incidence of allergies (12.5%) was observed as compared to the overall population (25.4-40.2%) [8,9].

Second-generation antihistamines were introduced to therapy in the 1980s. One of these second-generation antihistamines is loratadine, characterized by strong and long-lasting antiallergic activity. In contrast to the first-generation antihistamines, loratadine does not cross the blood-brain barrier, shows selectivity when used at therapeutic concentrations and reveals high affinity to peripheral H_1 receptors, allowing to avoid induction of somnolence (in the majority of population) [10-19]. The use of loratadine does not impair the ability to drive or use machines [13,16,20].

Loratadine has beneficial antiallergic properties – it inhibits the release of mediators from mast cells and basophils (animal studies) and is characterized by an additional anti-inflammatory effect [16,17,21]. It has no cholinolytic properties (allowing it to be used in glaucoma and prostatic hyperplasia) or antiserotonine properties (not causing a body mass increase). Loratadine is administered by oral route, and its long half-life allows for once-daily administration [17]. The efficacy of loratadine is identical as that of the first-generation drugs, although inter-individual differences may be observed [16]. Upon the use of loratadine, skin reactions to histamine and allergens (skin allergy tests) are suppressed for up to 7 days after discontinuation of the drug [21]. Loratadine was not shown to induce tolerance after administration for 28 days [13,22]. Loratadine has no cardiotoxic effects, even in combination with antifungals (ketoconazole, itraconazole) or macrolide antibiotics (erythromycin, clarithromycin) that inhibit the metabolism of loratadine, thus increasing its plasma levels [13,18,22,23].

The use of loratadine in pregnancy is allowed only in absolute necessity, because the drug is classified as FDA category B [10,24,25]. Category B includes drugs for which animal tests had been conducted showing no adverse effects on the fetus but there had been no tests on humans, or the animal tests had shown adverse effects on the fetus but studies in groups of pregnant women did not confirm any hazard for the fetus. [27,28]

Loratadine should not be used when breastfeeding as loratadine and its metabolite pass to mother's milk, and the concentration of loratadine in milk is higher than that in the serum [10].

Loratadine is used in the treatment of symptoms of allergic rhinitis, both seasonal and perennial (sneezing, running nose, itchy nose, rhinitis, nasal mucosal swelling, itching and burning sensation, lachrymation), as well as symptoms of acute and chronic hives (erythema, pruritus and blisters) [10,12, 13,15,20,28-30].

The drug is administered at a dose of 10 mg daily in adults and children (aged 2-12) with body mass of > 30 kg. Children with body mass of < 30 kg should receive 5 mg/day of loratadine. Dosing to patients with hepatic or renal insufficiency or to elderly patients should start at 10 mg every second day [13,18,20,21,24,31].

Contraindications for use include hypersensitivity to any of the ingredients of the product or pregnancy (pregnancy category B) [13,20].

Most common adverse effects include: somnolence, headaches, insomnia, increased appetite, nervousness. Much less common adverse effects include: headaches, anaphylactic reactions, tachycardia, palpitations, dry mouth, nausea, gastric mucositis, abnormal hepatic function, rash, alopecia, fatigue [10,13,20,24].

Pharmacokinetic parameters of loratadine

Loratadine is rapidly absorbed; only 40% of the dose is absorbed after oral administration [12]. The onset of action is observed after 1-3 hours

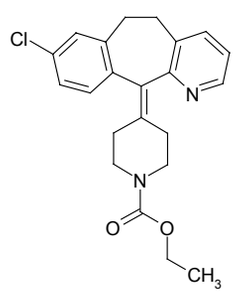

Figure 1: Structural formula of loratadine

and the maximum effect is observed 8-12 hours after administration [10,14,22,24,32]. The steady state concentration may be observed after 5 days of use [13,14,22]. Intake with meals may increase the absorption by up to 40%, and the amount of the metabolite by 15% [13]. The degree of plasma protein binding for loratadine is 97-99%, while decarboethoxyloratadine binds plasma proteins to a much lower extent - 73-76% [14,20,28]. Loratadine is metabolized in the liver, where it is transformed by cytochrome P-450 3A4 and 2D6 enzymes [12,14,25,18-21,33] to its main metabolite, decarboethoxyloratadine, which is also pharmaceutically active and contributes to loratadine activity persisting for over 24 hours [15,20,22,23,32,34,35].

About 40% of the ingested dose is excreted by kidneys and 42% by the gastrointestinal tract in the

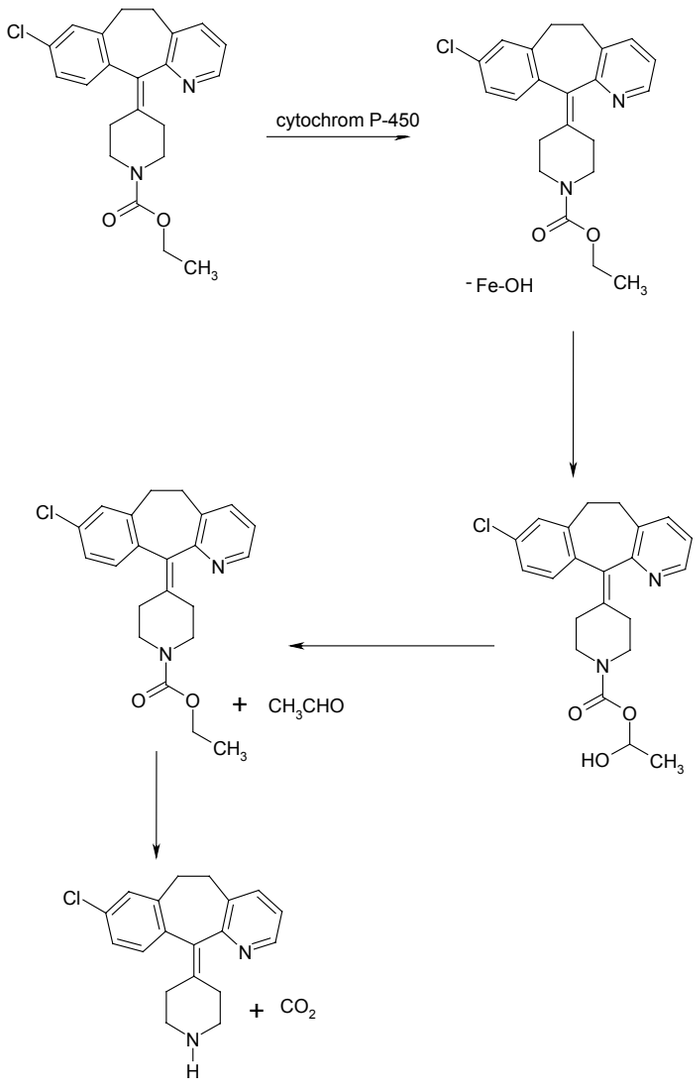

Figure 2: Metabolism of loratadinee

form of conjugated metabolites within 10 days from administration [13,20,22,28,32]. About 1% of the drug is excreted as unchanged compound. The half-life of loratadine is 8.4 h, and the half-life of its main metabolite is 28 h [13,20,22,24,32].

Physicochemical properties of loratadine

Loratadine is w white or nearly white crystalline powder with melting point of 131oC to 137oC, molecular weight of 382.89, virtually insoluble in water, poorly soluble in diethyl ether but well soluble in such organic solvents as ethanol (760 g/L), methanol, acetone, 2- propanol and chloroform [12,29, 43,44]. Experimental solubility of loratadine in water is 0.000011 mg/mL [12].

A broad pH range can be observed in the gastrointestinal tract; therefore, a question arose whether different pH values might affect solubility of loratadine in particular segments of the gastrointestinal tract, and thus whether they might enhance loratadine absorption. Loratadine was observed to have the lowest solubility at the pH of 6.5-7.5 (0.004-0.006 mg/mL) and the highest solubility, of 4.59 mg/mL, at the pH of 1.2. In addition, a significant difference in the pH value may be observed between the pH values of 1.2 and 2, with solubility dropping to 1.32 mg/mL at the latter value [38].

The octanol/water partition coefficient of 3.8 was determined experimentally for loratadine [12].

According to the biopharmaceutical classification system (BCS), loratadine is a class II drug (poorly soluble and well absorbable substance). Low solubility of the drug limits its bioavailability (despite good absorption, only about 40% of the dose enters circulation). In order to improve the bioavailability, solubility of loratidine should be improved. This may be achieved by addition of surfactants as micellar stabilizers or by the use of autoemulsification systems [38,39].

Commercial loratadine-containing products and their composition

Loratadine 10 mg is available in commercial products in the form of tablets, capsules and syrups. In addition, it is also present in combination with pseudoephedrine in Clarinase extended-release tablets at the dose of 5 mg. [28]

In most cases, solid oral formulations of loratadine are simple, with the most common excipients being lactose, starch (potato, maize, modified starch) and magnesium stearate. Surfactants are not used to increase solubility.

Formulation of loratadine syrups is based on plain syrup, with flavor-enhancing additives (peach flavor) and preservatives (sodium

benzoate), as well as sorbitol or glycerol to avoid crystallization of sugars.

Pharmaceutical loratadine-containing products, in which appropriate ratio of starch and lactose is used (plain granulate) are fully biodegradable and often referred to as residue-free products. Components of the granulate are a combination of excipients which may be safely administered to children above 4 months of age.

Table 1: Qualitative composition of commercial products formulated as tablets and capsules containing 10 mg of loratadine and extended-release tablets containing 5 mg of loratadine and 120 mg of pseudoephedrine.

Trade name	Excipients
Alerfan	lactose, potato starch, magnesium stearate
Aleric	microcrystalline cellulose, modified starch, lactose anhydrous, crosspovidone, colloidal silica, magnesium stearate, stearic acid
Claritine	hydrated lactose, maize starch, magnesium stearate
Flonidan	lactose, maize starch, gelatinized starch, magnesium stearate
LoraHEXAL	lactose, magnesium stearate, maize starch, silica
Loram	lactose, magnesium stearate, maize starch, silica
Loratadine	calcium hydrogen phosphate, maize starch, sodium benzoate, magnesium stearate, colloidal talc, silica, polyvidone
Loratine	microcrystalline cellulose, corsspovidone, magnesium stearate
Rotadin	lactose, potato starch, magnesium stearate
Loratan (capsules)	PEG 400, glycerol, 20% hydrochloric acid, gelatin, sorbitol, ethyl p-hydroxybenzoate sodium salt, propyl p-hydroxybenzoate sodium salt, Cochilean red, patent blue.
Clarinase (extended release tablets)	lactose, maize starch, polyvinympyrrolidone, magnesium stearate, butylparaben, calcium sulfate, Carnauba wax, acacia gum, oleic acid, granulated sugar, talc, titanium dioxide, microcrystalline cellulose, white wax, natural zeina soap.

Table 2: Qualitative composition of commercial syrups containing 1 mg of loratadine per 1 mL of syrup.

Trade name	Excipients
Claritine	propylene glycol, glycerin, citric acid monohydrate, sodium benzoate, sucrose, peach flavor, purified water
Loratan	sucrose, glycerin, propylene glycol, sodium benzoate, citric acid, peach flavor, purified water
Loratine	sucrose, glycerin anhydrous, propylene glycol, citric acid, methyl para-hydroxybenzoate, wild strawberry flavor, purified water
Rotadin	sodium benzoate, sucrose, propylene glycol, glycerol, citric acid anhydrous, vanilla flavor AB-710, strawberry flavor 22754-00, purified water.

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