REVIEW — New Drug and Recent Technique —

Pharmacological, Pharmacokinetic and Clinical Properties of Olopatadine Hydrochloride, a New Antiallergic Drug

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ABSTRACT—Olopatadine hydrochloride (olopatadine, 11-[(Z)-3-(dimethylamino)propylidene]-6,11-dihydro-dibenzo[b,e]oxepin-2-acetic acid monohydrochloride) is a novel antiallergic/histamine H₁-receptor antagonistic drug that was synthesized and evaluated in our laboratories. Oral administration of olopatadine at doses of 0.03 mg/kg or higher inhibited the symptoms of experimental allergic skin responses, rhinoconjunctivitis and bronchial asthma in sensitized guinea pigs and rats. Olopatadine is a selective histamine H₁-receptor antagonist possessing inhibitory effects on the release of inflammatory lipid mediators such as leukotriene and thromboxane from human polymorphonuclear leukocytes and eosinophils. Olopatadine also inhibited the tachykininergic contraction in the guinea pig bronchi by prejunctional inhibition of peripheral sensory nerves. Olopatadine exerted no significant effects on action potential duration in isolated guinea pig ventricular myocytes, myocardium and human ether-a-go-go-related gene channel. Olopatadine was highly and rapidly absorbed in healthy human volunteers. The urinary excretion of olopatadine accounted for not less than 58% and the contribution of metabolism was considerably low in the clearance of olopatadine in humans. Olopatadine is one of the few renal clearance drugs in antiallergic drugs. Olopatadine was shown to be useful for the treatment of allergic rhinitis and chronic urticaria in double-blind clinical trials. Olopatadine was approved in Japan for the treatment of allergic rhinitis, chronic urticaria, eczema dermatitis, prurigo, pruritis cutaneous, psoriasis vulgaris and erythema exsudativum multiforme in December, 2000. Ophthalmic solution of olopatadine was also approved in the United States for the treatment of seasonal allergic conjunctivitis in December, 1996 (Appendix: also in the European Union, it was approved in February 2002).

Keywords: Olopatadine, Allergic rhinoconjunctivitis, Chronic urticaria, Cutaneous diseases with pruritus

1. Introduction

Allergic rhinoconjunctivitis and chronic urticaria, as well as eczema and bronchial asthma, are associated with a hypersensitive response of the immune system. These type I hypersensitivities are characterized by the large quantities of IgE antibodies and begin with an acute IgE-mediated reaction. This occurs following the interaction of allergen with a specific antibody that has been adsorbed onto the surface of mast cells and basophils located in the tissue and blood, respectively. To a lesser extent, IgE also binds to eosinophils and macrophages. When an allergen binds with several antibodies attached to a mast cell or basophil, the cell degranulates and releases mediators of allergic inflammation. Following mast cell and basophil degranulation, released chemical mediators cause vasodilation and attraction of neutrophils, eosinophils, lymphocytes and monocytes to the active site and damage to local tissues. Other effects include increased vascular permeability that results in loss of fluid in the surrounding tissues and edema, increased glandular secretion, contraction of smooth muscle and stimulation of sensory nerve endings. Allergic rhinitis and conjunctivitis, which are the most common forms of atopic disease, are characterized by sneezing, rhinorrhea nasal obstruction and itching of the nose and
eyes. Seasonal allergic rhinoconjunctivitis can be induced by common air-borne allergens such as Japanese cedar pollen, grass and weed pollen. This type of allergic rhinoconjunctivitis usually occurs between February and October in Japan. On the other hand, perennial allergic rhinoconjunctivitis caused by house-dust mites, animal danders and insects generally occurs throughout the year. Allergic skin conditions are also extremely common and often manifest as urticaria. This reaction involves the lower layer of the surface of the skin and becomes present as localized swelling and as the development of wheals and flares, which are associated with severe pruritis. There are many antiallergic and antihistaminic drugs for the treatment of rhinoconjunctivitis, urticaria, eczema and bronchial asthma as follows: ketotifen fumarate, azelastine hydrochloride, oxatomide, emedastine fumarate, epinastine hydrochloride, terfenadine, astemizole, ebastine, cetirizine hydrochloride, fexofenadine hydrochloride, bepotastine besilate, loratadine, ramatroban, pranlukast hydrate, diphenhydramine hydrochloride, chlorpheniramine maleate and clemastine maleate. However, the incidence of these allergic diseases in general has been increasing. As the prevalence of these allergic diseases rises, efforts at the discovery of novel and effective medications for prevention and treatment of these conditions also rise.

Olopatadine hydrochloride (olopatadine, 11-[(Z)-3-(dimethylamino)propylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid monohydrochloride, CAS 140462-76-6, KW-4679, Fig. 1), a tricyclic compound, is an orally-active antiallergic/antihistaminic drug synthesized and evaluated in our laboratories (1). This review will focus on the pharmacological properties, pharmacokinetic profile and efficacy in clinical trials of olopatadine.

2. Pharmacological properties of olopatadine

2-1. Inhibitory effects on experimental allergic responses in sensitized animals

Type 1 hypersensitivity reactions have different clinical consequences depending upon the type of tissue in which the antigen-antibody reaction occurs. The skin, nose, eyes and bronchial lumen are the areas most commonly affected. Oral administration of olopatadine 1 h before antigen challenge showed a dose-dependent inhibition on the IgE-mediated 48-h homologous passive cutaneous anaphylaxis in rats, with an ID₅₀ value of 0.04 mg/kg (2). The significant inhibitory effect of olopatadine on passive cutaneous anaphylaxis persisted for 12 h (3). In guinea pigs passively sensitized with IgE-containing antiserum, instillation of antigen into nostrils caused the sneeze response, nasal rubbing behavior and increase in dye leakage. Oral administration of olopatadine significantly reduced the sneeze response, the nasal rubbing response and the increase in the nasal vascular permeability at 1 mg/kg or higher (4). In actively sensitized rats, oral administration of olopatadine caused a dose-dependent inhibition of antigen-induced increase in dye leakage into the nasal cavity, with an ID₅₀ value of 0.30 mg/kg (5). The nasal obstruction (blockage) is one of the major symptoms of allergic rhinitis. Engorgement of the venous sinuses within turbinates leads to soft tissue swelling, a reduced internal nasal diameter and increased resistance to airflow. It is apparent that many mediators have the potential to be involved in the nasal obstructive response in allergic rhinitis. It is on account of this duplicity of action that single mediator antagonists have proved poorly efficacious in the amelioration of this disorder. Both histamine H₁-receptor antagonists and leukotriene receptor antagonists have only partial effects (6). Kaise et al. investigated the effect of olopatadine on the nasal blockage induced by antigen challenge in the nostrils of actively sensitized guinea pigs. The change of the nasal
cavity volume caused by nasal mucosal swelling after antigen challenge was measured by acoustic rhinometry (7). The method involves measurements of acoustic reflections from the nasal cavity from a sound pulse created by a spark in a sound tube connected with the nasal cavity via a nosepiece. In adult humans, acoustic rhinometry has been used to evaluate nasal obstruction by determining nasal cavity dimensions in terms of cross-sectioned areas as a function of the distance from the nostril. Oral administration of olopatadine (0.1, 1 and 10 mg/kg) significantly inhibited the decrease in the nasal cavity volume at 10 min, 30 min and 6 h after antigen challenge (Fig. 2) (8). It is reported that the late-phase response in the nose associated with nasal swelling occurs in humans at several hours after the antigen challenge (9). The nasal blockage observed at 6 h after the antigen challenge in guinea pigs may correspond to the late phase response in the human nose. In rats actively sensitized by continuous inhalation of antigen for 7 days, infiltration of eosinophils in the nasal mucosa was observed. Successive oral administration of olopatadine at doses of 1, 3 and 10 mg/kg after first antigen inhalation inhibited the infiltration of eosinophils (10). The increase in resistance to airflow may also be due to the intraluminal hypersecretions. It is reported that olopatadine inhibited the nasal glandular secretion by an inhibitory action on the increase of intracellular Ca\(^{2+}\) concentration induced by acetylcholine in the isolated acini of guinea pig nasal glands (11). From these results, olopatadine may have inhibitory effects on sneeze, nasal irritation, rhinorrhea and nasal blockage in clinical use. When antigen was instilled in the eyes, a remarkable conjunctivitis developed in actively sensitized guinea pigs. Oral and topical administration of olopatadine inhibited the antigen-induced conjunctivitis with ID\(_{50}\) values of 0.09 mg/kg and 3.90 \(\mu\)g/mL, respectively (5). In asthmatic patients, a variety of pulmonary asthmatic response patterns can be developed after an appropriate antigen challenge. After an immediate asthmatic response (IAR), a late asthmatic response (LAR) can occur in some allergic subjects with asthma 3–6 h after the antigen challenge. LAR is known to be accompanied by an increase in bronchial responsiveness to non-specific stimulation and by the infiltration of inflammatory cells into the bronchial lumen. The effects of olopatadine on the development of bronchial hyperresponsiveness, airway inflammation and early and late asthmatic responses following aerosol antigen challenge in guinea pigs which were actively sensitized by the inhalation of aerosolized ovalbumin were investigated (12, 13). As an index of bronchoconstriction in conscious guinea pigs, respiratory resistance (\(R_L\)), was automatically measured by a whole-body plethysmograph (14). The airway responsiveness was determined by measuring \(R_L\) in response to doubling.

![Fig. 2](image_url)
the concentration of methacholine. The minimum provocative concentration of methacholine at which the Rt exceeds 200% of the baseline was calculated and expressed as PC200 (µg/mL). PC200 values were determined 24 h before and 24 h after antigen challenge. In the control group, the mean PC200 value was significantly reduced from 194.9 to 85.4 µg/mL after antigen challenge. When olopatadine was administered at 10 mg/kg 1 h before antigen challenge, the mean PC200 values before and after antigen challenge were 148.1 and 182.9 µg/mL, respectively, indicating that olopatadine inhibits antigen-induced development of bronchial hyperresponsiveness (12). Kawasaki et al. also investigated the effect of olopatadine on antigen-induced airway hyperresponsiveness to inhaled acetylcholine using Rt and dynamic lung compliance (Cdyn) in actively sensitized guinea pigs under anesthesia. Oral administration of olopatadine (0.1 and 1 mg/kg) significantly inhibited the development of airway hyperresponsiveness to inhaled acetylcholine in Rt and Cdyn (13). Examination of the bronchoalveolar lavage fluid 24 h after antigen challenge revealed the inhibitory effect of olopatadine (1, 3 and 10 mg/kg, p.o.) on the infiltration of eosinophils into the airway (12). Olopatadine at doses of 1 and 10 mg/kg clearly inhibited the increase in Rt at IAR and LAR (12). These results indicate that olopatadine could be useful in the treatment of bronchial asthma. Taken together, it is suggested that olopatadine is a useful drug for the treatment of skin allergy, allergic rhinitis, conjunctivitis and bronchial asthma.

2-2. Mode of action
2-2-1. Histamine H1-receptor antagonistic effects

Histamine, which is derived from mast cells and basophils, is recognized as a primary mediator of allergic diseases. Macrophages, T lymphocytes and neutrophils also produce histamine when activated by bacterial endotoxin or various cytokines through induced histidine decarboxylase (15, 16). The H1-subtype of the four subclasses of histamine receptor appears to be the most important in mediating the pro-inflammatory and allergic effects of histamine. In vitro receptor binding studies have demonstrated the affinity of olopatadine for the histamine H1 receptor with a Ki value of 16 nmol/L in guinea pig cerebellum membranes (17). Additionally, the selectivity of olopatadine for histamine H1 receptor has been shown, and a lack of significant interaction with H2- and H3-histaminergic, α-adrenergic, dopaminergic, muscarinic and numerous other receptors has been demonstrated (18). It is assumed that the G-protein-coupled receptors with a common structural feature of seven transmembrane domains should also have a common mechanism of interaction with their ligands. The histamine H1 receptor has an aspartate residue in the third transmembrane helix, which is well-conserved among biogenic amine receptors. The aspartate residue is one of the most crucial amino acids for ligand binding (19). The tested histamine H1-receptor antagonists with tri- and tetracyclic antagonists such as epinastine and ketotifen were not selective for histamine H1 receptors and showed affinity for several other biogenic amine receptors. 3H-Olopatadine had high affinity (Kd value of 2.5 ± 0.12 nmol/L) for wild-type human histamine H1 receptors transfected into Chinese Hamster Ovary cells. In the 3H-olopatadine binding assay, replacement of aspartate by alanine by site-directed mutagenesis greatly reduced the affinities (420- and 2100-fold) of tri- and tetracyclic compounds such as epinastine and ketotifen, whereas this mutation led to a comparatively small reduction (14-fold) in olopatadine affinity. These results demonstrate that tested tri- and tetracyclic histamine H1-receptor antagonists that have a tight interaction with the aspartate residue are not selective for histamine H1 receptor. The high selectivity of olopatadine might be explained by a unique binding pocket, which consists of the aspartate residue and other sites in the histamine H1 receptor (20). In the functional assay, olopatadine showed several antagonistic actions via histamine H1 receptor. Olopatadine competitively antagonized histamine-induced contraction in isolated guinea pig trachea and ileum with pKb values of 8.89 and 7.70, respectively. Olopatadine inhibited histamine-induced increase in intracellular calcium concentration in cultured guinea pig tracheal smooth muscle cells with an IC50 value of 170 nmol/L (21). Olopatadine also antagonized histamine-induced phosphoinositide turnover in cultured human conjunctival epithelial cells (IC50 = 9.5 nmol/L), human corneal fibroblast (IC50 = 19 nmol/L) and transformed human trabecular meshwork cells (IC50 = 39.9 nmol/L) (18). Oral administration of olopatadine showed inhibitory effects on the increase in vascular permeability and paw edema induced by histamine in rats with ID50 values of 0.02 and 0.1 mg/kg, respectively (21).

Cell adhesion molecules play an important role in leukocyte adhesion to vascular endothelial cells and migration to organs. Expression of intercellular adhesion molecule-1 (ICAM-1, CD54), vascular cell adhesion molecule-1 (VCAM-1, CD106), P-selectin (CD62P) and E-selectin (CD62E) was induced on endothelial cells by proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-1 (22). Miki et al. showed that histamine by itself did not induce expression of ICAM-1 and E-selectin, whereas histamine enhanced the TNF-α-induced expression of ICAM-1 and E-selectin on human umbilical vein endothelial cells through histamine H1 receptors (23). Olopatadine inhibited the histamine-enhanced expression of ICAM-1 and E-selectin with IC50 values of 2.3 and 4.4 nmol/L, respectively (23). In addition, it is reported that histamine caused a dose-dependent stimulation of
IL-6 and IL-8 release by normal and transformed human bronchial epithelial cells that appeared to occur via histamine H₁-receptor activation (24). The proinflammatory properties of IL-6 and IL-8 are well documented. Elevated IL-6 levels have been reported to be associated with a variety of inflammatory conditions, including bronchial asthma and allergic rhinitis. IL-8 is a member of the C-X-C family of chemokines. It promotes integrin expression, neutrophil degranulation, and chemotaxis of basophils and eosinophils. Yanni et al. reported that olopatadine inhibited the histamine-induced secretion of IL-6 and IL-8 from human conjunctival epithelial cell with IC₅₀ values of 5.5 and 1.7 nmol/L, respectively (25). Results presented herein indicate that the compound is more potent as an inhibitor of cytokine secretion than would have been predicted from its histamine H₁-receptor affinity (36 nmol/L). Olopatadine was also more potent as an inhibitor of histamine-enhanced TNF-α-stimulated adhesion molecule expression than predicted from drug’s receptor binding affinity (17). These data suggest that olopatadine may offer additional therapeutic benefits that complement histamine H₁-receptor antagonistic activities.

2-2-2. Inhibitory effects on the production and release of chemical mediators from various inflammatory cells

As mentioned above, histamine, which is derived from mast cells and basophils, is recognized as a primary mediator of allergic diseases. Moreover, there is evidence that lipid mediators such as platelet-activating factor (PAF), leukotrienes (LTs) and thromboxane (TX) A₂ participate in immediate and late phase allergic responses in human subjects and experimental animals. Histamine and these lipid mediators have many biological activities, such as increase in vascular permeability, mucus secretion and stimulation of chemotaxis for eosinophils (26, 27). Olopatadine inhibited antigen-induced histamine release from sensitized rat peritoneal exudate cells (28) and rat basophilic leukemia cells (29). Olopatadine also inhibited anti-human IgE-induced histamine release from human conjunctival tryptase/chymase-containing mast cells (29). Ikemura et al. investigated the effects on the production of lipid mediators from neutrophil-enriched human polymorphonuclear leukocytes (PMNs) induced by Ca ionophore A23187 (30). Olopatadine at 10 μmol/L reduced the amount of cell-associated PAF by 52.8%. Olopatadine also inhibited the release of LTB₄ and TXB₂, a stable metabolite of TXA₂, with IC₅₀ values of 5.9 and 6.0 μmol/L, respectively. Olopatadine failed to inhibit PAF acetyltransferase, 5-lipoxygenase and TX synthase, but inhibited the arachidonic acid release from human PMNs in a concentration-dependent manner at a similar concentration as that inhibiting production or release of lipid mediators (29). These results indicate that olopatadine suppresses LTs and TXA₂ release and PAF formation by reducing arachidonic acid release from membrane phospholipids, probably through interference with phospholipase A₂ (PLA₂). Whether olopatadine inhibits PLA₂ in PMNs, or in the process of PLA₂ activation, needs to be clarified in further experiments. Recently, Miyake et al. reported that olopatadine inhibited the release of peptide LTs from human eosinophils (31). Human eosinophils were purified from venous blood of healthy donors by negative selection using anti-CD16-bound immunomagnetic beads. When human eosinophils were stimulated with A23187, the amount of peptide LTs was approximately 1200 pg/10⁵ cells, while TXB₂ release was under the detection limit (<20 pg/10⁵ cells). Olopatadine inhibited the A23187-induced peptide LTs release with an IC₅₀ value of 4.5 μmol/L (31).

In order to investigate the mechanism for the amelioration of allergic rhinitis by olopatadine, its effects on the increase in histamine, peptide-LTs and TXB₂ concentrations in nasal lavage fluid (NALF) following the intranasal antigen challenge in sensitized guinea pigs were investigated (32, 33). In actively sensitized animals, the concentrations of peptide-LTs and histamine increased 10 min after the antigen challenge (32). The concentrations of TXB₂ and histamine increased 10 min after antigen challenge in passively sensitized animals (33). Oral administration of olopatadine at 10 mg/kg significantly prevented the increase in histamine and tended to inhibit the increase in peptide LTs in actively sensitized animals. Olopatadine at 0.1, 1 or 3 mg/kg (p.o.) also inhibited the increase in the TXB₂ and histamine concentrations in passively sensitized animals (Fig. 3). It was necessary to use comparatively high concentrations of olopatadine that reduced the release and production of histamine and lipid mediators in isolated inflammatory cells. However, the oral doses of olopatadine that inhibited the increase in histamine and lipid mediators in NALF after antigen challenge in sensitized guinea pigs were nearly equivalent to the doses that inhibited the experimental allergic rhinitis in guinea pigs. Recently, the involvement of peptide LTs and TXA₂ have been suggested because pranlukast, a peptide LTs-receptor antagonist and ramatroban, a TXA₂-receptor antagonist, showed clinical efficacy in the treatment of nasal obstruction (34, 35). Consequently, it is thought that the inhibitory effects of olopatadine on the release of peptide LTs and TX may contribute to the suppressive effect of olopatadine on nasal obstruction.

2-2-3. Effect on tachykinin release from peripheral sensory nerve endings

Tachykinins such as substance P (SP) and neurokinin A (NKA) induce bronchoconstriction and neurogenic inflammation (36). Barnes proposed that stimulation of the sensory nerves in airways may lead to tachykinin release via an axon reflex (37). Laitinen et al. reported that tachykinin may contribute partly to the inflammatory response in the
airway of asthmatic patients (38). Bertrand et al. demonstrated that antigen-induced bronchoconstriction in guinea pigs involved neurogenic inflammation (39). Taken together, modulation of the actions of tachykinins in airways should lead to the attenuation of the neurogenic inflammation and bronchoconstriction. It was reported that electrical field stimulation (EFS) elicited a biphasic contraction in guinea pig bronchus. The fast phase and slow phase of contraction are mediated by acetylcholine released from parasympathetic nerves and tachykinins released from unmyelinated sensory nerves, respectively (40). Ikemura et al. examined the effect of olopatadine on contractile responses induced by EFS in guinea pig bronchial muscles (41). EFS (8 Hz, 0.5 ms, 15 V, for 15 s) evoked biphasic contractile responses in the guinea pig main bronchus in the presence of indomethacin to prevent the formation of contractile prostaglandins. The contractions consisted of a fast phase of an atropine-sensitive transient contraction and a slow phase of a sustained contraction that was inhibited by a combination of the tachykinin NK1-receptor antagonist (±)-CP-96,345 (dihydrochloride salt of a racemic mixture containing both (2S,3S-cis- and (2R,3R-cis-2(diphenylmethyl))-N-(2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine) and the NK2-receptor antagonist SR 48968 ((S)-N-methyl-N-[4-(4-acetylamino-4-phenylpiperidino)-2-(3,4-dichlorophenyl)butyl]benzamidine (42). Olopatadine preferentially inhibited the slow phase in a concentration-dependent manner by 43.2 ± 7.7% at 10 μmol/L, whereas olopatadine had no effect on the fast phase at concentrations up to 10 μmol/L. In the presence of atropine, olopatadine at concentrations of 10 and 100 μmol/L inhibited the EFS-induced contraction. Olopatadine (10 and 100 μmol/L) did not affect SP-induced or NKA-induced contraction. The inhibitory effect of olopatadine was suppressed by treatment with small conductance Ca2+-activated K+ channel blockers, apamin (0.5 μmol/L) or scyllatoxin (0.3 μmol/L). Apamin or scyllatoxin per se did not influence the slow phase contraction. These results suggest that olopatadine preferentially inhibits the release of tachykinins from the bronchial sensory nerves through activation of small conductance Ca2+-activated K+ channel (41). Electrical stimulation of the vagus nerve in atropine-treated and propranolol-treated guinea pigs under anesthetization caused a 38.1% decrease in Cdyn, which was suppressed by the combination of (±)-CP-96,345 and SR 48968. Olopatadine at a dose of 3 mg/kg significantly reduced the decrease in Cdyn. Olopatadine did not inhibit SP or NKA-induced decrease in Cdyn. This study provides in vivo evidence indicating that olopatadine inhibits the tachykinin release from airway sensory nerves (43).

There are some results suggesting the involvement of neuropeptides in the pathogenesis of nasal obstruction, although the effectiveness of an antagonist against neuropeptide receptor has not been elucidated in humans. Nerve fibers containing neuropeptides such as SP, NKA and calcitonin gene-related peptide (CGRP) have been found in the human nasal mucosa (44, 45). Their receptors, that is, tachykinin NK1, NK2 and CGRP receptors, respectively, have also been shown to exist in human nasal mucosa (44, 45). Moreover, the intranasal administration of SP, NKA
or CGRP has been reported to cause nasal obstruction in humans (46 – 48). Recently, Kaise et al. found that neuropeptides are involved in the allergic nasal obstruction in guinea pigs as well as in humans (49). The decrease in nasal cavity volume was determined by acoustic rhinometry as an index of nasal obstruction. In non-sensitized guinea pigs, SP, NKA and CGRP caused the nasal obstruction 10 to 30 min after their intranasal application. At a dose of 1 mg/kg of LY303870 ((R)-1-[N-(2-methoxybenzyl)acetylamino]-3-[(1H-indol-3-yl)-2-[N-(2-(4-(piperidin-1-yl)piperidin-yl)acetamino)-propane], a novel tachykinin NK1-receptor antagonist (50), SR 48968 (1 mg/kg) and CGRP(8 – 37) (50 nmol/kg), a CGRP1-receptor antagonist (51), administered intravenously before the intranasal application of neuropeptides, inhibited the responses induced by SP, NKA and CGRP, respectively. In the actively sensitized guinea pig with dinitrophenyl-coupled Ascaris suum allergic extract, the intranasal antigen challenge caused nasal obstruction. The response was biphasic and consisted of the early phase reaction (EPR) and late phase reaction (LPR), which developed 30 min and 6 h after the antigen challenge, respectively. As mentioned above, oral administration of olopatadine significantly inhibited the EPR and LPR (8). LY303870 inhibited the EPR, while it partly suppressed the LPR. SR 48968 inhibited the LPR without affecting EPR. CGRP(8 – 37) inhibited the LPR, while it slightly ameliorated the EPR. These results suggest that neuropeptides are involved in allergic obstruction. Kaise et al. also investigated the effect of olopatadine on the sneezing and the rubbing responses induced by the intranasal administration of capsaicin in conscious guinea pigs (52), in which the release of tachykinins from sensory nerves are involved (53). Olopatadine at 10 mg/kg significantly reduced the number of the capsaicin-induced sneezes by 57%, and the drug tended to inhibit the response (Table 1). On the other hand, olopatadine did not affect the nasal rubbing response. The histamine H1-receptor antagonistic action of olopatadine is unlikely to be involved in the inhibition by this drug of the sneeze response, as the conventional histamine H1-receptor antagonists such as chlorpheniramine and clemastine did not affect the response. The sneezing is assumed to be a nerve reflex involving the sneeze center in the central nervous system following the stimulation of sensory nerve endings (54). In this study, LY303870 (10 mg/kg, i.v.) tended to inhibit the capsaicin-induced sneezing response. The previous studies in guinea pigs demonstrated that the intranasal capsaicin challenge released SP (55), the intranasal application of SP caused the sneezing response (54), and the capsaicin-induced sneezing response was abolished by the systemic pretreatment with capsaicin (53). The capsaicin-induced sneezing response is assumed to be mediated by the release of SP and/or other tachykinins. The mechanism for the capsaicin-induced nasal rubbing response has not fully been elucidated. In this study, morphine at 3 mg/kg (s.c.) caused significant inhibition of the capsaicin-induced nasal rubbing response, which was antagonized by naloxone (52). Capsaicin not only stimulates the nasal C-fiber afferent nerves to release tachykinins but also transmits the information to the central nervous systems through the trigeminal dorsal horn in the medulla, leading to the sense of pain. Geppetti et al. reported the intranasal capsaicin challenge caused the sense of pain in humans (56). Aicher et al. recently demonstrated that the μ-opioid receptor was often co-located with the NK1 receptor, on the dendrites, which often existed in close contact with SP-containing axon terminals in the trigeminal dorsal horn of the rat (57). These reports suggest that morphine inhibits the capsaicin-induced nasal rubbing response by the postsynaptic inhibition of SP-mediated nociceptive signals through the activation of the μ-opioid receptor. Alternatively, the inhibitory effect of morphine on the rubbing response may be due to the action of this substance at the cerebral cortex. Thus, the nasal rubbing response induced by capsaicin is likely to reflect the sense of pain. Taken together, it is suggested that olopatadine inhibited the capsaicin-induced sneezing response by suppressing the tachykinin release presynaptically and that the nasal rubbing response seemed to be caused by the sense of pain, which olopatadine did not affect.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Sneezing (times in 30 min)</th>
<th>Nasal rubbing (times in 30 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>10</td>
<td>8.6 ± 1.8</td>
<td>55.0 ± 8.4</td>
</tr>
<tr>
<td>Olopatadine, 10 mg/kg (p.o.)</td>
<td>10</td>
<td>3.7 ± 0.7* (57)</td>
<td>57.3 ± 9.5 (–4)</td>
</tr>
<tr>
<td>Vehicle</td>
<td>10</td>
<td>11.5 ± 2.2</td>
<td>52.3 ± 5.1</td>
</tr>
<tr>
<td>Olopatadine, 1 mg/kg (p.o.)</td>
<td>10</td>
<td>6.7 ± 1.4 (42)</td>
<td>66.9 ± 7.4 (–28)</td>
</tr>
</tbody>
</table>

N means the number of the animals. Results are the mean ± S.E.M. The number in the parenthesis represents the inhibitory percentage as compared with the response in the vehicle group. Olopatadine or its vehicle was administered orally 1 h before the capsaicin challenge. *P<0.05, compared with the number in the vehicle group. Modified from ref. 52 with permission.
In the patients with pruritic allergic dermatitis, the deposition of major basic protein (MBP), which is one of the eosinophil granule proteins, is frequently observed around the sites of skin lesions (58). Delayed pressure urticaria is characterized by the development of deep, indurated tender wheals 3–12 h after the application of sustained pressure. Sequential biopsy of delayed urticaria showed eosinophil infiltration with extensive MBP deposition (59). MBP, when intradermally injected into human skin, elicits a dose-related wheal-and-flare reaction (60). MBP is a highly cationic protein containing 17 arginine residues (61). Coyle et al. reported that MBP induced airway hyperresponsiveness, which was inhibited by anionically charged heparin (62). This observation suggests that the MBP-induced airway hyperresponsiveness depends on the cationic nature of this protein, and, thus, the synthetic cationic polypeptides have been used as tools to study the biological properties of MBP. In fact, the synthetic cationic polypeptides poly-L-lysine (PL) and poly-L-arginine (PA) are reported to elicit airway hyperresponsiveness in rats (62, 63). In the skin, PL and PA increase cutaneous vascular permeability in rats and rabbits (64), and PA induces wheal and flare in human skin (65). Histamine, serotonin and SP are known to induce flare and itch in human skin. PL, PA and MBP induce histamine release from human skin mast cells (66), while MBP and PL induce SP release from cultured rat dorsal root ganglia (67). These observations suggest that MBP and the synthetic polycations may induce skin inflammation by the activation of mast cells to release biogenic amines and/or sensory C-fibers to release SP. Hayashi et al. investigated whether the polycation PA elicited cutaneous vascular hyperpermeability (plasma leakage) and scratching behavior and, if so, whether these responses involved mast cells and sensory nerves in rats (68). The scratching behavior was recorded using an 8-mm video camera for 30 min after injection of PA. Intradermal injections of PA at doses of 50 and 200 μg/site induced plasma leakage and scratching behavior, respectively. The study showed that treatment of chlorpheniramine (10 mg/kg, p.o.) and methysergide (1 mg/kg, p.o.) inhibited the PA-induced plasma leakage by 46.4% and 45.8%, respectively, and their combination almost completely inhibited the plasma leakage. Capsaicin desensitization or the treatment of LY303870 (10 mg/kg, i.v.) partially inhibited the leakage. In mast cell-deficient rats (WsRC/Slc-Ws/Ws), PA only minimally induced plasma leakage. On the other hand, capsaicin desensitization and LY303870, but not chlorpheniramine or methysergide, suppressed the PA-induced scratching. Moreover, PA elicited the scratching even in mast cell-deficient rats. Phosphoramidon (2.5 mg/kg, i.v.), an inhibitor of neutral endopeptidase, enhanced the PA-induced scratching approximately fourfold. These results suggest that SP is partly involved in both the cutaneous plasma leakage and the scratching behavior induced by PA. Moreover, mast cell-derived amines are suggested to be involved in the plasma leakage but scarcely, if any, in the scratching behavior (68).

Hayashi et al. also investigated the effects of olopatadine on the PA-induced plasma leakage and scratching behavior (69). Olopatadine at oral doses of 0.03, 0.1 and 1 mg/kg significantly inhibited the plasma leakage by 69.2%, 72.8% and 77.5%, respectively (Fig. 4). Olopatadine at a dose of 1 mg/kg significantly inhibited the scratching behavior (68.2%), and the drug tended to inhibit the response at 0.1 mg/kg (Fig. 4). From these results, it is suggested that the suppression of tachykinin release, in addition to the antagonism of histamine H1 receptors, is to be involved in the inhibitory effect of olopatadine on the PA-induced responses.

In conclusion, olopatadine showed inhibitory effects on tachykinin release from sensory nerve endings in isolated guinea pig bronchi and in vivo various experimental allergic models. The inhibitory effects of olopatadine on tachykinin release may contribute to the treatment of allergic diseases such as bronchial asthma, allergic rhinitis and skin allergic diseases.

2.3. Tolerability and adverse events

Olopatadine showed little effect on central nervous, autonomic nervous, peripheral nervous, cardiovascular, digestive and urogenital systems in dogs, mice, rats, guinea pigs, rabbits and cats at doses that elicit the antiallergic actions (70, 71). An extensive systemic and topical ophthalmic toxicology profile has been developed for olopatadine, including evaluations of mutagenicity, single- and repeated-dose toxicity in various species, effect on fertility, reproduction, fetal development (72–77) and local ocular tolerance. Based on these findings, olopatadine is safe for use. Recently, serious ventricular arrhythmia has been reported in patients taking terfenadine and astemizole (78). These proarrhythmic effects of terfenadine and astemizole have been seen in patients with overdose, liver disease, or concomitant administration of medications that interfere with hepatic cytochrome P-450 enzymatic metabolism such as ketoconazole and erythromycin. Terfenadine and astemizole may act by blocking the rapidly activating component of the delayed rectifier potassium current, leading to the increase in action potential duration (APD) (78). Terfenadine (30 nmol/L–1 μmol/L) increased concentration-dependently APD in isolated guinea pig ventricular myocytes. On the other hand, olopatadine (0.1 μmol/L–100 μmol/L) exerted no significant effects on action potential parameters (79). Terfenadine at 10 μmol/L or higher decreased the maximum rate of rise of action potential and the sinus rate in isolated guinea myocardium preparation. Olopatadine, even up to 100 μmol/L, exerted no signifi-
Olopatadine, a Novel Antiallergic Drug

3. Pharmacokinetic properties of olopatadine

3-1. Pharmacokinetics

After single oral administration of olopatadine to healthy male volunteers at doses of 5, 10, 20, 40 and 80 mg under fasting conditions, olopatadine was absorbed rapidly, reached $C_{\text{max}}$ values at 0.5–2 h, and decreased thereafter biexponentially (83). The elimination half-lives ($t_{1/2}$) were 7.13–9.36 h within this dose range. The $C_{\text{max}}$ and AUC$_{0-\infty}$ values increased in proportion to the dose administered. Therefore, the pharmacokinetics of olopatadine were considered to be linear at the doses from 5 to 80 mg in healthy volunteers. In plasma after oral administration at a dose of 80 mg, the N-oxide form (M3) and N-monodesmethyl form (M1) were detected at amounts of about 7% and 1% of the unchanged drug, respectively (84). The plasma concentrations of both metabolites decreased in parallel to the decrease of the unchanged drug. The N-didesmethyl form (M2) was not detected in the plasma. The protein binding ratios in human plasma were in a range of 54.7–55.2%, and the main binding protein was a human albumin. The mean ratios of cumulative urinary excretion of the unchanged drug up to 48 h after oral administration of olopatadine at doses of 5, 10, 20, 40 and 80 mg were high values of 58.7–73.4% of the dose (83). In contrast to many other antiallergic drugs that are eliminated by hepatic clearance, olopatadine was eliminated by the renal clearance. The mean ratios of urinary excretion of M1 and M3 were 0.17–1.67% and 2.23–4.62% of dose, respectively. The metabolite M2 was not detected in the urine. These results indicated that olopatadine is excreted mainly through a renal route without receiving extensive metabolism after absorption and, therefore, that the drug-drug interaction in drug metabolism is very unlikely to occur. After oral administration under the non-fasting condition, a delayed $T_{\text{max}}$ (by about 0.3 h), decreased AUC$_{0-\infty}$ (by about 16%) and decreased ratio of cumulative urinary excretion within 48-h post-dose (by about 9%) was observed compared to those parameters under fasting conditions (83). The renal clearance was found to be constant under both fasting and non-fasting conditions. The food effects on the absorption of olopatadine were not considered to be remarkable. During repeated oral administration of olopatadine to healthy male volunteers at doses of 10 and 20 mg twice daily, the plasma concentration reached the steady state until day 4 after starting the repeated administration (83). The repeated administration at a dose of 10 mg twice a day caused the
increases of $C_{\text{max}}$ and $C_{12h}$ by 1.14- and 1.72-fold, respectively. The repeated administration at a dose of 20 mg twice a day caused the increases of $C_{\text{max}}$ and $C_{12h}$ by 1.19- and 1.85-fold, respectively. The plasma concentrations of olopatadine during and after repeated administration agreed with those predicted from the plasma concentrations after single administration, demonstrating that the effects of the repeated administration on the pharmacokinetics are small. In both studies of repeated oral administration of olopatadine to healthy volunteers at doses of 10 and 20 mg twice a day, the ratios of cumulative urinary excretion of the unchanged drug and M3 were almost the same as those observed after single administration. In elderly subjects, after single oral administration of olopatadine at a dose of 10 mg/body, the plasma concentrations were found to be higher than those after administration to the healthy volunteers, and the $C_{\text{max}}$ and AUC values were about 1.3- and 1.8-fold higher, respectively, than those in the healthy volunteers (85). However, the $t_{1/2}$ values were almost equal. The ratio of urinary excretion of the unchanged drug in the elderly subjects was 62.5%, which was slightly lower than the urinary excretion ratio after administration to the healthy male volunteers (69.6%). With high correlation with creatinine clearance, the renal clearance of olopatadine in the elderly subjects was about 0.5-fold that of the healthy male volunteers, and it was significantly lower than that of the healthy male volunteers. This fact may be caused by the decreased renal function associated with aging. After starting the repeated oral administration of olopatadine for a total of 10 times to the elderly subjects at a dose of 10 mg twice daily, the plasma concentration of the unchanged drug reached the steady state on day 3, as similarly observed in the healthy male volunteers. The $C_{12h}$ value after the final administration was 1.27-fold the value after the first administration, demonstrating only a small change in the pharmacokinetics after repeated administration. The $C_{\text{max}}$ and $C_{12h}$ values in the elderly subjects after the final administration were about 1.4- and 2.5-fold higher than those values in healthy male volunteers. The mean ratio of cumulative urinary excretion of the unchanged drug in the elderly subjects was 66.6%. The ratios of M1 and M3 were 0.01% and 3.65%, respectively. The N-didesmethyl form (M2) was not detected in the urine after administration to the elderly subjects. After oral administration of olopatadine to the patients with renal dysfunction, before hemodialysis, at a single dose of 10 mg, the pharmacokinetics of the unchanged drug were compared with that after administration to healthy male volunteers at a dose of 10 mg (86). The $C_{\text{max}}$ value in patients before hemodialysis was 2.3-fold higher than that in healthy male volunteers. The AUC$_{0-\infty}$ and $t_{1/2}$ values in patients with renal dysfunction were 8-fold higher and 1.3-fold longer, respectively, than those values in healthy male volunteers.

The bioavailability in experimental animals, rat, guinea pig, monkey and dog, was in a range of 60.8 – 100% after oral administration of olopatadine at 1 mg/kg (87). In rats, dogs and guinea pigs, oral administration (rats and dogs: 0.3 – 3 mg/kg, guinea pigs: 1 – 10 mg/kg) led to an increase in both $C_{\text{max}}$ and AUC$_{0-\infty}$ increased in proportion to the dose. The main site of absorption was considered to be the duodenum to the jejunum, where the absorption ratio was high, more than 91% in rats (88). The main route of excretion after oral administration of $^{14}$C-olopatadine was through the urine tract in dogs (0 – 24 h: 71.9%) (89), while in rats, the ratio of fecal excretion (0 – 24 h: 46.1%) was slightly higher than the ratio of urinary excretion (0 – 24 h: 41.7%) (88). The ratios of urinary excretion of the unchanged drug were 51.6% in dogs and 27.3% in rats. Urinary excretion was completed within 24 h after administration, demonstrating a rapid elimination of the unchanged drug and metabolites from the body after administration. In rats, 46% of the radioactivity dosed was excreted in the bile by 72 h after oral administration of $^{14}$C-olopatadine. The radioactivity excreted in the bile was partly re-absorbed in rats, showing an enterohepatic circulation. As the causes for the species difference in the excretion among rats, dogs and humans, the following factors could be considered: 1) molecular weight dependency of biliary excretion (m.w. 373.87), 2) extensive metabolism in rats in contrast to poor metabolism in dogs and humans and 3) active secretion and reabsorption in the renal tubule by cation or anion transporters as a twitter ion type-compound.

After oral administration of $^{14}$C-olopatadine to rats at 1 mg/kg, the tissue concentration of the radioactivity reached the highest concentration at 0.5 h in most tissues and organs (88). Of the tissues and organs, except for the gastrointestinal system, the concentrations in the liver, kidneys and urinary bladder were higher than the plasma concentration. The concentrations of the radioactivity was lowest in the brain, and the $C_{\text{max}}$ value in the brain was a low value, about 1/25 of that of the plasma concentration. In the case of other antiallergic drugs, the brain concentrations of the radioactivity relative to the plasma concentration as the $C_{\text{max}}$ ratio has been reported to be 1/5 for $^{14}$C-epinastine (90) and 1/17 for $^{14}$C-emedastine (91). In the case of $^{14}$C-terfenadine, the brain concentration of the radioactivity has been reported to be 1/3 that of the plasma concentration of the radioactivity at 2 h after oral administration to rats at 10 mg/kg (92). These results suggested that the blood-brain barrier is relatively impermeable to olopatadine compared the other above-described anti-allergic drugs. Olopatadine is an amphoteric compound and has a low lipophilicity as indicated by a low logP oct value of 0.3 in Britton-Robinson buffer (pH 7.4). These characteristics may explain a low incidence of the side effects of
the central nervous system. The concentrations of radioactivity in the tissues and organs decreased in parallel to the plasma concentration. After oral administration of $^{14}$C-oloapatadine to pregnant rats, the concentrations of the radioactivity in the fetal plasma and those in the fetal tissues and organs were in a range of 0.07–0.38-fold greater than that of the plasma concentrations of dam rats (93). After oral administration of $^{14}$C-oloapatadine to lactating rats, AUC$_{0\rightarrow\infty}$ of the concentration of the radioactivity in the milk was about 1.5-fold greater than that in plasma (93). The AUC$_{0\rightarrow24h}$ value for the unchanged drug in the milk after oral administration of olopatadine to lactating rats was 66.3% of the AUC$_{0\rightarrow24h}$ value for the total radioactivity in the milk, demonstrating a relatively high milk transfer. The milk transfer of olopatadine is due to the lipophilic nature under a weakly acidic condition. The blood cell distribution ratios of the radioactivity after oral administration of $^{14}$C-oloapatadine were 20.5–37.8% in rats (88) and 31.7–35.5% in dogs (89). The serum protein binding ratios in vivo after oral administration of $^{14}$C-oloapatadine were 60.5–70.0% in rats (88) and 53.1–56.8% in dogs (89). The serum protein binding ratios of $^{3}$H-oloapatadine in vitro were in a range of 47.3–66.7% in rats, guinea pigs, monkeys, dogs and humans.

3-2. Metabolism

In dogs and humans, olopatadine is a renal clearance drug, showing poor metabolism. The radioactivity in the plasma, urine and feces after oral administration of $^{14}$C-oloapatadine to rats and dogs was mainly detected as the unchanged drug. Like the metabolites, the N-monodesmethyl form (M1) and the hydroxylated form (M5) were detected at relatively high proportions (94). The N-oxide form (M3) and N-monodesmethyl form (M1) were detected in human plasma and urine after oral administration of olopatadine (84). The metabolic pathway of olopatadine after oral administration was assumed to consist of 1) N-demethylation at the side chain moiety, 2) hydroxylation at the dibenzoxepine ring, 3) sulfate-conjugation of the hydroxylated metabolite and 4) N-oxidation of the side chain moiety. In the in vitro metabolism study using rat liver, kidney, lung, small intestine and brain homogenates and their 9000xg supernatant fractions, the metabolism of olopatadine was found to proceed only in the supernatant of the liver homogenate. The main metabolite in this fraction was M1. In female rats after repeated oral administration of olopatadine at 0.1, 1 and 25 mg/kg once daily for 7 days, no effects of the repeated administration were found on the drug metabolizing enzyme system in the liver microsomes (95). Like the metabolites in dogs, M1, M3, M2 and M5 have been detected (94).

Inhibitory effects of olopatadine on the activities of human cytochrome P450 isoforms, CYP1A2, CYP2C8/2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4, to metabolize their typical substrates, phenacetin (O-deethylation), tolbutamide (hydroxylation of methyl group), S-mephenytoin (4’-hydroxylation), bufuralol (1’-hydroxylation), chlorzoxasone (6-hydroxylation) and testosterone (6β-hydroxylation), respectively, were examined using human liver microsomes. The inhibitory effects of olopatadine were compared with those of the selective inhibitors of the cytochrome P450 isoforms, furaphylline, sulfaphenazole, tranylcypromine, quinidine, diethylthiocarbamate and ketoconazole. Olopatadine showed no inhibitory effect on the drug-metabolizing activities catalyzed by these isoforms of cytochrome P450. The isoforms of human cytochrome P450 involved in the generation of M1 from olopatadine were estimated in the inhibition experiments using isoform-selective inhibitors and in the experiments using the microsomes expressing each isoform of human liver cytochrome P450. Troleandomycin and ketoconazole, the selective inhibitors of CYP3A4, strongly inhibited the generation of M1. On the other hand, furaphylline (CYP1A2 inhibitor), sulfaphenazole (CYP2C9 inhibitor), quinidine (CYP2D6 inhibitor), tranylcypromine (CYP2C19 inhibitor) and diethylthiocarbamate (CYP2E1 inhibitor) showed almost no effect on the generation of M1. In addition, the generation of M1 was observed in the microsomes expressing CYP1A2 and CYP3A4. These results indicated that CYP3A4 was mainly involved in the generation of M1. On the other hand, the generation of M3 was mainly catalyzed by CYP1A2 in the system containing human liver microsome. Although the involvement of flavin-containing monoxygenase was also considered, details are still not known. The renal clearance and non-renal clearance of olopatadine in healthy volunteers are 14.4 and 5.92 L/h, respectively (86). It has been demonstrated that the C$_{max}$ and AUC$_{0\rightarrow\infty}$ values in healthy male volunteers after single oral administration of olopatadine at a dose of 20 mg increase by 1.7 and 1.9 times, respectively, compared to those values after administration at a dose of 10 mg, while there were no risk in the safety (83). Therefore, the increased plasma concentration of olopatadine by 1.4 times as a consequence of the hepatic drug interaction was not considered to cause a serious safety problem since the clinical dose level is set at 10 mg (b.i.d.).

4. Clinical usefulness of olopatadine

4-1. Clinical pharmacology

The effects of three different oral doses of olopatadine at concentrations considered to have both histamine H$_1$-receptor antagonistic and antiallergic properties were compared with terfenadine and placebo in a double-blind cross-over trial in 15 volunteers with seasonal allergic rhinitis (96). Comparison of the effect of the treatments with either 2.5,
5, or 10 mg (b.i.d.) of olopatadine, 60 mg (b.i.d.) of terfenadine or placebo was made on the response to histamine and grass pollen skin-prick testing. Nasal provocation testing with grass pollen was performed on the eighth day of treatment. Nasal airway resistance (NAR) was measured using active posterior rhinomanometry and the dose of grass pollen which caused a 200% increase in NAR was determined. The number of sneezes in the first 12 min was counted. Compared with placebo, all doses of olopatadine and terfenadine significantly inhibited the skin weal response to histamine and grass pollen \((P<0.001)\). The inhibitory effect of olopatadine on both histamine and allergen-induced skin weals was significantly greater than that of terfenadine \((P = 0.001\) and \(P<0.05\), respectively). The results of nasal challenges with grass pollen showed that all doses of olopatadine and terfenadine were effective in reducing sneeze counts \((P<0.001)\), although there were no significant effects on allergen induced increase in NAR. The results of measurements of NAR were highly variable \((96)\). More detailed clinical studies are necessary to ascertain the effect of olopatadine on the nasal blockage. All three doses of olopatadine were generally well tolerated.

4-2. Clinical studies in patients with perennial allergic rhinitis

An early phase II study was conducted in patients with perennial allergic rhinitis (a total of 148 patients) \((M.\ Okuda et al., unpublished data)\). For preliminary investigation of safety and efficacy, three groups were observed for one week and then treated with olopatadine at a daily dose of 5, 10 or 20 mg (b.i.d.) for two weeks. As a result, the efficacy rates were 46.3% in the 5 mg/day group, 60.6% in the 10 mg/day group and 48.6% in the 20 mg/day group; the incidence of adverse reactions was 10.2%, 11.4% and 25.0%, respectively, showing no significant differences among the three groups; and the major adverse reaction was drowsiness. None of the groups showed any serious adverse reactions or serious abnormal changes in clinical laboratory values. A late phase II study was conducted under a double-blind design for the purpose of objectively investigating the usefulness of olopatadine in the treatment of perennial allergic rhinitis \((M.\ Okuda et al., unpublished data)\). The doses were set at 10 mg (b.i.d.) for olopatadine and 60 mg (b.i.d.), i.e., the approved dose, for oxatomide, and the study period was set as a 1-week observation period and 4-week administration period as in the late phase II study. As a result, no significant differences were noted between the two groups either in incidence of adverse reactions (olopatadine: 29.1%, oxatomide: 30.7%) or incidence of abnormal changes in clinical laboratory values. Olopatadine is equivalent in efficacy to oxatomide \((P<0.05,\ equivalency\ test\ (\Delta = 10\%))\) for which usefulness has already been established (efficacy rate: 62.4% for olopatadine, 56.6% for oxatomide). Based on the results, olopatadine was considered to be clinically useful for the treatment of perennial rhinitis. Among the major symptoms of allergic rhinitis, nasal obstruction is the symptom least relieved by antiallergic drugs. Olopatadine treatment led to a great reduction of nasal obstruction than other drugs of the same category studied using the same protocol in previously published studies \((improvement\ ratings\ of\ other\ drugs\ of\ the\ same\ category\ are\ shown\ in\ Table\ 2)\). As shown in Table 2, among the latest drugs of the same category having the same indications, olopatadine showed the highest improvement rating against nasal obstruction, and also the preclinical data supported this result.

4-3. Clinical studies in patients with chronic urticaria or pruritic diseases

An early phase II study was conducted in patients with chronic urticaria \((a\ total\ of\ 73\ patients)\) \((97)\). The dose levels of olopatadine in this study were set at daily doses of 2, 5 and 10 mg (b.i.d.). The administration period was two weeks pursuant to the clinical studies of other drugs of the same category having the same indications. As a result, safety problems were tolerable and none of the groups showed serious adverse reactions. The efficacy rates were 91.7% in the 2 mg/day group, 86.4% in the 5 mg/day group and 87.0% in the 10 mg/day group, being similarly high in all groups. Based on the above results, olopatadine was considered to exhibit high usefulness in the dose range of 2 – 10 mg/day. A late phase II study was conducted for
the purpose of investigating the optimal dose for chronic urticaria (a total of 233 patients) (98). Based on the results of the early phase II study, three dose levels (0.4, 2 and 10 mg (b.i.d.)) were compared under a double-blind design to investigate dose-dependency. The administration period was 2 weeks. The efficacy rates were 58.9%, 77.1% and 76.5%; the safety rate was 92.0%, 89.2% and 78.6%; and the usefulness rate was 55.4%, 73.6% and 74.3%, of the patients in the 0.4 mg/day group, 2 mg/day group, 10 mg/day group, respectively. A significant difference was observed in efficacy rate not only between the 10 mg/day group and the 0.4 mg/day group (P<0.01, U-test) but also between the 2 mg/day group and 0.4 mg/day group (P<0.05, U-test), and the 0.4 mg/day group was significantly superior to the 10 mg/day group in safety rate (P<0.05, U-test). In addition, the 10 mg/day group was significantly superior to the 2 mg/day and 0.4 mg/day groups in disappearance rate of itching after one week of treatment (0.4 mg vs 10 mg, P<0.05; 2 mg vs 10 mg P<0.01; χ²-test). From these results, the optimal dose was estimated to be 10 mg/day. A phase III study was performed comparing ketotifen to olopatadine under a double-blind design (olopatadine group: 127 patients, ketotifen group: 129 patients) to objectively investigate the usefulness of olopatadine in the treatment of chronic urticaria (99). The doses were set at 10 mg (b.i.d.) olopatadine and 2 mg (b.i.d.); i.e., the approved dose, ketotifen, and the administration period was 2 weeks. Olopatadine was significantly superior to ketotifen in both efficacy (olopatadine: 77.7% and ketotifen: 66.9%, P<0.05, U-test) and safety (olopatadine: 77.2% and ketotifen: 53.9%, P<0.001, U-test). From this study, olopatadine was considered to be highly useful in the treatment of chronic urticaria. A long-term administration study was conducted using the 10 mg/day dose estimated to be optimal in the late phase II study for the purpose of investigating the safety and efficacy of olopatadine on long-term administration (a total of 82 patients) (100). The administration period was set at 8 weeks pursuant to the clinical studies of other drugs of the same category and having the same indications. The efficacy rate was 86.8% and increased with duration of administration, showing no reduction in effect. The adverse reactions observed after 20 days of administration were sleepiness and body weight increase noted in one patient each. No serious abnormal changes in clinical laboratory values were observed in either. These results suggested that olopatadine would also be highly useful on long-term administration. Compared with ketotifen, which has been highly appreciated in clinical practice for chronic urticaria, olopatadine showed significantly greater usefulness (P<0.05, U-test) and significantly lower incidence of adverse reactions (P<0.01, χ²-test). When compared to published data, as shown in Table 3, the final global improvement ratings of the other drugs observed in the phase III comparative studies were not significantly better than that of ketotifen, but the final global improvement rating of olopatadine was significantly better (P<0.05, U-test).

An open clinical study was conducted using the 10 mg
(b.i.d.) dose estimated to be optimal in the treatment of chronic urticaria to investigate the effect of olopatadine on various dermatosis with pruritis (a total of 398 patients) (101). The efficacy rate was 74.6% for the group of eczema/dermatitis, 50.8% for the group of prurigo, 49.3% for the group of pruritis cutaneous and 52.8% for the group of vulgar psoriasis, exhibiting almost the same efficacy as the other drugs of the same category and having the same indications; and the efficacy rate was a high 83.3% for erythema exsudativum multiforme. The incidence of drowsiness was 11.3%, but there were few patients who needed discontinuation of administration (0.8%, 3 events). The major abnormal changes in clinical laboratory values were increases of GOT and GPT, but they were not clinically significant. These results indicate that olopatadine is an effective drug for pruritis of the above dermatosis.

### 4-4. Clinical studies in patients with bronchial asthma

An early phase II study was conducted in patients with bronchial asthma (a total of 62 patients) (102). Based on the results in the phase I studies, the maximum dose was 20 mg (b.i.d.) and additional doses of 10 and 5 mg (b.i.d.), and the administration period was 4 weeks as the minimum duration allowing efficacy evaluation and the 2-week period before starting administration was the observation period. The efficacy rates were 23.5% in the 5 mg/day group, 36.8% in the 10 mg/day group and 50.0% in the 20 mg/day group, suggesting the presence of dose-dependency. A late phase II study was conducted for the purpose of investigating the optimal dose for bronchial asthma in a 60-institution collaborative study (a total of 242 patients) (103). In order to clarify the safety and efficacy, two dose levels (10 and 20 mg (b.i.d.)) were compared under a double-blind design using placebo as a comparator. The study period was a 2-week observation period and 6-week administration period pursuant to the clinical studies of other drugs of the same category and having the same indications. Taking into consideration the clinical laboratory findings in the early phase II study, laboratory tests were also to be performed after 2 weeks of administration, in addition to before starting administration and after completing administration to confirm influences on liver function test values. There were no significant differences in incidence and intensity of abnormality in liver function test values between the placebo group and the 10 or 20 mg/day group. The incidence of adverse reactions was significantly higher in the 10 mg/day group (14.6%) than in the placebo group (2.5%) (P<0.05, χ²-test), but not in the 20 mg/day group (8.8%). The major symptom of adverse reaction was sleepiness. The efficacy rates were 23.6% in the placebo group, 36.1% in the 10 mg/day group and 47.1% in the 20 mg/day group, significantly higher in the 20 mg/day group than in the placebo group (P<0.05, U-test). This study suggested that olopatadine was effective against bronchial asthma and the optimal dose seemed to be 20 mg/day. A phase III comparative study using terfenadine as a comparator was conducted under a double-blind design (olopatadine group: 106 patients, terfenadine group: 114 patients) for the purpose of objectively investigating the usefulness of olopatadine in the treatment of bronchial asthma (104). The doses were 20 mg (b.i.d.) for olopatadine and 120 mg (b.i.d.), i.e., the approved dose, terfenadine, and the study period was set as a 2-week observation period and a 6-week administration period as in the late phase II study. As a result, olopatadine was judged to be equivalent in efficacy to terfenadine, which is widely used in clinical practice and has already been appreciated to a certain extent (olopatadine: 31.9% and terfenadine: 28.7%). There were no significant differences between the two groups in incidences of adverse reactions including drowsiness. Although these results suggested that olopatadine would be effective against bronchial asthma, it was not sufficiently demonstrated that olopatadine is superior in usefulness to the anti-asthmatic agents currently in use. Bronchial asthma was therefore excluded from the indications submitted for approval at this time. A phase III open clinical study was conducted to investigate the safety and efficacy of long-term administration (105, 106). The dose was 20 mg (b.i.d.), and after a 2 week observation period, the administration period was 24 weeks or longer, up to 48 weeks if possible, pursuant to the clinical studies of other drugs of the same category and having the same indications. The

### Table 3. Results of phase III comparative studies of antiallergic drugs using ketotifen as a comparator in patients with chronic urticaria

<table>
<thead>
<tr>
<th>Drug name (daily dose)</th>
<th>Olopatadine (10 mg)</th>
<th>Cetirizine (10 mg)</th>
<th>Ebastine (10 mg)</th>
<th>Astemizole (10 mg)</th>
<th>Epinastine (20 mg)</th>
<th>Emedastine (4 mg)</th>
<th>Azelastine (2 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final global improvement ratio</td>
<td>Tested drug</td>
<td>77.7% (87/112)</td>
<td>82.2% (88/107)</td>
<td>73.7% (87/118)</td>
<td>71.3% (97/136)</td>
<td>79.8% (95/119)</td>
<td>71.7% (81/113)</td>
</tr>
<tr>
<td>Final global improvement ratio</td>
<td>Ketotifen</td>
<td>66.9% (81/121)</td>
<td>79.0% (79/100)</td>
<td>66.7% (78/117)</td>
<td>69.8% (97/139)</td>
<td>73.0% (84/115)</td>
<td>64.2% (77/120)</td>
</tr>
<tr>
<td>Significant difference (U-test)</td>
<td>OL&gt;KT</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>H-test:</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

The number in the parenthesis indicates the number of patient rated as improved/number of patients included in analysis.
mean administration period was 30.3 weeks, the incidence of adverse reactions was 19.5% and the efficacy rate was 47.5%. No serious adverse reactions were noted and the efficacy was maintained. Olopatadine was also considered to be safe and effective following long-term administration.

4-5. Clinical studies in patients with allergic conjunctivitis

Olopatadine was licensed to Alcon Laboratories, Inc. (Fort Worth, TX, USA), where the drug was evolved as ophthalmic solution for the treatment of allergic conjunctivitis. Allergic conjunctivitis often occurs simultaneously with rhinitis in seasonal allergy sufferers. Therapy for allergic conjunctivitis has evolved from primarily systemic agents to topical ocular preparations. Oral administration of antiallergic and histamine H<sub>1</sub>-receptor antagonistic drugs have been shown to be efficacious; however, side effects and slow onset of action are drawbacks to their use in treating ocular signs and symptoms of allergic conjunctivitis (107). Double-masked, randomized, placebo-controlled, contralateral eye comparison studies were conducted using the conjunctival allergen challenge model in order to evaluate the effectiveness and safety of olopatadine and to determine its optimal concentration, onset and duration (108). A total of 96 subjects received 0.01%, 0.05%, 0.1% or 0.15% olopatadine solution, which was administered in one eye while placebo was administered in the opposite eye. Itching and redness were scored for both eyes after conjunctival allergen challenge. All four concentrations of olopatadine were clinically and significantly (P<0.05) superior to placebo in preventing itching and redness at most evaluations immediately and 8 h after drug administration. There were no serious or drug-related ocular or nonocular adverse events in the study. The 0.1% concentration was found to be most effective. These results indicated that olopatadine ophthalmic solution is safe and effective in the treatment of allergic conjunctivitis, with the 0.1% concentration of olopatadine being optimal. The rapid onset and at least 8-h duration of action of olopatadine indicates that the drug can be used twice daily (108). Moreover, the study was conducted to compare the efficacy and safety of olopatadine ophthalmic solution (0.1%) with ketorolac ophthalmic solution (0.5%) in a clinical model of acute allergic conjunctivitis. Kitorolac is a non-steroidal anti-inflammatory drug approved in the United States for the relief of ocular itching associated with seasonal allergic conjunctivitis. The study demonstrated that olopatadine was significantly (P<0.05) more effective and more comfortable than ketorolac (109). Recently, it has been reported that olopatadine eye drops adjunctive to loratadine tablets for 7 days is superior to therapy with loratadine tablets alone (110). The three-center, observer-masked, treatment-controlled, randomized, parallel-group study involved 94 patients with seasonal allergic conjunctivitis. Patients were treated for 7 days with either olopatadine (b.i.d.) adjunctive to loratadine once daily or only loratadine once daily. Results from this clinical study showed that patients receiving olopatadine twice daily in addition to loratadine once daily exhibited less ocular itching (P<0.05) and rated their ocular condition as more improved compared with those receiving loratadine alone (P<0.05). Twenty minutes after initial dosing, olopatadine plus loratadine relieved ocular itching and redness significantly better than loratadine alone (P<0.05). Both treatment groups showed clinically meaningful improvements in the overall quality of life in all but one of the rhinoconjunctivitis quality of life questionnaire domains. Compared with loratadine alone, olopatadine adjunctive to loratadine provides greater relief of ocular itching and redness, better quality of life, and is well tolerated in patients with seasonal allergic conjunctivitis. Abelson and Lanier also reported the added benefit of local olopatadine therapy in the treatment of ocular allergic symptoms in patients receiving systemic histamine H<sub>1</sub>-receptor antagonists for concomitant systemic allergies (111).

5. Conclusion

Oral administration of olopatadine inhibited the symptoms of experimental allergic skin responses, rhinoconjunctivitis and bronchial asthma in sensitized guinea pigs and rats. Olopatadine also inhibited the antigen-induced infiltration of eosinophils into the nasal mucosa and bronchoalveolar lavage fluid. Olopatadine is a selective histamine H<sub>1</sub>-receptor antagonist possessing inhibitory effects on the release of inflammatory lipid mediators such as LTs and TX from human polymorphonuclear leukocytes and eosinophils. Eosinophil is one of the pivotal cells in allergic inflammation. To our knowledge, olopatadine is the first antiallergic drug that inhibits both the infiltration and activation of eosinophils, and inhibits the skin responses induced by PA that mimics the actions of major basic protein which is one of the eosinophil granule proteins. Olopatadine also inhibited the tachykinin release from sensory nerve endings in isolated guinea pig bronchi and various experimental allergic animal models in vivo. Olopatadine also inhibited release of newly formed and preformed mediators from human conjunctival mast cells. These mast cells are predominantly tryptase- and chymase-containing and similar to mast cells in the skin. This fact provides a rationale for the enhanced efficacy of olopatadine in dermatological conditions. Olopatadine exerted no significant effects on action potential duration in isolated guinea pig myocardium, ventricular myocytes and HERG channel. Olopatadine was highly and rapidly absorbed in healthy volunteers. The urinary excretion of olopatadine accounted
for not less than 58% and the contribution of metabolism was considerably low in the clearance of olopatadine in humans. Olopatadine was shown to be highly useful for the treatment of allergic rhinitis, chronic urticaria and conjunctivitis in double-blind clinical trials. Olopatadine (Allelock®) was also approved in the United States for the treatment of seasonal allergic conjunctivitis in December, 1996. Patanol® is now available in 32 countries.

Appendix

During the editorial process of this manuscript, ophthalmic solution of olopatadine (Patanol®) was approved also in the European Union for the treatment of seasonal allergic conjunctivitis (February 2002).

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