Histamine (H₁) receptor antagonists are one of the commonly used drugs. The second generation histamine H₁ receptor antagonists, the so called ‘non sedating’ antihistamines, have high potency and additional antiallergic properties. In fact these have replaced the older drugs because they lack sedation and cardiovascular side effects.

**Ebastine** (1,2) is an effective non sedating H₁ receptor antagonist marketed for the treatment of allergic rhinitis and urticaria. After oral administration it is extensively and rapidly metabolized to its active metabolite, carebastine. After ingestion of ebastine 10mg, the carebastine Cmax of 120µg/litre is obtained in 3-6 hours. Bioavailability is good and food ingestion seems to increase the bioavailability. Carebastine has Vd (volume of distribution) of 90-143 litre and 98% plasma protein bound (PPB). In hepatic or renal dysfunction its dose adjustment may not be necessary. Moreover, it does not appear to interact with alcohol (ethanol), diazepam or cimetidine. A significant increase in plasma carebastine concentration may occur when ketoconazole 400mg/day or erythromycin 500mg 6 hourly are concomitantly administered with ebastine. It has a dose related suppressive effect on histamine induced wheals and flares over the dose range of 3-30 mg. After a single dose, the maximum suppressive effect occurs at 6-8 hours. After a short course of ebastine, the residual effect lasts for 3-4 days. Tachyphylaxis to ebastine has not been reported.

**Levocabastine** (1) has a terminal t₁/₂ of 35-40 hours and is only available as a topical application administered intranasally or ophthalmically in patients with rhinoconjunctivitis. Absorption from nasal or ophthalmic formulations occur within 1-2hours. Steady state plasma concentration achieved in 7-10 days are approximately 10.5µg/litre after 2 nasal sprays (50µg/spray) per nostril three times daily and 1.6µg/litre after application of 0.05% ophthalmic suspension, 1 drop (15µg) per eye three times daily. Oral and intravenous formulations are not used clinically because of potential sedative effects. Sixty to seventy percent of it is excreted unchanged in urine and 10-20% appears unchanged in faeces because of biliary excretion. After single or repeated doses the t₁/₂ of levocabastine is between 35-40 hours regardless of the route of administration.

**Mizolastine** (1,3,4), another second generation antihistaminic is a potent and selective H₁ receptor antagonist lacking affinity for H₂, H₃, muscarinic and serotonergic receptors. In addition at usual clinical doses it inhibits neutrophil migration, mast-cell histamine release and the activity of 5-lipoxygenase in animal models. The anti 5-lipoxygenase activity might explain the inhibition of the arachidonic acid induced cutaneous inflammatory reactions by mizolastine. After oral administration, it is rapidly absorbed with a mean peak plasma concentration (Cmax) of 276µg/litre. Bioavailability is 65.5% and is not affected by age or concomitant ingestion of food or alcohol. It has Vd of 1.4litre/kg with 98.4% PPB. It is extensively metabolized by glucuronidation with less than 0.5% of the administered dose excreted unchanged in urine. Clinical studies have demonstrated lack of diffusion into the CNS, lack of anticholinergic activity, the rapidity of onset and prolonged duration of action allowing once daily administration. Its t₁/₂ is prolonged (but with in the normal range) by 47% in patients with renal disease and no dose adjustment is required. It has no effect on pharmacokinetics of theophylline, digoxin, R-(+)- and S-(-)-warfarin or diltiazem. Mizolastine 10mg suppresses histamine induced wheals and flares significantly with in 1hour of administration. Peak effect occurs in 3-12 hours and suppression lasts for 24 hours. It also produces dose...
related bronchodilation and protection against histamine induced broncho-constriction. Tachyphylaxis to mizolastine has not been reported. The suppressive effect of mizolastine on wheals and flares induced by histamine, codeine or allergen remains highly significant even after 3 months of regular administration.

**Levocetirizine** (5-7), a new, once-daily, non-sedating antihistamine is the active enantiomer of cetirizine, a potent histamine H1-receptor antagonist. Cetirizine is a racemic mixture of levocetirizine and dextrocetirizine. Recent data has demonstrated that the antihistaminergic activity of the racemate is primarily due to levocetirizine. Levocetirizine is rapidly and extensively absorbed, poorly metabolized, and not subject to racemization. Its apparent Vd is smaller than that of dextrocetirizine (0.41 litre/kg vs. 0.60 litre/kg. Moreover, the non-renal (mostly hepatic) clearance of levocetirizine is also significantly lower than that of dextrocetirizine (11.8 mL/min vs. 29.2 mL/min). Levocetirizine has been found to be equally effective as desloratadine and fexofenadine in attenuating the response to nasal adenosine monophosphate (AMP) challenge as well as in an nasal provocation test (NPT) with grass pollen allergen. In the comparative trials in patients with seasonal allergic rhinitis, 5 mg levocetirizine has been found to be equivalent to 10 mg cetirizine.

**Desloratadine** (8), a new H1 receptor antagonist, is the primary active metabolite of loratidine. Early studies have demonstrated that desloratadine is approximately 10-20 times more potent in H1 receptor binding than loratidine in vitro and has 2.5-4 times more antihistaminic potency in animals. In clinical trials with desloratadine, there were no clinically relevant changes in cardiac conduction at doses up to 9 times the recommended clinical doses.

**Fexofenadine** (1) is the active metabolite of terfenadine. It is readily absorbed after oral administration, with tmax of 1 to 3 hours. Absorption is not affected by food and about 70% PPB. It gets primarily eliminated unchanged in faeces and urine and has a terminal half life t½ of ~14 hours and duration of action of 24 hours making it suitable for once or twice daily administration. Tachyphylaxis to fexofenadine has not been observed.

**Olopatadine** (9), is an agent that exerts both a mast cell stabilization effect and an anti-histaminic effect. In a controlled double blind study, topical olopatadine 0.05% and 0.1% solutions assessed in patients with allergic conjunctivitis using conjunctival allergen challenge model to determine efficacy. Both concentrations were significantly better than placebo in alleviating itching and redness in test subjects. It was effective if administered within 30 minutes of allergen challenge and was effective for up to 8 hours. The fact that it displayed a low affinity for 38 nonhistamine receptor binding sites suggests that it will have few adverse effects. It thus appears to be a promising new agent for the treatment of ocular allergy. Other interesting future therapeutic possibilities include single chemical entities with clinically relevant intrinsic dual pharmacological activity for example combined H1 and H3 antagonism, H1 antagonism and cysteinyl leukotriene antagonist activity or H1 antagonism and 5-lipoxygenase activity. Introduction of these novel therapeutic strategies would be a therapeutic miracle of the new millenium.

**References**