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Review Article

Levo Cetirizine - the Drug with Numerous Plus to Cure Allergic Syndrome Compared to other Treatment Systems

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ABSTRACT

Many drugs are available to treat allergic condition. This review focused on why antihistaminics are best choice for treatment of allergic disorder especially allergic rhinitis (AR). AR is a chronic inflammatory disease. AR can be detected by its characteristics of nasal congestion, nasal itching, sneezing, rhinorrhoea, pruritis, redness, tearing and itching of eyes. This is very common and increases day after day. Allergic rhinitis is not lethal but interferes with daily schedule in a sustained manner. It is also observed that after COVID-19, stimuli reactions such as allergic condition, breathing difficulties and nasal irritation are quite common. It is very necessary to treat AR with an effective and powerful medicine because nowadays, many factors trigger these responses such as the environment, food products, pollution, etc. Before treatment of any symptoms it is very necessary to know it pathogenesis. Hence, in this review, we discuss the introduction of AR, its pathogenesis, diagnostics, classification and treatment. We also understand why levocetirizine, a third-generation antihistamine, is superior to all other antihistamines and the most favourable in paediatric patients in many ways.

Keywords: Allergic rhinitis; Antihistaminic; Levocetirizine; COVID19; Asthma; Nasal congestion

INTRODUCTION

Allergic Rhinitis

Allergic rhinitis (AR) is currently one of the most frequently reported chronic diseases in children. The paediatric population exhibits differences in metabolism, renal clearance, and other drug disposal mechanisms associated with anatomical, physiological, and developmental differences. Anti-allergic drugs, particularly the antihistamines that are given by nasal route are among the most commonly prescribed medications in children. Compared with other commonly used second-generation antihistamines, levocetirizine is characterized by a favourable pharmacokinetic profile, with a shorter elimination half-life than desloratadine, ebastin, fexofenadine, and loratadine.[1]

The physical complications (chronic sinusitis, snoring and asthma) and the mental complications (sleep, poor school performance, learning, performance, behaviour and mood hyperactivity) are also observed.[2]

Allergic Rhinitis (AR) is a major, widespread and long standing chronic type 2 inflammatory heterogeneous disorder but still appreciated highly enough.[3] It is also observed that chances of having asthma also increased up to 40% in those diagnosed with AR. AR is common, long but unnoticed condition.[4]

AR is characterized by mucosal infiltration and action of eosinophils, plasma cells, and mast cells. Basically, it is a disorder of nasal mucosa triggered by inhalation of allergen. The prevalence of allergic rhinitis peaks in the second to fourth periods of life and then slowly moderates.[5]

AR Disorder is characterized by different symptoms such as nasal congestion, nasal itching, sneezing, rhinorrhea, pruritus, redness, tearing and itching of the eyes. Other symptoms such as rubbing of the nose, swelling of the nasal lining, pale and thin secretions, persistent breathing by mouth, clearing of the throat, snoring and dark circles are also noticed.[6] It is also observed that the irritating characteristics of AR result in decreased patient interest or compromised productivity at school and at work for children

and seniors respectively.[7]

In the past, AR was considered a localized condition, but recent updates have shown that AR is a systemic illness of the respiratory tract.[8] It is also observed that 19-39% of patients with RA were found to have concurrent asthma.[9] In RA Eustachian tube blockage, cough, and a feeling of pressure in the sinuses result from swelling and venous engorgement of the nasal mucosa defects.[10]

Allergic rhinitis show global impact on person's health as well as economical condition. The high incidence of AR imposes a heavy burden to general well-being and has a significant financial impact from both direct and indirect costs for management of the disease.[11,12]

In all aspects, there is a need to focus on possible relevant allergens including pollen, fur creatures, floor/textile fabrics, tobacco smoke, moisture changes at home and also food products.[8]

Evidence shows that change in climate (temperature, humidity, wind speed, thunderstorms, desert dust, pollution, microorganism etc), exposure to environment and lifestyle factor (diet, type of food, spending too much time indoors, use of antibiotic and sanitizers, hygienic, less contact to rodents) increase the chances to get allergic disorder.[12,13] Patients with family history of AR are more prone to allergy responses. Whereas, big family with older siblings shows opposite effect. Growing in farming or wild field lowers the threat of allergy symptoms.[14]

During this pandemic when whole world is fighting with COVID-19 and its symptoms, data shows that AR patients protected from COVID-19 infection didn't face risk of unfortunate scenarios. It is also documented that the Sino-Nasal Test 22 (SNOT 22) score is higher for patients with COVID-19 than for patients with AR.[12] The refluxes are quite comparable as COVID 19 patients stated about smell loss, fatigue, fever and cough while in AR sneezing and nose blowing are mostly observed.[15]

Research data shows allergic rhinitis occurrence increased theatrically day by day as shown in Table 1.

Table 1: Allergic Rhinitis increased rate in different country

S.No.	Country	Initial	Progressiveness
1	Europe (Danish)[16]	19%	32%
2	America[17]	10%	30%

Pathophysiology

This (AR) type of hypersensitivity reaction occurs by immunoglobulin E (IgE).[17] IgE release is a reaction of cytokine secretion (Interleukin) that occurs when numerous inflammatory cells (mast cells, T cells, CD4 macrophages and infiltrated eosinophils, etc.) are exposed to the allergen.[18]

When individual remain unguarded to allergen mostly airborne dust, faeces of mite, cockroach residue, mould, pollens, food, and animal hackles then IgE is secreted by plasma which initiates the release of cysteinyl leukotrienes, prostaglandin D2 and histamine etc. This release is responsible for triple response (dilation of arteriole, flare and increase of vascular permeability) and for critical characteristics of AR which is itching, runny nose, red eyes, sneezing, nasal pruritus, air flow obstruction, blockage and mucous secretion. These symptoms appear within minutes after exposure.[19] The pathogenesis of AR is shown in Figure 1.

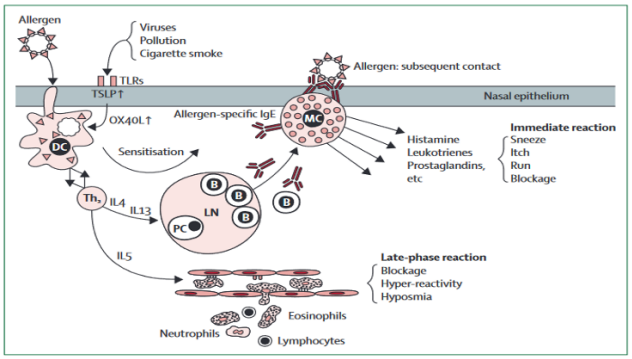

Fig. 1: Pathogenesis of Allergic Rhinitis

Classification

There are different ways to classify rhinitis.

- According to etiology: automatic, IgE mediated and idiopathic
- Traditional: seasonal and perennial
- According to pathophysiological mechanism
- According to symptoms

It is very difficult to fit patients in one system so nowadays according to symptoms like duration and severity they are classified as shown in Table 2.

Table 2: Classification of allergic rhinitis according to symptoms duration and severity [3,8]

Intermittent	**Persistent**
Symptoms less than 4-6 weeks	More that 4-6 weeks
Mild	**Moderate-severe**
Ordinary sleep Ordinary daily activities Ordinary work and school	Irregular sleep Struggle in daily activity Concentration issues Upsetting warning sign

AR is differentiated in two ways, first by what pathophysiological mechanism it arises and the second intensity of the critical symptoms or observable features. Personalized medicine is also drug of choice nowadays.[20,21]

Duration and severity can be estimated using numerical values (with 0 representing none, 1 for mild or less than

30min, 2 moderates, 3 for severe condition). They are judged according to interferences with daily activity.[22]

Many factors are responsible for AR. Some components that must be examined to suspect main allergen are shown in Table 3.

Table 3: Component of a complete physical examination for suspected rhinitis[6]

Component	Examination
Personal	Nasal itch, Rhinorrhoea, Sneezing,
Family	Specific Allergy and history of Asthma
Environmental	Pollens, Animals, Flooring/fabric, Mould, Humidity and exposure of tobacco
Medication	Beta-blockers, ASA, NSAIDs, ACE inhibitors, Hormone therapy and Recreational cocaine use
Comorbidities	Asthma, Mouth breathing, Snoring, Sinus involvement, Otitis media, Nasal polyps, and Conjunctivitis
Response to previous medications	Second-generation oral antihistamines, Intranasal corticosteroids
Outward signs	Mouth breathing, Rubbing the nose, Frequent sniffling and/or throat clearing and Allergic shiners (dark circles under eyes)
Nose	Mucosal swelling, bleeding, Pale, thin secretions
Ears	Generally normal, Pneumatic otoscopy to evaluate Eustache tube dysfunction, Valsalva maneuver to assess for fluid behind the ear drum
Sinuses	Palpation of sinuses for signs of tenderness and Maxillary tooth sensitivity
Posterior oropharynx	Postnasal drip, Lymphoid hyperplasia ("cobblestoning"), Tonsillar hypertrophy
Chest and skin	Atopic disease and Wheezing

Diagnosis

Diagnosis is easy when symptoms are clearly observed after exposure to the triggering allergen. Spirometer and computed tomography are used to detect subclinical asthma and sinusitis respectively.[22] Basically, AR diagnosis depends on indication of sensitivity, presence of IgE in serum and by positive epicutaneous skin test where triple response is observed using allergen extracts.[23]

It is also diagnosed according to its typical history and "sneezers and runners". Some tests are mentioned below to test nasal obstruction

- Nasal examination (Anterior rhinoscopy, nasal endoscopy)
- Functional tests (peak nasal inspiratory flow. Rhinomanometry or acoustic rhinometry)
- Immediate hypersensitivity skin test or IgE mediated reaction (radio allergosorbent testing, RAST)
- Chronic rhinosinusitis and tumours (Computerized tomography (CT) scan)[3]
- • Non allergic in nature (Non inflammatory rhinopathy or vasomotor rhinitis) (chronic rhinosinusitis)[24]
- • Molecular allergy diagnosis by immuno solid-phase allergen chip (ISAC) to measure aeroallergen specific IgE in nasal fluid[25]

Treatment Goals

The main aim of any drug is relief of symptom. The rationale for treatment choice mostly depends on its level of efficacy, affordability and presence of drug in WHO essential list of drugs.[26]

If we see the therapeutic option presented possibility to treat AR it incorporates avoidance, Pharmacotherapy (intranasal corticosteroid, leukotriene receptor antagonist, antihistaminic, decongestants, mast cell stabilizer, cromolyn) and allergen immunotherapy.[8,17] Every line of treatment has different pharmacological response, advantages and disadvantages as shown in Table 4.

Histamine and antihistaminics

Histamine is biological amine (L-histidine) produced by decarboxylation in presence of enzyme histidine decarboxylase (HDC).[29] Basically histamine receptors are of 4 sub types (heptahelical G-protein coupled receptors) namely H1 (chromosome 3) (anti-allergic & anti-inflammatory), H2 (gastric acid related disorder), H3 (cognitive disorder) and H4 (immune and inflammatory disorder). Histamine is responsible for contraction of smooth muscle, gastric acid secretion, neurotransmitter activity (itching and sneezing), glandular secretions (rhinorrhea) in nose and enhancement of vascular permeability (edema and blockage). Histamine through the H1 release down regulates humoral immunity and upregulates TH1 proliferation, interferon-production, cellular adhesion molecule expression, and chemotaxis of eosinophils and neutrophils. Through transcription factor, nuclear factor-kB, they also decrease antigen presentation, expression of proinflammatory cytokines and cell adhesion molecules, and chemotaxis.[30]

Effect of food (grapefruit juice) and drug is also observed on antihistaminic response of drug. Ketoconazole, cyclosporine, verapamil, itraconazole, erythromycin, azythromycin or rifampin alter the plasma concentration of drug.[31] It is main key which is responsible of immunomodulation, allergy [generation of (IgE)], inflammation, haematopoiesis, cell proliferation embryonic development, regeneration, and wound healing. Histamine exposure leads to erythema, pruritus, nasal congestion, flushing,

Table 4: Treatment of AR with their adverse effect and mechanism of action [18,27,28]

Pharmacotherapy	Minimum age	Mechanism of action	Adverse effect
Intranasal corticosteroids	2-12 year	Inhibit the influx of inflammatory cell	Biter after taste, burning, epistaxis, headache, nasal dryness, potential risk of systemic absorption, rhinitis medicamentosa, stinging, throat irritation
Oral antihistaminic	6 months to 12 years	Block H1 receptor, onset of action is 15 to 30 minutes	Dry mouth, sedation at higher than recommended doses
Oral decongestants	12 years	Vasoconstriction,	Arrhythmias, dizziness, headache, hypertension, insomnia, nervousness, tremor, urinary retention
Intranasal cromolyn	2 years	Inhibit histamine release. Results typically noted in one	Epistaxis, irritation of the nose, sneezing.
Intranasal anticholinergic	6 years	Blocks acetylcholine receptor	Epistaxis, headache, nasal dryness
Leukotriene receptor antagonist	6 months	Block leukotriene receptor, onset of action is two hours	High levels of alanine transaminase, aspartate transaminase and bilirubin.

headache, hypotension, tachycardia and bronchoconstriction.[32]

Symptoms occur due to activation of H1-receptor-coupled $G_{q/11}$ which trigger inositol phospholipid signalling pathway and increases intracellular calcium concentration by formation of Inositol-1,4,5-triphosphate (InsP3) and diacylglycerol (DAG). Phospholipase D and phospholipase A2 are also activated.[33]

Histamine producing neuron (~64000) presents tuberomammillary nucleus of the human brain in cerebrum, cerebellum, posterior pituitary and spinal cord and released when activated.[34]

As present in brain H1-receptors responsible for circadian sleep/wake cycle, reinforcement of learning and memory, fluid balance, suppression of feeding, control of body temperature, control of cardiovascular system and mediation of stress-triggered release of ACTH and β-endorphin from the pituitary gland.[35]

H1 antihistaminics are inverse agonist/neutral antagonist or receptor antagonists still a theory to justify. Antihistaminic is effective and safe in treatment of nasal itch, watery eye, sneezing and rhinorrhoea but less effect on nasal congestion. It is popular in children (aged 3-13) specially.[28]

H1 antihistamines are extensively used in relieving from different condition such as seasonal and perennial allergic rhinitis, urticaria, mild-moderate seasonal asthma and angioedema etc.

According to classification both first and second generation antihistaminics are over the counter (OTC) drug. But choosing second generation is for considering it on daytime also and have more advantage which will be discussed later.[22]

First generation antihistaminics

These drugs are usually classified as older 'first-generation H1-antihistamines'. They are widely used in the treatment of allergic rhinitis, allergic conjunctivitis, urticaria, cough, cold and insomnia. They cross (blood brain barrier) BBB easily but show poor selectivity toward receptor. As they are derived from the same chemical stem from which cholinergic muscarinic antagonists, tranquillizers, antipsychotics and antihypertensive agents were developed so has side effect of these drugs. Drowsiness, sedation, somnolence, fatigue, hang-over are also observed with altered sleep/wake cycle.[36]

It is also reported that whenever accident happen excluding alcohol/drug there is always first-generation H1-antihistaminic was found in post-partum report. Study shows there were 338 accidents (6% of total) where the pilot's blood sample was found to contain first-generation H1-antihistamine responsible for plane crash.

Many first-generation H1-antihistamines are found dangerous to children like in US promethazine comes with 'boxed warning' and from studies in 3000 patients, diphenhydramine (cardiac repolarization) and chlorpheniramine were reported causing 27 and 11 deaths, respectively.[37]

First-generation H1 antihistamines are highly liposoluble, they have low molecular weight and a high degree of affinity for cerebral H1 receptors, as a result sedation occurs frequently, even at therapeutic doses.[38]

They also show adverse effect on cardiac system like Cardiac arrhythmias caused by hydroxyzine, diphenhydramine, orphenadrine, pheniramine and chlorpheniramine while promethazine cause syncopal attacks with frequent ventricular tachycardia and torsade de pointes. On CNS Seizure was also observed in cases of hydroxyzine, diphenhydramine and orphenadrine.[39]

Second generation antihistaminic

Second-generation H1 antihistamines, in contrast, have high molecular weight, low liposolubility and low affinity for cerebral H1 receptors. Therefore, the majority of compounds in this generation, at therapeutic doses, are apparently devoid of significant side effects on the CNS.[37]

Second-generation compounds act as inverse agonist. They are less sedating due to limited penetration to BBB and also highly specific to H1 receptor. Hopefully there is no report found related to accident related to second-generation H1-antihistamines side effect. They also have additional anti-allergic properties different from antihistaminic activity.[39,40] It is used in the treatment of Allergic rhinitis, Atopic dermatitis, Acute and chronic urticaria, Insect bites, stings and Seasonal asthma with allergic rhinitis. They also produce rapid onset of action.[41]

In patients with AR, H1 antihistamines improve itching, sneezing and watery rhinorrhoea except nasal obstruction. They affect on symptoms nasal and ocular both.[40] All second-generation H1 antihistamines, with the exception of cetirizine, levocetirizine and fexofenadine, are metabolized via the cytochrome system. The P4503A (CYP3A) cytochrome, is known to be involved in the metabolism of many drugs used on humans.[42]

After oral administration at usual dosages, they rapidly achieve peak concentration in tissues. The majority of them begin to act within 1 to 2 hours after administration, with effects up to 24 hours, and hence can be taken once a day. Their activity does not diminish with regular, daily use for prolonged periods. These compounds maintain the capacity both to suppress the wheal and flare induced by histamine and to control the symptoms of persistent allergic rhinitis and chronic urticaria, for weeks and months.[43]

It is observed that second generation H1 antihistaminic show adverse effect on cardiac system. But three drugs namely cetirizine, levocetirizine and fexofenadine are safe. The other problem like drying of mouth, tachycardia and urinary retention which is reported in use of First generation H1 antihistaminic are countered by second generation.[44]

These reports contrast markedly with the report of an 18-month-old boy, weighing only 13 kg, who drank approximately 18 ml of cetirizine solution, corresponding to a dose of 180 mg, some 50 times the recommended dose. The toddler tolerated the overdose with virtually no complications. Levocetirizine and loratadine also show same result.[45]

The most frequently used Four second-generation H1 receptor antagonists are desloratadine, loratadine, fexofenadine, cetirizine and levocetirizine.[46]

Second generation antihistaminics also have some side effect related to cardio and CNS disorder like Astemizole, Desmethylastemizole, Terfenadine (also observed convulsion) and Fexofenadine shows prolonged QT effect. Different comparative tolerability of second/third generation H1 antihistaminic drugs is shown in Table 5.

Why Levocetirizine is good choice for AR

Levocetirizine (Xyzal®) 'third generation' is the active R-enantiomer of cetirizine with chemical formula $C_{21}H_{25}ClN_2O_3$ and chemical name of piperazine class.[46] It is 2-(2-{4-[(R)-(4-chlorophenyl) (phenyl)methyl] piperazin-1-yl} ethoxy) acetic Acid as shown in fig 2.

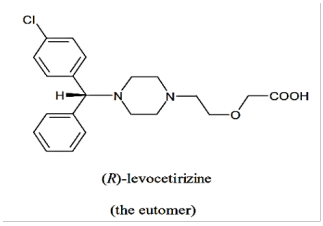

Fig. 2: Chemical structure oflevocetirizine[47]

Levocetirizine (5mg) has demonstrated a 2-fold higher affinity, less sedative effect[48] for the human H1-receptor compared to cetirizine, and an approximately 30-fold higher affinity than dextrocetirizine.[49]

Comparison of the neurological event like somnolence (2.3, 0), nervousness (1.3, 0.4) and fatigue(3.3,0) between cetirizine and levo cetirizine were found respectively.

A New Drug Application (NDA) to the United States Food and Drug Administration (FDA) for approval of levocetirizine was granted in May, 2007. Comparative studies shows that levocetirizine had a higher clinical response rate than loratadine in allergic rhinitis, and a more pronounced and longer lasting inhibition of histamine mediated wheal and flare skin reactions than loratadine 10 mg.[47] Many studies demonstrate that the antihistaminic properties noted for cetirizine in the management of seasonal and perennial allergic rhinitis are probably due to the levocetirizine enantiomer.[50]

It is selective, potent, oral histamine H1 antagonist of the latest generation receptor which is allowed for symptomatic treatment of chronic idiopathic urticaria, seasonal allergic rhinitis, and hay fever. Levocetirizine is non-sedating, selective histamine H1 receptor antagonist, with antihistamine, antiangiogenic and additional anti-inflammatory activities.[46,50]

Levocetirizine have lower volume of distribution may be due to high protein binding compared to both isomers. Great configurational stability of levocetirizine is also observed in body.[51]

The most frequently used second-generation H1 receptor antagonists are desloratadine, loratadine, fexofenadine, cetirizine and levocetirizine.[46]

Binding-affinity constants were found to be 0.9 nmol/L for desloratadine, 5.0 nmol/L for fexofenadine and 0.6 nmol/L for levocetirizine at a pH of 5.8. Increasing the pH to

Table 5: Different comparative tolerability of second/third generation H1 [40,44]

Drug	Performance impairment	On Cardio vascular system	Chronic renal	liver impairment	Pregnancy	In nursing mother	Body weight
Acrivastine	Yes	No	Yes	Yes	Teratogenic	Possible	No
Astemizole	No	Yes	No	No	Category C	Yes	3.6%
Azezlastine	Yes	Yes	Possible	Possible	Category C	Yes	No
Cetrizine	No	No	No	No	Category B	Possible	0.4%
Levocetrizine	No	No	No	No	Category B	possible	No
Ebastine	No	Possible	No	No	-	-	No
Fexofenadiene	No	Possible*	No	No	Category C	-	No
Loratadine	No	Possible*	Yes	Yes	Category B	Yes	Yes
Mizolastine	No	Yes	No	Possible	-	-	No
Terfenadine	No	Yes	Possible	Yes	No teratogenic effect	-	No

*fexofenadine causes blockage of potassium channel.
*loratadine causes CYP450 mediated metabolism.
*category B is Favourable FDA category.

7.4 resulted in a binding affinity constant of 7.4 nmol/L for levocetirizine. Desloratadine has a higher H1 receptor affinity than other second-generation antihistamines at nearly 200 times that of fexofenadine, >50 times that of loratadine and cetirizine, and three times that of levocetirizine.[52]

In 2005, Potter published a 4-wk clinical trial of the efficacy and safety of levocetirizine and health-related quality of life in children aged 6–12 yr with perennial allergic rhinitis.[4] His study showed that levocetirizine had significant improvement in 2- and 4-week of total four symptom scores compared with a placebo. In conclusion, a 12-wk treatment program showed that cetirizine was more efficacious than levocetirizine. Twice daily for oral intake of levocetirizine may be an alternative way to well control the symptoms of perennial allergic rhinitis in age 6- to 12-yr-old children.[53]

Fexofenadine and levocetirizine are devoid of any clinically relevant anticholinergic activities but desloratadine (due to high potency).[54]

Levocetirizine is approved in the US and EU for relief of symptoms of SAR, perennial/persistent AR and CIU patients aged ≥6 years.[46,53]

Levocetirizine has shortest onset of action as compared to other drugs. But on CNS effects like somnolence, drowsiness and psychomotor impairment was reported high for levocetirizine compared to other.[46]

Desloratadine, fexofenadine and levocetirizine are not considered to be significant P-gp inhibitors. On long use decrease plasma concentration and bioavailability is observed in case of desloratadine.[46]

Levocetirizine does not undergo extensive metabolism. It is notably not metabolized by the Cytochrome P450 system. It does not show any drug -drug interaction either.[51]

Comparison of these drugs for every age shows that levocetirizine is suitable in every age especially for younger ones. Even compared to its isomer there is no need to increase dose in children for clearance issue.

Levocetirizine undergoes a low degree of first pass metabolism in the liver; it is metabolized to a limited extent by oxidative dealkylation to metabolite with negligible antihistaminic activity. It is approximately 93% bound to plasma proteins and has a plasma elimination half-life of 8-9 h that does not change with multiple dosing. Food had no effect on the extent of levocetirizine exposure (AUC) but T_{max} was delayed by 1.7 hours and C_{max} was decreased by 23% in the presence of food.[50,51,55,56]

As compared to cetirizine is shows high selectivity and twice affinity for H1 receptors. It is rapidly absorbed have prolonged effect as prescribed once a day(5 mg/day).[47] Levocetirizine have significant improvement in nasal flow and symptom score compare to other. Additionally, it also uses in prevention of immediate and late symptoms resulting from insect bites. Levocetirizine does not interact significantly with any of the muscarinic receptor subtypes and therefore does not exhibit strong anticholinergic effects. It is safe and well-tolerated compound compare to other. It does not cause sedation or other harmful effects on cognitive and psychomotor abilities of healthy volunteers. In patients with persistent AR and chronic idiopathic urticaria, it significantly enhances quality of life and reduces the cost of prolonged treatment.[40,48]

There are many types of formulation of Levocetirizine nowadays available which show good effectiveness and safety for long term use as compare to other drug shown in table 6.

CONCLUSION

The pharmacological characteristics of antihistaminics show that second generation are better as compare to first generation. They show less toxic and sedative effect. Second generation H1 antihistaminics are highly effective and safe

Table 6: Different types of formulation related to levocetirizine

Dosage form	Method	Advantage
orally dissolving fibrous web[57]	Nanofiber-based system core–shell type hydrophilic polymer-based fibrous systems.	Reduced bitter taste
Topical delivery[58]	Microemulsion	Enhanced penetration
Oral dosage form[59]	Nanoparticles by spray drying	Improved disintegration
Topical delivery[60]	Noisome (loaded polymeric nanoparticle gel)	Penetration enhancement
Topical delivery[61]	emulgel	Penetration enhancement
Oral dosage form[62]	Orodispersible tablets, direct compression technique containing synthetic superdisinte-grantscrospovidone	Improved disintegration
Oral dosage form[63]	in-situ floating gel	extended release
Oral dosage form[63]	fast-dissolving film	excellent stability, release
Oral dosage form[64]	mouth dissolving tablet	Reduced bitter taste, low disintegration time, wetting time and friability
Oral dosage form[65]	Fast releasing oral polymeric film	instant disintegration and dissolution
Ocular dosage form[66]	in situ thermosensitive hydrogel	Enhanced penetration, prolong action
Oral dosage form[67]	mouth dissolving tablets	Reduced bitter taste
Nasal drug delivery[68]	mucoadhesive microspheres by spray drying	Enhanced penetration, prolong action

with lesser interaction. Many type of such formulation are available in market related to treat AR. But most promising molecules are fexofenadine, loratadine and levocetirizine. If we compare these three, levocetirizine has many plus like used in insect bite, anti-inflammatory with zero drug-drug interaction and safest in paediatric purpose. The active component levocetirizine (R-isomer) possesses almost ideal pharmacological and pharmacokinetic properties as an antihistamine with low incidents of CNS side effects, because compared to cetirizine (88-90%), levocetirizine (91.2%) have high protein binding show low volume of distribution which decrease risk of drug-drug interaction and dose-dependent toxicity. Levocetirizine could serve as a good example for medicinal chemists to design zwitterion drugs from an acidic, basic or neutral lead molecule for various biological targets, particularly those requiring low CNS penetration for avoiding obvious CNS side-effects. It is an extensively investigated antihistamines for safety and efficacy in children of different ages ranging from 6 months to 12 years. Compared with cetirizine, desloratadine, fexofenadine and mizolastine; levocetirizine seems to have a favourable PK profile with respect to absorption, plasma protein binding or volume of distribution, suggesting a potentially greater therapeutic index for this antihistamine. Real-life studies have indicated good satisfaction levels with levocetirizine for the majority of patients.

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