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A Systematic Review On Pharmacokinetic, Pharmacodynamic, Interaction with Other Drugs, Toxicity and Clinical Effectiveness of Anti - Histamine Drug (H1 Antagonist)

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Abstract: *H1 antagonist antihistamines are a family of therapeutic drugs that are extensively used and clinically significant. They are intended to prevent and treat a wide range of allergic responses. Histamine is a key player in the physiological reactions that occur during allergen exposure, including bronchoconstriction, vasodilation, increased capillary permeability, and sensory neuron activation, all of which contribute to the typical symptoms of allergic illness. These drugs efficiently lessen symptoms, including sneezing, itching, rhinorrhea, urticaria, and conjunctival irritation, by specifically inhibiting H1 receptors on different target tissues, resulting in quick symptom alleviation.*

First-generation (sedating) and second-generation (non-sedating) antihistamines are the two major categories into which these medications are divided, mostly on the basis of their capacity to pass across the blood–brain barrier. Triprolidine and diphenhydramine are examples of first-generation H1 antagonists that easily enter the central nervous system and cause severe sleepiness, cognitive slowness, and anticholinergic side effects. Because of their quick start-up effect, they are nonetheless helpful in acute allergy situations, despite these disadvantages. Second-generation antihistamines, such as cetirizine and levocetirizine, on the other hand, show little penetration of the central nervous system and great selectivity for peripheral H1 receptors. They are therefore ideal for long-term treatment in patients with allergic rhinitis, chronic urticaria, and other persistent hypersensitivity disorders since they produce little to no drowsiness.

The foundation of contemporary pharmacological treatment of allergic illnesses is made up of H1 antihistamines, which are safe and effective in a variety of clinical contexts.

Keywords: Anti-Histamine, H1antagonist, Diphenhydramine, Cetirizine , Pharmacokinetic, Pharmacodynamic, Interaction with other drug, Toxocity, Clinical effectiveness

I. INTRODUCTION

A family of drugs known as antihistamines is used to treat symptoms brought on by the body's release of histamine, a substance released during allergic responses. Sneezing, itching, watery eyes, runny noses, and skin rashes are symptoms caused by histamine binding to H1 receptors when the body comes into touch with allergens, including dust, pollen, animal dander, or certain foods. Antihistamine medications reduce allergy symptoms by inhibiting these H1 receptors, which stops histamine from having its effects.

These medications are frequently used to treat conjunctivitis, urticaria (hives), allergic rhinitis (hay fever), bug bites, and occasionally in conjunction with other medications to relieve colds and coughs. First-generation and second-generation antihistamines are the two main categories. Second-generation antihistamines are less sedative and provide longer-lasting relief, but first-generation antihistamines frequently induce sleepiness due to their ability to pass the blood–brain barrier. All things considered, antihistamines are essential for controlling allergies and enhancing patient comfort.

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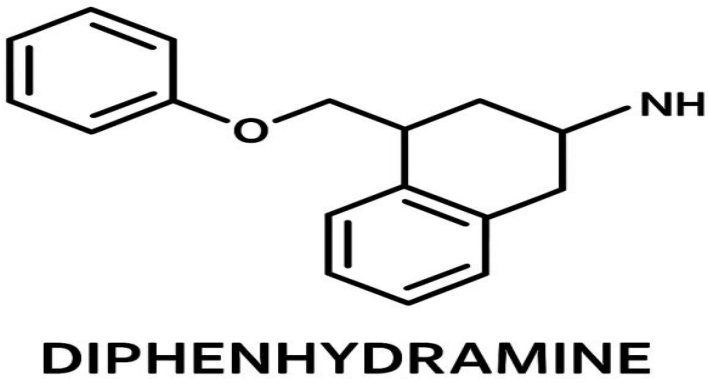
II. H1 ANTAGONIST

Histamine a significant family of antihistamine medications, H_2 antagonists are mainly used to treat and prevent allergic diseases. During allergic responses, histamine causes vasodilation, increased capillary permeability, bronchoconstriction, and sensory nerve activation. These medicines work by blocking H_2 receptors on target tissues. Consequently, symptoms including sneezing, itching, rhinorrhea, urticaria, and conjunctival irritation are successfully relieved by H_2 antagonists. Based on their capacity to pass across the blood–brain barrier, they are generally divided into first-generation (sedating) and second-generation (non-sedating) antihistamines.

First-generation H_2 antagonists like triprolidine and diphenhydramine are commonly used to treat colds and allergic reactions. They cause severe drowsiness and anticholinergic adverse effects because they penetrate the central nervous system. On the other hand, second-generation medications like cetirizine and levocetirizine offer strong and specific peripheral H_2 receptor blockage with little sedation, which makes them appropriate for long-term treatment of chronic urticaria and allergic rhinitis. Despite not being a traditional H_2 antagonist, cromolyn sodium is used prophylactically to treat allergic rhinitis and asthma by stabilizing mast cells and preventing histamine release. These medications collectively serve as the cornerstone of contemporary allergy treatment.

III. DIPHENHYDRAMINE



(Fig.1.12.Structure of Diphenhydramine)

Diphenhydramine, a first-generation H1 antihistamine belonging to the ethanolamine family, is well-known for its potent sedative and anticholinergic effects since it may pass across the blood–brain barrier. It was created in the 1940s and is still often used to quickly relieve allergy symptoms such as urticaria, rhinitis, watery eyes, sneezing, and itching. It is also useful for motion sickness, nausea, and vertigo due to its anticholinergic effects, and it is often used for acute dystonic responses. It is frequently found in over-the-counter sleep aids for temporary insomnia due to its CNS depressive properties. Hepatic CYP450 enzymes metabolize diphenhydramine, which is quickly absorbed and strongly protein-bound. Because abuse or excessive dosages can result in severe anticholinergic toxicity, arrhythmias, seizures, or coma, especially in sensitive populations, caution is crucial.

Medical Uses

- Diphenhydramine is frequently used to treat allergic responses to foods or insect bites, urticaria (hives),and allergic rhinitis (runny nose, sneezing).
- Skin rashes from mild allergies Redness, swelling, and itching are all lessened by its antihistamine activity.
- Symptoms of a Common Cold

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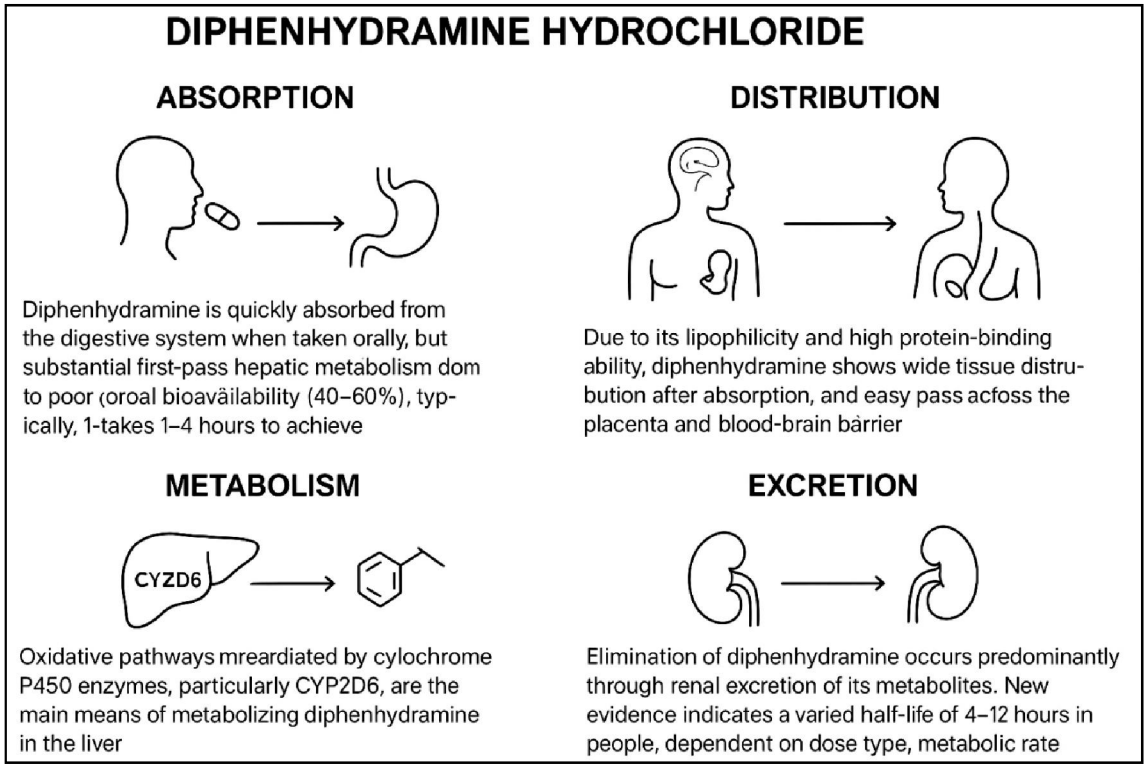
- Diphenhydramine prevents and cures motion sickness-related nausea, vomiting, and dizziness.
- It acts by altering the brain's vomiting center.
- It is frequently used as an over-the-counter sleep aid due to its sedative properties, particularly for: Occasional difficulties falling asleep

PHARMACOKINETIC



(Fig.1.2.Pharmacokinetic of Diphenhydramine)

Absorption

The gastrointestinal tract absorbs diphenhydramine effectively; however, the dose type affects how much of it is absorbed. It exhibits quick and effective stomach absorption when administered orally as a liquid solution, nearly entirely entering the hepatoportal system. Commercial capsule absorption, on the other hand, varies significantly according to formulation and individual characteristics; some people absorb almost the whole capsule dose, while others only absorb around 83% when compared to the solution. The liver metabolizes almost half of the oral dosage before it reaches the systemic circulation, indicating a strong first-pass impact even though GI absorption is usually good. Urinary recovery is not a good indicator of absorption since less than 4% of the medicine is eliminated in urine. First-pass metabolism is the primary cause of the overall decrease in systemic availability.

Distribution

Due to its high lipophilicity, diphenhydramine may quickly pass through biological membranes and disperse throughout the body after consumption. Only 1.5–1.8% of the medication is left unbound due to its extremely high plasma protein binding; this ratio is constant across doses, suggesting a continuously low free fraction. The medication is mostly restricted to plasma and extracellular fluid rather than entering blood cells since plasma levels are marginally greater than whole-blood levels (blood/plasma ratio 0.82). Since only free medication may pass through membranes, the

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restricted unbound percentage affects both distribution and pharmacological activity. Nevertheless, its lipophilicity allows for substantial tissue penetration, including the brain, resulting in strong CNS sedative effects. Strong protein binding may enhance the likelihood of drug-drug interactions through displacement and prolong the duration of activity.

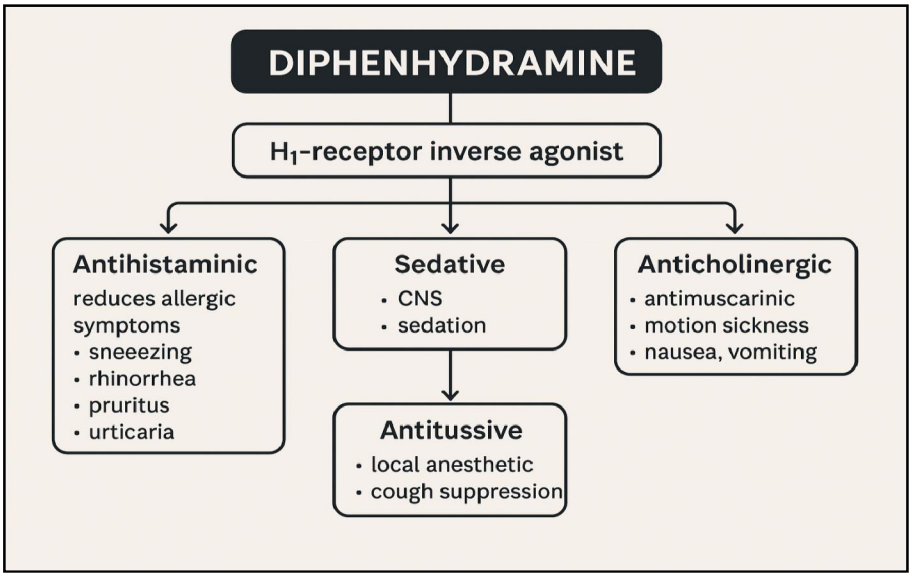
Metabolism

Diphenhydramine is extensively metabolized by the liver, and a significant first-pass impact significantly lowers the quantity of active medication that enters the bloodstream. Compared to intravenous dosing, which completely avoids first-pass metabolism, approximately half of the absorbed dosage is quickly digested after oral ingestion before reaching the bloodstream, resulting in much lower plasma levels. Diphenhydramine is transformed into inactive metabolites, including diphenylmethoxyacetic acid and N-demethylated derivatives, in the liver by CYP450 enzymes, particularly CYP2D6. The extremely tiny percentage of unaltered medication discharged in urine (<3–5%) indicates efficient metabolism rather than inadequate absorption since these metabolites are inactive. Despite slight variations in absorption, this substantial metabolism happens uniformly in all dose formulations. The intrinsic elimination half-life of diphenhydramine is very short (4–7 hours), while some oral investigations have longer apparent values because of slower absorption.

Excretion

Diphenhydramine's significant hepatic biotransformation is reflected in the renal excretion of its inactive metabolites, which is the main method of elimination. The parent medication contributes relatively little to total renal clearance since only a very little portion of the dosage is eliminated unaltered, usually less than 4%. Because it avoids first-pass metabolism, an intravenous dose produces a somewhat larger unmodified recovery (approximately 2–3%), while oral administration produces just around 1% unchanged drug in urine. These modest recoveries demonstrate the unreliability of using urine excretion of unaltered diphenhydramine to estimate absorption. It is confirmed that metabolism, not renal filtration, controls clearance since nearly the whole dosage is metabolized before excretion. Due to sluggish absorption, apparent oral half-lives appear to be longer (13–21 hours), while the actual elimination half-life following intravenous injection is substantially lower (4–7 hours).

PHARMACODYANMIC



(Fig.1.3. Pharmacodynamic of Diphenhydramine)

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A first-generation ethanolamine antihistamine, diphenhydramine functions as an inverse agonist at H_2 receptors, causing them to become inactive instead of only preventing histamine binding. It relieves sneezing, rhinorrhea, pruritus, and urticaria by counteracting histamine-induced vasodilation, increased capillary permeability, smooth muscle contraction, and sensory neuron activation through the reduction of histaminergic transmission. It successfully reduces the vascular and sensory aspects of allergy responses through this method. Its high lipophilicity, which enables simple blood-brain barrier crossing, is a crucial pharmacodynamic characteristic. It has powerful sedative, hypnotic, and psychomotor-impairing effects on the central nervous system (CNS) by inhibiting the histaminergic pathways responsible for alertness. This explains why it is frequently used as a short-term sleep aid. However, particularly in older persons, these same CNS effects may result in dizziness, delayed cognition, poor coordination, and an increased risk of falls.

Additionally, diphenhydramine exhibits significant antimuscarinic action across M_1–M_6 receptors. Motion sickness, nausea, and vomiting are efficiently treated by lowering cholinergic transmission in the vestibular nucleus and chemoreceptor trigger zone. However, negative symptoms such as dry mouth, impaired vision, tachycardia, constipation, urine retention, and disorientation are also explained by similar anticholinergic activities.

Additionally, diphenhydramine reduces peripheral neuronal excitability in airway pathways by blocking voltage-gated sodium channels, which gives it moderate local anesthetic and antitussive properties. By reestablishing the dopaminergic-cholinergic balance, its central anticholinergic action might also somewhat lessen extrapyramidal symptoms and offer limited symptomatic relief in Parkinsonism.

INTERACTION WITH OTHER DRUGS

Diphenhydramine is susceptible to serious medication interactions due to its sedative and anticholinergic properties. When taken with sleep aids like zolpidem or eszopiclone, sedation can become dangerously excessive, and taking many drugs containing diphenhydramine can result in an accidental overdose. While benzodiazepines like alprazolam or lorazepam further enhance disorientation and fall risk, opioids like oxycodone or tramadol significantly increase sleepiness, dizziness, and the risk of respiratory depression. Other anticholinergics, such as scopolamine and oxybutynin, might exacerbate impaired vision, constipation, disorientation, and urine retention, particularly in elderly or dementia patients. Additionally, antidepressants interact: sedation and anticholinergic effects are enhanced by SSRIs, SNRIs, MAOIs, and TCAs. Cyclobenzaprine and other muscle relaxants exacerbate sleepiness and poor coordination. Alcohol should be completely avoided since it significantly increases sedative effects.

TOXICITY

Diphenhydramine overdose can result in mydriasis, flushing, anxiety, tremor, dystonia, hallucinations, ECG abnormalities, and in extreme circumstances, rhabdomyolysis, convulsions, delirium, arrhythmias, coma, or circulatory collapse. It also produces lethargy, hyperpyrexia, and strong anticholinergic effects. Even at lower hazardous levels, children are particularly vulnerable and may have seizures or hallucinations. The drug crosses the placenta and enters breast milk, so it should only be used during pregnancy or lactation if the benefits to the mother outweigh the risks to the fetus or newborn. Even while young and old individuals have similar metabolisms, older folks are more likely to feel sleepy and disoriented; therefore, its usage should be avoided. Dosing intervals should be increased in renal failure, and half-life is prolonged in liver disease. Myocardial infarction, ventricular arrhythmias, unconsciousness, and even death can result from a significant overdose.

CLINICAL EFFECTIVENESS

First-generation H1 antihistamines like diphenhydramine are frequently used to treat allergy symptoms such as rhinorrhea, pruritus, and sneezing. In addition to acting as an adjuvant with corticosteroids and epinephrine in cases of anaphylaxis, it offers quick relief from urticaria, allergic rhinitis, and conjunctivitis; the CDC approves its intravenous usage for vaccine-related responses. Because of its sedative properties, it is used for short-term sleeplessness in addition to allergy treatment, while usage in children is advised. Additionally, it acts on the vestibular system to alleviate nausea and motion sickness, and it may be a part of chemotherapy or postoperative antiemetic regimens. Its sedative and

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sodium-channel-blocking properties facilitate its use in local anesthetic and procedural sedation. However, long-term usage is restricted by drowsiness, cognitive decline, anticholinergic effects, and cardiac concerns, which favor safer second-generation antihistamines.

IV. CETIRIZINE

Cetirizine, an active metabolite of hydroxyzine and a second-generation H_2-antihistamine, minimizes the sedative and anticholinergic effects of first-generation antihistamines while treating allergic disorders, including urticaria and allergic rhinitis. It blocks histamine-mediated symptoms like sneezing, itching, and nasal congestion by acting as a selective H_2 receptor antagonist and inverse agonist. Cetirizine has high bioavailability, minimal hepatic metabolism, and is generally eliminated unaltered in urine, making once-daily dosage simple. It is taken orally and reaches peak plasma levels in approximately an hour. Clinical trials attest to its effectiveness and safety in both adults and children, with very minor adverse effects such as slight sleepiness or gastrointestinal distress. It has little effect on heart rhythm, in contrast to earlier antihistamines. Cetirizine, which comes in pills, syrup, and oral solution, guarantees long-lasting symptom alleviation and excellent compliance and is advised as a first-line treatment for allergic illnesses.

Medical Uses :

1. Allergic Rhinitis (Nose Allergies)

Sneezing, runny or clogged noses, itchy noses, seasonal allergies (pollen), and perennial allergies (dust, pets, mold) are all treated with it.

2. Allergic Conjunctivitis (Eye Allergies)

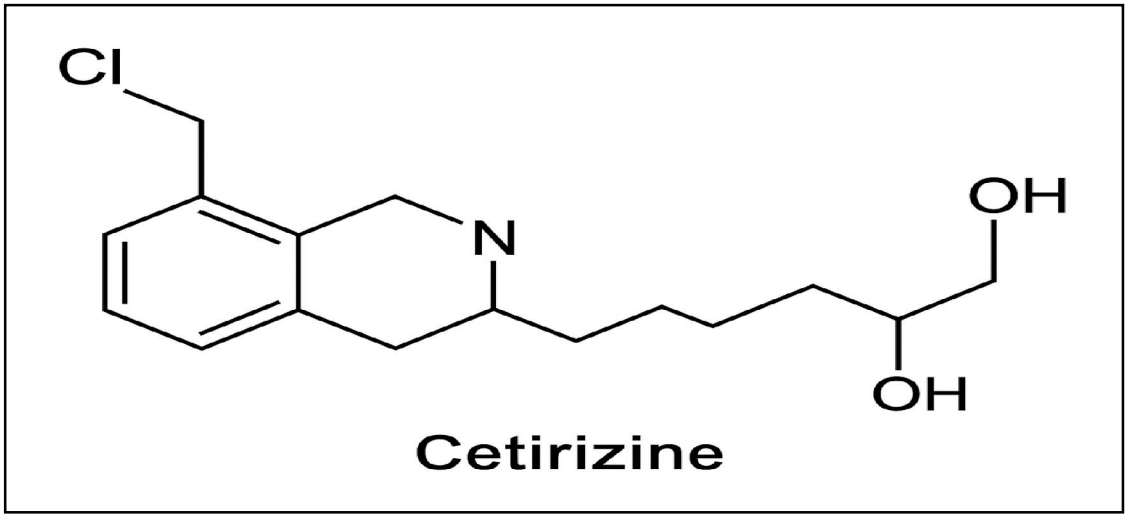
helps lessen redness and watery or itchy eyes.

3. Urticaria (Hives)

Extremely successful in treating red, itchy skin bumps, swelling, and chronic urticaria (long-term itching).

4. Skin Allergies

used to treat nonspecific allergic skin responses, such as rashes, itching, and dermatitis-related irritation.



(Fig.3.1.Structure of Cetirizine)

PHARMACOKINETIC

Absorption

Cetirizine is easily absorbed orally and has a bioavailability of 70–85%, indicating little first-pass metabolism. Although formulation and individual variations may somewhat alter this, peak plasma concentrations (C_max) are usually attained in around an hour. Food may postpone peak concentration (T_max) by about an hour, but it has no

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effect on total absorption or bioavailability. Because of its intermediate lipophilicity and poor passive diffusion, absorption mostly takes place in the small intestine by carrier-mediated transport. Cetirizine has linear pharmacokinetics at therapeutic dosages (5–20 mg), providing consistent plasma levels and symptom alleviation. While low interindividual variability guarantees a dependable once-daily dose and consistent therapeutic effects in adults, children, and the elderly, rapid absorption enables action within 30 to 60 minutes.

Distribution

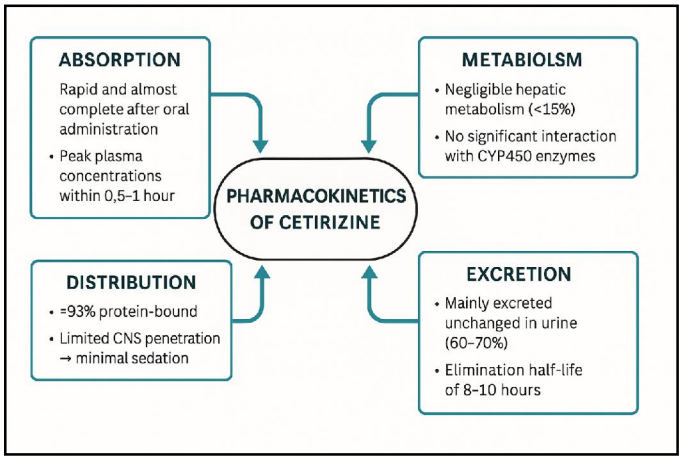
Cetirizine's poor tissue penetration and small volume of distribution (0.4–0.5 L/kg) suggest that it mostly stays in extracellular fluid. It has fewer sedative and psychomotor effects than first-generation antihistamines because of its hydrophilic nature and P-glycoprotein efflux at the blood-brain barrier (BBB), which limits CNS penetration. Approximately 93% of cetirizine is protein-bound, primarily to albumin, which restricts the amount of free medication but prolongs its effects and lessens interactions that are clinically important. Age, body composition, and plasma protein levels all affect distribution; infants have a comparatively higher volume of distribution, but small variations in elderly or liver-impaired people are typically not clinically significant. By focusing on H_2 receptors and reducing cerebral side effects, cetirizine's actions are primarily peripheral.

Metabolism

The liver metabolizes only 10–15% of cetirizine, mostly by oxidative O-dealkylation; however, it is unknown which CYP450 isoenzymes are involved. Pharmacokinetic interactions with other CYP450-metabolized medicines are less likely when hepatic metabolism is minimal. Predictable pharmacokinetics are supported by the parent compound's continued pharmacological activity and the metabolites' relative inactivity. Low metabolic clearance in healthy people leads to a half-life of 8–10 hours, which makes once-daily dosage practical and improves adherence. Cetirizine is safe for a variety of patient demographics because of its low hepatic dependency. Pharmacokinetics are mostly unaffected by hepatic impairment; however, concomitant renal dysfunction may somewhat delay elimination. Cetirizine's low metabolism reduces buildup and side effects, making it safer than first-generation antihistamines in cases of liver illness or poly pharmacy.

Excretion

Renal clearance is the primary elimination mechanism for cetirizine, with around 70% being removed unaltered in urine and 10–13% in feces. With a renal clearance rate of 30–40 mL/min, excretion happens via active tubular secretion and glomerular filtration. The half-life is 8–10 hours in healthy adults and 12–15 hours in older or renally impaired people. Children have a shorter half-life of five to six hours due to their increased renal clearance per kilogram. Drug buildup brought on by renal impairment may require dosage modifications to ensure safety and effectiveness. Cetirizine is not effectively removed by hemodialysis for quick clearance. Overall, steady pharmacokinetics and safe therapeutic usage are ensured by cetirizine's consistent renal clearance, low metabolism, and low inter individual variability.



(Fig.3.2. Pharmacokinetic of Cetirizine)

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PHARMACODYNAMIC

A popular second-generation antihistamine, cetirizine is important for treating allergic diseases such as urticaria, allergic rhinitis, and other hypersensitivity disorders. Its unique activity on histamine H_1 receptors, which are important mediators of allergic inflammatory reactions, is the main source of its therapeutic benefits. Cetirizine's pharmacodynamic mechanism includes inhibiting histamine activity, which lessens the physiological impacts of allergic responses.

Histamine is released by mast cells and basophils as part of the immune response when the body comes into contact with allergens such as dust, pollen, or animal dander. Following its binding to H_1 receptors found in smooth muscles, vascular endothelium, and sensory neurons, histamine causes symptoms such as nasal congestion, pruritus, increased vascular permeability, and vasodilation.

A strong, reversible, and specific antagonist of peripheral H_1 receptors is cetirizine. It alleviates allergy symptoms such as sneezing, itching, watery eyes, and swelling by competing with histamine at these locations and preventing histamine-mediated effects. Because of its polar shape and low lipophilicity, cetirizine has limited blood–brain barrier penetration and strong peripheral selectivity, which means that it causes less sedation and psychomotor deficits than first-generation antihistamines. It enables simple once-daily dosing and better adherence because it starts to work within an hour and has benefits that continue for roughly 24 hours. Cetirizine's overall efficacy in managing allergy symptoms is attributed to its modest anti-inflammatory and histamine-induced vascular permeability reduction at the cellular level. Additionally, cetirizine decreases the production of endothelial adhesion molecules and limits eosinophil migration, which lessens the infiltration of inflammatory cells at allergic sites. Its long-term benefits in chronic illnesses like urticaria are a result of these effects. Because of its low affinity for muscarinic, serotonergic, or adrenergic receptors, it is less likely to cause non-selective antihistamine-related side effects such dry mouth, impaired vision, or urine retention. Cetirizine reduces the risk of QT interval lengthening associated with earlier antihistamines like terfenadine since it has no discernible effect on cardiac ion channels. Clinically, it lowers wheal and flare in urticaria and efficiently improves nasal congestion, rhinorrhea, and sneezing, which are symptoms of allergic rhinitis. Cetirizine is a safe and efficient antihistamine because of its strong peripheral H_1 antagonism, low level of sedation, and extended duration.

INTERACTION WITH OTHER DRUGS

Cetirizine is a second-generation H_2-antihistamine that limits sedation and anticholinergic effects by selectively inhibiting peripheral H_1 receptors to treat allergic diseases. Its racemic structure contains the active R-enantiomer, levocetirizine, which has a piperazine ring that increases receptor affinity and a carboxyl group that decreases blood-brain barrier permeability. Food has little effect on oral bioavailability, which ranges from 70 to 85%. Changes in pH or GI motility may cause a little delay in absorption. Only 10–15% is metabolized by the liver (CYP3A4/CYP2D6), and 70% is eliminated unaltered by the kidneys by tubular secretion and glomerular filtration. Approximately 93% is protein-bound. Strong CYP3A4 inhibitors, CNS depressants, anticholinergics, and drugs that influence renal clearance (such as probenecid and cimetidine) can all cause minor drug interactions. Children, the elderly, and people with renal or hepatic impairment are more likely to experience sedation, necessitating dosage adjustments or monitoring.

TOXICITY

Cetirizine is a second-generation H_2-antihistamine that specifically blocks peripheral H_1 receptors to successfully relieve urticaria, allergic rhinitis, and associated disorders. It is typically safe and well-tolerated. Its poor CNS penetration and low anticholinergic action lessen sedation and systemic side effects, which are often modest and dose-dependent and include headache, weariness, dry mouth, and mild drowsiness. CNS toxicity (drowsiness, disorientation, restlessness, seizures), uncommon hepatotoxicity (hyperbilirubinemia, increased ALT/AST, cholestasis), and mild cardiovascular symptoms (palpitations, tachycardia) might result from overdose or idiosyncratic responses. Usually, toxic levels are more than 50–100 mg for adults or 0.5 mg/kg for children. Activated charcoal within an hour after consumption, monitoring, and hydration are all part of supportive management. Strong protein binding renders hemodialysis inefficient, and the majority of side effects are reversible when stopped.

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CLINICAL EFFECTIVENESS

By selectively inhibiting peripheral H_1 receptors, cetirizine, a second-generation H_1-antihistamine, successfully cures allergic disorders like atopic dermatitis, chronic urticaria, and allergic rhinitis, alleviating symptoms like watery eyes, nasal congestion, sneezing, and itching. It supports once-daily dosage and good patient compliance by acting quickly—within an hour—and controlling symptoms for up to 24 hours. While low blood-brain barrier penetration reduces CNS sedation and cognitive impairment, cetirizine also has moderate anti-inflammatory effects, decreasing eosinophil migration and inflammatory mediator release. Dry mouth, exhaustion, or moderate drowsiness are common side effects that are dose-dependent; in rare instances, palpitations or mood swings are reported. In order to prevent additive drowsiness, concomitant use of alcohol or sedatives should be avoided, and dosage modification is advised for renal or hepatic impairment.

V. CONCLUSION

H1 antihistamines are still used to treat allergy diseases because of their ability to suppress histamine-induced reactions. Despite their effectiveness, first-generation drugs have severe sedation and anticholinergic side effects. Second-generation antihistamines, on the other hand, are more suited for long-term treatment since they offer focused peripheral H1 blockage with little central side effects. All things considered, the safety, tolerability, and efficacy of allergy therapy have significantly increased due to the ongoing development of H1 antagonists. Additionally, their wider therapeutic application has improved overall clinical results and patient compliance. Their relevance in contemporary allergy care has been further reinforced by developments in pharmacokinetics and receptor specificity. Newer drugs may offer even more accuracy and fewer side effects in the future with continued study.

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