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Antihistamine: New Advancement in H1&H2 Receptor used for Pregnancy

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Abstract: ***The function of histamine in allergic inflammation, neurotransmission, and immunological regulation has since been better known one of the most typical skin conditions is urticaria. It may be sudden, recurring, caused by physical stimulation, or brought on by contact with an urticant. A small vessel vasculitis may be the cause of certain instances. As knowledge about this disorder grows, autoimmune pathways are now understood to contribute to chronic urticaria. This study shows that H antihistamine therapy alone is not statistically better to combined H2 and H antihistamine therapy for the treatment of chronic urticaria symptoms. Histamine has been one of the biological amines most extensively studied in medicine. It encourages the contraction of smooth muscles and the release of stomach acid, enhances vascular permeability, functions as a neurotransmitter, and has a range of actions in the control of the immune system, allergies, inflammation, haematopoiesis, and cell division. Histamine works by attaching to the H1, H2, H3, and H4 receptors. H3 and H4 receptors are predominantly presynaptic and haematopoietic, respectively, whereas H1 and H2 receptors are widely dispersed. Human H1- and H2-histamine receptors were cloned and described in the early 1990s, followed a few years later by human H3- and H4-histamine receptors. The main treatment for chronic urticaria is second-generation non-sedating non-impairing H antihistamines. Then, the H antihistamines permitted dosage is raised by a factor of up to four.***

Keywords: Allergic inflammation, chronic urticaria, presynaptic, antihistamine, haematopoietic

I. INTRODUCTION

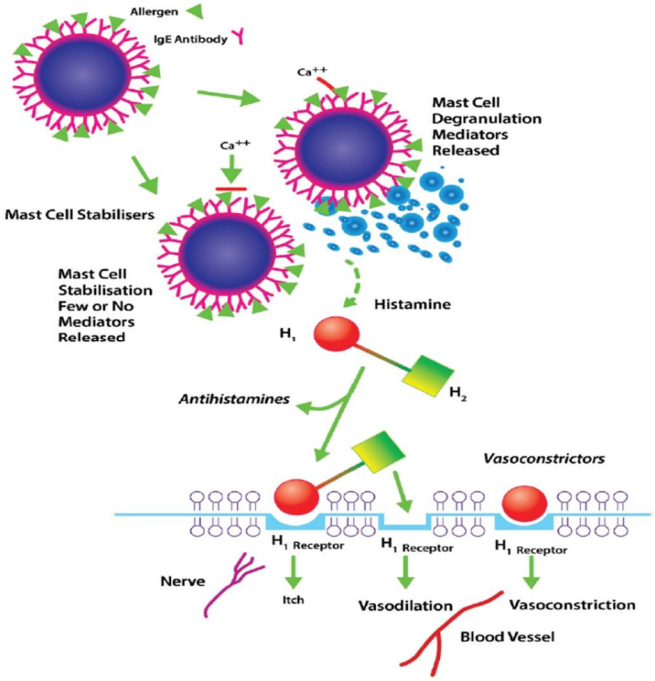
Histamine decarboxylase, an enzyme, creates histamine, a substance that occurs naturally in the body, entirely from l-histamine. It is expressed in cells all throughout the body, including basophils, mast cells, neurons in the central nervous system, and parietal cells in the stomach mucosa [1]. Histamine is a low-molecular-weight amine [2]. Histamine has a significant biological function in maintaining human health by acting on four different types of receptors. Cell proliferation and differentiation, haematopoiesis, embryonic development, regeneration, and wound healing are all impacted by it. In Histamine is produced by the mammalian central nervous system, neurons that only contain cell bodies in the posterior hypothalamic tuberomamillary nucleus, and axons that deliver histamine to the frontal and temporal cortexes and other regions of the brain. [3,4]. With the identification of certain histamine receptors, we have learned a lot more about the effects of histamine in the past ten years. Now, it is known that histamine binds to four distinct binding sites (H 1 -, H 2 -, H 3 -, and H 4 -receptors)[5,6,7]. Sneezing, nasal obstruction, itching, and rhinorrhoea are the primary early allergic response symptoms caused by activation of the H 1 -receptor by histamine binding. Leukotrienes, prostaglandins [8, 9], and other cytokines are also produced in greater amounts when H 1 receptors are activated, which also occurs before the late phase of an allergic reaction [10,11]. Several physiological and pathological processes, including skin allergies, “septic inflammation, and various neutral transmission and digestion [15, 16]. The histamine receptors found in the skin are partially blocked by H1 antihistamines. The purpose of this clinical trial was to determine whether a combination therapy using H1 (hydroxyzine) and H2 (cimetidine) antihistamines is more effective than H1 antihistamines alone in treating patients with refractory chronic idiopathic urticaria [20,21]. Histidine decarboxylase, an enzyme, catalyses a reaction in which the amino acid L-Histidine is decarboxylated to produce histamine (HDC). Mast cells, Histamine are produced in large numbers by basophiles, enterochromaffin-like cells of the stomach mucosa, and histaminergic neurones. These cells also store histamine within the cells in specialised storage granules. [22, 23].

A. Mode Of Action

Based on how well they interact with the H1 and H2 histamine receptor subtypes, antihistamines can be categorised. Antihistamines work in different ways on H1 and H2 receptors [29,30].

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1) *H1 Antihistamines:* First-generation antihistamines also referred to as H1 antihistamines, function by inhibiting H1 receptors. Histamine attaches to H1 receptors on different cells in the body when it is released after an allergic reaction, causing symptoms like itching, sneezing, and runny nose. H1 antihistamines lessen or prevent these symptoms by obstructing the H1 receptors. H1 antihistamines are also used to treat various forms of anxiety, motion sickness, and sleeplessness. They can, however, impact the central nervous system and breach the blood-brain barrier, which can result in drowsiness and sedation. Diphenhydramine, chlorpheniramine, and hydroxyzine are a few H1 antihistamines [32,33].
2) *H2 Antihistamines:* Also referred to as second-generation antihistamines, H2 antihistamines function by inhibiting H2 receptors. Since they encourage the secretion of stomach acid, H2 receptors are mostly present in the stomach. Histamine promotes the production of stomach acid when it binds to H2 receptors, which can cause acid reflux and heartburn. H2 antihistamines can ease these symptoms by decreasing the formation of stomach acid by inhibiting H2 receptors. Famotidine, cimetidine, and ranitidine are a few H2 antihistamines. They are typically used to treat illnesses like Zollinger-Ellison syndrome, peptic ulcers, and gastroesophageal reflux disease (GERD) [36,37].



B. Classification Of Antihistamine

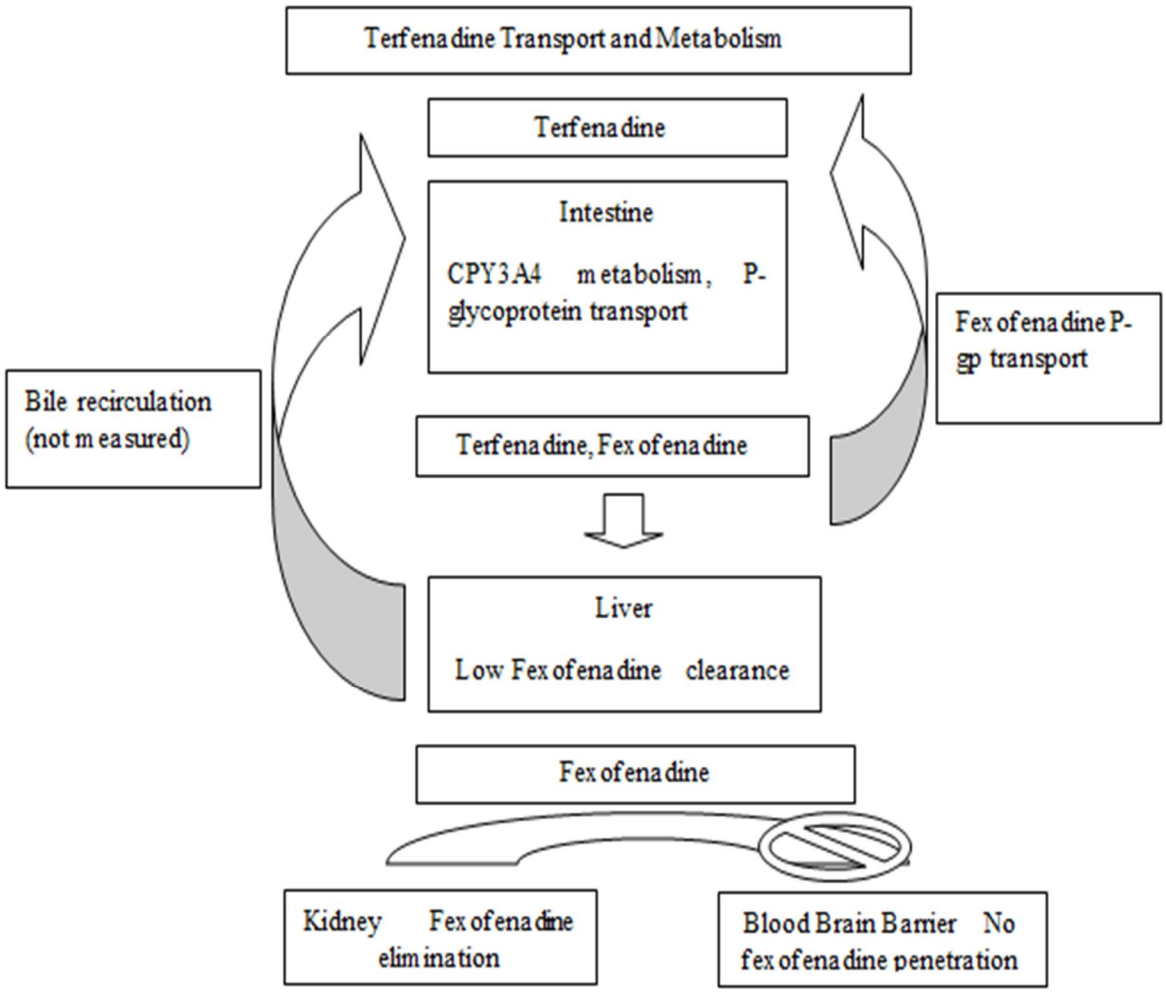
There are two types of h1 antihistamine classified are first generation sedating and second generation non-sedating antihistamines [38].

SR.NO.	GENRIC NAME	BRAND NAME	GENERATION
1	FEXOFENADINE	ALLEGRA	2^{ND} generation
2	LEVOCITRIZINE	XYZAL	2^{ND} generation
3	LORATIDINE	CLARITIN	2^{ND} generation
4	CITRIZINE	ZYRTEC	2^{ND} generation
5	CHLORPHENIRAMINE	CHLOR-TRIMETON	1^{ST} generation
6	CYPROHEPTADINE	ACMETIN-ACME	1^{ST} generation
7	HYDROXYZINE	VISTARIL	1^{ST} generation

1) Fexofenadine

The carboxylate metabolite of terfenadine is fexofenadine HCl, a novel second-generation H1-receptor antagonist that is produced as a hydrochloride salt. It efficiently prevents histamine-induced cutaneous wheals and is nonsedating [39].

a) *Mode of action:* The H1 histamine receptor mediates allergic and hypersensitive reactions. Mast cells and basophils release histamine and other inflammatory mediators when exposed to an allergen by degranulating. Histamine binds to and activates basophils and mast cells, which in turn causes them to release pro-inflammatory cytokines such interleukins. Histamine also stimulates H1 receptors. Among the myriad allergy symptoms brought on by these histamine binding's downstream effects are pruritus, rhinorrhea, and watery eyes. Fexofenadine is referred to be a "inverse agonist" of the H1 receptor because it binds to and stabilises the inactive form of the receptor, preventing activation and the related downstream effects. Despite having a strong and specific affinity for H1 receptors, there is no evidence that it has an antidopaminergic, antiserotonergic, anticholinergic, sedative, or adrenergic blocking function. Fexofenadine is unlikely to have a significant effect on the central nervous system since it cannot cross the blood-brain barrier [40].



b) *Food interaction:* Avoid drinking fruit juice. Fruit juices including grapefruit, orange, and apple may reduce the medication's overall exposure and rate of absorption. Take with or without food. Co-administration with meals has little to no effect on absorption [40].

2) *Levocitrizine*

Levocetirizine, an H1-receptor antagonist, is used to treat allergic rhinitis symptoms as well as mild cases of chronic idiopathic urticaria [41].

Mode of action: Histamine H1 receptors are specifically inhibited by levocetirizine.This action stops histamine from activating this receptor and has consequences including smooth muscle contraction, increased vascular endothelium permeability, basophile Histidine absorption, cough receptor activation, and stimulation of neurological flare-up reactions [42].

3) Loratidine

An antihistamine of the second generation called lotatadine is used to treat allergic rhinitis symptoms [43].

Mode of action : Epithelial, endothelial, eosinophil, neutrophil, airway, and vascular smooth muscle cells are among the different kinds of cells, all have H1 histamine receptors that loratadine binds to. The G-protein coupled receptors, of which the H1 histamine receptor is a subset, are in equilibrium between their active and inactive states. When histamine binds to the H1-receptor, stabilising the receptor's active form, transmembrane domains III and V can cross link more readily. Antihistamines, on the other hand, favour the inactive form by attaching to a specific site on the H1 receptor [44].

4) Citrizine

Mode of action: An antihistamine, cetirizine is a metabolite of hydroxyzine. The main mechanism of action is the selective inhibition of peripheral H1 receptors. In numerous tests on both humans and animals, cetirizine has proven to have antihistamine properties. Only marginally anticholinergic and antiserotonergic effects are seen in in vivo and ex vivo animal models. Clinical studies, however, revealed that cetirizine frequently induced dry mouth compared to a placebo. According to in vitro receptor binding tests, cetirizine has no apparent affinity for histamine receptors other than the H1 receptors. Cerebral penetration was barely detected in studies utilising radiolabel cetirizine injection in rats. Ex vivo mice studies show that systemically administered cetirizine does not significantly occupy brain H1 receptors [45].

5) Chlorpheniramine

An antihistamine, chlorpheniramine lessens the effects of the body's natural chemical histamine [46].

Mode of action: Chlorpheniramine binds to the histamine H1 receptor. As a result, the symptoms that histamine is known to cause temporarily improve. This stops endogenous histamine from activating [47].

6) Cyproheptadine

A combination serotonin and histamine antagonist known as cyproheptadine is used to relieve allergy symptoms, increase appetite, and treat serotonin syndrome off-label.

Mode of action: Cyproheptadine appears to exert its antihistamine and antiserotonin effects by competing with free histamine and serotonin for binding at their respective receptors. Serotonin's negative effects on the hypothalamic centre for appetite may account for cyproheptadine's ability to enhance appetite.

7) Hydroxyzine

The antihistamine hydroxyzine is used to treat psychoneuroses-related anxiety and stress as well as allergic illnesses such pruritus and chronic urticaria [48].

Mode of action: The H1 histamine receptor mediates allergic and hypersensitive reactions. Mast cells and basophils release histamine and other inflammatory mediators when exposed to an allergen by degranulating. Basophils and mast cells generate pro-inflammatory cytokines such interleukins after basophils and mast cells are bound to and activated by histamine, which also activates H1 receptors. The downstream effects of this histamine binding include pruritus, rhinorrhea, and watery eyes, among other allergy symptoms [49].

C. Antihistamines During Pregnancy

Diphenhydramine, cyproheptadine, promethazine, chlorpheniramine, and hydroxyzine are examples of first generation antihistamines. Although they are fast acting, they have a very strong impact and high lipophilicity. The microsomal cytochrome P-450 system in the liver breaks them down into smaller molecules. These antihistamines typically have sedative and anticholinergic side effects, such as dry mouth, blurred vision, constipation, and urine retention. The first-generation antihistamines have been categorised by the FDA based on pregnancy issues. Due to a lack of rigorous human trials, promethazine and hydroxyzine have been classified as pregnancy category C substances. A Michigan Medicaid Birth Defects research has connected hydroxyzine to newborn cleft palate [50]. Pregnancy category B denotes the absence of adequate and well-controlled studies in pregnant women, the failure to show a risk to the foetus in any trimester in animal reproduction studies, and the lack of well-controlled studies in pregnant women. Animal studies may have shown an adverse effect. Pregnancy category C indicates that there are no adequate and well-controlled human trials, animal reproduction studies have demonstrated a negative effect on the foetus, but potential advantages may still make it appropriate to use the medicine in pregnant women despite possible risks [52,53].

Medications like loratadine, fexofenadine, cetirizine, and azelastine are second generation antihistamines. They are nonsedating, have extremely selective effects, and a high therapeutic index. Despite being inadequately lipophilic and having a short half-life, they have no access to the central nervous system. The second generation of antihistamines have photosensitivity, tachycardia, and Q-T interval lengthening as side effects. The second generation of antihistamines have been classified by the FDA. Desloratidine and fexofendine are both considered pregnancy category C drugs. Fexofenadine caused weight loss in pups and increased survival. Fexofenadine and loratadine cannot be classified as safe during pregnancy due to a lack of human data [54,53].

Table 2: FDA pregnancy category classification for the first-generation antihistamines

Sr. No.	Drug Name	Pregnancy category
1	Chlorpheniramine	B
2	Cyproheptadine	B
3	Dexchlorpheniramine	B
4	Hydroxyzine	C
5	Promethazine	C
6	Tripelennamine	B

The increased incidence of hypospadiasis in offspring of pregnant women who used loratadine had previously been linked to loratadine. Recent research, however, suggests that this is not the case and that there is no significant teratogenic risk associated with this drug. The FDA still classifies loratadine as a category B medication, nevertheless [55,56].

Table 3: FDA pregnancy category classification for second-generation antihistamines

Sr. No.	Drug Name	Pregnancy category
1	Cetirizine	B
2	Fexofenadine	B
3	Loratidine	B
4	Levocetrizine	C
5	Desloratidine	C

1) Pregnancy-Safety Of Antihistamines

Even while pruritus is not a serious medical disease, it can cause a lot of problems for expectant mothers. Precaution must be taken when treating pruritus during pregnancy due to potential negative effects on the foetus. The doctor will eventually have to provide antihistamines and balance their advantages with their teratogenic side effects [57,58].

The choice between a more established, older antihistamine that is regarded to be generally safe during pregnancy and a more recent drug with less detrimental effects on quality of life but potential teratogenic potential must be made by doctors [59].

First generation antihistamines are recommended and supported by several studies for usage during pregnancy. They call attention to the fact that these antihistamines are more often used during pregnancy and have been available for a longer time. The potential negative effects of first-generation antihistamines during pregnancy are well understood. Additionally, several of the second generation drugs have been linked to a rise in the frequency of a few congenital abnormalities [60,61].

Based on their long-term availability as well as reassuring animal and human data, the National Asthma Education and Prevention Programme (NAEPP) Working Group on Asthma and Pregnancy recommended the first-generation antihistamines chlorpheniramine and tripelennamine as the antihistamines of choice during pregnancy in 1993.

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Due to their poor selectivity, sedative, and anticholinergic effects, Even in the non-pregnant population, the older antihistamines have an overall negative risk/benefit ratio., according to the Allergic Rhinitis and Its Impact on Asthma (ARIA) recommendations, which were released in 2001. No longer should first-generation antihistamines be used administered, according to ARIA. Second-generation antihistamines often have a higher potency, a longer duration of action, and little to no drowsiness [62].

Pregnant women should take tripelennamine and chlorpheniramine, according to the American College of Obstetricians and Gynaecologists (ACOG) and the American College of Allergy, Asthma, and Immunology (ACAAI).Additionally, they advise cetirizine and loratadine for individuals who are unable to tolerate or do not respond to tripelennamine or chlorpheniramine at their maximum dosages after the first trimester [63,64].

Other studies argue that the evidence is insufficient to support cetirizine and loratadine as the first-line therapy for morning sickness during pregnancy, and they suggest that if an antihistamine is necessary, chlorpheniramine, tripelennamine, or hydroxyzine should be considered first [65].

II. CONCLUSION

Through the H1-receptor, histamine plays a key role in physiologic responses such as neurotransmission, allergic inflammation, and immunomodulation. Patients, medical professionals, and anybody else looking to select an H1-antihistamine should be aware that many of the medications in this class have not undergone the greatest research. There are clinically significant differences in the pharmacologic characteristics and safety profiles of H1-antihistamines, despite the fact that most of them are similarly effective in treating allergic rhino conjunctivitis and chronic urticaria.

Primary generation medications like chlorpheniramine, dexchlorpheniramine, and hydroxyzine should be the primary choices in the event that antihistamines must be provided. Additionally, the patient should be advised to drink enough of water in order to counteract the anticholinergic side effects of taking antihistamines while pregnant.

In addition, they must be told to seek immediate gynaecological assistance if they experience an increase in contractions or a change in the frequency of the baby's movements after taking the drugs.

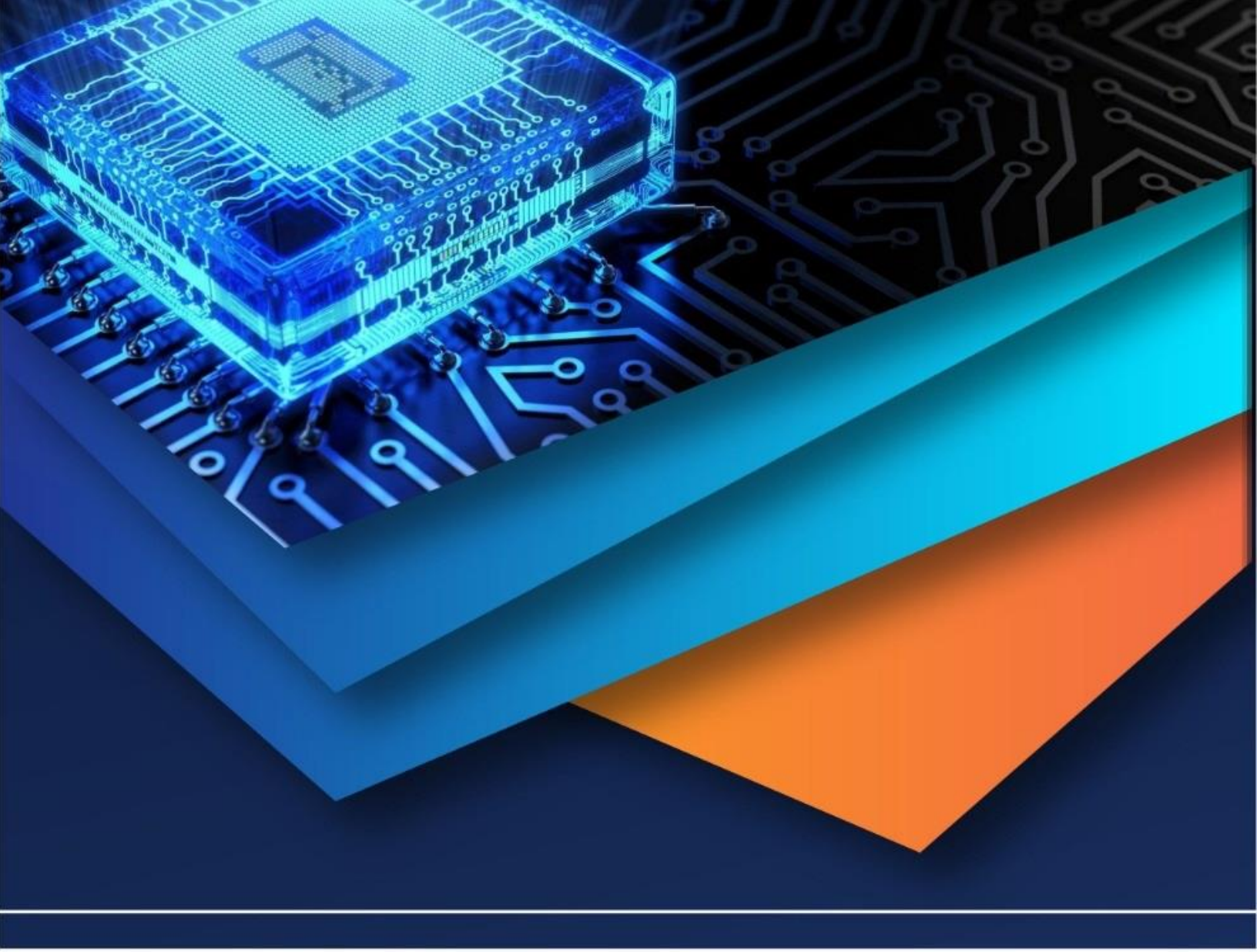
If a second-generation agent is required, loratadine or cetirizine should be utilised because extensive study on them has demonstrated that they are not currently teratogenic. These two chemicals are classified as Category B during pregnancy. Second-generation medications should only be used if absolutely essential and only after the first trimester, when organogenesis is still occurring. To sum up, the safest antihistamines to use during pregnancy are those from the first generation, namely chlorpheniramine, hydroxyzine, and dexchlorpheniramine.

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