Volume 1

This book is printed in 2 volumes

Postgraduate Dermatology

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Foreword
S Premalatha

JAYPEE

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11 CHAPTER

Skin through Ages

KN Sarveswari

INTRODUCTION

From birth till death, the skin and its appendages show many structural and functional alterations. Aging modifications in the skin reflect analogous changes that occur in internal organs.

EMBRYOLOGY

In the embryo, signaling pathways including the wingless-related (Wnt) signaling pathway, the bone morphogenic pathway, Sonic Hedgehog pathway, Notch pathway as well as the receptor tyrosinase kinase and fibroblast growth factors are used frequently to develop various structures in the body.[1]

Epidermis

- In 2 weeks, a single layer of cuboidal epithelium is present.
- In 4 weeks, the second outer layer periderm is formed.
- In 8 weeks, stratum intermedium starts to appear.
- In 9 weeks, rudimentary hair begins to develop.
- In 12 weeks, dendritic cells begin to appear.
- Between the 16th and 28th weeks, Merkel cells are seen.
- In 24 weeks, the granular and the horny layers form after the periderm sloughs.

Dermis

- In 4–8 weeks, stellate mesenchymal cells embedded in a matrix of hyaluronic acid and glycogen is seen.
- In 12 weeks, immature elastic fibers are present.
- In 16–20 weeks, papillary and reticular compartments are distinguished.
- During the fourth week, subcutaneous fat cells appear beneath dermis.

SKIN IN PRETERM INFANTS, NEONATES, AND INFANTS

Infants born before 37 weeks of pregnancy are considered "preterm infants". The first month after birth is considered the "neonatal period", while the whole of the first year is considered "infancy".

Skin of Preterm Infants[2]

- Stratum corneum is thin, leading to barrier dysfunction.
- The infants are susceptible to infections, react easily to irritants and are prone to toxicity from topically applied substances.
- Transepidermal water loss (TEWL) is increased.
- They have high blood flow through the skin and more water per kilogram body mass which aggravates TEWL.
- Skin damage such as removal of dressings, tapes, and monitors increases TEWL.[3]
- Application of emollients enhances barrier function.
- Sweat glands are functionally immature and sweating is not an effective mechanism for thermoregulation in preterm infants. Strict care should therefore be taken to avoid overheating.
- Vernix is very minimal.
- Vernix consists of lipids and prevents infections.

Skin of Neonates and Infants

- Thin stratum corneum
- Papillary dermis is thinner than adults
- Collagen fibers are smaller
- Elastic fibers are immature
- TEWL is similar to that of adults
- Infants are more susceptible to percutaneous toxicity
- High surface area to volume ratio, decreased subcutaneous fat stores, and immature drug metabolism system—these factors increase absorption while decreasing the volume of drug or toxin. It is thus important to apply only essential products to the skin during the first year of life.[4]
- In infants, the subcutaneous fat is rich in saturated fats which have higher melting point (unlike unsaturated fats of adults) and can freeze easily. This causes fat necrosis easily in infants manifesting as "subcutaneous fat necrosis of newborn", when they are exposed to lower temperatures. Hence, it is essential to avoid extreme cold exposure.

Disorders in Neonates and Infants

- Certain infantile disorders like infantile acne occur between 3 months and 1 year.
- Comedones and inflammatory papules occur similar to adult skin.

- Infantile acne is thought to be triggered by endogenous androgens.
- Prompt search for signs of hyperandrogenism should be made in an infant with severe acne.[5]
- Neonatal acne lacks comedones and is due to *Malassezia* yeast species. This condition can be treated with topical ketoconazole.
- Staphylococcal scalded skin syndrome caused by "exfoliatin", a toxin from *Staphylococcus,* can occur in infants. Prompt diagnosis and treatment with systemic antibiotics is important.
- Infantile skin is fragile and is susceptible to irritant dermatitis, especially napkin dermatitis.
- Other pustular eruptions in infants include transient neonatal pustulosis, eosinophilic pustular folliculitis, candidiasis, and congenital syphilis.

SKIN DURING CHILDHOOD

There is gradual acquisition of structural and functional features of the adult prior to development of sexual characteristics of puberty.

- Children are likely to be more exposed to infections and pyodermas, warts, molluscum contagiosum, tinea capitis, scabies, and chickenpox.[6]
- Endogenous eczemas such as atopic eczema, seborrheic eczema, and pityriasis alba occur increasingly.
- There is also increased incidence of exogenous eczema due to contact and irritant dermatitis.
- Other causes of eczemas maybe due to genodermatoses such as Leiner's disease, Hartnup syndrome, and phenylketonuria.
- Skin diseases maybe due to nutritional and endocrine disorders.
- Increased stress levels brought on by factors including competitive education, family issues, and peer pressure can lead to psychocutaneous disorders such as "dermatitis artefacta".
- One must also keep in mind symptoms of sexual abuse in children.

SKIN DURING ADOLESCENCE[7]

With the onset of puberty, the childhood skin undergoes several changes to transform into adult skin. These changes are due to a surge in the sex hormones such as estrogen, testosterone, and progesterone which bring about maturation of hair follicles, sebaceous glands, and sweat glands in the skin.

- In adolescent boys, testosterone derived from the Leydig cells of the testis causes secondary sexual changes such as growth of pubic hair, axillary hair, moustache, beard, and enlargement of larynx and penis.
- Testosterone is also responsible for axillary hyperhidrosis and increased sebaceous secretion.
- In girls, development of breasts is the first sign of puberty. It is due to the secretion of estrogen from the ovaries and occurs between 8 and 13 years of age.
- Sex hormones also cause development of apocrine gland which becomes localized in the axillary and pubic region. They produce the thick apocrine sweat, which along with bacteria on the surface of the skin is responsible for body odor.
- Sebaceous gland activity and sex hormones are also responsible for the common teenage problem acne vulgaris.
- In puberty, there is also a risk of sexually transmitted diseases. Teenagers are also exposed to new exogenous hazards.
- Androgenic alopecia occurs in genetically susceptible males and females.
- Certain disorders such as atopic dermatitis tend to improve during puberty.
- Becker's Nevus starts during puberty.
- Other disorders that tend to occur in puberty include seborrheic dermatitis, hidradenitis suppurativa, polymorphic light eruptions, and Fox-Fordyce disease.

SKIN DURING MENSTRUAL CYCLE

Cyclical fluctuations in estrogen and progesterone levels that occur during the menstrual cycle are responsible for many of the cutaneous changes and disorders like autoimmune progesterone dermatoses.

- Many women report premenstrual flare of acne.
- Some report dry skin while others find their skin and hair more greasier.
- Diseases which undergo premenstrual flare include psoriasis, recurrent aphthae, rosacea, herpes simplex, and atopic dermatitis.
- Premenstrual edema involving feet, ankles, and even face and ankles can occur.
- Some women experience premenstrual flushing as part "premenstrual syndrome". This might be due to hormonal influences, nutritional changes like depletion of essential fatty acids, fluid balance abnormalities, neurotransmitters, and psychological factors or a complex of all this into related problems.
- Increased melanocyte-stimulating activity can cause darkening of skin around eyes and nipples premenstrually.
- Autoimmune progesterone dermatitis consists of variable skin manifestations such as pompholyx-like eczema, erythema multiforme, and urticarial dermatitis herpetiformis.[8] These lesions occur premenstrually in some women and are thought to be due to hypersensitivity to progesterone. It is refractory to treatment with topical steroids and antihistamines, but some respond to estrogen or tamoxifen.

SKIN AND MENOPAUSE[9]

Menopause marks the end of reproductive life and is characterized by cessation of menses for 12 months. Average age of onset is around 50 years (45–55 years), and most women will live at least one-third of their lives in the post-menopausal state. Phase of waning ovarian activity 2–3 years before and 2–5 years after menopause is called as "climateric" or "menopause transition (MT)".

Hormones during Menopause[10]

- Ovaries become atrophic, resulting in decreased levels of ovary-derived estrogen.
- Progesterone production by corpus luteum ceases. This results in increased production of follicle-stimulating hormone and luteinizing hormone (LH).
- Relative increase of testosterone due to reduced estrogen.
- Estrogen is now derived from the conversion of androstenedione of the adrenals into estrogen.

Effect of Estrogen on Skin

- Estrogen receptors are found in keratinocytes, sebaceous glands, eccrine and apocrine glands, hair follicles, dermal fibroblasts, and melanocytes.
- Skin thus appears to be the target organ for estrogens and its decrease during menopause may aggravate the deleterious effect of intrinsic and extrinsic aging.
- Estrogens are essential for essential hydration because of their increased water retaining capacity, increased production of glycosaminoglycans, and improved barrier function of stratum corneum.
- They prevent aging by increasing collagen content, skin thickness, and their hydrating capacity.
- Low estrogen levels cause atrophy of the vagina epithelial cells.
- pH of vagina increases and can cause recurrent infections.
- Decreased estrogen levels also cause thin epidermis and dermis, loss of elastic tissue, and reduced vasculature.
- These receptors are found in greater numbers in women than in men.

Disorders Common in Menopause[9]

- Pruritus
- Menopausal flushing (due to pulsatile release of LH)
- Atrophic vaginitis
- Hirsutism
- Androgenic alopecia
- Chronic telegenic effluvium
- Brittle nails
- Frontal fibrosing alopecia
- Impaired wound healing
- Keratoderma climactericum
- Lichen sclerosus et atrophicus
- Hormone replacement therapy (HRT) used to treat menopausal symptoms can cause urticaria or eczematous reactions.
- HRT can also exacerbate chloasma, acanthosis nigricans, and spider angioma.

AGING SKIN

As in other organs, passage of time does not leave the skin unaltered. Both its structure and functions are affected.

Skin aging can be:

- *Intrinsic (chronological)* ***(Flowchart 1):***
  - Genetic background
  - Time bound
  - Inevitable
- *Extrinsic (results in premature aging)*:
  - Photodamage
  - Constant facial movements
  - Poor nutrition
  - Stress
  - Pollution
  - Smoking

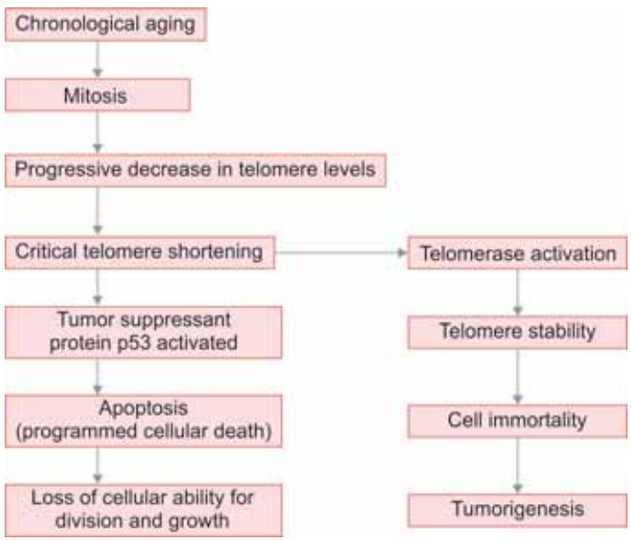
Photoaging

Photoaging is premature aging of the skin caused by repeated exposure to ultraviolet (UV) radiation, primarily from the sun but also from artificial UV sources. It is the super imposition on intrinsic aging triggered by chronic sun exposure. Photoaging is different from chronological aging, as the damaging effects of UV rays from the sun (or artificial tanning sources) alter the normal structures of the skin **(Flowchart 2)**.

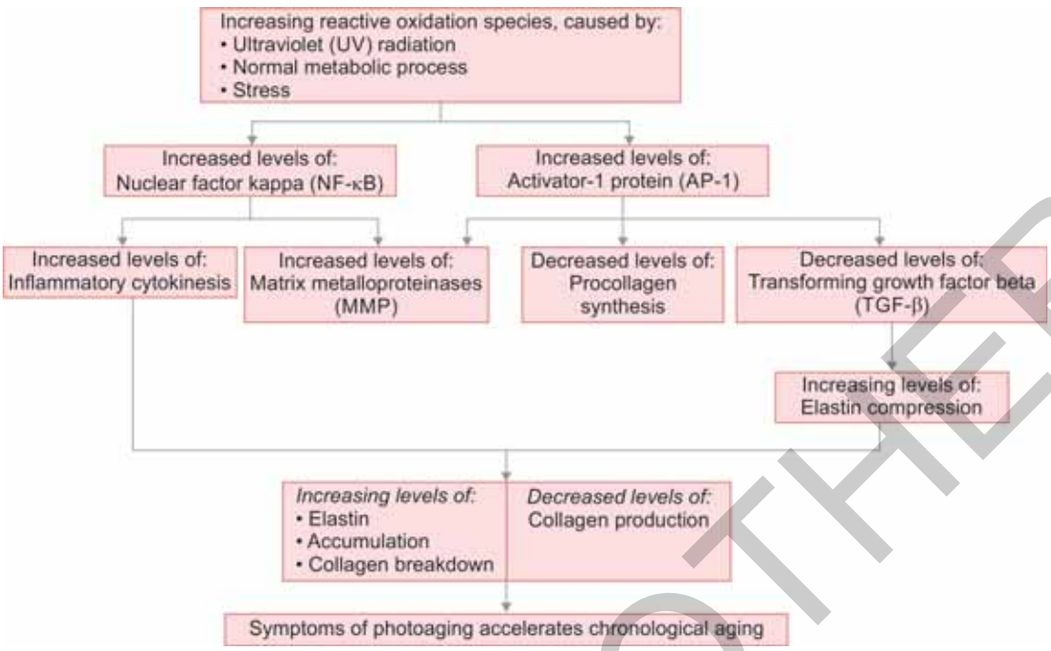
Features of Photodamaged Skin

- Coarse skin
- Furrows

Flowchart 1: Chronological aging pathogenesis.



Flowchart 2: Photoaging pathogenesis.



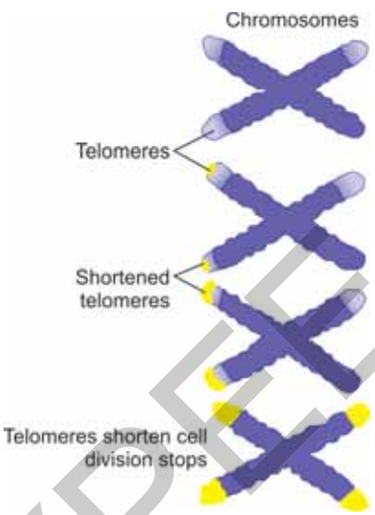


Fig. 1: Telomere shortening.

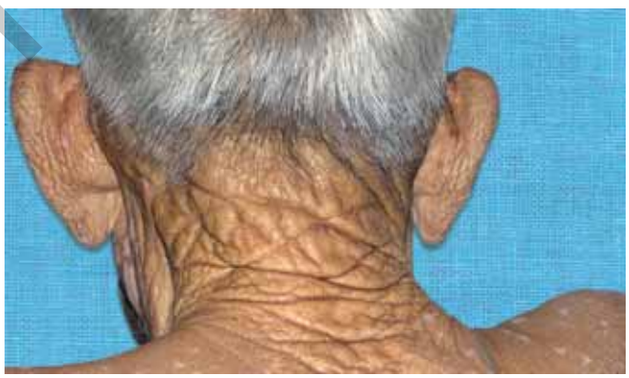


Fig. 2: Cutis rhomboides nuchae.
Courtesy: Dr Koushik Lahiri.

- Deep wrinkles
- Dry
- Lax and sagging
- Freckles
- Solar lentigines
- Telangiectasia (over cheeks)
- Seborrheic keratosis
- Cutis rhomboidalis nuchae (sun-induced wrinkling on back of neck in a rhomboidal pattern) **(Fig. 2)**
- Favre–Racouchot disease (cysts and comedones in the periorbital region due elastic degenerative changes)
- Tendency to develop premalignant and malignant neoplasms

Cutaneous Disorders in Old Age

- Senile pruritus (probably due to increased touch and pain thresholds)
- Senile lentigines (over dorsal of hands and face)
- Graying of hair
- Xerosis (avoid harsh soaps)
- Brittle nails, trachyonychia, onychogryphosis, onycholysis, onychauxis, infections, subungual hematomas, splinter hemorrhages, subungual exostosis, and malignancies
- Asteatotic eczema (rule out internal malignancy, if severe)
- Allergic contact eczema (from products containing perfumes, lanolin, and local anesthetics)
- Stasis eczema (due to insufficient venous drainage)

TABLE 1: Cutaneous problems related to chronological aging.

Chronologic changes	*Problems in skin*
Epidermis	
• Reduced epithelial melanocytes • Reduced adhesion of epithelial corneocytes	• Increased cancer susceptibility • Skin gets dry
Disappearance of rete ridges with reduced adhesion of epidermis and dermis	Wound healing gets delayed and blisters occur easily
Increased skin permeability	Occurrence of allergic contact dermatitis is common
• Reduced photosynthesis of vitamin D • Reduced Langerhans cell	• Bone fractures and osteomalacia • Increased susceptibility of infection
Dermis	
Disappearance of capillary network	Persistence of allergens
Increased matrix metalloproteinases (MMPs)	Loss of collagen
Muffled inflammatory response	Increased sunburns and irritant eczema
Delayed "dermal clearance"	Persistence of topical medications persist ("depot formation")
• Fragmented collagen fibers • Reduced collagen and elastic fibers	• Purpura and wound healing gets delayed • Reduced tensile strength in wounds
Reduced secretion of eccrine gland	Thermoregulatory disorders
Solid state of hyaluronic acid	• Reduced water-binding capacity • Appearance of more wrinkles
Disappearance of Pacinian corpuscles	Lead to more injuries and reduced sensations
Reduced cell-mediated immunity	Increased carcinomas, infections, and allergic contact dermatitis
Reduced subcutaneous fat	Hypersensitivity to cold
Immune dysfunction of B-cell, autoantibodies	Increased autoimmune disease
Disappearance of antibodies to common infections	Increased chance of infections

Source: Sarveswari KN, Premalatha S. Skin at different ages. In: Sacchidanand S (Ed). IADVL Textbook of Dermatology, 4th edition. New Delhi: Bhalani Publishing House; 2015. p. 179.

- Leg ulcers (due to venous hypertension and arterial diseases)
- Decubitus ulcers
- Infections like bacterial cellulitis due to venous stasis, candidal intertrigo in skin folds (unable to reach and dry skin folds, especially toe webspaces)
- Herpes zoster (especially postherpetic neuralgia)
- Ectoparasitic infestations such as scabies and pediculosis
- Bullous disorders such as bullous pemphigoid
- Benign and malignant skin tumors

Cutaneous problems related to chronological aging are given in **Table 1**.

CONCLUSION

The integumentary system typically reflects the process of aging that occurs through all the tissues and organs of the body. While this intrinsic chronological aging is progressive, protection from sun damage and environmental toxins can slowdown the progress of aging.

KEY POINTS

- The skin and its appendages show many structural and functional changes from womb to tomb.
- In the full-term infant, the epidermis, the epidermal appendages, and dermoepidermal junction are fully developed. But the dermis is thinner than that of adults.
- The ratio of skin surface area to volume is high in infants thus making them more susceptible to toxicity from absorption of toxins and drugs.
- During childhood there is a gradual acquisition of structural and functional features of the adult prior to development of sexual characteristics of puberty.
- Low levels of estrogen during menopause accelerate intrinsic aging.
- Both intrinsic (chronological) and extrinsic (environmental) factors contribute to skin aging.

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EXAMINATION QUESTIONS

1. What are the skin manifestations associated with aging?
2. Discuss the physiological neonatal disorders.

153 CHAPTER

Antihistamines

Prerna Raj, Aarti Sarda, Abhishek De

HISTAMINE

Histamine is synthesized from histidine by mast cells through the process of decarboxylation, and stored inside them, covalently bound to its granules. Stimulation of cutaneous mast cells cause release of granule-linked histamine, along with other chemoreactants such as chymase, tryptase, eicosanoids, and cytokines. Cutaneous mast cells can get stimulated immunologically or nonimmunologically. For immunological stimulation, they express on its surface FcER1 receptors, which binds to IgE, anti-FcER1 IgG, or anti-IgE antibodies.[1] However, they may also get stimulated nonimmunologically by substance-P, complements C3a, C4a, C5s, radiocontrast media, stem cell factor, salicylates, and NSAIDs.

Histamine Receptors

Histamine expresses its effect through histamine receptors. Both H_1 and H_2 receptors are expressed in human skin.[2,3] Histamine-induced itching and axon reflex is evoked by H_1 receptors whereas both H_1 and H_2 receptors produce vasodilatation and increased vascular permeability in the skin.[4-9] H_2 receptors also regulate T-lymphocyte activity by decreasing its proliferation and cytotoxicity thereby showing effectiveness in treatment of verruca vulgaris with cimetidine,[10-12] an H_2 antihistamine. Gastric parietal cells also express H_2 receptors thereby establishing the role of H_2 selective antihistamines for treatment of peptic ulcer disease and gastroesophageal reflux. H3 receptors express negative feedback effect on biosynthesis and release of histamine at the axon terminal. H_4 receptors are expressed on skin mast cells and neurons.[4]

Pharmacological attempts to block histamine synthesis has been largely unsuccessful. Thus, antihistamines serve the mainstay in blocking the action of histamine in the body once released.

ANTIHISTAMINES

Chronic idiopathic urticaria patients have an elevated tissue histamine levels producing the triple response of Lewis, characterized by erythema, edema, and axon reflex flare.[5] Histamine also plays a role in urticarial vasculitis where increased vessel permeability causes extravasation of inflammatory cells, neutrophils, complements thereby causing vessel wall damage and extravasation of RBCs at the site. Substances which reverse the effects of histamine, are called antihistamines. Earlier believed to be competitive antagonist of histamine, they are now known to be inverse agonists of the same, at their respective receptor sites.[13]

First Generation Antihistamines

First generation antihistamines consist of ethers based on the imidazole ring structure of histamine. Mepyramine was the first ever clinically used H_1 antihistamine, followed by diphenhydramine which got FDA approval. Cimetidine was the first ever H_2 antihistamine.

The 1st generation H_1 antihistamine can be divided into five categories **(Table 1)**.

Being highly lipophilic, they readily cross the blood–brain barrier inducing sedation by blocking the histamine stimulatory effects on brain H_1 receptors. They reach peak plasma concentration in about 2 hours, therefore used as preventives, then rescue medication. Metabolism occurs by cytochrome P450, including CYP2D6. Thus, their plasma half-life can be prolonged in patients of liver disease or those taking CYP3A4 inhibitors such as erythromycin and ketoconazole. Because of their persistence in tissues, the therapeutic effect can last longer than their plasma half-life **(Table 2)**. They may interfere with hypothalamic function, thus causing increased appetite and weight gain. Cyproheptadine in addition has anti-serotonin property as well, thereby being more effective in cold-induced urticaria and other physical urticarias.[14]

Adverse Effects

- *Central nervous system*: Sedation, impaired cognition, increased appetite
- *Gastrointestinal*: Dry mouth, constipation
- *Genitourinary*: Urinary retention, dysuria, erectile dysfunction

TABLE 1: Categories of 1st generation H_1 antihistamine.

Ethanolamine	Diphenhydramine
Piperidine	Cyproheptadine
Phenothiazine	Promethazine
Alkylamine	Chlorpheniramine
Piperazine	Hydroxyzine

- *Cardiac*: Arrythmia, tachycardia
- *Others*: Blurred vision

Second Generation Antihistamines

Developed by alteration of the imidazole ring structure of histamine. They are poorly lipophilic, thus do not cross blood–brain barrier, making them less sedative as a class. Also, they are highly selective at H_1 receptor, having negligible anticholinergic effect **(Table 2)**.

Currently five molecules are in use:

Active drug	*Derived from*
1. Fexofenadine	Terfenadine
2. Cetirizine	
3. Levocetirizine	Hydroxyzine
4. Loratadine	
5. Desloratadine	Loratadine

Fexofenadine

- Active metabolite of terfenadine that got discontinued due to cardiotoxicity.
- Readily absorbed orally, peak plasma concentration achieved in 1–3 hours.[15]
- Elimination half-life is 11–15 hours.[16]
- Single therapeutic dose of 40 mg can suppress wheal flare reaction of CIU by 80%.
- Does not undergo liver metabolism, no adverse cardiac effects.

Cetirizine

- Carboxylic acid metabolite of hydroxyzine
- Excreted unchanged in urine
- Peak onset of action in 1 hour.[17,18]
- Plasma half-life is 8 hours
- Pharmacological action lasts for 24 hours
- Normal therapeutic dosage is 10 mg in patients of hepatic or renal failure, 5 mg is sufficient.[19-21]
- Despite having minimal anticholinergic activity, drowsiness has been reported.
- Additionally it also inhibits eosinophil accumulation in tissues.

TABLE 2: Different drug and their uses.

Drug	*Peak plasma levels in (hours)*	*Half-life*	*Metabolism*	*Excreted in*	*Sedation*	*Pregnancy class*
1st Generation Antihistamines						
Diphenhydramine	0.6–2.8	4	Hepatic	Minimal renal	Yes	B
Cyproheptadine	2–3	1–4	Hepatic	40% renal	Yes	B
Promethazine	2–3	10–14	Hepatic	Predominantly renal	Yes	C
Chlorpheniramine	2–3.6	15–25	Liver	Predominantly renal	Yes	B
Hydroxyzine	1.7–2.5	20–25	Cetirizine is active metabolite	70% renal	Yes	C
2nd Generation Antihistamines						
Fexofenadine	1–3	14.4	Terfenadine is prodrug	80% feces	Minimal	C
Cetirizine	0.5–1.5	8.3	Levocetirizine is active metabolite	70% renal	Minimal	B
Levocetirizine	0.75	11	Active metabolite of cetirizine	Largely renal	Minimal	B
Loratadine	0.7–1.3	2–14	Desloratadine is active metabolite	Negligible in urine	Minimal	B
Desloratadine	2–3	19–34	No interaction with CYPs	Minimal renal	Minimal	C
Bilastine	1	14.5	No interaction with CYPs	Unchanged in urine and stool	No	
TCAs						
Doxepin	2	11–23	Nordoxepin an active metabolite	Minimal in urine	Yes	C
Mirtazapine						
Mast cell stabilizer						
Cromolyn sodium	0.25	1–2		Significant renal	No	B
Olopatadine		2.9–3.4		Significant renal	No	
Bepotastine	1	2.4	Piperidine derivative	Unchanged in urine	No	

Levocetirizine

- New 2nd generation H_1 antihistamine[22-24]
- R-enantiomer of cetirizine, and its active metabolite
- It is more potent than others even at 5 mg
- It has minimal sedative and anticholinergic side-effects

Loratadine

- It is a tricyclic, piperidine derivative, long-acting selective H_1 antihistamine.
- Peak plasma concentration of 10 mg therapeutic dose achieved by 0.7–1.3 hours.
- Its plasma half-life 8–11 hours, action lasts up to 12 hours.[25]
- Safe in renal hepatic impairment or advanced age.
- Minimal sedative or anticholinergic effect.

Desloratadine

- Active metabolite of loratadine
- Therapeutic dose of 5 mg is sufficient.[26-28]
- 5 times more potent than loratadine.
- It has no sedative, anticholinergic or cardiac side-effect
- Not metabolized by CYP enzyme, thus no drug interaction.

Bilastine

- It is a novel 2nd generation H_1 antihistamine. Got approval for use in chronic urticaria and allergic rhinitis in 2015.[29]
- Has highly selective H_2 receptor action. Thus, minimal or no adverse effects. Safe for long-term administration
- Therapeutic dose of 20 mg once daily for as long as 52 weeks showed no reduction in efficacy or tachyphylaxis
- Safe in patients aged >12 years, or in patients with hepatic or renal compromise, and in elderly.

Olopatadine

- Structural analog of doxepin
- Selective H_1 antagonist and mast cell stabilizer.[30]
- Efficient in attenuating inflammatory and allergic reactions of chronic spontaneous urticaria.

Bepotastine

- Topical and oral 2nd generation H_1 antihistamine with mast cell stabilizing properties[31]
- In addition also have other immunoactive properties, such as inhibition of eosinophil migration, interleukin-5 (IL-5), leukotrienes (e.g., LTB4), and platelet-activating factor (PAF)
- Approved as a safe and effective treatment option for use in allergic rhinitis and urticaria in Japan
- Non-sedative, minimal side-effect, does not cross blood–brain barrier.
- Quick onset of action with prolonged effect

Contraindications

- Hypersensitivity to drug or its component.
- Newborn or premature infants (1st generation only)
- Pregnancy or lactating (1st generation only)
- Angle closure glaucoma (1st generation only)

Warnings/Precautions

- Promethazine should be avoided in <2 years children for the fear of respiratory depression
- *Neurologic*: Neuroleptic malignant syndrome
- *Cardiac*: Ischemic heart disease
- *Metabolic*: Thyroid dysfunction
- *BPH*: May cause urine retention
- COPD/sleep apnea

Pregnancy/Lactation

- Among 1st generation antihistamines, diphenhydramine and chlorpheniramine has maximum evidence supporting safety (Classified as Pregnancy Category B).[32,33]
- Among 2nd generation antihistamines, cetirizine and loratadine are Category B classified
- Doxepin, hydroxyzine, fexofenadine and desloratadine are Category C classified, and should be avoided
- Cetirizine and loratadine are excreted least in breast milk, thus safer alternatives in lactating mothers.[34-36]

H_2 ANTIHISTAMINES

They are selective inverse agonist on H_2 receptor downregulating its activity on epithelial, endothelial and parietal cells of gastric mucosa. They have also been implicated in altering cellular recruitment, antigen presentation, inflammatory mediator release because of presence of H_2 receptor on lymphocyte, monocyte, neutrophils, mast cells and dendritic cells. H_2 antihistamines available are:

- Cimetidine
- Ranitidine
- Famotidine
- Nizatidine

Their peak plasma concentration is achieved within 2 hours of oral intake. They do not cross blood–brain barrier, thus have low risk of CNS side-effect. However, dosage reduction maybe required in patients of hepatic or renal compromise[37,38] Unique adverse effect of cimetidine at high doses include galactorrhea, decreased libido, and decreased sperm count. Famotidine carries risk of QT prolongation and Torsades de pointes.[39,40] Because of CYP metabolism, they have huge drug interactions, thus increases serum levels of warfarin, BB, SSRI, metformin.

Tachyphylaxis/Subsensitivity

It is the development of a reduced response to prolonged antihistamine therapy perceived by patients. However, clear evidence for tachyphylaxis or subsensitivity in patients taking daily antihistamines is unsubstantiated, and recent reviews have either omitted mention of this condition or denied its existence.[41–43]

Miscellaneous Drugs

Doxepin

- It is a tricyclic antidepressant with H_1 and H_2 antihistamine activity, seen to be 800 times more potent than diphenhydramine. Thus, used in refractory cases of chronic idiopathic urticaria (CIU), physical urticarias and systemic disease associated pruritus.[44-46]
- Topical doxepin is found to be effective in atopic dermatitis (AD) and lichen simplex chronicus (LSC).[46]
- Sedation is the most common adverse effect, although this improved with continued use.
- Oral doxepin is Category-C whereas topical doxepin is considered Category-B drug.[47]
- Avoided in pregnancy, lactating, elderly, and children <12 years of age.

Mirtazapine

- It is a tetracyclic antidepressant with H_1 antihistamine property[48]
- Beneficial in reducing nocturnal itch in patients with chronic pruritus[49]

Mast Cell Stabilizer: Cromolyn Sodium

- It blocks mast cell degranulation, thereby preventing wheal flare reactions
- It is and extremely rapidly acting drug. Reaches peak plasma levels in 0.25 hours, and has a half-life of 1–2 hours.
- Produces no sedation
- It is pregnancy category B drug.

Uses

In Urticaria

H_1 antihistamines remain the cornerstone of treatment in chronic idiopathic urticaria or even in other physical urticarias.[50-52] However, they are seen to be less effective in preventing angioedema episodes, that occur in about 40% patients of CIU. In refractory cases, higher doses of 2nd generation. H_1 antihistamines are prescribed, up to four-folds.[53] In cases suffering from insomnia or anxiety, 10–25 mg of doxepin can be prescribed. A preferred strategy is prescription of fexofenadine in the morning and cetirizine at night, to deal with sedative effects relating to cetirizine.[54] Another strategy is of using a combination of H_1 and H_2 receptor antagonist in resistant CIU. Beyond urticaria, concomitant H_1 and H_2 antihistamines have been found to be effective in relieving abdominal pain of cutaneous mastocytosis.[55-57]

In Atopic Dermatitis

The effectiveness of H_1 antihistamines as antipruritics in AD is at best ambiguous.[58,59] One study, however, did demonstrate decreased pruritus in AD patients treated with four times the recommended dose of cetirizine, but the reduction in pruritus was attributed to cetirizine's sedative effects.[60] Yet, H_1 antihistamines may be beneficial for AD patients with other manifestations of atopy, such as allergic rhinitis or allergy induced asthma.

KEY POINTS

- Histamine is synthesized from histidine by the process of decarboxylation, and stored inside the mast cells.
- Antihistamines act as inverse agonists rather than antagonist of histamine. They form the mainstay of treatment in urticaria.
- The older first generation H1 antihistamines penetrate readily into the brain causing sedation, drowsiness, fatigue and impaired concentration.
- The newer second generation H1 antihistamines are safer, more efficacious and cause less side effects.
- Though every drug in pregnancy carries the risk of teratogenicity, cetirizine, levocetirizine and loratidine are relatively safer in pregnancy.
- Cardiotoxicity is an observed adverse effect. Fexofenadine, cetirizine, loratidine are relatively safer in children.

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EXAMINATION QUESTIONS

1. Write a short note on second generation antihistamincs.
2. Discuss antihistamines.

Postgraduate Dermatology

Salient Features

- With 15 sections and 180 chapters, the book covers all aspects of dermatology including Clinical Dermatology, Sexually Transmitted Diseases, Leprosy, Procedural Dermatology, and Dermato-therapeutics.
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