Chapter 11 Histamine and Antihistaminics

HISTAMINE

Histamine, meaning 'tissue amine' (*histos*—tissue) is almost ubiquitously present in animal tissues and in certain plants, e.g. stinging nettle. Its pharmacology was studied in detail by Dale in the beginning of the 20th century when close parallelism was noted between its actions and the manifestations of certain allergic reactions. Histamine was implicated as a mediator of hypersensitivity phenomena and tissue injury reactions. It is now known to play important physiological roles.

Histamine is present mostly within storage granules of *mast cells*. Tissues rich in histamine are skin, gastric and intestinal mucosa, lungs, liver and placenta. Nonmast cell histamine occurs in brain, epidermis, gastric mucosa and growing regions. Turnover of mast cell histamine is slow, while that of nonmast cell histamine is fast. Histamine is also present in blood, most body secretions, venoms and pathological fluids.

Synthesis, storage and destruction Histamine is β imidazolylethylamine. It is synthesized locally from the amino acid histidine and degraded rapidly by oxidation and methylation (Fig. 11.1). In mast cells, histamine (positively charged) is held by an acidic protein and heparin (negatively charged) within intracellular granules. When the granules are extruded by exocytosis, Na^+ ions in e.c.f. exchange with histamine to release it free (Fig. 11.2). Increase in intracellular cAMP (caused by β adrenergic agonists and methylxanthines) inhibits histamine release. Histamine is inactive orally because liver degrades all histamine that is absorbed from the intestines.

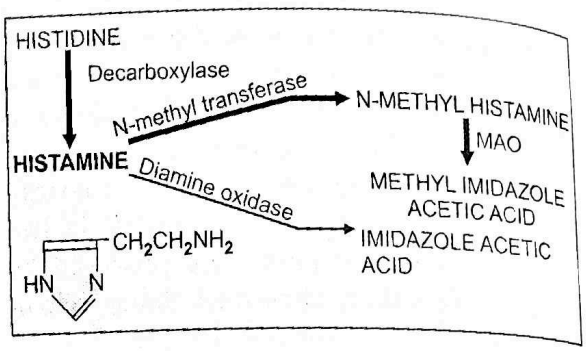

Fig. 11.1: Synthesis and degradation of histamine
MAO—Monoamine oxidase

Histamine receptors *Four* types of histaminergic receptors have now been clearly delineated and cloned. Analogous to adrenergic α and β receptors, histaminergic receptors were classified by Asch and Schild (1966) into H_1 and H_2 : those blocked by then available antihistamines were labelled H_1. Sir James Black (1972) produced the first H_2 blocker burimamide and confirmed this classification. Till now, only these two receptors are clinically relevant. A third H_3 receptor, which serves primarily as an autoreceptor controlling histamine release from neurones in the brain was identified in 1983. Though some selective H_3 agonists and antagonists have been produced, none has found any clinical application. Features of these 3 types of histaminergic receptors are compared in Table 11.1.

Molecular cloning has revealed yet another (H_4) receptor in 2001. It has considerable homology with H_3 receptor and binds many H_3 ligands. 4-Methyl histamine, earlier

Table 11.1: Distinctive features of three types of histaminergic receptors

	H_1	H_2	H_3
1. Selective agonists (relative selectivity H_1: H_2)	2-Methyl histamine (8:1) 2-Pyridylethylamine (30:1) 2-Thiazolyl ethylamine (90:1)	Dimaprit (1:2000) Impromidine (1:10,000)	(R) α-Methyl histamine (H_1: H_3 1:3000) Imetit
2. Selective antagonists (relative selectivity H_1: H_2)	Mepyramine (6000:1) Chlorpheniramine (15000:1)	Cimetidine (1: 500) Ranitidine (I : >500)	Thioperamide (H_1: H_3 1: 23000) Impromidine (also H_2 agonist) Tiprolisant, Clobenpropit
3. Receptor type	Gq-protein coupled	Gs-protein coupled	Gi/Go-protein coupled
4. Effector pathway	PIP_2 hydrolysis → IP_3/DAG : Release of Ca^{2+} from intracellular stores; Protein kinase-C activation NO release→cGMP	Adenylyl cyclase activation — cAMP ↑—phosphorylation of specific proteins	a. Restricting Ca^{2+} influx b. K^+ channel activation c. cAMP ↓
5. Distribution in body: actions mediated	a. Smooth muscle (intestine, airway, uterus)—contraction b. Blood vessels • Endothelium: Release of NO and, PGI_2—vasodilatation. widening of gap junctions—increased capillary permeability • Smooth muscle of larger vessels—vasoconstriction. c. Afferent nerve endings—stimulation. d. Ganglionic cell—stimulation. e. Adrenal medulla—release of CAs. f. Brain (postsynaptic)—impulse.	a. Gastric glands—acid secretion b. Blood vessels (smooth muscle)—dilatation c. Heart Atria: +ive chronotropy Ventricles: +ive inotropy d. Uterus (rat)—relaxation e. Brain (postsynaptic)—impulse	a. Brain (presynaptic)—inhibition of histamine release—sedation b. Lung, spleen, skin, gastric mucosa —decrease histamine release c. Ileum—inhibition of ACh release from myenteric plexus neurones d. Certain blood vessels—inhibit NA release—vasodilatation

PIP_2—Phosphatidyl inositol bisphosphate; IP_3—Inositol trisphosphate; DAG—Diacylglycerols; NO—Nitric oxide; PGI_2—Prostacyclin; CAs—Catecholamines; cAMP —Cyclic 3', 5' adenosine monophosphate; ACh—Acetylcholine

CHAPTER 11

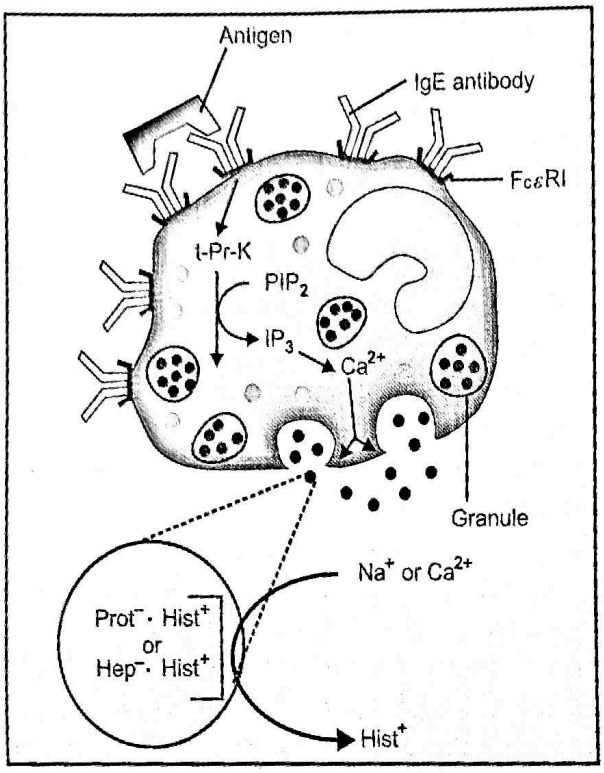

Fig. 11.2: Mechanism of antigen-antibody reaction induced release of histamine from mast cell
In sensitized atopic individual, specific reaginic (IgE) antibody is produced and gets bound to Fc epsilon receptor I (FcεRI) on the surface of mast cells. On challenge, the antigen bridges IgE molecules resulting in transmembrane activation of a tyrosine-protein kinase (t-Pr-K) which phosphorylates and activates phospholipase$C\gamma$. Phosphatidyl inositol bisphosphate (PIP_2) is hydrolysed and inositol trisphosphate (IP_3) is generated which triggers intracellular release of Ca^{2+}. The Ca^{2+} ions induce fusion of granule membrane with plasma membrane of the mast cell resulting in exocytotic release of granule contents. In the granule, positively charged histamine ($Hist^+$) is held complexed with negatively charged protein ($Prot^-$) and heparin (Hep^-) molecules. Cationic exchange with extracellular Na^+ (and Ca^{2+}) sets histamine free to act on the target cells.

considered to be a specific H_2 agonist, has shown greater affinity and selectivity for the H_4 receptor, and is now labelled a H_4 agonist. Eosinophils, mast cells and basophils are the primary cells expressing H_4 receptors. Activation of H_4 receptors enhances chemotaxis of these cells. The H_4 receptor may be playing a role in allergic inflammation. Some H_4 antagonists are being explored as potential drugs for allergic inflammatory conditions like rhinitis and asthma. Intestines and brain are the other sites where H_4 receptors have been located.

PHARMACOLOGICAL ACTIONS

1. Blood vessels Histamine causes marked dilatation of smaller blood vessels, including arterioles, capillaries and venules. On s.c. injection flushing, especially in the blush area, heat, increased heart rate and cardiac output, with little or no fall in BP are produced. Rapid i.v. injection causes fall in BP which has an early short lasting H_1 and a slow but more persistent H_2 component. With low doses only the H_1 component is manifest since H_1 receptors have higher affinity. Fall in BP due to large doses is completely blocked only by a combination of H_1 and H_2 antagonists. Dilatation of cranial vessels causes pulsatile headache.

Like many other autacoids and ACh, vasodilatation caused by histamine is partly (H_1 component) indirect, mediated through 'endothelium dependent relaxing factor' (EDRF), i.e. NO; the receptor being located on the endothelial cells. H_2 receptors mediating vasodilatation are located directly on the vascular smooth muscle.

Larger arteries and veins are constricted by histamine. This is mediated by H_1 receptor on vascular smooth muscle. Histamine also causes increased capillary permeability due to separation of endothelial cells resulting in exudation of plasma. This is primarily a H_1 response.

Injected intradermally, it elicits the *triple response* consisting of:

Red spot: due to intense capillary dilatation.
Wheal: due to exudation of fluid from capillaries and venules.
Flare: i.e. redness in the surrounding area due to arteriolar dilatation mediated by axon reflex.

2. Heart Direct effects of histamine on *in situ* heart are not prominent, but the isolated heart, especially of guinea pig, is stimulated—rate as well as force of contraction is increased. These are primarily H_2 responses but a H_1 mediated negative dromotropic (slowing of A-V conduction) effect has also been demonstrated.

3. Visceral smooth muscle Histamine causes bronchoconstriction; guinea pigs and patients of asthma are highly sensitive. Large doses cause abdominal cramps and colic by increasing intestinal contractions. Guineapig uterus is contracted while that of rat is relaxed; human uterus is not much affected as are most other visceral smooth muscles.

Smooth muscle contraction is a H_1 response. In few instances H_2 mediated relaxation is also seen, e.g. bronchial muscle of sheep, human bronchi after H_1 blockade when H_2 response is unmarked.

4. Glands Histamine causes marked increase in gastric secretion—primarily of acid but also of pepsin (*see* Ch. 47). This is a direct action exerted on parietal cells through H_2 receptors, and is mediated by increased cAMP generation, which in turn activates the membrane proton pump (H^+ K^+ ATPase).

Histamine can increase other secretions also, but the effect is hardly discernable.

5. Sensory nerve endings Itching occurs when histamine is injected i.v. or intracutaneously. Higher concentrations injected more deeply cause pain. These are reflections of the capacity of histamine to stimulate nerve endings.

6. Autonomic ganglia and adrenal medulla These are stimulated and release of Adr occurs, which can cause a secondary rise in BP.

7. CNS Histamine does not penetrate blood-brain barrier—no central effects are produced on i.v. injection. However, intracerebroventricular administration produces rise in BP, cardiac stimulation, behavioural arousal, hypothermia, vomiting and ADH release. These effects are mediated through both H_1 and H_2 postsynaptic receptors.

PATHOPHYSIOLOGICAL ROLES

1. Gastric secretion Histamine has dominant physiological role in mediating secretion of HCl in the stomach (*see* Fig. 47.1). Nonmast cell histamine occurs in gastric mucosa, possibly in cells called 'histaminocytes' situated close to the parietal cells. This histamine has high turnover rate. It is released locally under the influence of all stimuli that evoke gastric secretion (feeding, vagal stimulation, cholinergic drugs and gastrin) and activates the proton pump (H^+K^+ ATPase) through H_2 receptors.

H_2 blockers not only suppress acid secretion induced by histamine but also markedly diminish that in response to ACh and gastrin. By a mutually synergistic interaction the three secretagogues amplify responses to each other with histamine playing the dominant role. As such, antimuscarinic drugs dampen the response to histamine and gastrin as well. All three secretagogues activate the same proton pump (H^+K^+ATPase) in the parietal cell membrane, but through their own receptors.

2. Allergic phenomena Mediation of hypersensitivity reactions was the first role ascribed to histamine. It is an important, but only one of the mediators of such phenomena. Released from mast cells following AG : AB reaction on their surface (involving IgE type of reaginic antibodies; Fig. 11.2) in immediate type of hypersensitivity reactions, histamine is causative in urticaria, angioedema, bronchoconstriction and anaphylactic shock. The H_1 antagonists are effective in controlling these manifestations to a considerable extent, except asthma and to a lesser extent anaphylactic fall in BP in which leukotrienes (especially LTD_4) and PAF appear to be more important. Histamine is not involved in delayed or retarded type of allergic reactions.

3. As transmitter Histamine is believed to be the afferent transmitter which initiates the sensation of itch and pain at sensory nerve endings.

Nonmast cell histamine occurs in brain, especially hypothalamus and midbrain. It is involved in maintaining wakefulness; H_1 antihistaminics owe their sedative action to blockade of this function. In the brain H_1 agonism suppresses appetite. This may explain the appetite promoting action of certain H_1 antagonists. Histamine also appears to participate as a transmitter regulating body temperature, cardiovascular function, thirst, and possibly other functions, mainly through H_2 (postsynaptic receptors) and H_3 (presynaptic autoreceptors and heteroreceptors).

4. Inflammation Histamine is a mediator of vasodilatation and other changes that occur during inflammation. It promotes adhesion of leukocytes to vascular endothelium by expressing adhesion molecule *P-selectin* on endothelial cell surface, sequestrating leukocytes at the

inflammatory site. It may also regulate microcirculation according to local needs.

5. Tissue growth and repair Because growing and regenerating tissues contain high concentrations of histamine, it has been suggested to play an essential role in the process of growth and repair.

6. Headache Histamine has been implicated in certain vascular headaches, but there is no conclusive evidence.

USES

Histamine has no therapeutic use. In the past it has been used to test acid secreting capacity of stomach, bronchial hyperreactivity in asthmatics, and for diagnosis of pheochromocytoma, but these pharmacological tests are risky and obsolete now.

Betahistine It is an orally active, somewhat H_1 selective histamine analogue, which is used to control vertigo in patients of Meniére's disease. It possibly acts by causing vasodilatation in the internal ear. It is contraindicated in asthmatics and ulcer patients.

VERTIN 8 mg tab., 1/2 to 1 tab. QID.

HISTAMINE RELEASERS

A variety of mechanical, chemical and immunological stimuli are capable of releasing histamine from mast cells.

1. Tissue damage: trauma, stings and venoms, proteolytic enzymes, phospholipase A.
2. Antigen: antibody reaction involving IgE antibodies.
3. Polymers like dextran, polyvinyl pyrrolidone (PVP).
4. Some basic drugs—tubocurarine, morphine, atropine, pentamidine, polymyxin B, vancomycin and even some antihistaminics release histamine by displacing it from the binding site, and not by an immunological reaction. This release is not exocytotic, and does not require Ca^{2+}.
5. Surface acting agents like Tween 80, compound 48/80 etc. The primary action of these substances is release of histamine from mast cells, therefore they are called *'histamine liberators'*. They produce an 'anaphylactoid' reaction—itching and burning sensation, flushing, urticaria, fall in BP, tachycardia, headache, colic and asthma.

H_1 ANTAGONISTS (Conventional antihistaminics)

These drugs competitively antagonize actions of histamine at the H_1 receptors. Recent evidence indicates that histamine H_1 receptor exhibits some degree of constitutive activity at certain sites, and few H_1 antagonists are also inverse agonists. The first H_1 antagonists were introduced in the late 1930s and have subsequently proliferated into an unnecessary motley of drugs. Nevertheless, they are frequently used for a variety of purposes. More commonly employed now are the less sedating/nonsedating second generation H_1 antihistamines added after 1980. Seemingly, H_1 antihistaminics have diverse chemical structures, but majority have a substituted ethylamine side chain. They are classified and listed in Table 11.2.

PHARMACOLOGICAL ACTIONS

Qualitatively all H_1 antihistaminics have similar actions, but there are quantitative differences, especially in the sedative property.

1. Antagonism of histamine The H_1 antagonists effectively block histamine induced bronchoconstriction, contraction of intestinal and other smooth muscle and triple response—especially wheal, flare and itch. Fall in BP produced by low doses of histamine is blocked, but additional H_2 antagonists are required for complete blockade of that caused by higher doses. Pretreatment with these drugs protects animals from death due to i.v. injection of large doses of histamine. Release of Adr from adrenal medulla in response to histamine is abolished. Constriction of larger blood vessel by histamine is also antagonized. Action of histamine on gastric secretion is singularly not affected by these drugs. Cyproheptadine had additional 5-HT_2 receptor blocking activity (*see* p. 189).

2. Antiallergic action Many manifestations of immediate hypersensitivity (type I reactions) are suppressed. Urticaria, itching and angioedema are well controlled. Anaphylactic fall in BP is only partially prevented. Asthma in man is practically unaffected, though anaphylactic bronchoconstriction in guinea pig is largely prevented. This tissue and species dependence of response probably reflects extent of involvement of histamine in the reaction. It is now well established that leukotrienes (LTC_4, LTD_4) and PAF are more important mediators for human asthma.

Table 11.2: Clinical classification, doses and preparations of antihistaminics

Drug	Dose and route	Preparations
I. *HIGHLY SEDATIVE*		
Diphenhydramine	25–50 mg oral	BENADRYL 25, 50 mg cap., 12.5 mg/5 ml syr.
Dimenhydrinate	25–50 mg oral	DRAMAMINE 16 mg/5 ml syr, 50 mg tab, GRAVOL 50 mg tab
Promethazine	25–50 mg oral, i.m. (1 mg/kg)	PHENERGAN 10, 25 mg tab., 5 mg/ml elixir, 25 mg/ml inj
Hydroxyzine	25–50 mg oral, i.m.	ATARAX 10, 25 mg tab., 10 mg/5 ml syr, 6 mg/ml drops, 25 mg/ml inj.
II. *MODERATELY SEDATIVE*		
Pheniramine	20–50 mg oral, i.m.	AVIL 25 mg, 50 mg tab, 15 mg/5 ml syr, 22.5 mg/ml inj.
Cyproheptadine	4 mg oral	PRACTIN, CIPLACTIN 4 mg tab., 2 mg/5 ml syrup
Meclozine (Meclizine)	25–50 mg oral	In DILIGAN 12.5 mg + niacin 50 mg tab In PREGNIDOXIN 25 mg + Caffeine 20 mg tab
Cinnarizine	25–50 mg oral	STUGERON, VERTIGON 25 and 75 mg tab.
III. *MILD SEDATIVE*		
Chlorpheniramine	2–4 mg (0.1 mg/kg) oral, i.m.	PIRITON, CADISTIN 4 mg tab
Dexchlorpheniramine	2 mg oral	POLARAMINE 2 mg tab, 0.5 mg/ 5 ml syr
Triprolidine	2.5–5 mg oral	ACTIDIL 2.5 mg tab.
Clemastine	1–2 mg oral	TAVEGYL 1 mg tab., 0.5 mg/5 ml syr
IV. *SECOND GENERATION ANTIHISTAMINICS*		
Fexofenadine	120–180 mg oral	ALLEGRA, ALTIVA, FEXO 120, 180 mg tab
Loratadine	10 mg oral	LORFAST, LORIDIN, LORMEG, 10 mg tab, 1 mg/ml susp.
Desloratadine	5 mg oral	DESLOR, LORDAY, NEOLORIDIN 5 mg tab
Cetirizine	10 mg oral	ALERID, CETZINE, ZIRTIN, SIZON 10 mg tab, 5 mg/5 ml syr.
Levocetirizine	5–10 mg oral	LEVOSIZ, LEVORID, TECZINE 5, 10 mg tab LEVOCET 5 mg tab, 2.5 mg/5 ml syr.
Azelastine	4 mg oral 0.28 mg intranasal	AZEP NASAL SPRAY 0.14 mg per puff nasal spray
Mizolastine	10 mg oral	ELINA 10 mg tab
Ebastine	10 mg oral	EBAST 10 mg tab
Rupatadine	10 mg oral	RUPAHIST 10 mg tab

3. CNS The older antihistamines produce variable degree of CNS depression. This appears to depend on the compound's ability to penetrate the blood-brain barrier and its affinity for the central (compared to peripheral) H_1 receptors. Individual susceptibility to different agents varies considerably. The same drug and dose may incapacitate some subjects, while others may remain alert. An overall grading of the sedative property of H_1 antihistaminics is presented in Table 11.2. Some individuals also experience stimulant effects like restlessness and insomnia. Excitement and convulsions are frequently seen at toxic doses. The second generation antihistaminics are practically nonsedating.

Certain (*see* below) H_1 antihistamines are effective in preventing *motion sickness*. It is not clear whether this is due to antagonism of histamine in the brain or reflects antimuscarinic property of these drugs. Promethazine also controls vomiting of pregnancy and other causes.

Promethazine and few other antihistaminics reduce tremor, rigidity and sialorrhoea of *parkinsonism*. Anticholinergic and sedative properties underlie the benefit.

Some older antihistamines, especially cyproheptadine, have *appetite stimulating* effect.

Some H_1 antihistamines are also effective *antitussives* (*see* Ch. 16).

4. Anticholinergic action Many H_1 blockers in addition antagonize muscarinic actions of ACh. The antimuscarinic action can be graded as:

High	*Low*	*Minimal/ Absent*
Promethazine	Chlorpheniramine	Fexofenadine
Diphenhydramine	Triprolidine	Astemizole
Dimenhydrinate	Cyproheptadine	Loratadine
Pheniramine	Cinnarizine	Cetirizine
		Mizolastine

If used concurrently with atropine or its substitutes, phenothiazines, tricyclic antidepressants or disopyramide, the anticholinergic action adds up.

5. Local anaesthetic Some drugs like pheniramine, promethazine, diphenhydramine have strong while others have weak membrane stabilizing property. However, they are not clinically suitable local anaesthetics because they cause irritation when injected s.c.

Membrane stabilizing activity confers antiarrhythmic property to these compounds.

6. BP Most antihistaminics cause a fall in BP on i.v. injection (direct smooth muscle relaxation or α adrenergic blockade). Promethazine has significant α blocking activity. However, this is not evident on oral administration, though postural hypotension can occur in susceptible individuals.

PHARMACOKINETICS

The conventional H_1 antihistaminics are well absorbed from oral and parenteral routes, metabolized in the liver and excreted in urine. They are widely distributed in the body and enter brain. The newer compounds penetrate brain poorly accounting for their low/absent sedating action. Duration of action of most agents is 4–6 hours, except meclozine, chlorpheniramine, mesolastine, loratadine, cetirizine and fexofenadine which act for 12–24 hours or more. The H_1 antihistaminics are mainly administered orally, but few are available for i.m./i.v. use as well.

SIDE EFFECTS AND TOXICITY

Side effects of first generation H_1 antihistaminics are frequent, but generally mild. Individuals show marked differences in susceptibility to side effects with different drugs. Some tolerance to side effects develops on repeated use.

Sedation, diminished alertness and concentration, light headedness, motor incoordination, fatigue and tendency to fall asleep are the most common. Objective testing shows impairment of psychomotor performance. Patients should be cautioned not to operate motor vehicles or machinery requiring constant attention. Alcohol synergises in producing these effects as do other CNS depressants. Few individuals, however, become restless, nervous and are unable to sleep. Second generation compounds are largely free of CNS effects.

Regular use of conventional antihistamines is not advisable in children, because the CNS depressant property may interfere with learning and academic tasks.

Dryness of mouth, alteration of bowel movement, urinary hesitancy and blurring of vision can be ascribed to anticholinergic property of older antihistaminics.

Epigastric distress and headache may be felt. Local application can cause contact dermatitis. Some drugs like hydroxyzine, cyclizine and fexofenadine are teratogenic in animals; but there is no evidence of excess malformations in humans. Caution is nevertheless to be exercised in prescribing an antihistaminic during pregnancy.

Acute overdose produces central excitation, tremors, hallucinations, muscular incordination, convulsions, flushing, hypotension, fever and some other features of belladonna poisoning. Death is due to respiratory and cardiovascular failure.

SECOND GENERATION ANTIHISTAMINICS

The second generation antihistaminics (SGAs) may be defined as those H_1 receptor blockers marketed after 1980 which have one or more of the following properties:

- Absence of CNS depressant property.
- Higher H_1 selectivitiy: no anticholinergic side effects.
- Additional antiallergic mechanisms apart from histamine blockade: some also inhibit late phase allergic reaction by modifying release/action of leukotrienes, platelet activating factor (PAF) and cytokines, etc.

As per an international consensus group of experts, no compound developed so far merits labelling as 'third generation antihistaminic'.

These newer drugs have the advantage of not impairing psychomotor performance (driving, etc. need not be contraindicated), produce no subjective effects, no sleepiness, do not potentiate alcohol or benzodiazepines. Some patients do complain of sedation, but incidence is similar to that with placebo. However, they have a narrow spectrum of therapeutic usefulness which is limited by the extent of involvement of histamine (acting through H_1 receptors) in the disease state. Their principal indications are:

(i) Allergic rhinitis and conjunctivitis, hay fever, pollinosis: they control sneezing, runny but not blocked nose, and red-watering-itchy eyes.
(ii) Urticaria, dermographism, atopic eczema.
(iii) Acute allergic reactions to drugs and foods.

The SGAs have poor antipruritic, antiemetic and antitussive actions.

Fexofenadine It is the active metabolite of terfenadine, the first nonsedating SGA that was withdrawn because of several deaths due to polymorphic ventricular tachycardia *(Torsades de pointes)* occurring with its higher doses or when it was coadministered with CYP3A4 inhibitors (erythromycin, clarithromycin, ketoconazole, itraconazole, etc.). This toxicity is based on blockade of delayed rectifier K^+ channels in the heart at higher concentrations. Astemizole is another SGA banned for the same reason. Fexofenadine has a low propensity to block delayed rectifier K^+ channels, does not prolong QTc interval. Since it is minimally metabolized, no interaction with CYP3A4 inhibitors have been reported. It is largely free of arrhythmogenic potential, but some cases of ventricular arrhythmia in patients with preexisting long QT interval have been reported. Thus, it is not entirely safe in patients with long QT, bradycardia or hypokalemia.

Fexofenadine penetrates blood-brain barrier poorly; produces minimal sedation or impairment of psychomotor performance. It is free of atropinic side effects. Oral absorption is rapid. It is mainly excreted unchanged in urine and bile, has plasma t½ 11–16 hours and duration of action 24 hours.

Dose: For allergic rhinitis 120 mg OD; for urticaria and other skin allergies 180 mg OD.

Loratadine Another long-acting selective peripheral H_1 antagonist which lacks CNS depressant effects and is fast acting. It is partly metabolized by CYP3A4 to an active

metabolite with a longer t½ of 17 hr, but has not produced cardiac arrhythmia in overdose, though seizures are reported. No interaction with macrolides or antifungals has been noted. Good efficacy has been reported in urticaria and atopic dermatitis.

Desloratadine It is the major active metabolite of loratadine effective at half the dose. Noninterference with psychomotor performance and cardiac safety are documented.

Cetirizine It is a metabolite of hydroxyzine with marked affinity for peripheral H_1 receptors; penetrates brain poorly, but mild sedation and subjective somnolence is experienced by many recipients. It is not metabolized; does not prolong cardiac action potential or produce arrhythmias when given with erythromycin/ketoconazole.

Cetirizine in addition inhibits release of histamine and of cytotoxic mediators from platelets as well as eosinophil chemotaxis during the secondary phase of the allergic response. Thus, it may benefit allergic disorders by other actions as well. It attains high and longer lasting concentration in skin, which may be responsible for superior efficacy in urticaria/atopic dermatitis, as well as for once daily dosing despite elimination t½ of 7–10 hr. It is indicated in upper respiratory allergies, pollinosis, urticaria and atopic dermatitis; also used as adjuvant in seasonal asthma.

Levocetirizine is the active R(–) enantiomer of cetirizine. It is effective at half the dose and appears to produce less sedation and other side effects.

Azelastine This newer H_1 blocker has good topical activity; in addition it inhibits histamine release and inflammatory reaction triggered by LTs and PAF. After intranasal application it has been shown to down regulate intracellular adhesion molecule-1 (ICAM-1) expression on nasal mucosa. Its t½ is 24 hr, but action lasts longer due to active metabolite. Its metabolism is inhibited by CYP 3A4 inhibitors. Given by nasal spray for seasonal and perennial allergic rhinitis it provides quick symptomatic relief lasting 12 hr. Stinging in the nose and altered taste perception are the local side effects. Some somnolence has been reported on nasal application and a tendency to weight gain noted after oral use.

Mizolastine This nonsedating antihistaminic is effective in allergic rhinitis and urticaria by single daily dosing despite a t½ of 8–10 hr and no active metabolite.

Ebastine Another newer SGA that rapidly gets converted to the active metabolite carbastine having a t½ of 10–16 hr. It is nonsedating and active in nasal and skin allergies. Animal studies have found it to prolong Q-Tc interval which makes it liable to arrhythmogenic potential and CYP3A4 interaction, but actual reports are still few.

Rupatadine This recently introduced antihistaminic has additional PAF antagonistic property, and is indicated in allergic rhinitis.

USES

The uses of H_1 antihistaminics are based on their ability to block certain effects of histamine released endogeneously, as well as on their sedative and anticholinergic properties.

1. *Allergic disorders* Antihistaminics do not suppress AG: AB reaction, but block the effects of released histamine—are only palliative. They effectively control certain immediate type of allergies, such as itching, urticaria, seasonal hay fever, allergic conjunctivitis and angioedema of lips, eyelids, etc. However, their action is slow, therefore Adr alone is life-saving in laryngeal angioedema, while intravenously administered antihistaminic may have adjuvant value. Similarly, they cannot be relied upon in anaphylactic shock and have a secondary place to Adr. Benefits are less marked in perennial vasomotor rhinitis, atopic dermatitis and chronic urticarias; combination with an H_2 antagonist succeeds in some cases of chronic urticaria not responding to H_1 antagonist alone.

The antihistaminics are ineffective in bronchial asthma: reasons may be—

- Leukotrienes (LTC_4, D_4) and PAF are more important mediators in humans than histamine.
- Concentration of antihistamines attained at the site may not be sufficient to block high concentration of histamine released locally in the bronchi.

Certain newer compounds like cetirizine have adjuvant role in seasonal asthma.

Antihistaminics are also ineffective in other types of humoral and cell mediated allergies because histamine is not involved. They do suppress urticaria and swellings in serum sickness, but have no effect on other components of the syndrome.

Type I hypersensitivity reactions to drugs (except asthma and anaphylaxis) are suppressed. Some skin rashes also respond.

2. *Other conditions involving histamine* Antihistaminics block symptoms produced by histamine releasers (*see* p. 178); afford symptomatic relief in insect bite and ivy poisoning. Abnormal dermographism is suppressed. They also have prophylactic value in blood/saline infusion induced rigor.

3. *Pruritides* Many conventional antihistamines have antipruritic action independent of H_1 antagonism. Though relief is often incomplete, older antihistaminics chlorpheniramine, diphenhydramine, cyproheptadine remain the first choice drugs for idiopathic pruritus.

4. *Common cold* Antihistaminics do not affect the course of the illness but may afford symptomatic relief by anticholinergic (reduce rhinorrhoea) and sedative actions. The newer nonsedating antihistamines are less effective in this respect.

5. *Motion sickness* Promethazine, diphenhydramine, dimenhydrinate and meclozine have prophylactic value in milder types of motion sickness; should be taken one hour before starting the journey. Promethazine can also be used in morning sickness, drug induced and postoperative vomiting, radiation sickness.

An 'off label' (unapproved) use of cyproheptadine is often made in anorectic/convalescent patients for improving appetite. Such use in underweight children is inappropriate, because its CNS depressant action can affect learning.

6. *Vertigo* Vertigo is typically felt as a spinning sensation or rotation of surroundings, or sense of movement when there is none. Mild vertigo is often reported as 'dizziness'. Vertigo is mostly of vestibular origin, but may also be due to a variety of peripheral or central causes, and is generally accompanied by nausea and vomiting.

The long term therapy of vertigo occurring in Ménière's disease and other conditions is imperfect. A variety of approaches have been tried.

1. Labyrinthine suppressants These drugs suppress end-organ receptors or inhibit central cholinergic pathway (in vestibular nuclei).
   - *Antihistaminics* (with anticholinergic action)—cinnarizine, dimenhydrinate, diphenhydramine, promethazine.
   - *Anticholinergics*— hyoscine, atropine.
   - *Antiemetic phenothiazines*—prochlorperazine.
2. Vasodilators They improve blood flow to labyrinth and brainstem—betahistine is quite frequently used in Ménière's disease.
3. Diuretics They decrease labyrinthine fluid pressure —acetazolamide, thiazides, amiloride.
4. Anxiolytics, antidepressants These drugs appear to modify the sensation of vertigo; may also depress end-organ receptors—diazepam, amitriptyline.
5. Corticosteroids They decrease intralabyrinthine edema due to viral infection or other causes.

Labyrinthine (vestibular) suppressant medications are the principal drugs for management of vertigo as well as that of attendant nausea and vomiting. The H_1 antihistaminic *cinnarizine* and *dimenhydrinate* are the most commonly used vestibular suppressants in this condition. Betahistine (*see* p. 178) is specifically used in Mèniére's disease.

Cinnarizine: This H_1 antihistamine has additional weak antimuscarinic, anti-5HT, sedative and vasodilator properties. It modulates Ca^{2+} fluxes and attenuates vasoconstrictor action of many endogenous mediators. The antivertigo property may be due to calcium channel blockade. Cinnarizine inhibits vestibular sensory nuclei in the inner ear, suppresses postrotatory labyrinthine

reflexes, possibly by reducing stimulated influx of Ca^{2+} from endolymph into the vestibular sensory cells. Beneficial effects have been reported in Ménière's disease and other types of vertigo. Side effects are sedation and mild g.i. upset.

Prochlorperazine: This D2 receptor blocking neuroleptic has additional H_1 antihistaminic and labyrinthine suppressant property which is useful in the short-term control of vertigo as well as the associated nausea and vomiting.

Parenteral prochlorperazine is the most effective drug for controlling violent vertigo and vomiting. It is also used in other types of nausea and vomiting (*see* Ch. 48)

7. *Preanaesthetic medication* Promethazine has been used for its anticholinergic and sedative properties.

8. *Cough* Antihistaminics like chlorpheniramine, diphenhydramine and promethazine are constituents of many popular cough remedies. They have no selective cough suppressant action, but may afford symptomatic relief by sedative and anticholinergic property (*see* Ch. 16).

9. *Parkinsonism* Promethazine and some others afford mild symptomatic relief in early cases—based on anticholinergic and sedative property.

10. *Acute muscle dystonia* Caused by antidopaminergic-antipsychotic drugs is promptly relieved by parenteral promethazine, diphenhydramine or hydroxyzine. This is again based on central anticholinergic action of the drugs.

11. *As sedative, hypnotic, anxiolytic* Antihistamines with CNS depressant action have been used as sedative and to induce sleep, especially in children. However, promethazine has produced serious respiratory depression in young children; few deaths are on record; it is not indicated in children aged 2 years or less. For promoting sleep, antihistaminics are not as dependable as benzodiazepines. Hydroxyzine has been used in anxiety associated with autonomic manifestations.

(Combinations of antihistaminics with antidiarrhoeals or bronchodilators, or those containing more than one antihistaminic are banned in India.)

H_2 antagonist The first H_2 blocker *Burimamide* was discovered by Black in 1972. *Metiamide* was the next, but both were not found suitable for clinical use. *Cimetidine* was introduced in 1977 and gained wide usage. *Ranitidine, famotidine, roxatidine,* and many others have been added subsequently. They are primarily used in peptic ulcer, gastroesophageal reflux and other gastric hypersecretory states. They are described in Ch. 47.

H_3 antagonist Though some selective H_3 antagonists have been produced, they have not found any clinical utility.

PROBLEM DIRECTED STUDY

11.1 A taxi driver aged 30 years presented with sudden onset running and itchy nose, bouts of sneezing, partial nasal blockage, redness and watering from the eyes, but no fever, bodyache or malaise. He gave history of similar episodes occurring off and on during the spring season. A diagnosis of seasonal allergic rhinitis was made and the doctor prescribed an oral antiallergic medication to be taken once a day till symptoms subside.

(a) Which antiallergic medicine would be suitable for this patient? Which antiallergic drugs should be avoided?

(b) Will the above medication prevent/reduce recurrent episodes of rhinitis that this patient gets during spring. If not, can some medications be added to prevent/subdue the episodes during the vulnerable season.

(see Appendix-1 for solution).