

causing release of catecholamines (adrenaline and noradrenaline) into circulation. Normally the response is insignificant, but in patients with a pheochromocytoma a large amount of catecholamines is released and the blood pressure sharply rises (see later).

Anaphylactic Shock

The similarity between anaphylactic shock and the actions of histamine prompted Laidlow in 1910 to suggest that histamine may be a *mediator of anaphylactic shock*. In addition, other autacoids like *bradykinin*, *prostaglandins*, *5-hydroxytryptamine* (serotonin) and an unsaturated fatty acid called *slow reacting substance of anaphylaxis* (SRS-A) are liberated in varying amounts. Lately, an *eosinophil chemotactic factor of anaphylaxis* (ECF-A) has been described. The limited efficacy of antihistamines in some cases of *allergy* may be partly due to the mediation of other autacoids, the action of which the antihistamines are unable to antagonize, e.g., SRS-A may be involved in human bronchial asthma. In anaphylaxis the antigen reacts with the mast cell membrane-bound antibody, and histamine storage granules undergo *exocytosis*. This released *free histamine* is responsible for the various cellular and tissue manifestations of anaphylactic shock. Certain studies suggest that cyclic-AMP and drugs that activate adenylcyclase have an inhibitory action on histamine release. The *catecholamines may be inhibiting histamine release* in addition to their well known antagonism of histamine action in anaphylaxis.

It has been suggested that histamine also plays a role in *inflammatory reactions, regulation of microcirculation, tissue repair and growth*. It functions as a neurotransmitter at certain synapses. In certain diseases like hepatic cirrhosis, carcinoid tumours, urticaria pigmentosa, and chronic myelogenous leukaemia a defect in histamine turnover has been observed.

Histamine Releasing Drugs

Endogenous histamine may be released by certain drugs, chemicals and physical agents. The major source of the histamine liberated are the *mast cells*, from which *heparin*, *SRS-A* and *vasoactive kinins* are also released in varying amounts. Such a histamine release may be of a magnitude to precipitate an *anaphylactic reaction*. The most active compound known to release histamine is compound 48/80 (Table 11.1-2). A feature of drug / chemical-induced histamine release is the development of *tachyphylaxis*.

Clinical Uses

1. Gastric Analysis

Histamine is useful for the differential diagnosis of pernicious anaemia from other stomach diseases on the basis of achlorhydria. If the fasting aspirated sample of gastric juice contains no acid, histamine, 0.5 mg is injected subcutaneously (histamine is available as 1 mg/ml of the base in 1 ml ampoules and 10 ml vials). Samples are collected for the following hour or until acid is present in the aspirate. The side effects of histamine (flushing, tachycardia, hypotension, throbbing headache) may be minimized by pre-treatment with *pyrilamine* which antagonizes H₁-receptor responses but does not interfere with the acid secretion which is an H₂-receptor response. In the "augmented" (maximal histamine test) test, 0.04

mg/kg of histamine is injected SC 30 minutes after *pyrilamine* (100 mg IM), and the test is done in the usual manner. This test measures the total number of functioning parietal cells (parietal cell mass) present and identifies patients with *true achlorhydria*, defined as the failure to lower the gastric pH below 6 to maximal histamine stimulation. *True achlorhydria* (histamine-fast achlorhydria) is *pathognomic of pernicious anaemia*. The test is reliable but the passage of a gastric tube causes inconvenience to the patient.

Betazole hydrochloride (Histalog), an isomer of histamine, may be used as an *alternative* to histamine for gastric analysis, in a dose of 0.5 mg/kg SC. It has negligible systemic side effects, and an antihistaminic is not required. Betazole is being replaced by *gastrin* for this test. A "tubeless" method of gastric analysis by using the dye *azuresin* (Diagnex blue) orally has also been developed. Its limitation is that though a positive test is reliable, a negative test has to be confirmed by the conventional gastric tube analysis.

Table 11.1-2. Chemical and physical agents releasing endogenous histamine

Chemical agents	Physical agents
Chymotrypsin	Mechanical trauma
Compound 48/80	Radiant energy
Atropine	Thermal energy
Dextran	
Morphine	
Codeine	
Polymyxin B	
Polyvinylpyrrolidone	
Reserpine	
Tubocurarine	
Toxins and Venoms	

2. Diagnosis of Pheochromocytoma

Histamine (3 mcg/kg, IV) *tyramine* (1.0 mg IV), *glucagon* (0.5–1.0 mg IV) or *phenolamine* (5 mg, IV) may be employed for the diagnosis of pheochromocytoma. These tests have to be carried out cautiously (Chap. 3.5)

Preparation. *Histamine phosphate* is available as a solution for injection containing 100 mcg, 200 mcg or 1 mg/ml. Doses of histamine are expressed conventionally in terms of base and 2.75 mg of the phosphate salt are equivalent to 1 mg of histamine base.

ANTIHISTAMINES

The actions of histamine can be antagonized in three ways: (i) by preventing or reducing histamine release, e.g., *glucocorticoids* can suppress the tissue effects of antigen/antibody reactions (Chap. 7.5) and *cromolyn sodium* (see later) stabilizes the mast cell membranes; (ii) by receptor antagonism, e.g., by antihistamines; and (iii) by using *physiological antagonists* which oppose the actions of histamine, e.g., *adrenaline* (Chap 3.4).

All the antihistamines are *competitive antagonists* at the histamine receptors, and can be divided into two groups: *H₁-receptor antagonists*, which comprise the large group of older classic agents; and the *H₂-receptor antagonists* namely *cimetidine* and *ranitidine*, which are newer agents exclusively used to suppress gastric acid secretion in the treatment of peptic ulcer.

Allergic Disorders

The term "allergy" refers to an exaggerated susceptibility to a substance which may be attributable to some underlying **antigen/antibody reaction**. The provoking substance or **allergen** may come from diverse sources including inhalants, foods, and drugs. An antigen is a large molecule, usually a protein capable of stimulating the formation of specific antibodies. Most drug molecules (haptens) are too small to be antigenic, but they may combine with a body protein (carrier) to form a **drug-protein complex** which is antigenic. When the antigen is introduced into the body for the first time, antibodies are formed and the body becomes **sensitized** to the antigen. This protein antibody may circulate in the plasma or be **fixed** in tissues. Thus the body becomes hypersensitive to the presence of the antigen, and on **re-exposure** to the specific antigen, an antigen/antibody reaction occurs, resulting in the release of many **mediator substances** which are responsible for the allergic symptoms and resultant cellular damage (Fig. 11.1.2).

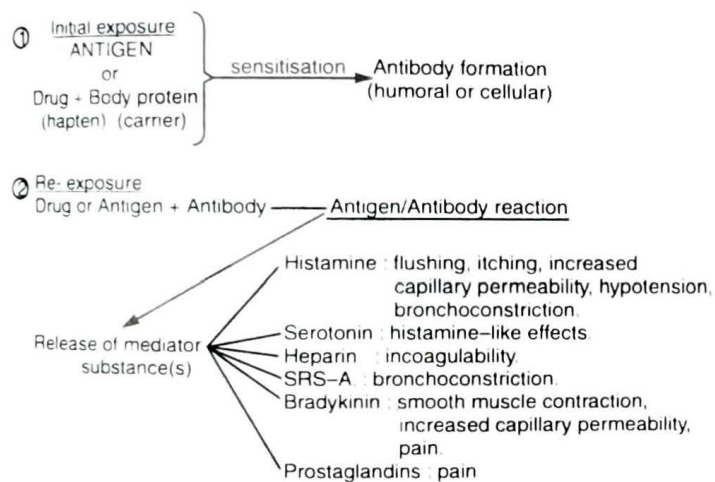


Fig. 11.1.2: Mechanism of allergic reactions.

In humans, SRS-A is generally considered to be an important mediator. Allergic reactions are often categorized as being either **immediate** or **delayed**. Immediate reactions such as anaphylactic shock, occur within minutes after reexposure to the antigen and the patient complains of anxiety and headache, which is rapidly followed by circulatory and respiratory failure and shock. In delayed hypersensitivity reactions, there is a slowly developing cellular response independent of formation of antibody. The sensitized mononuclear cells infiltrate the target area causing chronic inflammation and tissue damage. Histamine is not involved in the delayed reactions.

Mode of Action

Both H_1 - and H_2 - receptor antagonists do not influence the formation or release of histamine, but **selectively** and **competitively** antagonize its actions presumably at specific receptor sites. The effectiveness of antihistamines in blocking the actions of injected histamine is greater than in combating the various manifestations of anaphylaxis and allergy. This may be due to the liberation of **other autacoids** like SRS-A against which antihistamines are ineffective.

The antihistamines effectively block the actions of **exogenously** administered histamine in animals and man.

The effects mediated through H_2 -receptors are only antagonized by cimetidine and related drugs. However, the H_1 -receptor antagonists are **minimally effective** against the symptoms of anaphylaxis or histamine release by histamine releasing chemicals, or drugs, or other conditions which release **endogenous** histamine. Generally, urticaria and pruritus are antagonized by antihistamines, but bronchoconstriction and hypotension are not controlled. *The gastric acid hypersecretion induced by endogenous histamine is unaffected by H_1 -receptor antagonists.*

H_1 -receptor Antagonists (Antihistamines)

Prior to 1937, nothing but the physiological antagonist adrenaline was available to antagonize the actions of histamine. Bovet and Staub in 1937 introduced the compound 929F, which protected guinea pigs against five lethal doses of histamine. This compound was too toxic for clinical use. Antergan, introduced in France in 1942, was the first compound successfully used clinically as an antihistamine, and was 20 times more active than 929F and was less toxic. Later, dozens of histamine antagonists have been made available. Most of the important antihistamines contain a **substituted ethylamine** - $CH_2 CH_2 N =$ which is also present in histamine. However, this sequence may be present in compounds with no antihistamine activity.

Classification

1. **Alkylamines.** Chlorpheniramine, triprolidine, pheniramine, dimethindine, dexchlorpheniramine, and brompheniramine.
2. **Phenothiazines.** Promethazine, mequitazine, dimethothiazine, trimeprazine, and methdilazine.
3. **Piperazines.** Cyclizine, chlorcyclizine, meclozine, buclizine, and cinnarizine.
4. **Ethylenediamines.** Tripelennamine, mepyramine, pyrilamine, methapyrilene, and antazoline.
5. **Ethanolamines.** Diphenhydramine, dimenhydrinate, clemastine, carbinoxamine, and embramine.
6. **Miscellaneous.** Cyproheptadine, azatidine, terfenadine, astemizole, fexofenadine, loratadine, mizolastine, and cetirizine.

The above is a partial list of antihistamines. The older agents (**Classical or First-Generation Antihistamines**) cause appreciable sedation - **dimenhydrinate**, **promethazine**, and **trimeprazine** are more sedating, whereas **chlorpheniramine**, **cyclizine**, and **mequitazine** are less sedating. The non-sedating agents (**Second-Generation Antihistamines**) like **acrivastine**, **astemizole**, **cetirizine**, **fexofenadine**, **terfenadine**, **loratadine**, and **mizolastine** cause least sedation and psychomotor impairment, as they penetrate the blood-brain barrier only to a slight extent. **Fexofenadine**, an active metabolite of terfenadine, has been introduced recently.

Pharmacological Actions

Antihistamines offer palliative relief from allergic symptoms, but are not as potent and prompt in their action as **adrenaline**, which is a **physiological antagonist** of histamine. In addition, these agents exert effects on the **central** and **peripheral nervous system**.

Table 11.1-3. Pharmacological profile and dosage of some commonly used antihistamines

Drugs	Single adult dose (mg)	Dosing interval (hrs)	Potency	Sedative effects	Anticholinergic activity	Antiemetic effects
FIRST-GENERATION ANTIHISTAMINES						
Alkylamines						
Chlorpheniramine	4	4-6	++	+	++	—
Tripolidine	2.5	4-6	+++	++	++	—
Pheniramine	40	3-4	++	+	+	—
Phenothiazines						
Promethazine	25-50	6-12	+++	+++	+++	++++
Methdilazine	8	8-12	++ to +++	+	+++	++++
Trimeprazine	2.5	6	++ to +++	++	+++	++++
Piperazines						
Cyclizine	50-100	6-8	++	+	+	+++
Chlorcyclizine	50	8-12	++	+	+	+++
Meclozine	25-50	8-16	++	+	+	+++
Ethylenediamines						
Tripelennamine	50	4-6	++	++	+	—
Pyrilamine	25-50	4-6	+	++	+	—
Methapyrilene	25-50	4-6	+	+	+	—
Ethanolamines						
Diphenhydramine	25-50	6-8	++	+++	+++	++ to +++
Dimenhydrinate	50	4-6	++	++	++	—
Clemastine	1.0	12	+ to ++	++	+++	++ to +++
Miscellaneous						
Cyproheptadine	4	8	++	+	++	—
Azatidine	1-2	12	++	++	++	—
Phenindamine	25	4-6	++	±	++	—
SECOND-GENERATION ANTIHISTAMINES						
Miscellaneous						
Astemizole	10	24	++ to +++	±	±	—
Terfenadine	60	12	++ to +++	±	±	—
Loratadine	10	24	++ to +++	±	±	—
Cetirizine	10	12-24	++ to +++	±	±	—

++++ = very high; +++ = high; ++ = moderate; + = low; ± = low to none; — = none

Central Nervous System

In therapeutic doses the antihistamines produce *depression* and *sedation* of the central nervous system like the antipsychotic tranquillizers. Some antihistamines (see later) suppress nausea and vomiting resulting from labyrinthine disturbances, without producing sedation. Motion sickness is also suppressed. The agents diphenhydramine and phenindamine improve spontaneous movement and speech in patients of *Parkinson's disease*, and related drug-induced extrapyramidal disorders. Their atropine-like activity may be playing an additional role.

Peripheral Nervous System

The antihistamines have *anticholinergic*, *local anaesthetic* and *antiserotonin* actions in different measures. The anticholinergic activity may be related to their usefulness in motion sickness. Some antihistamines, given

intravenously in high doses may produce a *quinidine-like effect* due to their local anaesthetic activity. The compound cyproheptadine has significant antiserotonin activity in addition to its antihistamine action.

Absorption, Metabolism and Excretion

The antihistamines are readily absorbed on oral or parenteral administration. The actions are manifested within 30 minutes, but their potency, duration of action and sedative effect varies with different agents (Table 11.1-3). They are metabolized in the liver by *hydroxylation*, and may stimulate the hepatic microsomal enzymes.

Therapeutic Uses

The antihistamines have a widespread popularity in the symptomatic treatment of many *hypersensitivity states*, *parkinsonism*, *insomnia*, and *motion sickness*.

Hypersensitivity states. Antihistamines are used to treat allergic symptoms produced by the release of histamine, e.g., increased capillary permeability, oedema, pruritus, smooth muscle contraction and urticaria.

Antihistamines are effective in the management of hay fever, vasomotor rhinitis, acute and chronic urticaria, atopic and contact dermatitis, and for treating the pruritus, erythema and oedema of insect bites, but are of little value in erythema multiforme and exfoliative dermatitis. There is little evidence that any one of the older antihistamines is superior to another, and patients vary widely in their responses.

The antihistamines play only a secondary role in the therapy of **anaphylactic shock**, **angioneurotic oedema**, **serum sickness** and **bronchial asthma**. As probably autacoids other than histamine are involved, the antihistamines are ineffective against hypotension and bronchoconstriction, which are serious features of these immediate allergic reactions. In these conditions the drugs of choice are: **adrenaline** in the treatment of anaphylactic shock, angioneurotic oedema and serum sickness; and **adrenaline**, **theophylline** and **isoprenaline** in the treatment of bronchial asthma. For an acute anaphylactic reaction **adrenaline** 0.3 to 0.6 mg (1:1000 solution) is injected IM or IV. The **glucocorticosteroids** may also be used.

Antihistamines like diphenhydramine have been used in the treatment of **parkinsonism** and drug-induced extrapyramidal reactions. The piperazines (cyclizine and others), **promethazine** and **diphenhydramine** are useful in the prevention of **motion sickness**, and nausea and vomiting following radiation exposure. Antihistamines have been used to treat nausea and vomiting of pregnancy, but it is preferable to avoid them. **They may be used to manage mild blood transfusion reactions.** Antihistamines are ineffective in the treatment of migraine, but may be of some use in **Meniere's disease** and other types of vertigo. Promethazine and diphenhydramine have been used for their sedative effect and for **preoperative medication**. There is little evidence that the antihistamines influence the course of common cold, although some symptomatic benefit may be obtained. Cyproheptadine accelerates weight gain and stimulates linear growth in children. However, most patients lose weight when the drug is discontinued.

Adverse Reactions

The incidence and severity of untoward effects varies with the preparation and the individual. Thus it is advisable to determine by trial and error, the preparation tolerated best by the patient. Usually, depression of the CNS, **dizziness**, **tinnitus**, **incoordination**, **diplopia** and **fatigue** develop. Very rarely central excitement, **euphoria**, **insomnia** and tremors may occur. Sedation is by far the most common adverse effect. Hence the patient using antihistamines should be **warned not to drive a vehicle or operate**

machinery, as accidents may occur.

Some antihistamines (diphenhydramine, promethazine) possess appreciable anticholinergic activity and produce **xerostomia**, **dysuria**, **blurring of vision**, **impotence** and **constipation**. Depression of bone marrow, **leucopenia** and **agranulocytosis** occur rarely. Since some antihistamines have been found to be **teratogenic** in animals, the use of these agents is contraindicated during pregnancy. Topical use leads to hypersensitivity. **Accidental acute poisoning** is not uncommon with antihistamines. **Treatment is symptomatic**, and directed towards combating the impending cardio-circulatory collapse.

Warning: Rare hazardous ventricular arrhythmias and death have been associated with **astemizole** and **terfenadine** administration, specially with increased blood concentrations consequent upon overdosing. These two antihistamines should not be taken concomitantly, and the long half-life of astemizole (24 hrs) should be borne in mind. The recommendations are: (i) **not to exceed the recommended doses**; (ii) **avoid concomitant administration of ketoconazole, itraconazole and other imidazole antifungals, the macrolides erythromycin and clarithromycin, the protease inhibitors like ritonavir and saquinavir, and selective serotonin-reuptake inhibitor (SSRI) antidepressants like fluoxetine and paroxetine**; (iii) **to be avoided if hypokalaemia or other electrolyte imbalance is evident, or the QT interval is known to be prolonged**; (iv) **avoid concomitant administration of arrhythmogenic drugs or diuretics**; and (v) **to be avoided in patients with significant hepatic dysfunction**.

Drug Interactions

Alcohol and certain CNS depressants can potentiate the sedative effect of antihistamines, and the patients should be warned about concomitant use of **alcoholic beverages**. Some antihistamines antagonize the antihypertensive effect of **guanethidine**, and blood pressure control may be lost.

H₂-receptor Antagonists

The H₁-receptor antagonists (classical antihistamines) do not block the gastric secretory effect of histamine. To explain this it was proposed that histamine acts on two types of receptors (Table 11.1-4). Later, Black and his co-workers in 1972 introduced the first antagonist, **burimamide**, which competitively antagonized the effects of histamine on parietal cells of the stomach and guinea pig atria. These histamine receptors were called H₂-receptors. The next antagonist was metiamide, but several patients on **metiamide** developed agranulocytosis, and it was withdrawn. In 1975 **cimetidine**, a non-thiourea H₂-receptor antagonist was introduced. In contrast to the H₁-antagonists, the H₂-receptors antagonists are less lipid-soluble compounds, and do not cross the blood-brain barrier, and as such do not cause sedation.

Table 11.1-4. Actions of histamine mediated by H₁- and H₂-receptors*

H ₁ actions	H ₂ actions
1. Contraction of smooth muscle of gut	1. Stimulation of gastric acid secretion
2. Contraction of smooth muscle of bronchi	2. Stimulation of cardiac atrial rate
3. Relaxation of smooth muscle of vascular resistance vessels	3. Relaxation of smooth muscle of vascular resistance vessels
4. Increase in permeability of postcapillary venules	4. Inhibition of contraction of uterus

* The fall in blood pressure produced by histamine involves both H₁- and H₂-receptors, thus both H₁- and H₂-blockers have to be used to abolish this response.

13

DRUGS ACTING ON THE RESPIRATORY SYSTEM

<p>Bronchodilator Drugs Classification Anticholinergics: Atropine, Ipratropium Sympathomimetics: Adrenaline, Ephedrine, Isoprenaline, Orciprenaline, Salbutamol, Terbutaline, Isoetharine, Rimiterol Methylxanthines: Aminophylline, Choline Theophyllinate, Diprophylline Disodium Cromoglycate Ketotifen Drug Therapy of Bronchial Asthma Prophylaxis Treatment of Acute Attack</p>	<p>Status Asthmaticus Treatment of Chronic Asthma Corticosteroids in Bronchial Asthma Antihistamines in Bronchial Asthma Antitussive Drugs Classification Centrally-acting Antitussives Peripherally-acting Antitussives Expectorants and Mucolytic Agents Inhalation Agents Oral Agents Oxygen Therapy Hyperbaric Oxygen Respiratory Stimulants</p>
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Chronic obstructive lung diseases (COLD) include *bronchial asthma, chronic bronchitis and emphysema*. These *three* disorders differ in their aetiology but have one common characteristic, *i.e.*, airway obstruction which blocks effective pulmonary ventilation. *Coughing, wheezing and dyspnoea* are the symptoms, and become progressively worse, leading to acidosis and electrolyte imbalances. Proneness to frequent respiratory infections can precipitate acute pulmonary failure, congestive heart failure, and even cardiac arrest. The *bronchodilator drugs* are the mainstay in the drug management. The other drugs employed are the *expectorants and mucolytic agents, antibacterials, anti-inflammatory agents and antitussives*.

Bronchodilator Drugs

The *tone* of the bronchial muscle is controlled by *humoral factors* and by the *autonomic nervous system*. In health the bronchial calibre is mainly controlled by the *balance* between the *parasympathetic and sympathetic* nervous systems (Table 13-1).

Table 13-1. Control of the bronchial smooth muscle

Factor	Constriction	Dilatation
<i>Neurogenic (ANS)</i>		
Parasympathetic	+	
Sympathetic	-	
<i>Autonomic receptors</i>		
Cholinergic (muscarinic)	+	
Adrenergic alpha	+	
beta2	-	
<i>Humoral</i>		
Histamine	+	
Serotonin (5-HT)	+	
Bradykinin	+	
SRS-A	+	
Prostaglandins	+	
	(FGF ₂ alpha)	+
		(PGE ₂)

+ = activity; - = no activity

The parasympathetic system causes *bronchoconstriction* mediated by acetylcholine. The sympathetic stimulation mediated by noradrenaline causes increased pulmonary blood flow, *bronchodilatation*, and vasodilatation of the pulmonary circulation. The *humoral* factors are mainly operative in diseased states.

Classification

The bronchodilators may be classified as under:

I. Anticholinergic agents

Atropine

Ipratropium

II. Sympathomimetic amines

(a) *Drugs stimulating alpha- and beta-receptors*

Adrenaline

Ephedrine

(b) *Drugs stimulating beta₁- and beta₂-receptors*

Isoprenaline

Orciprenaline

(c) Drug stimulating β_2 -receptors

Salbutamol
Terbutaline
Isoetharine
Rimiterol

III. Theophylline derivatives (Methylxanthines)

Aminophylline
Choline theophyllinate
Diprophylline

Mode of Action

Ahlquist (1948) introduced the concepts of alpha- and beta-adrenergic receptors to account for the excitatory and inhibitory actions of sympathomimetic amines at different sites. Later, Lands (1967) further subdivided the beta-receptors into β_1 responsible for cardiac stimulation and lipolysis, and β_2 responsible for bronchodilatation and vasodepression (Chaps. 3.1, 3.4). Isoprenaline is an agent with mixed β_1 and β_2 agonistic action, and the cardiac stimulation thus caused is a serious limitation when used for bronchial asthma. Now specific β_2 stimulants like salbutamol are available, which produce bronchodilatation with minimal cardiac side effects.

Beta-adrenoceptor activity is mediated by c-AMP. The beta-adrenergic drugs increase adenylcyclase activity, which promotes the conversion of ATP to active c-AMP, and this in turn relaxes the bronchial muscle (Fig. 13.1). Cyclic-AMP also inhibits the secretion of SRS-A, histamine, and the eosinophil chemotactic factor (ECF-A) from the mast cells. Cyclic-AMP is broken down by the enzyme phosphodiesterase. The methylxanthines inhibit this enzyme, thereby conserving c-AMP in the bronchial muscle cell. Thus, the adrenergic agonists cause bronchodilatation by promoting the formation of c-AMP, and the methylxanthines act by inhibiting the destruction of c-AMP.

There is evidence that stimulation of the alpha-receptors located in the bronchial muscle, is responsible for bronchoconstriction, and release of chemical mediators (histamine, SRS-A, ECF-A) from the mast cells. This action is just opposite to that of beta-adrenergic stimulation, as discussed above. It is postulated that bronchial asthma is a disturbance in the homeostatic control mechanisms maintaining bronchial tone, as a result of the imbalanced function of alpha-and beta-adrenoceptors, and that there is a progressive beta-adrenoceptor blockade and hyposensitivity leading to bronchoconstriction.

Cellular cyclic guanosine monophosphate (c-GMP) is under control of the parasympathetic nervous system. Its

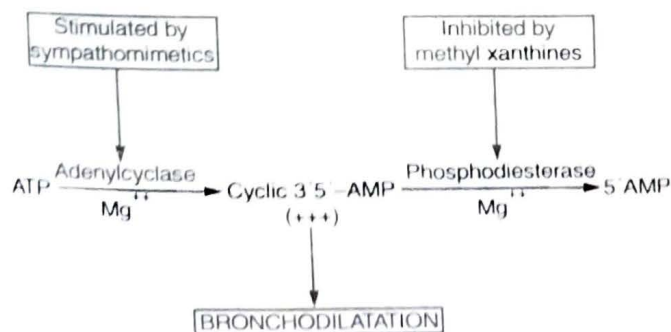


Fig. 13.1: Mode of action of sympathomimetics and methylxanthines as bronchodilators.

concentration is increased by vagal stimulation or by cholinergic drugs like carbechol and methacholine. Cyclic-GMP causes constriction of the bronchial muscle. The resting state of the bronchial muscle is probably regulated by a balance between c-AMP and c-GMP, and thus between sympathetic and parasympathetic stimuli. The anticholinergic agents may be acting by reducing the concentration of c-GMP in the bronchial muscle, although they are not very effective bronchodilators.

Anticholinergics

Atropine

Atropine relaxes the bronchial smooth muscle and reduces the secretions in the respiratory tract, which is its undesirable effect in bronchial asthma. Side effects of cholinergic blockade (tachycardia, xerostomia, blurred vision, difficulty in micturition) occur. Because of the side effects and slow onset of action, atropine today has no place in the management of bronchial asthma.

Ipratropium (Atrovent)

Ipratropium is a new synthetic anticholinergic agent. It prevents the increase in c-GMP resulting from parasympathetic activation. It is claimed that ipratropium has some bronchoselectivity, producing bronchodilation without unwanted anticholinergic side effects. It is more potent than atropine. Ipratropium is available in a metered dose inhaler delivering 0.02 mg per inhalation. The usual dosage is one or two puffs three or four times daily.

SYMPATHOMIMETICS

Adrenaline

The detailed pharmacology of the sympathomimetic bronchodilators is discussed in Chapter 3.4. Adrenaline has powerful bronchodilator action. It acts both on the alpha- and beta-receptors, and in addition to bronchodilatation, it produces vasoconstriction and cardiac stimulation. It has a short duration of action, and the maximum potential for harmful cardiac effects. It is now usually not included in most of the therapeutic regimens for bronchial asthma as it has been superseded by selective β_2 -receptor stimulants. It can be given subcutaneously 0.2 to 0.5 ml of a 1:1000 solution. A sustained release form of adrenaline is available, or it may be even administered as an aerosol. Adrenaline is still valuable in the treatment of anaphylactic shock.

Ephedrine

Ephedrine resembles adrenaline, and stimulates both alpha- and beta-receptors. In addition, it stimulates the release of noradrenaline from the sympathetic nerve endings. It is readily and completely absorbed after oral or parenteral administration. Side effects include CNS stimulation, vomiting, sweating, tremors, nervousness, insomnia and cardiac irregularities.

Ephedrine is used mainly as a chronic medication for mild or moderately severe bronchial asthma, specially in children. The usual adult dose is 30 to 60 mg orally three or four times daily. Resistance (tolerance) may develop, but can be controlled by discontinuing the therapy.

Isoprenaline

Isoprenaline has a powerful effect on beta-receptors and almost no action on alpha-receptors. As it stimulates *both* β_1 - and β_2 -receptors, in addition to producing bronchodilatation, it *increases the heart rate and cardiac output*. The major toxic effects are due to β_1 (cardiac) stimulant activity, producing *tachycardia, cardiac arrhythmias including ventricular fibrillation*.

For many years isoprenaline was a very useful drug in the treatment of bronchial asthma. It may be administered by *metered aerosol* in a dose of 0.08 to 0.24 mg (one to three puffs) upto eight times daily, with at least 30 minutes between two puffs. Between 1959 and 1966 when isoprenaline inhalers were in wide use in Great Britain, there was an increased death rate from bronchial asthma. Isoprenaline now is no longer a drug of choice in bronchial asthma. It has been *replaced* by the more specific β_2 stimulant drugs.

Orciprenaline (Alupent)

Orciprenaline is a long-acting derivative of isoprenaline. It stimulates both β_1 - and β_2 -receptors, although it is claimed that it has little effect on the heart muscle. It is not inactivated by catechol-O-methyl transferase (COMT), and is more stable in the body. Orciprenaline given orally reduces the frequency and severity of asthmatic attacks. Inhaled as an *aerosol*, it acts promptly and the action lasts for 3 to 6 hours. Orally it is given in a dose of 20 mg every 6 hours. The metered aerosol produces 0.75 mg per dose, and adults may take upto 12 doses in 24 hours.

Beta₂ Agonists

Salbutamol (Ventolin)

Salbutamol is probably the most widely used β_2 -receptor stimulant. It is effective by *oral, intravenous and aerosol* inhalation routes of administration, and has a much longer duration of action than isoprenaline. It is virtually devoid of cardiovascular effects in usual doses. The *oral* dose in the treatment of bronchial asthma is 2 to 4 mg three times daily. For *inhalation* 100 to 200 mcg may be repeated 4 hourly with a maximum of 8 inhalations in 24 hours. Salbutamol may be used by *slow intravenous infusion* (10 to 45 mcg/minute) to inhibit uterine contractions in *premature labour*.

Salmeterol (Salmeter)

Salmeterol is a *longer-acting* β_2 -receptor agonist. It is about 50 times more selective than salbutamol as a β_2 -agonist. In addition, it also inhibits the IgE-dependent release of mast cell mediators like histamine, leukotrienes, and prostaglandin D₂. Salmeterol reduces bronchial oedema by suppressing vascular permeability. It is used for the *prophylaxis of reversible bronchospasm including nocturnal asthma, exercise-induced asthma, and chronic bronchitis*. Dose. 50 mcg by *inhalation* bid, may be increased to 100 mcg bid in severe cases. *Adverse reactions* include headache, nervousness, muscle cramps, hypersensitivity reactions, urticaria, and paradoxical bronchospasm. *Formoterol* is another longer-acting β_2 -agonist with similar indications, and administered by *inhalation* in a dose of 12 mcg bid, increased to 24 mcg bid in more severe cases.

Terbutaline (Bricanyl)

Terbutaline is closely related chemically to orciprenaline, but is reputedly *more* β_2 -selective. Its pharmacological actions and therapeutic uses resemble those of salbutamol. *Orally* it is given in a dose of 2.5 to 5 mg two or three times daily. It may be administered subcutaneously (250 to 500 mcg) or by inhalation (200 or 250 mcg metered dose).

Isoetharine (Numotac)

Isoetharine is a *selective* β_2 -receptor stimulant and is effective by mouth, but its duration of action is short due to rapid inactivation in the body mainly by COMT. Orally it may be given in a dose of 10 mg *delayed release tablets*, with an effective duration of action of 4 to 6 hours. *Aerosol* preparation (350 mcg metered dose) is also available.

Rimiterol (Pulmadil)

Rimiterol is a short acting β_2 -receptor stimulant, not active by mouth, but produces potent bronchodilator effect of rapid onset and short duration on inhalation. Its activity is similar to that of *salbutamol* and *terbutaline*, and is used to relieve bronchospasm of bronchial asthma and chronic bronchitis. Plasma half-life is less than 5 minutes. The *dose* is 0.2 to 0.6 mg (one to three inhalations from a metered aerosol) with not more than 8 inhalations in 24 hours.

Other β_2 stimulants used as bronchodilators are *fenoterol, reproterol and tulobuterol*.

Methylxanthines

The methylxanthines act by *inhibiting the enzyme phosphodiesterase*, and hence have actions which resemble the sympathomimetics. They cause bronchodilatation, myocardial stimulation and CNS stimulation.

Aminophylline

Aminophylline is a combination of theophylline and ethylenediamine, and has useful bronchodilator properties in conditions like *bronchial asthma* and *pulmonary oedema*. It is often used by *slow intravenous injection* (250 to 500 mg) as a first line treatment in patients with severe asthmatic attacks. It is effective and acts rapidly, but may produce more side effects than the β_2 -receptor stimulants. When a large intravenous dose of aminophylline is given rapidly, *convulsions, arrhythmias or cardiac arrest* may occur. *Aminophylline suppositories* in strengths of 50, 100, 150 and 360 mg may be used to avoid gastric irritation and nausea caused by oral aminophylline.

Choline Theophyllinate (Cholelyl)

Choline theophyllinate is used for the relief and prophylaxis of mild to moderate bronchospasm. The *adult oral dose* is 400 to 1600 mg daily in divided doses. It has been observed that when a maximal bronchodilator effect has been achieved by a β_2 -receptor stimulant, an *additional effect* can be obtained by administration of aminophylline or choline theophyllinate.

Diprophylline (Dyphylline)

Diprophylline is a theophylline derivative which is used like aminophylline. It causes less of nausea and gastric irritation. It is better tolerated by mouth and by injection. The usual dose is upto 15 mg/kg every 6 hourly.

DISODIUM CROMOGLYCAT

Disodium cromoglycate (DSCG, Intal, Cromolyn sodium, sodium cromoglycate) is *not a bronchodilator*; it does not antagonize the mediators like histamine, serotonin, SRS-A and ECF-A involved in bronchial asthma; it has no anti-inflammatory activity; but is commonly used in the management of bronchial asthma. Its main action is prophylactic, reducing the incidence and severity of allergic asthmatic attacks. DSCG administration permits the **reduction in the dosage of corticosteroids and bronchodilators** being used in asthmatic patients. It is of little value in the treatment of acute attacks of asthma.

DSCG *inhibits the release of histamine and SRS-A* from the sensitized mast cells, possibly by *stabilizing the mast cell membrane*, and thereby preventing exocytosis. It also prevents exercise-induced bronchoconstriction in normal and asthmatic patients, possibly by *inhibiting the local release of prostaglandins*.

DSCG is very poorly absorbed from the gut. It has to be administered by *inhalation* from a special dispenser, the *spinhaler*, in which a propeller activated by suction creates a cloud of powder from the punctured capsule, which is inhaled. About 5 to 10 per cent of the inhalation reaches the lungs, the remainder is deposited in the mouth and oropharynx and is swallowed. DSCG is rapidly absorbed from the lungs, and is excreted unchanged in the urine and bile. It has *no serious toxic effects*, but may cause irritation of the throat and coughing. Isolated cases of *hypersensitivity* have been reported.

DSCG is used in the prophylaxis of allergic bronchial asthma. The initial dose is 20 mg four times daily. DSCG has also been tried in other disorders with an allergic basis including *hay fever, allergic rhinitis, food allergy, allergic conjunctivitis and ulcerative colitis*.

Nedocromil is a new compound with actions like cromolyn, used for *prophylaxis of asthma* by aerosal inhalation in a dose of 4 mg (2 puffs) tid or qid.

Ketotifen (Zaditen)

Ketotifen has actions similar to cromolyn sodium, and acts primarily by inhibition of mediator release. It also has antihistamine properties. It is used in the *prophylaxis of bronchial asthma* (Dose: 2 mg bid orally).

Drug Therapy of Bronchial Asthma

Bronchial asthma is a *bronchial hypersensitivity disorder*

Table 13-2. Characteristics of extrinsic and intrinsic asthma

Parameter	Extrinsic type	Intrinsic type
External allergens	Yes	No
Positive skin test	Yes	No
Serum IgE	Raised in 60%	Normal or low
Age group affected	Children and youth	Older adults
Pattern of asthma	Intermittent	Continuous
Family history of allergy	Common	Uncommon
Drug response to:		
Beta-sympathomimetics	Yes	Poor
Corticosteroids	Yes	Yes
DSCG	Yes	Poor

characterized by variable dyspnoea due to widespread airway obstruction, which is reversible spontaneously or as a result of treatment. In addition, most asthmatics show increased bronchial irritability in response to changes in atmospheric conditions and other trigger factors including *allergens*.

Based on clinical grounds, and the measurement of IgE, there are two major types of asthma: (i) *Extrinsic asthma* (reagin-mediated), in which symptoms develop only on exposure to a specific allergen. The extrinsic asthmatics rarely suffer from status asthmaticus, and require infrequent medication. They have a positive skin test and bronchial challenge tests; and (ii) *intrinsic asthma* (perennial asthma), in which the symptoms are often *precipitated by infection*, the frequency of status asthmaticus is higher, and no allergic aetiology is detectable. Both these types behave differently to antiasthmatic drugs (Table 13-2). Mixed features of both the types may be seen in some patients.

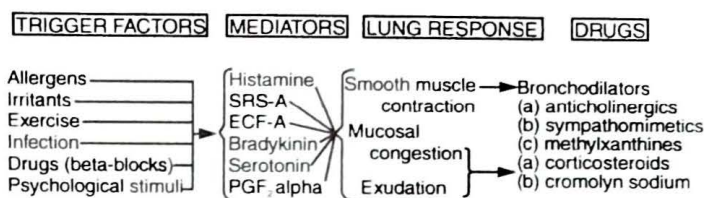


Fig. 13.2: Factors involved in the causation of bronchial asthma, and their drug management.

Three factors contribute to the reduction in airway calibre irrespective of the type of bronchial asthma—*smooth muscle constriction, mucosal congestion* and *exudation* (Fig. 13.2). The therapy is primarily directed at reversing bronchoconstriction by using bronchodilators, which are of three main types—*anticholinergics, sympathomimetics* and *methylxanthines*.

Prophylaxis

The incidence and severity of attacks may be reduced by regular administration of: (i) *disodium cromoglycate* which inhibits the release of mediators from the mast cells; (ii) *bronchodilators* like ephedrine orally, orciprenaline orally or by aerosol, or salbutamol orally or by aerosol. *Oral aminophylline* may be given, and the serum levels adjusted between 9 to 18 mcg/ml to obtain safe bronchodilator effect; (iii) *corticosteroids* like prednisolone may be administered orally, but there is a risk of adrenocortical suppression. *Beclomethasone* may be administered by

aerosol as a prophylactic without producing significant adrenocortical suppression; and (iv) *Desensitization* to an allergen is sometimes feasible.

Treatment of Acute Attack

In the treatment of the acute attack some authorities still advocate the use of subcutaneous *adrenaline*, while others advocate *salbutamol* inhalation. Respiratory infection is to be treated by *antibiotics*. An advocated regimen is outlined below:

(a) *Adrenaline* (1: 1000) 0.2 to 0.5 ml subcutaneously. May be repeated every 1 to 2 hours.

(b) *Aminophylline* 0.25 g in 10 to 20 ml of saline slowly IV may be used.

(c) *Nebulized drugs* like isoetharine, isoprenaline or salbutamol may be given.

(d) *Corticosteroids*. In a moderate to severe attack hydrocortisone sodium succinate 100 to 200 mg IV may be effective.

(e) *Other drugs*. Methylxanthines may be tried. Sedation should be avoided in severe asthma. In mild to moderate attacks *phenobarbital* (30 mg), or *diazepam* (5 mg) may be useful. Fluids are administered to avoid dehydration and to liquefy secretions. *Oxygen inhalations* by mask or by intermittent positive pressure breathing (IPPB) is indicated if symptoms are severe.

Status Asthmaticus

Aminophylline may be administered by intravenous infusion spread over 8 hours. *Hydrocortisone sodium succinate* 100 mg or *methyl prednisolone sodium succinate* 80 mg may be given IV every hour. Beta₂-adrenoceptor stimulants may be given by mouth, aerosol or injection. Other measures include IPPB and *bronchial lavage* to remove tenacious mucus plugs; and *broad spectrum antibiotic therapy*. *Sedatives* and *antianxiety* drugs should be used cautiously.

Treatment of Chronic Asthma

Whenever possible the obvious trigger factors should be avoided. *Desensitization* to allergens may be tried. The main drug treatment of chronic asthma is to interfere with the immune mechanisms, which can be achieved by (i) sympathomimetics; (ii) disodium cromoglycate; and (iii) corticosteroids.

Corticosteroids in Bronchial Asthma

The glucocorticoids and their synthetic analogues have an established place in the treatment of bronchial asthma. They are *life-saving* in an acute attack or status asthmaticus. It is not known exactly as to how the glucocorticoids affect the major components of reversible airway obstruction in asthma, namely bronchospasm, congestion and exudation. Probably they function as *non-specific anti-inflammatory agents* to provide relief from congestion and exudation (Chap. 7.5).

✓ **Beclomethasone dipropionate (Becotide)** is a chlorinated analogue of betamethasone. It acts *locally* on the respiratory mucosa, and the metered-dose inhaler delivers 42 or 50 mcg/puff. Two or three puffs a day are sufficient in mild asthma. Beclomethasone inhalation allows 'topical' treatment without major adverse effects like the suppression of the

pituitary adrenal axis. It is highly effective locally but *poorly absorbed*, and the amount swallowed is largely inactivated during passage through the liver. However, topical corticosteroids may lead to *local atrophy* of the pharyngeal mucosa and *superinfection* with candida.

Regarding the *mode of action* of glucocorticoids in bronchial asthma, the views put forward are that: (i) they *augment the responsiveness* of the tissues (including the bronchial tissue) to catecholamine action; (ii) they *overcome or partially reverse the beta-adrenoceptor blockade* (which is supposed to progressively occur in an asthmatic patient in the natural course of the disease); and (iii) they *slow the rate of catecholamine metabolism* by COMT, thus facilitating the activation of adenylylase. These three factors tend to increase the levels of c-AMP in the catecholamine sensitive bronchial tissue thereby antagonizing bronchoconstriction. In addition it has been shown that the corticosteroids *inhibit the re-accumulation of histamine in the mast cells*. In short, the corticosteroids inhibit the inflammatory and immune response, and reverse the resistance (beta-blockade) developed on prolonged exposure of the asthmatic to beta-receptor stimulants. Patients who develop persistent and severe airway obstruction, and do not respond to bronchodilators and disodium cromoglycate, should be considered for *long-term* corticosteroid therapy.

Other corticosteroids for inhalation (aerosol) treatment of steroid-dependent bronchial asthma are *dexamethasone*, *flunisolide*, *triamcinolone*, and *budesonide*.

Antihistamines in Bronchial Asthma

The antihistamines are almost ineffective in the treatment of bronchial asthma. This is probably because histamine is released from the sensitized mast cells in very high concentrations near the target cells, and the competitive blockade produced by mepyramine and other antihistamines is *ineffective*. In addition, many other chemical mediators are liberated from the sensitized mast cells (not antagonized by antihistamines) which may be more important in chronic asthma than histamine itself.

Antitussive Drugs

Coughing is a *protective reflex* which may be initiated by irritation in the pharynx or in the deepest level of the respiratory tract. The *cough receptors* (chemo- and mechano-receptors) lie in the mucosa of the bronchial tree, from the nose to the distal bronchi. The impulses from these receptors are transmitted through the *vagus* and the *glossopharyngeal nerve* to the cough centre in the medulla. The cough centre has a *coordinating network with the respiratory and vomiting centres*. The different pathway involves the nerves supplying the abdomen, thoracic muscles, diaphragm and the glottis. It is often not advisable to completely suppress cough in cases of *chronic bronchitis* or *bronchiectasis*, as it may result in the retention of secretions in the tracheobronchial tree.

Classification

Antitussive agents can be divided into two groups: (i) the *centrally-acting* drugs which suppress the cough centre, and increase the cough threshold; and (ii) the *peripherally-acting* drugs which increase the threshold of the cough receptors, or act by relieving the irritation.

I. Centrally-acting-antitussives

- (i) *Narcotic antitussives*
Codeine, hydrocodone, ethylmorphine, oxycodone.
- (ii) *Non-narcotic antitussives*
Dextromethorphan, noscapine, propoxyphene, caramiphen.

II. Peripherally-acting antitussives

- (i) *Mucosal anaesthetics*
Benzonatate, chlorphedianol.
- (ii) *Bronchodilators*
Ephedrine.
- (iii) *Hydrating agents*
Steam, aerosols, fluids
- (iv) *Miscellaneous*
Bromhexine, candy, syrup

The *central* antitussives are clinically more popular, compared to the *peripheral* antitussives, which only have a local soothing and demulcent effect and are employed as lozenges and syrups.

Narcotic Antitussives

Codeine

Codeine is an opium alkaloid, available both as sulphate and phosphate in *tablet*, *elixir* or *syrup* form. It is a very effective antitussive agent and *depresses the cough centre* in the medulla, resulting in an elevation of the cough threshold. When large doses are used *respiratory depression* may occur. Codeine has a potential for the development of dependence like the opioids, and should be used with caution. Codeine causes lesser analgesia, euphoria, hypnosis, respiratory depression, constipation, nausea and vomiting compared to morphine. (Chap 2.6). Its antitussive effect equals that of morphine. Thus morphine is hardly ever employed as an antitussive. The *usual adult dose* is 10 to 15 mg orally every 4 to 6 hours. The *side effects* include nausea and vomiting, constipation, drowsiness, pruritus and respiratory depression. It is *contraindicated* in bronchial asthma as it induces bronchospasm.

Hydrocodone bitartrate is similar to codeine in its action, but possesses a *greater* dependence liability. The dose is 5 to 10 mg every 4 to 6 hours, and the side effects are the same as those of codeine.

Ethylmorphine and *oxycodone* have codeine-like antitussive actions, but do not appear to have an advantage over codeine.

Non-narcotic Antitussives

Dextromethorphan (Romilar)

Dextromethorphan is a synthetic morphine derivative, and a very useful antitussive agent. It is devoid of an analgesic and sedative effect. Dextromethorphan (10 mg) is comparable to 15 mg of codeine in its antitussive activity. It has a very *low addiction liability*. The usual adult dose is 10 to 30 mg every 4 to 6 hours. The *side effects* include slight drowsiness, nausea and dizziness. It is a widely used antitussive.

Noscapine (Nectadin)

Noscapine (narcotine) is an opium alkaloid and belongs to the benzyloquinoline fraction. It has a *potent antitussive action*, almost equalling that of codeine. Although it is derived from opium, noscapine has no narcotic or analgesic effect. It is well absorbed from the gut. The usual *adult dose* is 15 to 30 mg three or four times daily. It has a wide margin of safety. *Side effects* include drowsiness, headache, nausea and allergic rhinitis.

Propoxyphene Napsylate (Novrad)

Propoxyphene is separable into its *l*-form and *d*-form. The *laevoform* has antitussive properties, while the *dextroform* has analgesic action. The antitussive action of *l*-propoxyphene (50 mg) was found to be equivalent to 15 mg of codeine. It does not depress the CNS and respiration. The usual *adult dose* is 50 to 100 mg every 4 hours. The *side effects* include nausea, epigastric discomfort, skin rashes, urticaria, drowsiness and dizziness.

Caramiphen Ethanedisulfonate (Taoryl)

Caramiphen raises the threshold of the cough reflex, and is less active than an equal dose of codeine. It has an *atropine like action* and exerts antisecretory and mydriatic effects. The *oral dose* is 10 to 20 mg three or four times daily. The *side effects* include nausea, dizziness and drowsiness.

The *peripherally-acting antitussives* are mucosal anaesthetics, bronchodilators, hydrating agents or demulcents. They provide a soothing effect by correcting the irritation to the cough receptors. In the treatment of cough the first step is to determine the cause and institute specific treatment. The antitussive agents are usually ineffective against cough associated with bronchial asthma.

Expectorants and Mucolytic Agents (Mucokinetic Agents)

Expectorants and *mucolytic agents* alter the viscosity of the sputum, and promote the removal of secretions from the bronchial tree. A normal person is estimated to secrete almost 100 ml of mucus from the bronchial tree daily. In acute *non-bacterial bronchitis*, the secretions remain relatively thin, and the disease process is self-limited. In *infections* such as bacterial bronchitis, pneumonia, chronic bronchitis or bronchiectasis, the secretion is usually *thick, tenacious* and *frequently mucopurulent*. If it remains in the lungs, it becomes thicker and obstructs the airways. Blockade of larger airways may produce *segmental* or *lobar atelectasis*. It is in these situations that *expectorants* and *mucolytic agents* (collectively named as *mucokinetic agents*) play an important role. The mucokinetic agents are classified as under:

I. Inhalational agent: (also effective orally)

- (i) *Water*
- (ii) *Saline solutions* - hypotonic, isotonic, hypertonic.
- (iii) *Hygroscopic agents* - Glycerol guaiacolate, propylene glycol.
- (iv) *True mucolytic agent* - Acetylcysteine, pancreatic dornase, trypsin, chymotrypsin, streptodornase and streptokinase.
- (v) *Volatile agents* - Balsams and other volatile oils.

II. Oral agents

- (i) *Vagal stimulants* - Creosote derivatives, terpenes, ipecacuanha.
- (ii) *Direct mucokinetics* - Potassium iodide, ammonium chloride, bromhexine.

Glycerol guaiacolate is the most commonly used expectorant. It is used singly or in combination with *dextromethorphan*. The usual adult dose is 100 to 200 mg three or four times daily. *Side effects* are rare, but nausea, gastrointestinal discomfort and drowsiness may occur.

Propylene glycol is a *hygroscopic* agent with a sweet taste and demulcent properties. It potentiates the mucolytic actions of other mucokinetic agents. A 2 per cent solution in water is isosmotic with serum, and is therefore non-irritating to the airways. Thus 1 to 2 ml of 2 per cent propylene glycol can be added to the aerosols safely.

Acetylcysteine (Mucomyst) is a mucolytic agent, both effective *in vivo* and *in vitro*. It acts by opening the disulphide linkages in mucus, thereby lowering the viscosity. Acetylcysteine can be given by means of a *nebulizer* or *instilled* directly into the trachea. When given as an aerosol, it has a *bronchoconstrictive action*, and should be used with a bronchodilator. Special precautions must be observed when given to bronchial asthmatics. The *usual dosage* is 3 to 5 ml of 20 per cent solution with a bronchodilator and saline when nebulized. It may be repeated three or four times daily. One to 2 ml of a 10 or 20 per cent solution can be instilled directly into the trachea. *Side effects* include stomatitis, nausea, rhinorrhoea and sensitization to the drug.

Pancreatic dornase hydrolyses the deoxyribonucleoprotein of purulent sputum and thereby reduces its viscosity. The efficacy of the other enzymes listed above is doubtful.

Creosote derivatives. Hard woods such as beech are used as a source of creosote, which is a mixture of phenols having a characteristic odour. The most important components are *creosol* and *guaiacol*. *Creosote* is an antiseptic with an expectorant quality. When given orally it acts as a mucokinetic agent, both indirectly, by stimulating the gastric mucosa, and directly when the absorbed drug is secreted into the tracheobronchial tree. *Creosote* has been used in the past as an inhalational agent in the treatment of chronic bronchitis, but its use has fallen into disfavour without any good reason.

Guaiifenesin is a guaiacol derivative, which has replaced creosote as a mucokinetic agent. It is less irritating to the bowel and is absorbed more reliably. The usual *adult dose* is 100 to 200 mg every 3 to 4 hours.

Terpenes are volatile oils related to turpentine and are used in many cough remedies for their expectorant action. Such drugs include *anise oil*, *eucalyptus oil*, *lemon oil*, *pine oil*, *terpin hydrate* and *thymol*.

Terpin hydrate is the most popular agent. It is usually employed in combination with other agents in a dose of 125 to 300 mg every 6 hours.

Ipecacuanha. The extract of ipecacuanha (ipecac) is primarily used as an emetic (**Chap. 12**). In subemetic doses it is a potent stimulator of the *gastropulmonary mucokinetic vagal reflex*, and it promotes respiratory glandular secretion.

As an expectorant Ipecac syrup (ipecac, glycerine and syrup) is given in a dose of 0.5 to 2 ml orally three to four times daily. The emetic dose ranges between 15 to 20 ml.

Ipecac is a second line mucokinetic agent as it may induce nausea in some patients.

Potassium iodide increases bronchial secretions by *reflex stimulation of the gastric mucosa*. It also increases the volume and decreases the viscosity of salivary, nasal and lacrimal secretions. The use of potassium iodide may lead to unpleasant hypersecretion in the eyes, nose and mouth. *Sneezing, conjunctival irritation, parotid swelling, thyroid enlargement* and *brassy taste* may be troublesome. The usual *dosage* is 0.3 g as plain or enteric coated tablets 3 to 4 times daily.

Ammonium chloride and other ammonium salts are active expectorants, but less potent than potassium iodide.

Bromhexine is an oral mucokinetic agent. It is obtained from the plant *Adhatoda vasica*. It has been used in this country as *Vasaka* for many years as a remedy for cough and asthma. The active constituents were found to be *adhatodic acid* and the alkaloid *vasicine*, from which benzylamine bromhexine was obtained. Chronic bronchitic patients on bromhexine therapy expectorate larger amounts of sputum of a low viscosity. It acts by *depolymerization of the mucopolysaccharides* in the mucus, thereby lowering the viscosity. In addition, it also directly acts on the bronchial glands *liberating lysosomal enzymes* which digest the mucopolysaccharide fibres. The *usual dose* is 8 to 16 mg orally three times a day.

Ambroxol is a metabolite of bromhexine with similar actions and uses. *Dose.* 30 to 120 mg orally in 2 or 3 divided doses. It may be given by inhalation or rectally.

The use of expectorants in the treatment of chronic bronchitis and emphysema is probably beneficial. Whether the benefit is psychological or actual is debatable. Adequate hydration, postural drainage and chest physiotherapy are usually quite effective in acute and chronic conditions to mobilize bronchial secretions.

Oxygen Therapy

Supplemental oxygen is widely used in patients with *acute respiratory distress*. Mechanical ventilatory assistance may be needed in addition when the neural drive, muscle power or thoracic mechanics is disturbed or lost. There are many situations in which simultaneous mechanical assistance and oxygen is required, e.g., *central respiratory depression due to narcotic drugs, severe shock, acute and chronic pulmonary disease*. The pre-requisites for oxygen administration are, a patent and adequate airway, maintained if necessary by tracheal intubation or tracheostomy, and a positive pressure device and masks.

Technique of Oxygen Administration

The method of administration selected depends on the concentration of oxygen to be delivered to the lungs, and the need for ventilatory assistance. Oxygen from the cylinder should preferably be *bubbled through water* to humidify it before it is delivered to the patient's airway.

(i) **Oxygen tent.** Concentration of 25-50 per cent oxygen can be reached, depending on the rate of inflow of oxygen.

(ii) **Head tents or hoods.** Concentrations from 50-80 per cent can be reached, as they are smaller than tents.

(iii) **Nasal catheter or cannula (Prongs).** Concentrations from 40-60 per cent can be reached, and this technique is

adequate for most purposes and more acceptable to the patient.

(iv) **Endotracheal tube or facial masks.** 80 to 100 per cent concentrations can be delivered by these methods.

(v) **Hyperbaric oxygen.** Oxygen can be administered under pressures greater than 1 atmosphere, and as high as 3 atmospheres in special pressurized chambers.

Mode of Action

Atmospheric air contains 20.9 per cent oxygen, which exerts a partial pressure (PO₂) of 159 mm Hg in the inspired air. The PO₂ in the alveoli is about 100 mm Hg, and there is a gradient across the alveolar membrane, and the PO₂ in arterial blood is about 90 mm Hg. *Under usual conditions, haemoglobin is almost completely (96%) saturated with oxygen (except in anoxic anoxia).* Oxygen administration can act through the increase in dissolved oxygen which is from 0.3 to 2 ml/100 ml.

Therapeutic Uses

Oxygen administration is indicated in cases of anoxia: (i) *anoxic anoxia* due to inadequate ventilation, interference with diffusion, right-to-left shunts and ventilation-perfusion abnormalities; (ii) *anaemic anoxia*, when the blood haemoglobin content is low or in cases of carbon monoxide poisoning; (iii) *stagnant anoxia* as in cases of shock; and (iv) *histotoxic anoxia* as occurs in cases of *cyanide poisoning* which exerts its lethal effect due to inactivation of cytochrome oxidase.

The chief clinical indications for oxygen therapy are: *acute respiratory failure or arrest; arterial hypoxia due to acute or chronic respiratory disease; congestive heart failure or vascular insufficiency; severe anaemia or haemolysis; and certain poisons like cyanide and carbon monoxide.* Mixed venous PO₂ values are the best guide for adequate whole-body tissue oxygenation. Such a monitoring is advisable to avoid or recognize the adverse effects of oxygen excess.

Oxygen Toxicity

Adverse reactions induced by oxygen administration are: (i) *respiratory tract irritation* involving the nose, pharynx and the trachea; (ii) *respiratory depression* due to a carbon dioxide wash out; and (iii) *retrolental fibroplasia* in premature infants who are administered oxygen in high concentrations.

Preparation

Medical oxygen is available in cylinders which are painted white at the valve and down to the shoulder, and the remainder is painted black (white shoulder, black body) according to British convention. The chemical symbol O₂ is clearly stamped on the cylinder valve. According to American convention oxygen cylinders are painted green. Commercial oxygen or welding oxygen is equally pure and may be used, if necessary.

Hyperbaric oxygen. (Oxygen administration between 2 and 3 atmospheres but never more than 4 atmospheres) administered in pressure chambers is effective in the treatment of *carbon monoxide poisoning* and of *gas gangrene* of a diffuse type with spreading muscle necrosis. At 3 atmospheres pressure and 100 per cent oxygen, enough oxygen is dissolved in the blood (6 ml/100 ml) to meet the

tissue needs, without haemoglobin desaturation. **Oxygen toxicity is increased at higher pressures.** Other applications (like in peripheral vascular disease, cerebrovascular accidents, coronary thrombosis, tumour therapy, preservation of organs and tissues for transplantation) are under evaluation. The value of hyperbaric oxygen in clinical practice is due to *three* biologic effects: the *relief of hypoxia and anoxia*; the *potentiation of ionizing radiation effect (radiosensitization)*; and the *inhibition of bacterial growth and toxin production.*

RESPIRATORY STIMULANTS

The use of drugs to act as respiratory stimulants has been *disappointing*, as drugs which have a specific stimulant effect on the respiratory drive are not available.

The term "analeptic" is derived from the Greek work "analepticos" which means restorative or strengthening. Essentially analeptics are CNS stimulants, and some of them stimulate the respiratory centre in the medulla. They do not have a specific action on this area, and stimulate the cerebrospinal axis at all levels causing general arousal, and in larger doses produce convulsions (Chap. 2.9). The commonly employed analeptics are caffeine sodium benzoate and doxapram (Dopram).

Doxapram is a non-specific analeptic agent used to stimulate respiration. Its therapeutic index expressed as convulsant dose 50/respiratory stimulant dose 50, is as high as 25. Thus it has a wider margin of safety. *Side effects* include tachycardia, cardiac arrhythmias, hypertension and vomiting. Doxapram is administered by intravenous infusion at an initial rate of 5 mg/minute, reduced to 2 mg/minute later. It may be administered by intravenous injection in a dose of 1 to 1.5 mg/kg body weight. It is *contraindicated* in hypertension, coronary artery disease, thyrotoxicosis, status asthmaticus and cerebrovascular accidents.

Doxapram, and caffeine sodium benzoate may be used as *temporary* measures to correct *acute respiratory insufficiency* in chronic obstructive lung disease, and to hasten recovery from anaesthesia. According to current opinion analeptics have no place in the management of poisoning by CNS depressant drugs (sedative-hypnotic drugs). *Mechanical assistance* to antagonize drug-induced respiratory depression is safer, better and more reliable.

Suggested Reading

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