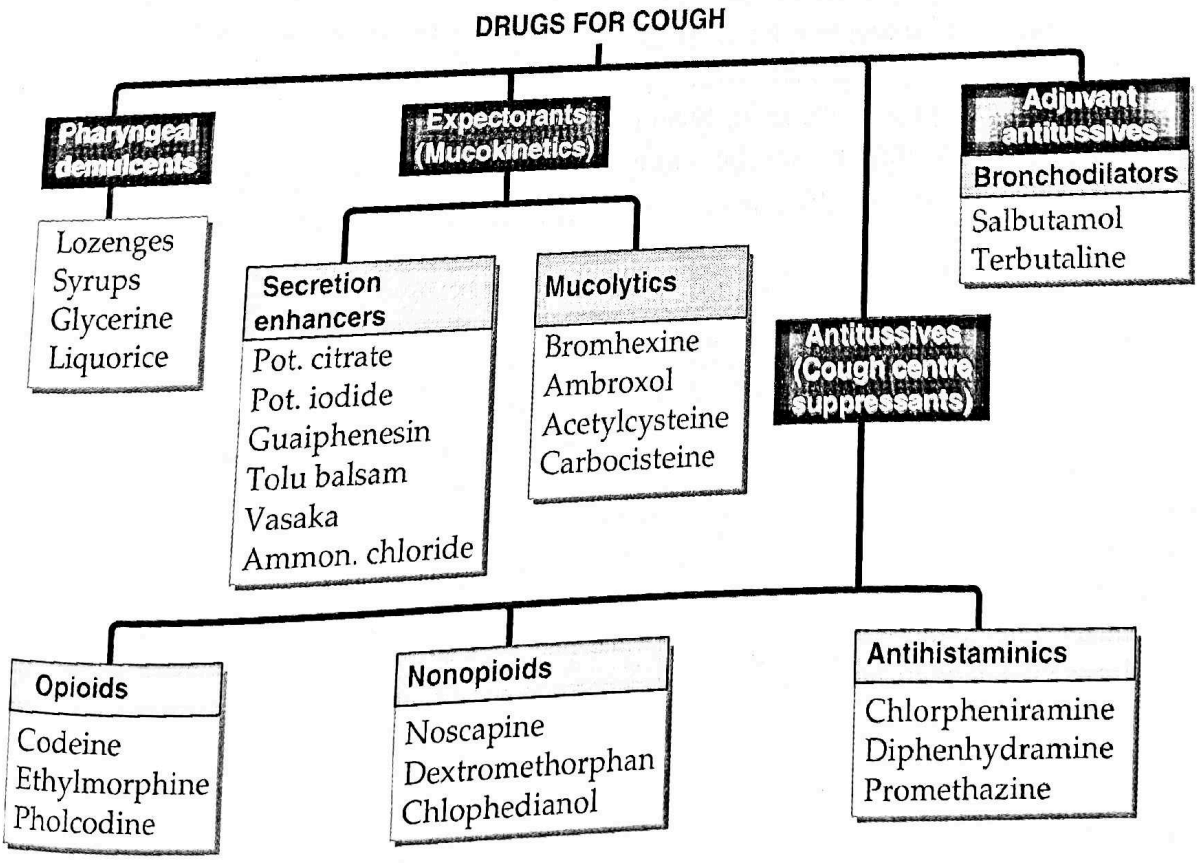
RESPIRATORY SYSTEM DRUGS

Chapter 16 Drugs for Cough and Bronchial Asthma

DRUGS FOR COUGH

Cough is a protective reflex, its purpose being expulsion of respiratory secretions and foreign particles from air passages. It occurs due to stimulation of mechano- or chemoreceptors in throat and respiratory passages or stretch receptors in the lungs. Cough may be useful or useless. Useless (nonproductive) cough should be suppressed. Useful (productive) cough serves to drain the airway; its suppression is not desirable; may even be harmful, except when the amount of expectoration achieved is small compared to the effort of continuous coughing. The commonest cause of acute cough (lasting < 3 weeks) is respiratory viral infections. Apart from specific remedies (antibiotics, etc. *see* box on p. 238), cough may be treated as a symptom (nonspecific therapy) with:



DEMULCENTS AND EXPECTORANTS

Pharyngeal demulcents soothe the throat and reduce afferent impulses from the inflamed/irritated pharyngeal mucosa, thus provide symptomatic relief in dry cough arising from throat.

Expectorants (Mucokinetics) are drugs believed to increase bronchial secretion or reduce its viscosity, facilitating its removal by coughing.

Sodium and potassium citrate are considered to increase bronchial secretion by salt action. Potassium iodide is secreted by bronchial glands and can irritate the airway mucosa. Prolonged use can affect thyroid function and produce iodism. It is not used now. Guaiphenesin, vasaka, tolu balsam are plant products which are supposed to enhance bronchial secretion and mucociliary function while being secreted by tracheobronchial glands. Ammonium salts are nauseating—reflexly increase respiratory secretions.

A variety of expectorant formulations containing an assortment of the above ingredients, often in combination with antitussives/antihistaminics are marketed and briskly promoted, but objective evidence of efficacy of expectorants is non-conclusive. The US-FDA has stopped marketing of all expectorants, except guaiphenesin. Steam inhalation and proper hydration may be more helpful in clearing airway mucus.

Mucolytics

Bromhexine A derivative of the alkaloid *vasicine* obtained from *Adhatoda vasica* (Vasaka), is a mucolytic and mucokinetic, capable of inducing thin copious bronchial secretion. It depolymerises mucopolysaccharides directly as well as by liberating lysosomal enzymes—network of fibres in tenacious sputum is broken. It is particularly useful if mucus plugs are present. *Side effects* are rhinorrhoea and lacrimation, nausea, gastric irritation, hypersensitivity.

Dose: adults 8 mg TDS, children 1–5 years 4 mg BD, 5–10 years 4 mg TDS.

BROMHEXINE 8 mg tablet, 4 mg/5 ml elixir.

Ambroxol A metabolite of bromhexine having similar mucolytic action, uses and side effects.

Dose: 15–30 mg TDS.

AMBRIL, AMBROLITE, AMBRODIL, MUCOLITE 30 mg tab, 30 mg/5 ml liquid, 7.5 mg/ml drops, ACOCONTIN 75 mg CR tab.

Acetylcysteine It opens disulfide bonds in mucoproteins present in sputum and makes it less viscid. It can be administered orally (200–600 mg TDS) as well as by inhalation of 10–20% nebulized solution. In intubated patients, the thick sticky secretion can be liquefied by instillation of 10–20% acetylcysteine solution directly into the respiratory tract.

MUCOTAB 600 mg tab, FLUIMUCIL 200 mg, 600 mg effervescent tab; MUCOMIX 200 mg/ml inj in 1,2,5 ml amps. The injectable solution can be nebulized/instilled through tracheostomy tube.

Specific treatment approaches to cough

Etiology of cough	*Treatment approach*
• Upper/lower respiratory tract infection	• Appropriate antibiotics
• Smoking/chronic bronchitis/ bronchiectasis	• Cessation of smoking/avoidance of pollutants, steam inhalation, postural drainage
• Pulmonary tuberculosis	• Antitubercular drugs
• Asthmatic cough	• Inhaled β_2 agonists/corticosteroids/ipratropium
• Cough in pulmonary eosinophilia	• Diethyl carbamazine citrate, inhaled corticosteroids
• Postnasal drip due to sinusitis	• Antibiotic, nasal decongestant, H_1 antihistaminic
• Postnasal drip due to allergic/perennial rhinitis	• Avoidance of precipitating factor(s), corticosteroid nasal spray, H_1 antihistaminic
• Gastroesophageal reflux	• Bed head elevation, light dinner, diet modification, H_2 blocker, proton pump inhibitor, mosapride
• ACE inhibitor associated cough	• Substitute ACE inhibitor by angiotensin receptor blocker, NSAIDs may reduce cough
• Post-viral cough	• No specific treatment, subsides by itself.

The gastric mucus barrier may be breached by orally administered acetylcysteine.

Carbocisteine It liquefies viscid sputum in the same way as acetylcysteine and is administered orally (250–750 mg TDS). Some patients of chronic bronchitis have been shown to benefit. It may break the gastric mucus barrier; therefore is contraindicated in peptic ulcer patients. Side effects are gastric discomfort and rashes.
MUCODYNE 375 mg cap, 250 mg/5 ml syr.
It is available in combination with amoxicillin or cephalexin for treatment of bronchitis, bronchiectasis, sinusitis, etc.
CARBOMOX: Carbocisteine 150 mg + amoxicillin 250 or 500 mg caps. CARBICEF: Carbocisteine 150 mg + cephalexin 250 or 500 mg caps.

Mucolytics are specifically useful in patients with tracheostomy, asthmatic bronchitis, cystic fibrosis, etc. who have thick tenacious sputum or mucus plugs.

ANTITUSSIVES

These are drugs that act in the CNS to raise the threshold of cough centre or act peripherally in the respiratory tract to reduce tussal impulses, or both these actions. Because they aim to control rather than eliminate cough, antitussive drugs should be used only for dry nonproductive cough or if it is unduly tiring, disturbs sleep or is hazardous (hernia, piles, cardiac disease, ocular surgery).

Opioid antitussives

Morphine and its congeners are the most effective antitussives, but morphine is not suitable for treating cough, because of its strong addicting and respiratory depressant property.

Codeine (*see* Ch. 34) An opium alkaloid, qualitatively similar to and less potent than morphine, but is more selective for cough centre. Codeine is regarded as the standard antitussive; suppresses cough for about 6 hours. The antitussive action is blocked by naloxone indicating that it is exerted through opioid receptors in the brain. That in certain opioid congeners, antitussive action can be dissociated from the analgesic-addicting action, indicates that the receptors mediating the two actions are not identical. Abuse liability is low, but present; constipation is the chief drawback. At higher doses respiratory depression and drowsiness can occur, especially in children. Driving may be impaired. Like morphine, it is contraindicated in asthmatics and in patients with diminished respiratory reserve; should be avoided in children.
Dose: Antitussive dose is lesser than analgesic dose. 10–30 mg; children 2–6 years 2.5–5 mg, 6–12 years 5–10 mg, frequently used as syrup codeine phos. 4–8 ml.
CODINE 15 mg tab, 15 mg/5 ml linctus.

Ethylmorphine It is closely related to codeine which is methylmorphine, and has antitussive, respiratory depressant properties like it, but is believed to be less constipating.
Dose: 10–30 mg TDS; DIONINDON 16 mg tab.

Pholcodine It has practically no analgesic or addicting property, but is similar in efficacy as antitussive to codeine and is longer acting—acts for 12 hours; dose: 10–15 mg.

Nonopioid antitussives

Noscapine (Narcotine) An opium alkaloid of the benzoisoquinoline series (*see* Ch. 34), which depresses cough but has no narcotic, analgesic or dependence inducing properties. It is nearly equipotent antitussive as codeine, especially useful in spasmodic cough. Headache and nausea occur occasionally as side effect. It can release histamine and produce bronchoconstriction in asthmatics.
Dose: 15–30 mg, children 2–6 years 7.5 mg, 6–12 years 15 mg.
COSCOPIN 7 mg/5 ml syrup, COSCOTABS 25 mg tab.

Dextromethorphan A synthetic central NMDA (N-methyl D-aspartate) receptor antagonist; the *d*-isomer has antitussive action while *l*-isomer is analgesic. Dextromethorphan does not depress mucociliary function of the airway mucosa and is practically devoid of constipating action. Though considered nonaddicting, some drug abusers indulge in it.

Side effect: Dizziness, nausea, drowsiness; at high doses hallucinations and ataxia may occur.
Dose: 10–20 mg, children, 6–12 years 5–10 mg. It is a common ingredient of many proprietary cough formulations (*see* antitussive combinations below), but not advocated for children < 6 years.

Chlophedianol It is a centrally acting antitussive with weak antihistaminic, anticholinergic and local anaesthetic properties. Onset of action is slow and duration longer.

Side effect: Dryness of mouth, vertigo, irritability.
Dose: 20–40 mg.

Prenoxdiazine A drug developed in Hungary which acts as antitussive by desensitizing the pulmonary stretch receptors. Tussal impulses originating in the lungs are suppressed. Efficacy, however, is not impressive.
Dose: 100–200 mg TDS; PRENOXID 100, 200 mg tab.

Antihistamines

Many H_1 antihistamines have been conventionally added to antitussive/expectorant formulations (*see* below). They afford relief in cough due to their sedative and anticholinergic actions, but lack selectivity for the cough centre. They have no expectorant property, may even reduce secretions by anticholinergic action. They have been specially promoted for cough in respiratory allergic states, though their lack of efficacy in asthma is legendary.

Chlorpheniramine (2–5 mg), Diphenhydramine (15–25 mg) and Promethazine (15–25 mg; PHENERGAN 5 mg/5 ml elixir) are commonly used. Second generation antihistamines like fexofenadine, loratadine, etc. are ineffective.

Bronchodilators Bronchospasm can induce or aggravate cough. Stimulation of pulmonary receptors can trigger both cough and bronchoconstriction, especially in individuals with bronchial hyperreactivity. Bronchodilators relieve cough in such individuals and improve the effectiveness of cough in clearing secretions by increasing surface velocity of airflow during the act of coughing. They should be used only when an element of bronchoconstriction is present and not routinely. Their fixed dose combinations with antitussives are not satisfactory because of differences in time course of action of the components and liability for indiscriminate use.

Fixed dose combinations of a centrally acting antitussive with a bronchodilator or with an antihistaminic having high atropinic activity have been banned in India, but many are still marketed.

Majority of the FDC cough formulations that are marketed and briskly advertized are irrational and have only placebo effect.

Aeromatic chest rub is widely advertized as a cough remedy. Though it has been shown to reduce experimentally induced cough in healthy volunteers, there is no evidence of benefit in pathological cough.

SOME ANTITUSSIVE-EXPECTORANT COMBINATIONS

ASTHALIN EXPECTORANT: Salbutamol 2 mg, guaiphenesin 100 mg per 10 ml syr; dose 10–20 ml.

ASCORIL-C: Codeine 10 mg, chlorpheniramine 4 mg per 5 ml syr.

AXALIN: Ambroxol 15 mg, guaiphenesin 50 mg, salbutamol 1 mg, menthol 1 mg per 5 ml syr.

BRONCHOSOLVIN: Guaiphenesin 100 mg, terbutalin 2.5 mg, bromhexine 8 mg per 10 ml susp.

CADICOFF, GRILINCTUS: Dextromethorphan 5 mg, chlorpheniramine 2.5 mg, guaiphenesin 50 mg, Amm. chloride 60 mg per 5 ml syr.

BENADRYL COUGH FORMULA: Diphenhydramine 14 mg, amm. chlor. 138 mg, sod. citrate 57 mg, menthol 1.1 mg per 5 ml syrup; dose 5–10 ml, children 2.5–5 ml.

BRO-ZEDEX: Bromhexine 8 mg, guaiphenesin 100 mg, terbutaline 2.5 mg, menthol 5 mg per 10 ml syrup; dose 10 ml.

CADISTIN EXPECTORANT: Chlorpheniramine 2 mg, glyceryl guaiacolate 80 mg, amm. chlor. 100 mg, sod. citrate 44 mg, menthol 0.8 mg, terpin hydrate 4 mg, tolu balsam 6 mg, Vasaka syrup 0.13 ml per 5 ml syrup; dose 10 ml.

CHERICOF: Dextromethorphan 10 mg, chlorpheniramine 2 mg, phenylpropanolamine 12.5 mg per 5 ml liq.

CLISTIN: Carbinoxamine 4 mg, amm. chlor. 240 mg, sod. citrate 240 mg per 10 ml syrup.

COREX: Chlorpheniramine 4 mg, codeine phos. 10 mg, menthol 0.1 mg per 5 ml syrup; dose 5 ml, children 1.25–2.5 ml.

COSCOPIN LINCTUS: Noscapine 7 mg, chlorpheniramine 2 mg, citric acid 29 mg, sod. citrate 3 mg, amm. chlor. 28 mg, per 5 ml syrup; dose 10–20 ml.

COSOME: Dextromethorphan 10 mg, phenylpropanolamine 25 mg, chlorpheniramine 4 mg per 10 ml syr; dose 10 ml.

GRILINCTUS: Dextromethorphan 5 mg, chlorpheniramine 2.5 mg, guaiphenesin 50 mg, ammon. chlor. 60 mg/5 ml syr; dose 5–10 ml.

GRILINCTUS SOFTCAPS: Dextromethorphan 10 mg, chlorpheniramine 2 mg, phenylpropanolamine 12.5 mg softcaps.

SOLVIN EXPECTORANT: Bromhexine 4 mg, pseudoephedrine 30 mg tablet and in 10 ml liquid; dose 1 tablet/5 ml liquid.

TOSSEX: Codeine phos 10 mg, chlorpheniramine 4 mg, menthol 1.5 mg, sod. citrate 75 mg per 5 ml liquid; dose 5 ml.

VENTORLIN EXPECTORANT: Salbutamol 2 mg, guaiphenesin 100 mg per 10 ml syrup; dose 10 ml, children 2.5–7.5 ml.

ZEET LINCTUS: Dextromethorphan 10 mg, guaiphenesin 50 mg, phenylpropanolamine 25 mg per 5 ml syr; dose 5 ml.

DRUGS FOR BRONCHIAL ASTHMA

Bronchial asthma is characterised by hyperresponsiveness of tracheobronchial smooth muscle to a variety of stimuli, resulting in narrowing of air tubes, often accompanied by increased secretion, mucosal edema and mucus plugging. Symptoms include dyspnoea, wheezing, cough and may be limitation of activity.

Asthma is now recognized to be a primarily inflammatory condition: inflammation underlying hyperreactivity. An allergic basis can be demonstrated in many adult, and higher percentage of pediatric patients. In others, a variety of trigger factors (infection, irritants, pollution, exercise, exposure to cold air, psychogenic) may be involved. Two principal varieties are recognised:

Extrinsic asthma: It is mostly episodic, less prone to status asthmaticus.

Intrinsic asthma: It tends to be perennial, status asthmaticus is more common.

The inflammation in bronchial asthma is initiated by mast cells (present in lungs), and the infiltrate is dominated by eosinophils, lymphocytes and mast cells. The initial inflammatory reaction produces a multitude of mediators by the following processes:

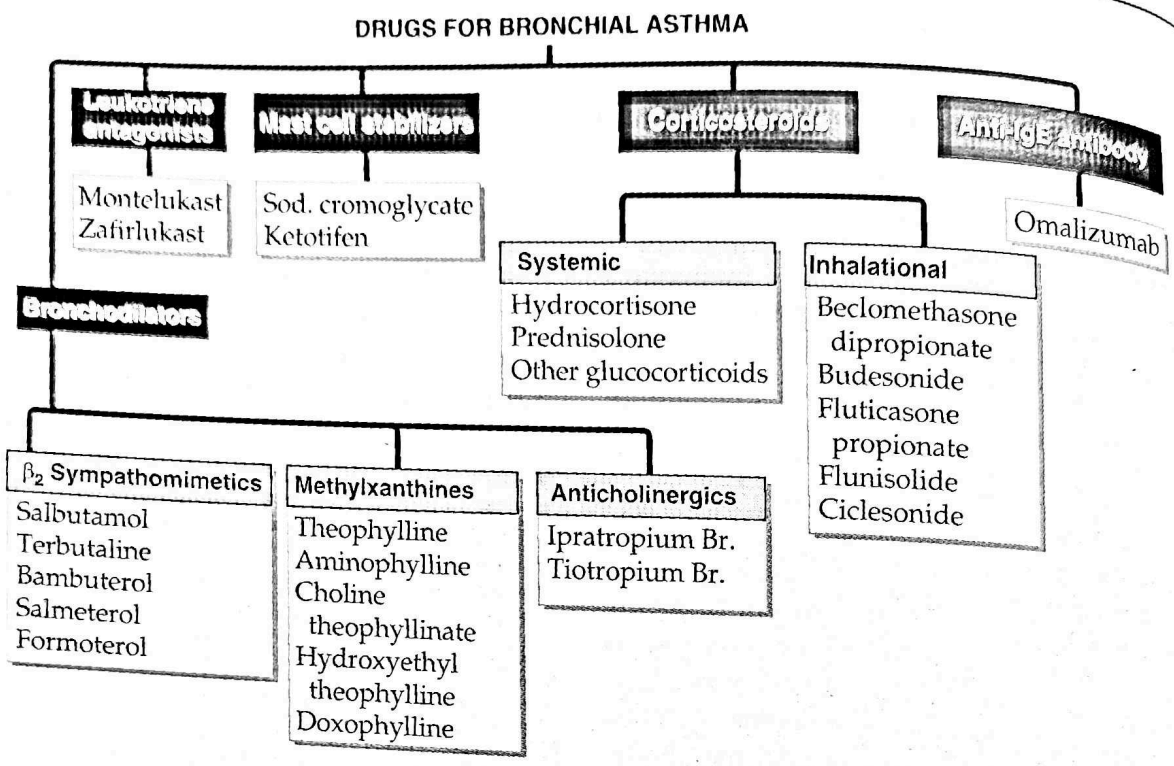
- Release of mediators stored in intracellular granules *(immediate):* histamine, protease enzymes, TNFα.
- Release of phospholipids from cell membrane followed by mediator synthesis *(within minutes):* PGs, LTs, PAF.
- Activation of genes followed by protein synthesis *(over hours):* Interleukins, TNFα.

These mediators together constrict bronchial smooth muscle, cause mucosal edema, hyperemia and produce viscid secretions, all resulting in reversible airway obstruction. The inflammation perpetuates itself by cell-to-cell communication and recruitment of more and more lymphocytes, eosinophils and neutrophils. Bronchial smooth muscle hypertrophy, increase in the population of mucus secreting cells and blood vessels occurs over time and damage to bronchial epithelium accentuates the hyperreactivity. Vagal discharge to bronchial muscle is enhanced reflexly. Airway remodeling progressively worsens the disease.

Chronic obstructive pulmonary disease (COPD) is also an inflammatory disease of the airways and lungs where inflammation is dominated by neutrophils, macrophages and cytotoxic lymphocytes. It is characterized by progressive emphysema (alveolar destruction) and bronchiolar fibrosis in variable proportions. Loss of bronchiolar elasticity leads to closure of smaller air tubes during expiration. The airway obstruction is accentuated during exercise causing shortness of breath. The expiratory airflow limitation does not fluctuate markedly over long periods of time, but there are exacerbations precipitated by respiratory infections, pollutants, etc. COPD is clearly related to smoking and characteristically starts after the age of 40. Quiting smoking reduces the rate of decline in lung function. Bronchodilators prevent closure of peripheral air tubes during expiration and afford symptomatic relief in COPD patients, but improvement in forced expiratory volume in 1st second (FEV_1) following inhalation of a shortacting β_2 agonist is generally <15%. An increasing part of airway obstruction is irreversible.

Approaches to Treatment

1. *Prevention of AG:AB reaction*—avoidance of antigen, hyposensitization—possible in extrinsic asthma and if antigen can be identified.
2. *Neutralization of IgE (reaginic antibody)*—Omalizumab.
3. *Suppression of inflammation and bronchial hyperreactivity*—corticosteroids.
4. *Prevention of release of mediators*—mast cell stabilizers.
5. *Antagonism of released mediators*—leukotriene antagonists, antihistamines, PAF antagonists.
6. *Blockade of constrictor neurotransmitter*—anticholinergics.
7. *Mimicking dilator neurotransmitter*—sympathomimetics.



8. *Directly acting bronchodilators*—methylxanthines.

SYMPATHOMIMETIC DRUGS (*see* Ch. 9)

Adrenergic drugs cause bronchodilatation through β_2 receptor stimulation → increased cAMP formation in bronchial muscle cell → relaxation. In addition, increased cAMP in mast cells and other inflammatory cells decreases mediator release. Since β_2 receptors on inflammatory cells desensitize quickly, the contribution of the latter action to the beneficial effect of β_2 agonists in asthma where airway inflammmation is chronic, is uncertain, and at best minimal. Adrenergic drugs are the mainstay of treatment of reversible airway obstruction, but should be used cautiously in hypertensives, ischaemic heart disease patients and in those receiving digitalis. The β_2 agonists are the most effective and fastest acting bronchodilators when inhaled.

Though adrenaline (β_1+β_2+α receptor agonist) and isoprenaline (β_1+β_2 agonist) are effective bronchodilators, it is the selective β_2 agonists that are now used in asthma to minimize cardiac side effects.

Salbutamol (Albuterol) A highly selective β_2 agonist; cardiac side effects are less prominent. Selectivity is further increased by inhaling the drug. Inhaled salbutamol delivered mostly from pressurized metered dose inhaler (pMDI) produces bronchodilatation within 5 min and the action lasts for 2–4 hours. It is, therefore, used to abort and terminate attacks of asthma, but is not suitable for round-the-clock prophylaxis. Muscle tremors are the dose related side effect. Palpitation, restlessness, nervousness, throat irritation and ankle edema can also occur. Hypokalaemia is a possible complication. Oral salbutamol undergoes presystemic metabolism in the gut wall, bioavailability is 50%. Oral salbutamol acts for 4–6 hours, is longer acting and safer than isoprenaline, but not superior in bronchodilator efficacy. Muscle tremor is the principal side effect.

Because of more frequent side effects, oral β_2 agonist therapy is reserved for patients who cannot correctly use inhalers or as alternative/adjuvant medication in severe asthma.

Dose: 2–4 mg oral, 0.25–0.5 mg i.m./s.c., 100–200 µg by inhalation.

ASTHALIN 2, 4 mg tab., 8 mg SR tab., 2 mg/5 ml syrup, 100 µg/metered dose inhaler; 5 mg/ml respirator

soln., 200 µg rota caps; CROYSAL 0.5 mg/ml inj, SALOL 2.5 mg/3 ml inj; VENTORLIN 2 mg/5 ml syr, 4 mg, 8 mg CR caps; DERIHALER 100 µg metered dose inhaler.

Single enantiomer preparation of R(–) salbutamol has also been marketed, because it is the active β_2 agonist and more potent bronchodilator which may produce fewer side effects than the racemate.

Terbutaline It is similar to salbutamol in properties and use.

Dose: 5 mg oral, 0.25 mg s.c., 250 µg by inhalation.

TERBUTALINE, BRICAREX 2.5, 5 mg tab., 3 mg/5 ml syrup, 0.5 mg/ml inj; MISTHALER 250 µg/metered dose, 10 mg/ml nebulizing soln.; BRICANYL 0.5 mg/ml inj, 2.5 mg, 5 mg tabs, 1.5 mg/5 ml syr.

Inhaled salbutamol and terbutaline are currently the most popular drugs for quick reversal of bronchospasm, but should not be used on a regular schedule. Regular use does not reduce bronchial hyperreactivity: may even worsen it. This may be responsible for the diminished responsiveness that occurs after long-term use of these drugs. Regular use also down regulates bronchial β_2 receptors. It is advised that patients requiring regular medication should be treated with inhaled steroids, with or without inhaled long acting β_2 agonists (e.g. salmeterol), while short acting β_2 agonist inhalers should be restricted to symptomatic relief of wheezing.

Bambuterol This biscarbamate ester prodrug of terbutaline is slowly hydrolysed in plasma and lungs by pseudocholinesterase to release the active drug over 24 hours. Reversible inhibition of pseudocholinesterase occurs in a dose dependent manner. It is indicated in nocturnal and chronic asthma as a single evening dose of 10–20 mg oral.

BAMBUDIL 10 mg, 20 mg tabs, 5 mg/5 ml oral soln; BETADAY 10, 20 mg tabs.

Salmeterol It is the first long acting selective β_2 agonist with a slow onset of action which is used by inhalation on a twice daily schedule for maintenance therapy, as well as for nocturnal asthma, but not for acute symptoms. It is more β_2 selective than salbutamol, as well as more lipophilic which probably accounts for its longer duration of action. Concern of asthma worsening due to regular use of inhaled β_2 agonists applies to salmeterol as well. Epidemiological studies indicate that risk of life-threatening asthma attacks may be increased by regular use of long acting β_2 agonists. Concurrent inhaled steroid appears to limit this risk. Excess mortality among asthmatics treated continuously with long acting β_2 agonist inhalations has been reported. Combined use of inhaled salmeterol with inhaled glucocorticoid produces effects equivalent to double dose of the corticoid alone. It is now advocated that long-acting β_2 agonists should be used only in combination with an inhaled steroid; combined formulations are available.

COPD: Long-acting β_2 agonists are superior to short-acting ones, and equivalent to inhaled anticholinergics in COPD. They reduce breathlessness by preventing expiratory closure of peripheral airways and abolishing the reversible component of airway obstruction.

SALMETER, SEROBID: Salmeterol 25 µg per metered dose inhaler; 2 puffs BD; severe cases 4 puffs BD; also SEROBID ROTACAPS 50 µg; 1–2 caps BD by inhalation.

SEROFLO—125/250/500 ROTACAPS: Salmeterol 50 µg + fluticasone 125 µg/250 µg/500 µg per rotacap

SEROFLO—125/250 INHALERS, COMBITIDE INHALER: Salmeterol 25 µg + fluticasone 125 µg/250 µg per puff MDI.

Indacaterol, Olodaterol and *Vilanterol* are new ultra long-acting selective β_2 agonists that have been approved for maintenance treatment of COPD. They are administered by inhalation in the powder form (indacaterol, vilanterol) or solution form (olodaterol) once a day. Cough, nasopharyngitis and dizziness are the side effects. Their efficacy and safety in the treatment of asthma has not been established.

Formoterol Another long-acting selective β_2 agonist which acts for 12 hrs when inhaled. In comparison to salmeterol, it has a faster onset of action. It is used on a regular morning-evening schedule for round-the-clock bronchodilatation.

Dose: 12–24 µg by inhalation twice daily.

FORATEC 12 µg rotacaps.

DERIFORM: 12 µg/puff MDI,

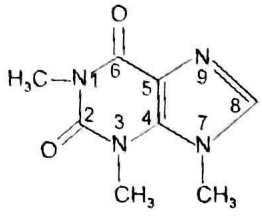
AIRTEC–FF, FORMOSONE: Formoterol 6 µg + fluticasone 125 µg or 250 µg/puff MDI

Ephedrine This oral sympathomimetic has $\alpha + \beta_1 + \beta_2$ actions which causes mild slowly developing bronchodilatation lasting for 3–5 hours. It is a constituent of older combination formulations and is used for mild to moderate chronic asthma. Because of low efficacy and frequent side effects, it is not preferred now.

METHYL XANTHINES

Theophylline and its compounds have been extensively used in asthma, but are now restricted to COPD and selected cases of asthma as adjuvant medication. Theophylline is one of

the three naturally occurring methylated xanthine alkaloids *caffeine*, *theophylline* and *theobromine*. The chemical relation between the three is depicted below:



THEOPHYLLINE (1,3, Dimethylxanthine)

THEOBROMINE (3,7, Dimethylxanthine)

CAFFEINE (1,3,7, Trimethylxanthine)

All three are consumed as beverages. The sources and average alkaloid contents of the beverages, as they are usually prepared are given below.

Source	Alkaloid content in beverage		
1. *Thea sinensis* (Tea leaves)	Caffeine Theophylline	50 mg 1 mg	in an average cup of tea
2. *Coffea arabica* (Coffee seeds)	Caffeine	75 mg	in an average cup of coffee
3. *Theobroma cacao* (Cocoa, chocolate)	Theobromine Caffeine	200 mg 4 mg	in an average cup of cocoa
4. *Cola acuminata* (Guru nuts)	Caffeine	30 mg	in 200 ml bottle of cola drink

All three alkaloids have qualitatively similar actions, but there are marked quantitative (Table 16.1) and pharmacokinetic differences.

Table 16.1: Comparative pharmacological actions of caffeine and theophylline

ACTION	CAFF.	THEO.
1. CNS—stimulation (low dose)	+++	++
—toxicity	++	+++
2. Heart—stimulation	++	+++
3. Blood vessel—relaxation	+	++
4. Bronchi—dilatation	+	+++
5. Kidney—diuresis	+	++
6. Sk. muscle—increased contractility	+++	++
7. Gastric mucosa—irritation	+	++
8. Phosphodiesterase inhibition	++	+++
9. Adenosine antagonism	++	+++

CAFF—Caffeine; THEO—Theophylline
Theobromine is of no therapeutic importance.

Pharmacological actions

1. *CNS* Caffeine and theophylline are CNS stimulants, primarily affect the higher centres. Caffeine 150–250 mg produces a sense of well-being, alertness, beats boredom, allays fatigue, thinking becomes clearer even when dullness has tended to prevail after a sustained intellectual effort. It tends to improve performance and increase motor activity. Caffeine is more active than theophylline in producing these effects. Higher doses cause nervousness, restlessness, panic, insomnia and excitement. Still higher doses produce tremors, delirium and convulsions. Theophylline has greater propensity to produce these adverse effects at higher doses and is definitely more toxic than caffeine.

These alkaloids also stimulate medullary vagal, respiratory and vasomotor centres. Vomiting at high doses is due to both gastric irritation and CTZ stimulation.

2. *CVS* Methylxanthines directly stimulate the heart and increase force of myocardial contractions. They tend to increase heart rate by cardiac action, but decrease it by causing vagal stimulation—net effect is variable. Tachycardia is more common with theophylline, but caffeine generally lowers heart rate. Cardiac output and cardiac work are increased. At high doses cardiac arrhythmias may be produced. While consumption of > 9 cups of coffee per day has been found to be associated with increased incidence of arrhythmias, moderate ingestion of caffeine (upto 500 mg/day) does not increase frequency or severity of cardiac arrhythmias even in patients with ischaemic heart disease or preexisting ventricular extrasystoles.

Methylxanthines, especially theophylline, dilate systemic blood vessels, including coronaries, by direct action: peripheral resistance is reduced. However, cranial vessels are constricted, especially by caffeine; this is one of the basis of its use in migraine.

Effect of methylxanthines on BP is variable and unpredictable—

- Vasomotor centre and direct cardiac stimulation—tends to raise BP.
- Vagal stimulation and direct vasodilatation—tends to lower BP.

Usually a rise in systolic and fall in diastolic BP is observed.

3. *Smooth muscles* All smooth muscles are relaxed; most prominent effect is exerted on bronchi, especially in asthmatics. Theophylline is more potent bronchodilator than caffeine. Slow and sustained dose-related bronchodilatation is produced, but the effect is much less marked compared to that of inhaled β_2 agonists. Vital capacity is increased. Biliary spasm is relieved, but effect on intestines and urinary tract is negligible.

4. *Kidney* Methylxanthines are mild diuretics. They act by inhibiting tubular reabsorption of Na^+ and water as well as increased renal blood flow and g.f.r. However, the action is brief.

5. *Skeletal muscles* Caffeine enhances contractile power of skeletal muscles. At high concentrations it increases release of Ca^{2+} from sarcoplasmic reticulum by direct action. At low doses, twitch response to nerve stimulation is augmented, while at toxic doses contracture is produced.

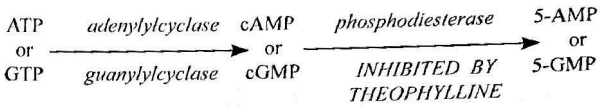
In addition, caffeine facilitates neuromuscular transmission by increasing ACh release. The central action of caffeine relieves fatigue and increases muscular work. Enhanced diaphragmatic contractility noted with theophylline in the therapeutic concentration range probably contributes to its beneficial effects in dyspnoea and COPD.

6. *Stomach* Methylxanthines enhance secretion of acid and pepsin in stomach, even on parenteral injection. They are also gastric irritants—theophylline more than caffeine.

7. *Metabolism* Caffeine and to a smaller extent theophylline increase BMR. Plasma free fatty acid levels are raised. They induce release of endogenous catecholamines, which appears to be partly responsible for these effects.

8. *Mast cells and inflammatory cells* Theophylline decreases release of histamine, other mediators and cytokines from mast cells and activated inflammatory cells. This may contribute to its therapeutic effect in bronchial asthma and COPD.

Mechanism of action Three distinct cellular actions of methylxanthines have been defined—
(a) Release of Ca^{2+} from sarcoplasmic reticulum, especially in skeletal and cardiac muscle.
(b) Inhibition of phosphodiesterase (PDE) which degrades cyclic nucleotides intracellularly.



Consequently the concentration of cyclic nucleotides is increased. Bronchodilatation, cardiac stimulation and vasodilatation occur and mediator release is inhibited when cAMP level rises in the bronchial/cardiac/vascular smooth muscle and in inflammatory cells, respectively. Several isoenzymes of the PDE superfamily exist in different tissues of which PDE3 and PDE4 appear to be involved in causing bronchodilatation and in inhibiting cytokine/inflammatory mediator release.

Some selective PDE4 inhibitors have been produced in the hope of finding an effective drug for asthma/COPD without the attendant toxicity as in theophylline. However, majority were clinically disappointing, but one of them *Roflumilast* has been approved by US-FDA for symptomatic treatment of COPD (but not bronchial asthma). It exerts antiinflammatory action, primarily in the lungs. Lung function is improved and risk of exacerbations is reduced. Most common adverse effect is diarrhoea. Psychiatric disturbances and weight loss are reported. Roflumilast appears to be a promising treatment option for moderate-to-severe cases of COPD. Theophylline is a subtype nonselective and weak PDE inhibitor.

(c) Blockade of adenosine receptors: adenosine acts as a local mediator in CNS, CVS and other organs. Adenosine contracts smooth muscles, especially bronchial; dilates cerebral blood vessels, depresses cardiac pacemaker and inhibits gastric secretion. Methylxanthines produce opposite effects.

Action (a) is exerted only at concentrations much higher than therapeutic plasma concentrations (range 5–20 μg/ml) of caffeine and theophylline. Action (b) and action (c) are exerted at concentrations in the therapeutic range and appear to contribute to bronchodilatation. Raised cAMP levels in inflammatory cells may

attenuate mediator release and promote eosinophil apoptosis, adding to the therapeutic effect of theophylline in asthma. Adenosine A_1 receptor antagonism is considered responsible for cardiac arrhythmias and seizures occurring in theophylline toxicity.

Recent evidence suggests that low concentrations of theophylline enhance histone deacetylation in airway inflammatory cells, suppressing proinflammatory gene transcription. Thus, even sub-bronchodilator doses of theophylline may exert some beneficial effect in asthma.

(Pharmacokinetics, adverse effects and uses of caffeine are described in Ch. 35)

Theophylline

Pharmacokinetics Theophylline is well absorbed orally; rectal absorption from suppositories is erratic. It is distributed in all tissues—crosses placenta and is secreted in milk (V 0.5 l/kg), 50% plasma protein bound and extensively metabolized in liver by demethylation and oxidation primarily by CYP1A2. Only 10% is excreted unchanged in urine. Elimination rate of theophylline varies considerably with age. At therapeutic concentrations, the t½ in adults is 7–12 hours. Children eliminate it much faster (t½ 3–5 hours) and elderly more slowly. In premature infants the t½ is markedly prolonged (24–36 hours). There are pronounced interindividual variations in plasma concentrations attained with the same dose.

Theophylline metabolizing enzymes are saturable, t½ is prolonged with higher doses (to as much as 60 hours) as kinetics changes from first to zero order. Plasma concentrations, therefore, increase disproportionately with dose.

Factors which need dose reduction are— age > 60 yr (× 0.6), CHF (× 0.6), pneumonia (× 0.4), liver failure (× 0.2–0.4).

Adverse effects Theophylline has a narrow margin of safety. Dose-dependent toxicity starts from the upper part of therapeutic concentration range (Fig. 16.1). Adverse effects are primarily referable to the g.i.t., CNS and CVS. Headache, nervousness and nausea are early symptoms. Children are more liable to develop CNS toxicity.

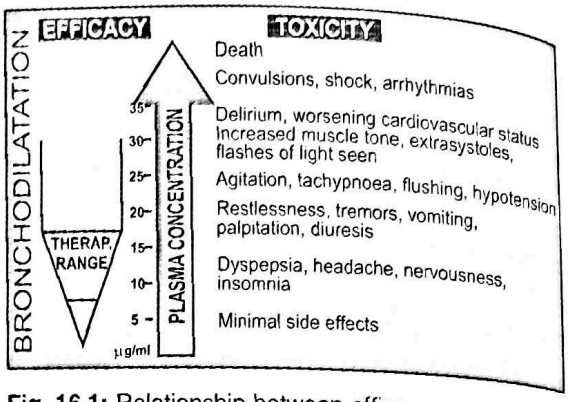


Fig. 16.1: Relationship between efficacy and toxicity of theophylline with its plasma concentration. The depicted concentration ranges are approximate

The irritant property of theophylline is reflected in gastric pain (with oral), rectal inflammation (with suppositories) and pain at site of i.m. injection. Rapid i.v. injection causes precordial pain, syncope and even sudden death—due to marked fall in BP, ventricular arrhythmias or asystole.

Interactions

1. Agents which enhance theophylline metabolism primarily by inducing CYP1A2 lower its plasma level: dose has to be increased by the factor given in parenthesis.
Smoking (1.6), phenytoin (1.5), rifampicin (1.5), phenobarbitone (1.2), charcoal broiled meat meal (1.3).
2. Drugs which inhibit theophylline metabolism and increase its plasma level are—erythromycin, ciprofloxacin, cimetidine, oral contraceptives, allopurinol; dose should be reduced to 2/3.
3. Theophylline enhances the effects of—furosemide, sympathomimetics, digitalis, oral anticoagulants, hypoglycaemics.
4. Theophylline decreases the effects of—phenytoin, lithium.
5. Aminophylline injection should not be mixed in the same infusion bottle/syringe with—ascorbic acid, chlorpromazine, promethazine, morphine, pethidine, phenytoin, phenobarbitone, insulin, penicillin G, tetracyclines, erythromycin.

Preparations and dose

(i) *Theophylline (Anhydrous)* 100–300 mg TDS (15 mg/kg/day) oral. THEOLONG 100, 200 mg SR cap., DURALYN-CR 400 mg continuous release cap, UNICONTIN 400 mg, 600 mg CR tabs, THEOBID 200 mg, 300 mg SR tabs. Only sustained release (SR) tab./caps. which produce effective blood levels for ~ 12 hours are used, because fast release tabs. produce high peak and low trough plasma concentrations.

Because solubility of theophylline is low, a number of soluble complexes and salts have been produced for oral and for parenteral use.

(ii) *Aminophylline (Theophylline-ethylenediamine; 85% theophylline)* water soluble, can be injected i.v. but not i.m. or s.c.—highly irritating. 250–500 mg oral or slow i.v. injection; children 7.5 mg/kg i.v.;
AMINOPHYLLINE 100 mg tab, 250 mg/10 ml inj.

(iii) *Hydroxyethyl theophylline (Etophylline, 80% theophylline)* water soluble; can be injected i.v. and i.m. (but not s.c.), less irritating; 250 mg oral/i.m./i.v.; DERIPHYLLIN 100 mg tab., 300 mg SR tab., 220 mg/2 ml inj.

(iv) *Theophylline ethanolate of piperazine* 250–500 mg oral or i.v.; CADIPHYLLATE 80 mg/5 ml elixir, ETOPHYLATE 125 mg/5 ml syrup.

Doxophylline A long-acting oral methylxanthine that is claimed not to interfere with sleep or stimulate gastric secretion.

Dose: 400 mg OD or BD, children 12 mg/kg/day; DOXOBID, DOXOVENT, DOXORIL 400 mg tab, 100 mg/5 ml syr.

The double salts/derivatives of theophylline are claimed to be less gastric irritant and better absorbed. However, anhydrous theophylline is completely absorbed and gastric irritancy of the salts is the same in terms of theophylline content.

Uses

1. *Bronchial asthma and COPD*: Theophylline may benefit by causing bronchodilatation as well as by decreasing release of inflammatory mediators, improving mucociliary clearance, stimulating respiratory drive and by augmenting diaphragmatic contractility. However, it has several limitations, *viz,* poor tolerability, narrow safety margin, lower efficacy and wide individual variability, because of which its use has declined. Sustained release theophylline is occasionally employed in mild-to-moderately severe asthma as an adjuvant drug, especially in patients with nocturnal asthma. It is more useful in COPD, and often added to other drugs.

Use of intravenous aminophylline in status asthmaticus is outmoded.

2. *Apnoea in premature infant*: Theophylline reduces the frequency and duration of episodes of apnoea that occur in some preterm infants in the first few weeks of life. Closely monitored oral or i.v. treatment is employed for 1–3 weeks. Caffeine is equally effective.

ANTICHOLINERGIC DRUGS (*see* Ch. 8)

Atropinic drugs cause bronchodilatation by blocking M_3 receptor mediated cholinergic constrictor tone. They act primarily in the larger airways (Fig. 16.2) which receive vagal innervation. However, some recent evidence points to presence of M_3 receptors on peripheral bronchiolar muscles as well, though these are not vagally innervated.

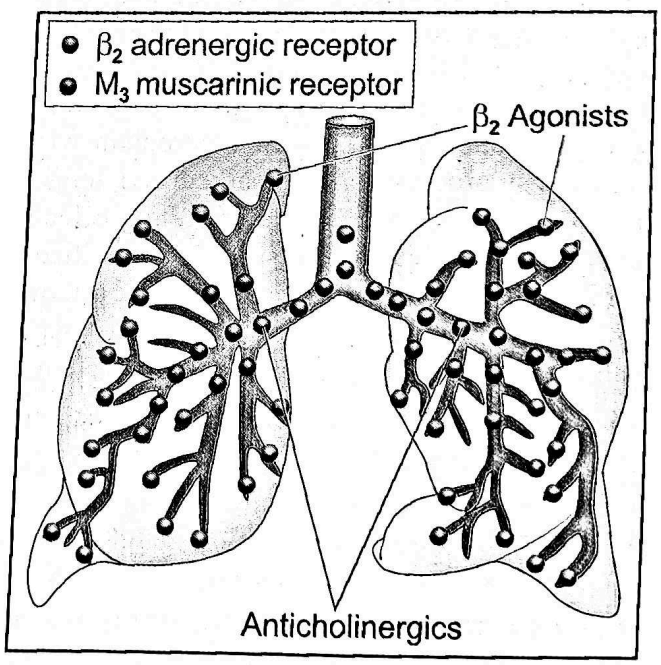


Fig. 16.2: Primary sites of bronchodilator action of inhaled adrenergic β_2 agonists and inhaled anticholinergics. Salbutamol mainly relaxes bronchiolar smooth muscle; Ipratropium blocks bronchoconstriction mainly in the larger airways

Ipratropium bromide is a short acting (duration 4–6 hours) inhaled anticholinergic bronchodilator, while *tiotropium bromide* is long acting (duration 24 hours). Administered as aerosol, they produce minimal antimuscarinic side effects due to poor systemic absorption. Anticholinergics are less efficacious than inhaled β_2 sympathomimetics in bronchial asthma. However, patients of asthmatic bronchitis, COPD and psychogenic asthma respond better to anticholinergics. Reflex cholinergic tone appears to be the major reversible component of airway obstruction in COPD. Inhaled anticholinergics are the bronchodilators of choice in COPD. Tiotropium is rated more effective than ipratropium in COPD; more suitable for severe cases (FEV_1<50% of predicted). No decline in its clinical efficacy has been noted over a period of 4 years. Regular maintenance therapy with long acting anticholinergic inhalations can also reduce episodes of COPD exacerbations.

The inhaled anticholinergics produce slower response than inhaled β_2 sympathomimetics and are better suited for regular prophylactic use (ipratropium 2–4 puffs 6 hourly or tiotropium 1 rotacap OD) than for quick relief of breathlessness. Combination of inhaled ipratropium with β_2 agonist produces more marked and longer lasting bronchodilatation; since their effects are additive. This synergism can be utilized for terminating severe exacerbations of asthma or COPD. Nebulized ipratropium mixed with salbutamol is employed in refractory asthma. Combined formulations are available.

Salbutamol + Ipratropium

DUOLIN INHALER, COMBIMIST INHALER — 100 µg + 20 µg per metered dose
DUOLIN ROTACAP: — 200 µg + 40 µg per rotacap
DUOLIN RESPULES, COMBIMIST RESPULES — 2.5 mg + 500 µg in 2.5 ml solution

Glycopyrronium Br., another long acting quaternary anticholinergic, has been recently approved (50 µg inhalation powder per cap) as once a day maintenance treatment of COPD.

LEUKOTRIENE ANTAGONISTS

Since it was realized that cysteinyl leukotrienes (LT-C_4/D_4) produced by macrophages, eosinophils and other inflammatory cells in the lungs are important mediators of bronchial asthma, efforts were made to develop their antagonists and synthesis inhibitors. Two *cys*LT_1 receptor antagonists *montelukast* and *zafirlukast* are now established drugs for asthma.

Montelukast and Zafirlukast Both have similar actions and clinical utility. They competitively antagonize *cys*LT_1 receptor (*see* p. 205) mediated bronchoconstriction, airway mucus secretion, increased vascular permeability and recruitment of eosinophils. Bronchodilatation, reduced sputum eosinophil count, suppression of bronchial inflammation, mucus and hyperreactivity are noted in asthma patients. Parameters of lung function show improvement to variable degree. Episodes of asthma exacerbations are reduced. Some studies have found that certain patients are 'responders' while others are 'nonresponders' to anti-LT therapy. This may reflect differing extent of involvement of LTs as asthma mediators.

Montelukast and zafirlukast are indicated for prophylactic therapy of mild-to-moderate asthma as alternatives to inhaled glucocorticoids. Though efficacy is low, they may obviate need for inhaled steroids, and may be more acceptable in children. In severe asthma, they have additive effect with inhaled steroids, may permit reduction in steroid dose and need for rescue β_2 agonist inhalations. However, the additive effect of long-acting β_2 agonists is greater. Montelukast/zafirlukast are not to be used for terminating asthma episodes. The *cys*LT_1 antagonists are effective in aspirin-induced asthma and exercise induced asthma, but are of no value in COPD. They afford relief in perennial allergic rhinitis as well.

Both montelukast and zafirlukast are very safe drugs; produce few side effects like abdominal pain, headache and rashes. Eosinophilia and neuropathy are infrequent. Few cases of Churg-Strauss syndrome (vasculitis with eosinophilia) have been reported.

Montelukast and zafirlukast are well absorbed orally, highly plasma protein bound and

metabolized by CYP2C9 (montelukast by CYP3A4 as well). The plasma t½ of montelukast is 3–6 hours, while that of zafirlukast is 8–12 hours.

Montelukast: 10 mg OD; children 2–5 yr 4 mg OD, 6–14 yr 5 mg OD to be taken in the evening.

EMLUKAST, MONTAIR, VENTAIR 4 mg, 5 mg, 10 mg tabs

Orally disintegrating strips (ODS) of montelukast 4 mg, 5 mg and 10 mg have also been approved for marketing.

Zafirlukast: 20 mg BD; children 5–11 yr 10 mg BD;

ZUVAIR 10 mg, 20 mg tabs.

Zileuton It is a 5-LOX inhibitor, blocks LTC_4/D_4 as well as LTB_4 synthesis. It therefore has the potential to prevent all LT induced responses including those exerted by activation of *cys*LT_1 receptor. However, clinical efficacy in asthma is similar to that of montelukast. The duration of action of zileuton is short and it has hepatotoxic potential. These limitations have restricted its use.

MAST CELL STABILIZERS

Sodium cromoglycate (Cromolyn sod.)

It is a synthetic chromone derivative which inhibits degranulation of mast cells (as well as other inflammatory cells) by trigger stimuli. Release of mediators of asthma like histamine, LTs, PAF, interleukins, etc. is restricted. The basis of this effect is not well understood, but may involve a delayed Cl^- channel in the membrane of these cells inhibiting activation. Long-term treatment decreases the cellular inflammatory response; bronchial hyperreactivity is reduced to variable extents. Bronchospasm induced by allergens, irritants, cold air and exercise may be attenuated. Cromoglycate is not a bronchodilator and does not antagonize constrictor action of histamine, ACh, LTs, etc. Therefore, it is ineffective if given during an asthmatic attack.

Sod. cromoglycate is not absorbed orally. For asthma it is administered as an aerosol through metered dose inhaler. Only a small fraction of the inhaled drug is absorbed systemically; this is rapidly excreted unchanged in urine and bile.

Uses

1. *Bronchial asthma:* Sod. cromoglycate is rarely used now as a prophylactic in mild-to-moderate asthma. Decrease in the frequency and severity of attacks is more likely in extrinsic (atopic) and exercise-induced asthma, especially in younger patients. Therapeutic benefit (when it occurs) develops slowly over 2–4 weeks and lasts 1–2 weeks after discontinuing.
2. *Allergic rhinitis:* Cromoglycate is not a nasal decongestant, but regular 4 times daily use as a nasal spray produces some symptomatic improvement in many patients after 4–6 weeks.
3. *Allergic conjunctivitis:* Regular use as eye drops is beneficial in some chronic cases.

FINTAL inhaler: 1 mg and CROMAL 5 mg/puff metered dose inhaler; 2 puffs 4 times daily.

FINTAL nasal spray: 2% CROMAL AQ 2.8 mg/dose; 2 squeezes in each nostril QID.

FINTAL eye drops: 2% CROMAL 2% and 4% eye drops; 1 drop in each eye QID.

Adverse effects Because of poor aqueous solubility, absorption of cromoglycate is negligible; systemic toxicity is minimal. Bronchospasm, throat irritation and cough occurs in some patients, especially with fine powder inhalation.

Ketotifen It is an antihistaminic (H_1) with some cromoglycate like action. Stimulation of immunogenic and inflammatory cells (mast cells, macrophages, eosinophils, lymphocytes, neutrophils) and mediator release are reduced. Ketotifen is not a bronchodilator. It is infrequently used now; may be tried in patients with multiple allergic disorders.

Ketotifen is generally well tolerated. Sedation and dry mouth are common. Other side effects are dizziness, nausea, weight gain.

Dose: 1–2 mg BD; children 0.5 mg BD.

ASTHAFEN, 1 mg tab, 1 mg/5 ml syrup; KETOVENT 1 mg tab, KETORID 0.25% eye drops.

CORTICOSTEROIDS

Glucocorticoids are not bronchodilators. They benefit by inhibiting inflammatory cytokine production and eosinophilic, lymphocytic infiltration of lungs. They also reduce bronchial hyperreactivity, mucosal edema and suppress inflammatory response to AG:AB reaction or to other trigger stimuli. Their mechanism of action is detailed in Ch. 20.

The realization that asthma is primarily an inflammatory disorder which, if not controlled, accentuates with time; as well as the availability of inhaled corticosteroids (ICS) that produce few adverse effects, has led to early introduction and more extensive use of glucocorticoids in asthma. Corticosteroids afford more complete and sustained symptomatic relief than bronchodilators and other drugs. They improve airflow, reduce asthma exacerbations and may influence airway remodeling, retarding disease progression. They also increase airway smooth muscle responsiveness to β_2 agonists and reverse refractoriness to these drugs. However, long-term systemic steroid therapy has its own adverse effects which may be worse than asthma itself.

Systemic corticosteroid therapy

Systemic steroid therapy is resorted to in asthma under the following two situations:

(i) *Severe chronic asthma:* not controlled by bronchodilators and ICS, or when there are frequent recurrences of increasing severity; start with prednisolone 20–60 mg (or equivalent) daily; attempt dose reduction after 1–2 weeks of good control and finally try shifting the patient onto an ICS. Only few patients require long term oral steroids—in them dose should be kept at minimum.

In patients requiring long-term glucocorticoid therapy, alternative treatment with immunosuppressants like methotrexate (low dose) or cyclosporine has been tried.

(ii) *Status asthmaticus/acute asthma exacerbation:* asthma attack not responding to intensive bronchodilator therapy: start with high dose of a rapidly acting i.v. glucocorticoid which generally acts in 6–24 hours—shift to oral therapy for 5–7 days and then discontinue abruptly or taper rapidly.

COPD A short course (1–3 week) of oral glucocorticoid may benefit some patients of COPD during an exacerbation.

Inhaled corticosteroids

These are glucocorticoids with high topical and low systemic activity (due to poor absorption and/or marked first pass metabolism). *Beclomethasone dipropionate, Budesonide, Fluticasone* and *Ciclesonide* are the commonly used ICS. Because airway inflammation is present in early mild disease as well, and bronchial remodeling starts developing from the beginning, it has been advocated that ICS should be the 'step one' for all asthma patients. However, currently ICS are not considered necessary for patients with mild and episodic asthma. They are indicated in all cases of persistent asthma when inhaled β_2 agonists are required almost daily or the disease is not only episodic. Start with 100–200 µg BD, titrate dose upward every 3–5 days; max. 400 µg QID, beyond which no further benefit generally occurs.

Inhaled corticosteroids suppress bronchial inflammation, increase peak expiratory flow rate, reduce need for rescue β_2-agonist inhalations and prevent episodes of acute asthma. However, they have no role during an acute attack or in status asthmaticus. Peak effect is seen after 4–7 days of instituting ICS and benefit persists for a few weeks after discontinuation. They can be started in patients who in the past have required oral corticosteroids as well as in those with no such history. Patients who are to be switched over from oral steroid should receive ICS in addition for 1–2 weeks before oral steroid is tapered, otherwise steroid withdrawal may manifest (precipitation of asthma, muscular pain, lassitude, depression, hypotension). This confirms lack of systemic activity of ICS (at doses < 600 µg/day). Long-term experience has shown that efficacy of ICS is maintained and reinstitution of oral steroids is seldom needed. Short courses of oral steroids may be added during periods of exacerbation. Some patients who remain well controlled for long periods can even stop ICS without worsening of asthma.

COPD: The airway inflammation in COPD is not very responsive to corticosteroids. As such, only high dose ICS are beneficial in advanced COPD with frequent exacerbations. They should not be used in early/mild cases. There is no proof that they retard progression of COPD.

Adverse effects Hoarseness of voice, dysphonia, sore throat, asymptomatic or symptomatic oropharyngeal candidiasis are the most common side effects. These can be minimized by the use of a spacer, and by gargling after every dose (to wash off the drug deposited on oral and pharyngeal mucosa). Oral candidiasis can be prevented as well as treated by topical nystatin/clotrimazole. There is no evidence of mucosal damage or increased incidence of chest infections, even on prolonged use of ICS.

Systemic effects of long-term ICS are clinically relevant only at doses > 600 µg/day. The significant ones are—mood changes, osteoporosis, growth retardation in children, early cataract,

bruising, petechiae, hyperglycaemia and pituitary-adrenal suppression. Several reports of adrenal crisis have appeared, especially in children, during stress (of an infection, etc).

Inhaled steroids are safe during pregnancy.

Beclomethasone dipropionate

BECORIDE 50, 100, 250 µg per puff inhaler.
AEROCORT INHALER 50 µg/metered dose inhaler with salbutamol 100 µg.
ECONASE 0.05% nasal spray.

Intranasal spray (50 µg in each nostril BD–TDS) is effective in perennial rhinitis.

Budesonide It is a nonhalogenated glucocorticoid with high topical: systemic activity ratio (greater first pass metabolism than beclomethasone). Small fraction that is absorbed is rapidly metabolized; less systemic effects are noted. It may be preferred in more severe cases.

PULMICORT 100, 200, 400 µg/metered dose inhaler, 0.25 mg/ml and 0.5 mg/ml respules.
FORACORT: Formoterol 6 µg + Budesonide 100 µg/200 µg rotacaps.
RHINOCORT 50 µg per metered dose nasal spray; BUDENASE AQ 100 µg metered dose aqueous nasal spray; 200–400 µg/day by intranasal spray for prophylaxis and treatment of seasonal and perennial allergic or vasomotor rhinitis, nasal polyposis; initially 2 puffs in each nostril every morning, maintenance 1 puff in each nostril in the morning.

Nasal irritation, sneezing, crusting, itching of throat and dryness may occur, especially in the beginning. It is contraindicated in presence of infection or nasal ulcers.

Fluticasone propionate This inhaled glucocorticoid has high potency (about double of beclomethasone); longer duration and negligible oral bioavailability. The dose swallowed after inhalation has little propensity to produce systemic effects. At high doses, systemic effects may be due to absorption from the lungs. It may be preferred in patients requiring higher doses.

FLOHALE INHALER 25 µg, 50 µg, 125 µg per actuation.
FLOHALE ROTACAPS 50 µg, 100 µg, 250 µg rotacaps.
FLOMIST 50 µg per actuation nasal spray.

Flunisolide This topical steroid is available for prophylaxis and treatment of seasonal and perennial rhinitis.

SYNTARIS 25 µg per actuation nasal spray; one spray in each nostril 2–3 times daily.

Ciclesonide This ICS utilizes a novel approach to improve topical: systemic activity ratio. It is a prodrug that is cleaved by esterases in the bronchial epithelium to release the active moiety. Though it is absorbed from the lungs, oral bioavailability is <1%. In the circulation it is extensively bound to plasma proteins, further minimizing exposure of tissue cells to the free and active drug.

CICLEZ 80 µg and 160 µg per metered dose inhaler with HFA propellant for once daily use, preferably in the evening.

The dose of the ICS depends upon the particular compound, its formulation, *viz.* metered dose inhaler (MDI) or dry powder inhaler (DPI), and the severity of asthma. The daily doses for each preparation can be categorized into low dose, medium dose or high dose, as presented in Table 16.2.

ANTI-IgE ANTIBODY

Omalizumab It is a humanized monoclonal antibody against IgE. Administered s.c., it neutralizes free IgE in circulation without activating mast cells and other inflammatory cells. On antigen challenge, little IgE is available bound to the mast cell surface receptors ($F_{\varepsilon}R1$) to trigger mediator release (*see* Fig. 11.2) and cause bronchoconstriction. In severe extrinsic asthma, omalizumab has been found to reduce exacerbations and steroid requirement. No benefit has been noted in nonallergic asthma. It is very expensive;

Table 16.2: Low, medium and high doses of inhaled corticosteroids for adults and adolescents (>11 years age)

Inhaled corticosteroid	*Daily doses (µg/day)*			
	Low	*Medium*	*High*	*Maximum*
1. Beclomethasone dipropionate—MDI	200–400	400–800	> 800	1600
2. Budesonide—MDI	200–400	400–800	> 800	1600
3. Fluticasone propionate—MDI	100–250	250–500	> 500	1000
—DPI	200–400	400–800	> 800	2000
4. Ciclesonide—MDI	80–160	160–320	> 320	640

MDI—Metered dose inhaler; DPI—Dry powder inhaler

use is reserved for resistant asthma patients with positive skin tests or raised IgE levels who require frequent hospitalization. It is being tried in other allergic diseases as well.

INHALED ASTHMA MEDICATION

Four classes of antiasthma drugs, *viz.* β_2 agonists, anticholinergics, cromoglycate and glucocorticoids are available for inhalational use. They are aimed at delivering the drug to the site of action so that lower dose is needed and systemic side effects are minimized. Faster action of bronchodilators can be achieved compared to oral administration. Most asthma patients are now maintained on inhaled medication only. Aerosols are of two types:

(i) use drug in solution: pressurized metered dose inhaler (MDI), nebulizers.

(ii) use drug as dry powder (DPI) spinhaler, rotahaler.

Pressurized metered dose inhalers use hydrofluroalkane (HFA) propellants and deliver a specified dose of the drug in spray form per actuation. Use of chlorofluorocarbon (CFC) propellants is now banned due to their effect on ozone layer. Device actuation has to be properly coordinated with deep inspiration, which many patients are unable to learn. A large volume 'spacer' (chamber interposed between the inhaler and the patient's mouth) can be used to improve drug delivery by obviating the need for precise coordination. Moreover, larger particles settle on the walls of the spacer reducing the fraction that deposits in the throat and is later swallowed. Local complications (candidiasis with inhaled steroids) as well as systemic exposure are reduced. Jet nebulizers produce a mist of the drug solution generated by pressurized air or oxygen which can be inhaled through a mouth piece, face mask or in a tent. Ultrasonic nebulizers use electrically vibrated crystals; pressurized air/oxygen is not needed. Metered dose inhalers are convenient handheld devices which can be carried along, while nebulizers are used at patient's bed side. Nebulizers are preferred for severe episodes of asthma as well as for children and elderly. More than one drug can be nebulized simultaneously.

Dry powder inhalers (DPIs) are also portable devices in which the capsule (rotacap) containing the drug is punctured/cut across and the powder is aerosolized by the inspiratory air flow of the patient. It requires high velocity inspiration which children, elderly and the very sick may not be capable of. The dry powder is also more likely to irritate the air passage—producing cough and bronchoconstriction.

Efficacy of aerosolized drug depends on the particle size: 1–5 μm diameter particles deposit on the bronchioles and effectively deliver the drug. Larger particles settle on the oropharynx, while very fine particles do not settle anywhere and are exhaled out. On an average only ~10% of the inhaled drug reaches the site of action. A considerable fraction is swallowed. Therefore, to minimize systemic action, the drug should have low oral bioavailability. Spacer devices improve inhaled to swallowed drug ratio. Slow and deep inbreathing after device actuation and holding the breath after inhalation also enhances efficacy of the inhaler. Greater proportion of smaller particles in a relatively narrow band width of 1–2 μM can be generated using the newer HFA propellant based MDIs. This improves delivery of the drug to the smaller bronchioles. However, systemic absorption from the peripheral lungs is also more.

CHOICE OF TREATMENT

The severity of asthma symptoms ranges from transient respiratory difficulty to incapacitating breathlessness, and characteristically fluctuates over time. The goals of drug therapy in asthma are to relieve the symptoms of breathlessness and wheezing, prevent recurrent exacerbations and to minimise need for emergency hospitalizations. A stepwise approach to assist the clinical decision-making in the treatment of asthma as per needs of the patient has been advocated.The following guidelines summarise the recommendations of the British Thoracic Society (2012)* as well as that of the National Asthma Education and Prevention Programme. Expert Panel Report (2007).[£] After the asthma is under control for 3–6 months, an attempt to reduce medication should be made in a stepwise manner.

1. *Mild episodic asthma* (symptoms less than once daily, normal in between attacks): Inhaled short-acting β_2 agonist at onset of each episode. Since asthma is intermittent, it does not require continuous prophylactic therapy (Step-1).

2. *Seasonal asthma* Start regular low-dose ICS 3–4 weeks before anticipated seasonal attacks and continue till 3–4 weeks after the season is over. Alternatively oral montelukast/zafirlukast may be tried, especially in children. Treat asthma episodes with inhaled short-acting β_2 agonist.

3. *Mild chronic (persistent) asthma with occasional exacerbations* (symptoms once

*British Thoracic Society and Scottish Intercollegiate Guidelines Network (Jan 2012; www.brit.thoracic.org.uk)

[£]National Asthma Education and Prevention Programme. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Institute of Health Pub No. 08-4051 (2007).

daily or so, subnormal ventilatory performance). Regular low-dose ICS (Step-2). Alternatively, montelukast/zafirlukast as above; but they may not be effective in some patients, or may afford less complete relief. Oral theophylline is a less satisfactory option. Episode treatment with inhaled short-acting β_2 agonist.

4. *Moderate asthma with frequent exacerbations* (attacks affect activity, occur > 1 per day or mild baseline symptoms persist). Low doses of ICS + inhaled long-acting β_2 agonist (Step-3), or medium dose ICS alone. In view of the potential risk of prolonged treatment with long-acting β_2 agonists, attempt should be made to discontinue it after maintaining asthma control over few months. Leukotriene antagonists may be tried in place of long-acting β_2 agonists, but their additive effect is less marked. Sustained release theophylline may be used as alternative additional drug to long-acting β_2 agonists, especially in nocturnal asthma.

5. *Severe asthma* (continuous symptoms; activity limitation; frequent exacerbations/ hospitalization) Regular high dose ICS through a large volume spacer device + inhaled long-acting β_2 agonist (salmeterol) twice daily. Additional treatment with one or more of the following (Step-4):

Leukotriene antagonist/sustained release oral theophylline/sustained release oral β_2 agonist.

Rescue treatment with short-acting inhaled β_2 agonist.

In patients not adequately controlled or those needing frequent emergency care—institute oral steroid therapy (Step-5) while continuing long acting β_2 inhalations and ICS. Efficacy of oral steroids is proven, but should be the last resort. Attempt to withdraw it should be made periodically. The British guidelines recommend continuing high dose ICS along with oral steroids.

6. *Status asthmaticus/Refractory asthma*

Any patient of asthma has the potential to develop acute severe asthma which may be life-threatening. Upper respiratory tract infection is the most common precipitant.

- Hydrocortisone hemisuccinate 100 mg (or equivalent dose of another glucocorticoid) i.v. *stat,* followed by 100–200 mg 4–8 hourly infusion; may take upto 6 hours to act.
- Nebulized salbutamol (2.5–5 mg) + ipratropium bromide (0.5 mg) intermittent inhalations driven by O_2.
- High flow humidified oxygen inhalation.
- Salbutamol/terbutaline 0.4 mg i.m./s.c. may be added, since inhaled drug may not reach smaller bronchi due to severe narrowing/ plugging with secretions.
- Intubation and mechanical ventilation, if needed.
- Treat chest infection with intensive antibiotic therapy.
- Correct dehydration and acidosis with saline + sod. bicarbonate/lactate infusion.

Aminophylline 250–500 mg diluted in 20–50 ml glucose (5%) solution injected i.v. over 20–30 min had been routinely used, but recent evidence shows that it does not afford additional benefit; may even produce more adverse effects; use is restricted to resistant cases.

Some antiasthma combinations

BRONKOPLUS: Salbutamol 2 mg, anhydrous theophylline 100 mg tab., also per 5 ml syrup.

BRONKOTUS: Bromhexine 8 mg, salbutamol 2 mg tab., also syrup—bromhexine 4 mg, salbutamol 2 mg per 5 ml.

TERPHYLIN: Terbutaline 2.5 mg, etophylline 100 mg tab, and per 10 ml syr.

THEO ASTHALIN: Salbutamol 2 mg, theophylline anhydrous 100 mg tab, and per 10 ml syr.

THEO ASTHALIN-SR: Salbutamol 4 mg, theophylline 300 mg SR tab.

THEO BRIC: Terbutaline 2.5 mg, theophylline 100 mg tab.

THEOBRIC SR: Terbutaline 5 mg, theophylline 300 mg SR tab.

DURASALYN-CR: Salbutamol 4 mg, theophylline 200 mg CR cap.

PROBLEM DIRECTED STUDY

16.1 A 30-year-old man presents with complaints of episodic breathlessness, often following exertion. One to three episodes occur daily and are accompanied by wheezing. Every 2–3 days, he wakes up at night with breathlessness. The episodes subside on taking 2 puffs of the inhaler prescribed by his family doctor (salbutamol 100 µg/puff). Lately, the episodes have become more frequent and are limiting his activities to some extent. Spirometry revealed FEV_1 to be 70% of predicted value at baseline, and 88% after 2 puffs of salbutamol (100 µg/puff) inhalation. He is diagnosed to be a case of moderate bronchial asthma.

(a) Is this patient receiving adequate treatment for his condition, or some other drug/drugs need to be used? If so, what should be the first line treatment for this patient?
(b) In case another drug is prescribed, should this patient continue to use salbutamol inhalations to relieve episodes of breathlessness, when they occur?
(c) Which alternative drugs can be used in this patient.

16.2 A 60-year-old male patient of moderately severe chronic obstructive pulmonary disease (COPD) with FEV_1 45% of predicted, who has quit smoking for the last 5 years, and is maintained on—Ipratropium br. 20 µg/puff metered dose inhaler, 2 puffs 3 times a day, and Theophylline 400 mg SR tab. twice a day, developed sore throat and fever. He was prescribed—

Tab Erythromycin 250 mg, one tab 4 times a day for 5 days
Tab Paracetamol 500 mg 3 times a day till fever persists.

After 3 days he presented with pain in epigastrium, restlessness, irritability, inability to sleep, palpitation, tremor of fingers and hand, and had vomited twice. His fever had subsided and throat was better.

(a) What could be the reason for his recent illness?
(b) Could this illness be prevented, if so, how?
(see Appendix-1 for solution)