Program	B. Pharmacy
Semester	VI
Subject /Course	Pharmacology-III
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Module No.	01
Module Title	Pharmacology of drugs acting on Respiratory system and GIT
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Learning Outcome of Module-1

LO	Learning Outcome (LO)	Course Outcome Code
LO1	Know about basics of respiratory and gastrointestinal tract, different diseases associated with them.	BP602.1
LO2	Different drugs and their pharmacological actions on respiratory and gastrointestinal tract.	BP602.1
LO3	Know about the different classes of the drugs with their mechanism of action, therapeutic uses and adverse effects.	BP602.1
LO4	To Understand the Pharmacokinetics and pharmacological action of different class of drugs.	BP602.1

Module Content Table

Topic
• Pharmacology of Anti -asthmatic drugs • Drugs used in the management of COPD • Expectorants and antitussives • Nasal decongestants • Respiratory stimulants • Antiulcer agent • Drugs for constipation and diarrhoea • Appetite stimulants and suppressants, • Digestants and carminatives, • Emetics and anti-emetics.

ANTI -ASTHMATIC DRUGS

Asthma is most common respiratory tract infection. It is the reversible obstruction of large and small airways. Bronchial asthma is characterized by hyperresponsiveness of tracheo-bronchial smooth muscle to a variety of stimuli, resulting in narrowing of air tubes, often accompanied by increased secretions, mucosal edema and mucus plugging.

1. Inflammation
2. Hyper reactivity
3. Bronchospasm

Types of Bronchial Asthma

1. Extrinsic Asthma: (allergic) It is mostly episodic, less prone to status asthmaticus

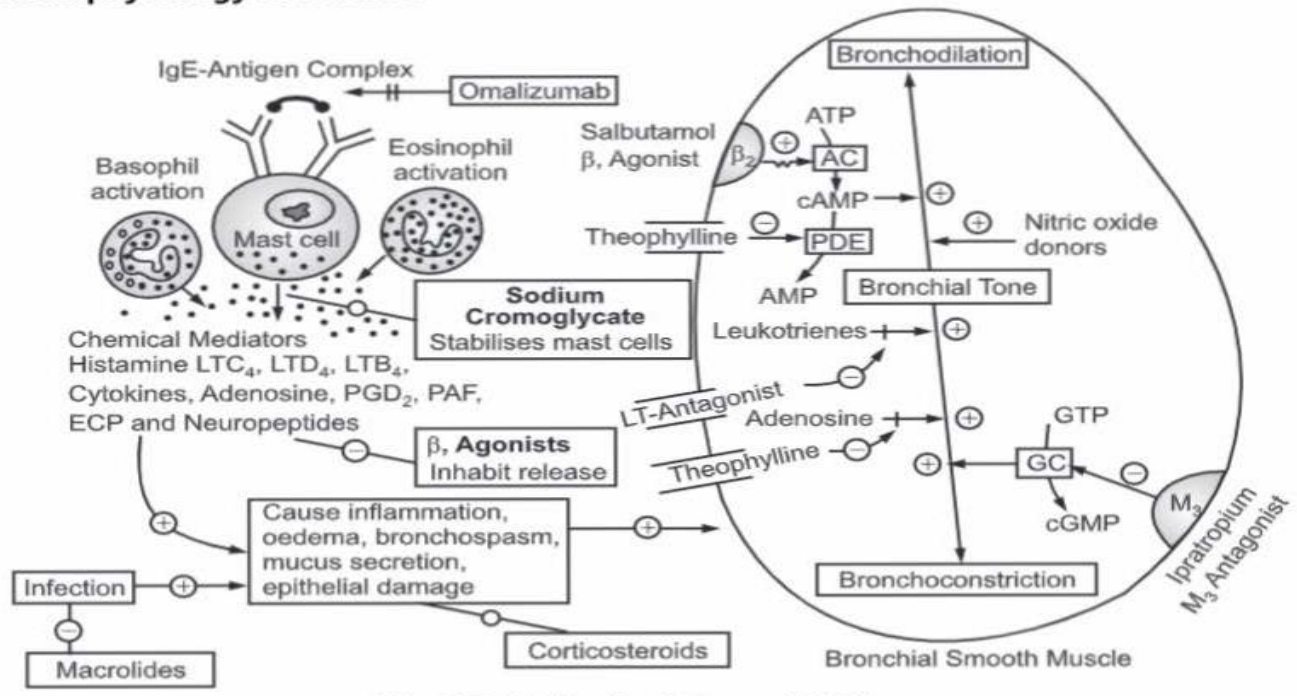
Atopic (immediate due to IgE antibody).

Nonatopic delayed for some hours, associated with production of precipitating antibodies

2. Intrinsic Asthma

It tends to be perennial, status asthmaticus is more common. Associated with COPD.

Pathophysiology of Asthma:



pathophysiology of asthma is depicted in fig. Antigen like pollen grains sensitize individuals by promtoting the production of IgE type of antibodies which remain circulating in the blood or are attached to the mast cells of nasal/ bronchial tissues and basophils. On subsequent exposure to the same antigen, there is an antigen-antibody reaction on the surface of lung mast cells causing release of mediators like histamine, serotonin, PGD2 and leukotrienes like LTC4/LTD4. Both leukotriene are powerful broncho-constrictors.

In the delayed phase, mast cells release leukotrienes like LTB4 and cytokines like IL-4, IL-5 and IL-13. Eosinophils, basophils and alveolar macrophages are rich in these mediators. There are few other mediators like adenosine, neurokinin-A and PAF which together cause inflammation, increased vascular permeability, chemotaxis of neutrophils and eosinophils, broncho-constriction and bronchial hypersensitivity.

Classification of Anti-asthmatic Drugs:

There are six classes of anti-asthmatic drugs. Details of these classes, along with sub-classification, wherever applicable along with relevant examples are mentioned below:

- Bronchodilators
  - Selective β2 agonists like Salbutamol
  - Non-selective sympathomimetics like Ephedrine
  - Anti-cholinergics like Ipratrotium
  - Methylxanthines like Theophylline
- Corticosteroids
  - Orally active corticosteroids like Prednisolone
  - Parenteral corticosteroids like Hydrocortisone
  - Inhalational corticosteroids like Beclomethasone
- Mast cell stabilisers like
  - Sodium cromoglycate
- Leukotriene modulators
  - 5-Lipoxygenase inhibitor like Zileuton
  - Cysteinyl leukotriene-antagonist like Zafirlukarst
- Monoclonal anti-IgE antibody like
  - Omalizumab
- Miscellaneous like
  - Nitric oxide donors

Sympathomimetics :Short Acting: Salbutamol, Terbutaline Long Acting: Formeterol, Salmetrol, Bambuterol Mechanism of Action

1. Beta-2 adrenoceptor agonist, when administered binds beta 2 receptors

- ✓ Stimulation of adenylate cyclase
- ✓ Increase cAMP
- ✓ Bronchodilation and decreased muscular tone

Methylxanthine: Aminophylline, Theophylline

Mechanism of Action

1. Inhibit Phosphodiestrase Enzyme (which catalyzes breakdown of cAMP).

- ✓ Increase cAMP
- ✓ Dephosphorylation of MLC
- ✓ Bronchodilation
- ✓ Increased intracellular calcium

Blockade of adenosine receptors: Decrease contractility of bronchiolar smooth muscles

Anticholinergics: Ipratropium, Oxytropiu, Tiotropium

Mechanism of Action

Blockade of muscarinic receptors present in bronchi and bronchioles

Decrease mucus viscosity

Increase mucociliary clearance

Leukotriene Receptor Antagonists

Montelukast – oral

Zafirlukast – (Cingular) oral administration for control of asthma

Leukotrines are products of arachidonic acid metabolism. They are released at the site of inflammation producing bronchoconstriction having contributory effect to inflammation and bronchoconstriction.

Mechanism of Action

Montelukast and Zafirlukast are competitive antagonists.

Inhibits cysteinlyl leukotriene Cys LT1 receptor relieving bronchospasm and bronchoconstriction.

Inhibit physiologic actions of LTC4, LTD4, LTE4

One drug blocks synthesis of 5 lipooxygenase and is hepatotoxic **Zileuton.** Half like is 2.5 hours

Drug Interactions

Zafirleukast has drug interaction with warfarin sodium, leading to increased prothrombin time, thus dose has to be monitored. Monteleukast is commonly used. ***Mast Cell Stabilizers***

- Na chromoglycate inhalation Nedocromil
- Ketotifen- (5HT action) oral Nedocromil and Ketotifen are not bronchodilators, not having direct effect. They are ineffective once antigen antibody reaction takes place.

Mechanism of Action

1. Inhibit transmembrane influx of Ca provoked by antigen antibody interaction on the surface of mast cells. This is prophylactic use and have to be given before antigen enters.
2. Stabilize mast cells membrane and inhibit release of chemical mediators
3. Depress exaggerated neuronal reflexes triggered by stimulation of irritant receptors
4. Depress axonal reflexes which release inflammatory neuropeptides.
5. Inhibit release of cytokines from T-CELLS

Corticosteroids

- Hydrocortisone **I/V**
- Prednisolone **oral**
- Betamethosone
- Beclomethasone **inhalation**
- Budesonide
- **Flucitasone** having affinity for glucocorticoids receptors in airways

Mechanism of Action

- Anti inflammatory action
- Decrease mucosal oedema, mucus secretion and reduce capillary permeability
- Stabilize mast cells
- Block immune response, decrease antibody formation
- Antagonise histaminergic and cholinergic responses

- Enhance beta-2 adrenoceptor responsiveness to agonists (Catecholamines)

Ciclesonide

Prodrug, when absorbed drug is acted upon by esterases in bronchial epithelial cells, less amount of drug absorbed gets bound to glucocorticoid receptors, bones, skin, eyes, and there are less chances of osteoporosis and cutaneous thinning.
It has some role in people predisposed to cataract and osteoporosis.

Status Asthmaticus Status asthmaticus is an acute exacerbation of asthma that remains unresponsive to initial treatment with bronchodilators. It is a life threatening form of asthma, because it can lead to respiratory failure and cardiac arrest. Status Asthmaticus requires immediate treatment (corticosteroids are essential as immediate treatment). Air trapping strains on breathing muscle which are fatigue and exhausted. Status asthmaticus is frequently associated with metabolic acidosis, and acidosis reduces the effectiveness of beta agonist.

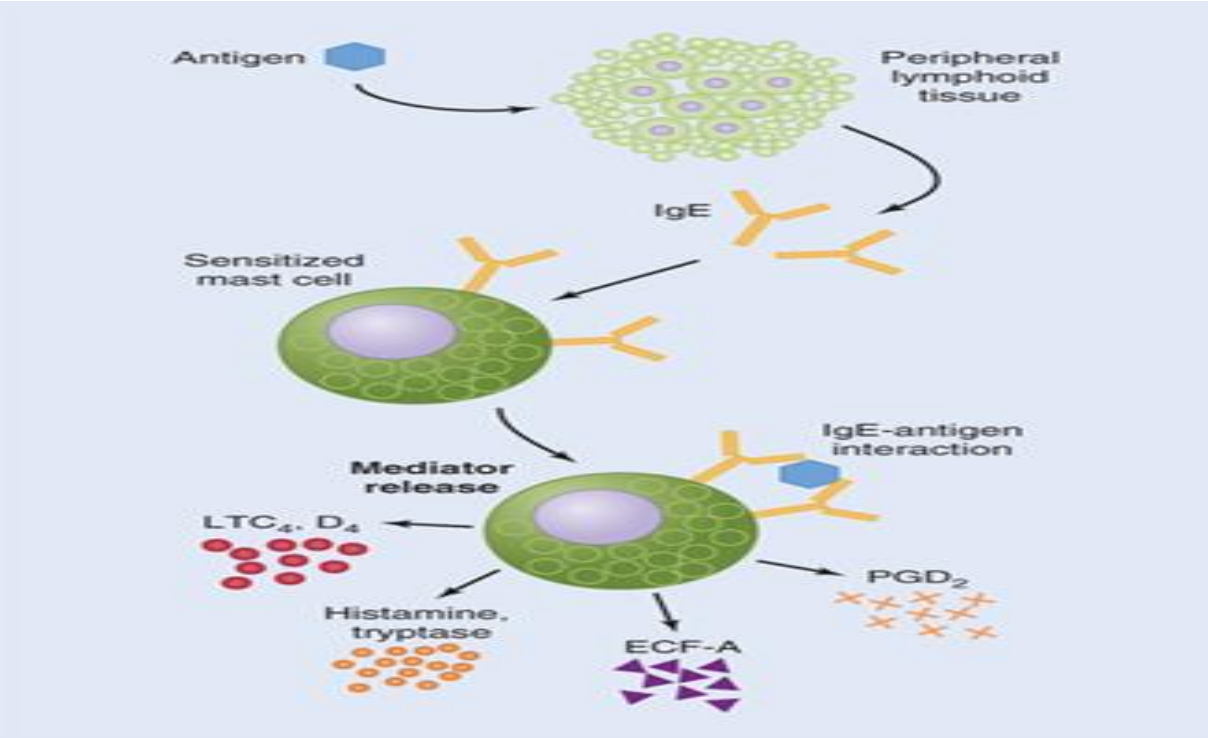
1. I/V $NaHCo_3$ added if pH is below 7.5 in patient with refractory status asthmaticus, but there is risk of hypercapnia, in children.
2. decrease in PCO_2 level corrected with nasal/Face mask oxygen (Helium)
3. Continuous nebulization of albuterol for the first few hrs
4. Switched to intermittent albuterol very 02 hrs. I/V
5. corticosteroids, inhaled ipratropium every 06 hrs

Monoclonal Antibodies: Omalizumab

They bind to IgE antibodies present on mast cells. If administered I/V or subcutaneously, humanized monoclonal antibodies decrease levels of IgE antibodies, decreasing tendency of severe asthma, in both phases (immediate/delayed).

DRUGS USED IN THE MANAGEMENT OF COPD

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is less reversible than in asthma and by a progressive course. However, many of the same drugs are used.In chronic obstructive pulmonary disease (COPD), airflow is obstructed during expiration. This increases the work of breathing and causes dyspnoea. In contrast to asthma, the airflow obstruction is not reversible and usually progresses over time. There are several mechanisms of airflow obstruction in COPD. Chronic bronchitis results in hypersecretion of mucus which fills and obstructs the airway lumen.



The objective of pharmacological treatment of chronic obstructive pulmonary disease (COPD) is to prevent and control symptoms, reduce the frequency and severity of exacerbations, and improve general health status and exercise tolerance. None of the classes of drugs currently used in the treatment of COPD are able to modify the progressive decline in lung function which is the hallmark of this disease. Smoking cessation is currently the only intervention which has been shown to reduce the progression of COPD. To achieve this objective, behavioral therapy and pharmacological treatment such as the administration of bupropion (an antidepressant), and nicotine replacement therapy have

proved useful. However, it is important to try to control symptoms of COPD with pharmacological treatment using the following general proposals:

1. There should be a stepwise increase in treatment, according to the severity of the disease. The step-down approach used in the chronic treatment of asthma is not applicable to COPD.
2. Treatment needs to be chronic and maintained at the same level for long periods of time, unless significant side effects or exacerbations occur.

3. Since individual patient response to the pharmacological treatment is variable, it is important to monitor pharmacological treatment closely and, if necessary, adjust it frequently.

Drugs currently recommended for the treatment of COPD are:

1. Bronchodilators (selective β_2-agonists, anticholinergic antimuscarinic agents and methylxanthines);
2. glucocorticoids;
3. Other types of medication (vaccines, antibiotics, α_1-antitrypsin augmentation therapy, mucolytic agents, antioxidants, immunoregulators, antitussives and vasodilators).

These drugs will be presented in the order in which they would normally be prescribed for the treatment of patients with COPD, based on the level of severity of the disease. Current knowledge on inhibitors of phosphodiesterase type 4 (PDE4), a new class of drugs for COPD which are in the late phase III of clinical development will be presented. However, it must be emphasized that each treatment regimen needs to be patient-specific as the relationship between the severity of symptoms and the severity of lung function is influenced by other factors, such as the frequency and severity of exacerbations, the presence of complications, the presence of respiratory failure, the presence of other diseases, and general health status.

Bronchodilators

Bronchodilators are currently the mainstay of the treatment of COPD. Bronchodilators are selective short-acting β_2-agonists such as salbutamol, metaproterenol, terbutaline, bambuterol, pirbuterol, isoetharine, bitolterol and fenoterol or selective long-acting β_2-agonists such as salmeterol and formoterol; anticholinergic antimuscarinic agents such as ipratropium bromide, oxitropium bromide and tiotropium bromide, and methylxanthines such as theophylline. Short- and long-acting β_2-agonists and antimuscarinic agents are generally administered by inhalation (aerosol, dry-powder or nebuliser solution). Bronchodilator therapy is most frequently delivered by pressurized metered-dose inhalers

(MDIs) or dry-powder inhalers (DPIs). Because of the lower bioavailability in asthma patients, the dose delivered by DPIs should be doubled compared with that of MDIs ; while a study comparing ipratropium bromide delivered by MDIs and by DPIs in COPD patients found that there was no difference between these two types of inhalers. The use of a spacer device to improve drug delivery proves particularly useful for patients who have poor inhalation technique. In a study on patients with COPD, inhalation of salbutamol through MDIs with spacer and dry-powder inhalers produced similar bronchodilating effects. However, further studies are necessary to establish deposition in the respiratory tract and the dose-effect relationship of drugs delivered by different inhalers in patients with COPD, as these are important factors in the choice of dosage. Short-acting β_2-agonists such as salbutamol and terbutaline are also available for oral or parenteral delivery. Theophylline is generally administered orally, mostly frequently in controlled release preparations which prolong the pharmacological effect of the drug, even if they do not significantly eliminate the interindividual variability of the bioavailability. For chronic administration, bronchodilators are the mainstay of treatment of COPD as they prevent and improve symptoms. One of the main therapeutic effects of bronchodilators, at least in severe COPD, is improvement in the emptying of the lungs during expiration. This causes a reduction in dynamic hyperinflation at rest and during exercise with consequent improvement in exercise tolerance. However, it is not easy to predict the extent of this improvement based on an increase in forced expiratory volume in one second (FEV_1) after a short period of bronchodilatory therapy. The evaluation of the efficacy of bronchodilators is generally based on questionnaires concerning symptom variation. COPD may require inhalation of a short-acting β_2-agonist on demand or, when airways obstruction is more severe, chronic administration of an antimuscarinic agent by inhalation or a long-acting β_2-agonist.

Selective β_2-agonists

There are no significant differences between the various β_2-agonists as far as selectivity for β_2-adrenoceptors is concerned, with the exception of metaproterenol and iso-etharine, which are less selective. Short-acting β_2-agonists have a bronchodilatory effect within 1 to 5 minutes and which lasts for up to 4 hours . Long-acting inhaled β_2-adrenergic agonists such as salmeterol and formoterol have a prolonged bronchodilatory effect for approximately 12 hours. Unlike salmeterol which has a slow onset of action, formoterol has a rapidly occurring bronchodilatory effect similar to that of short-acting β_2-agonists. Selective β_2-agonists mainly work by stimulating the β_2-adrenoceptors on the airway smooth muscle cells. The formation of the drug-receptor complex activates a stimulatory protein (Gs) which binds to guanosine triphosphate (GTP) with activation of the adenylate cyclase which leads to an

increase in intracellular cyclic adenosine monophosphate (cAMP) levels which, in turn, activates a cAMP-dependant protein kinase (PKA). Activation of the latter cause's myosin light chain kinase phosphorylation with a reduction in the affinity of this enzyme for the calcium–calmodulin complex, a reduction in the formation of active myosin light chain kinase, a reduction in myosin phosphorylation and, finally, a reduction in the interaction of actin and myosin filaments with consequent bronchodilation. In addition, PKA stimulation causes a reduction in intracellular calcium ion levels because of increased extrusion of calcium from the cell, reduction in the entry of calcium into the cell, and increase in the uptake of calcium by the smooth endoplasmic reticulum, which is the site at which calcium ions are deposited within the cell.

The reduction in the concentration of intracellular calcium causes a reduction in the formation of the calcium–calmodulin complex which produces the previously described effects. In addition to this main bronchodilation mechanism of selective β_2-agonists, other mechanisms may, in theory, contribute to reducing airway obstruction. Stimulation of β_2-adrenoceptors also increases potassium channel conduction with hyperpolarization and relaxation of the airway smooth muscle. This effect is, in part, independent from the increase in cAMP levels. The activation of β_2-receptors on inflammatory cells such as mast cells, basophils, eosinophils, neutrophils and lymphocytes cause an increase in cAMP levels and subsequent inhibition of the release of inflammatory mediators such as leukotrienes, histamine and cytokines. β_2-agonists increase mucociliary clearance, decrease microvascular permeability and may inhibit phospholipase A_2 with subsequent reduction in the synthesis of leukotrienes, prostaglandins and thromboxane A_2, which are important inflammatory mediators. The importance of these mechanisms on the therapeutic effect of β_2-agonists in humans, particularly in COPD, is not known.

Inhalation limits the absorption and therefore the systematic side effects of β_2-agonists. However, only about 10% of the aerosol enters the respiratory tract while the remainder is swallowed and may be absorbed in the intestinal tract with consequent systemic side effects. Furthermore, aerosolized particles less than 1μm in diameter reach the alveoli and may be absorbed in the pulmonary capillaries. The main side effect of selective β_2-agonists administered by inhalation at clinical doses is muscular tremor. However, this tends to diminish in intensity during prolonged treatment. This phenomenon is known as drug tolerance. It is not know if drug tolerance is due to the down regulation of the β_2-adrenoceptors on the muscle cytoskeleton or to adaptation phenomena in the central nervous system. Tachycardia is uncommon in clinical doses of β_2-agonists administered by inhalation. The absorption of β_2-agonists may cause tachycardia by stimulating the cardiac β_1-adrenoceptors, particularly at higher doses when

relative selectivity for β_2-adrenoceptors is lost. Although there are fewer cardiac β_2-adrenoceptors, their stimulation may also contribute to tachycardia. This type of side effect is particularly relevant in patients with ischemic heart disease or pre-existing arrhythmias. In these patients, β_2-agonists need to be administered with caution, even when inhaled. Bronchodilation may cause ventilation/perfusion mismatch with a consequent drop in the arterial partial pressure of oxygen. This is generally transitory and of little importance. Other side effects of systemically delivered β_2-agonists, such as hypokalemia, increase in the plasma concentrations of glucose, lactose, and free fatty acids are much less common when β_2-agonists are delivered by inhalation.

Antimuscarinic drugs

Antimuscarinics are delivered in the same way as bronchodilators. Antimuscarinics are quaternary ammonium derivatives which, after inhalation, undergo <1% absorption from the pulmonary or gastrointestinal tract. The parasympathetic nervous system has a role in the regulation of the bronchial tone. Vagal fibres activate nicotinic and M_1 muscarinic receptors on the parasympathetic ganglia of the respiratory tract; short postganglionic fibers release acetylcholine which stimulates the M_3 muscarinic receptors on the airway smooth muscle cells with consequent increase in motility. In addition, the airway submucosal glands have M_3 muscarinic receptors. M_3 muscarinic receptor stimulation increases bronchial secretion. Inflammatory mediators such as eicosanoids, histamine, and bradykinin may further produce parasympathetic reflexes which partly explains their bronchoconstriction effect. Antimuscarinic bronchodilators are non-selective antagonists of cholinergic muscarinic receptors. Their effect on airway obstruction is mainly due both to M_3 muscarinic receptor antagonism in the airway smooth muscle cells, with consequent bronchodilation, and to M_3 muscarinic receptor antagonism in the cells of the submucosal glands, with a reduction in the basal and stimulated cholinergic parasympathetic activity with consequent reduction in airway obstruction. Unlike atropine, antimuscarinic bronchodilators do not have an inhibitory effect on mucociliary clearance. The reason for this difference is not known. The effectiveness of antimuscarinic drugs depends on the role that cholinergic vagal tone has in the pathophysiology of bronchial obstruction. Antimuscarinic bronchodilators are generally considered to be more effective for COPD than for asthma. This could be partly due to the different pathophysiological role of the parasympathetic vagal system in these two diseases. The aerosol inhalation of ipratropium has a maximum effect 30–60 minutes after administration; its duration of action is 3 to 6 hours, making administration of the drug necessary 3 to 4 times a day. Ipratropium generally produces the same moderate bronchodilation as obtained with maximum doses of β_2-agonists. Oxitropium produces similar pharmacological effects to ipratropium

and can be administered twice a day. Tiotropium bromide, a new long-acting anticholinergic drug, which can be administered just once a day, has similar or greater efficacy compared with other bronchodilators and is useful in combination with formoterol for COPD treatment. A randomized, prospective, double-blind, placebo-controlled, multicenter trial to assess whether adding salmeterol or salmeterol–fluticasone to chronic therapy with tiotropium would provide additional clinical benefit to patients with moderate to severe COPD is currently being carried out. Tiotropium improves sleeping arterial oxygen saturation and, in combination with pulmonary rehabilitation, exercise tolerance in patients with COPD. Tiotropium bromide is indicated in the maintenance treatment of COPD, but it is not effective in relieving acute bronchospasms. However, as is the case with asthmatic patients, some authors raised doubts about chronic administration of bronchodilators which could be associated with worsening COPD. Because of their negligible absorption, antimuscarinics rarely cause systemic side effects and are generally well tolerated. Possible side effects include dry mouth, nausea, constipation, and headache. Antimuscarinic bronchodilators should be administered with caution in glaucoma, benign prostatic hypertrophy and urinary obstruction. Cases of acute angle-closure glaucoma have been reported with nebulized ipratropium, particularly when given with nebulized salbutamol.

Theophylline

Theophylline, a methylxanthine, is one of the least expensive bronchodilators. Given its very low solubility in water, theophylline is administered intravenously as aminophylline. Aminophylline is a theophylline and ethylenediamine mixture, which is 20 times more soluble than theophylline alone. The bronchodilatory effect of theophylline is due both to relatively non-selective inhibition of cyclic neucleotide phosphodiesterases and to competitive antagonism of adenosine receptors. At least eleven phosphodiesterase isozymes have been identified. The inhibition of phosphodiesterase isozymes type III and IV causes relaxation of the airway smooth muscle cells in vitro. Selective phosphodiesterase-4 inhibitors for COPD are currently in clinical trials. Adenosine receptor antagonism also contributes to the brochodilatory effect of theophylline. In addition to bronchodilation, theophylline may have anti-inflammatory effects at lower plasma concentrations in the respiratory tract as shown by the reduction both in the number of neutrophils and in the interleukin-8 concentration in induced sputum from COPD patients, where the same effects cannot be obtained after inhalation of high glucocorticoid doses. In vitro studies have shown that low doses of theophylline may enhance the anti-inflammatory effect of corticosteroids and antagonize the “resistance” to corticosteroids caused by smoking in COPD patients by activating histone deacetylases.

Theophylline is generally administered orally in conventional form or, more frequently, through sustained-release preparations or intravenously (like aminophylline). Sustained-release preparations are available for administration every 8, 12, or 24 hours. Intravenous administration of theophylline must be given very slowly, over at least a 20 minute period, because of the risk of serious toxic effects such as arrhythmias and convulsions. Inhalation of theophylline is not effective and intramuscular injection is not possible because of its irritant effect at the site of injection. Absorption of theophylline from conventional formulations is fast and complete with a plasma concentration peak within two hours of administration. Absorption of theophylline from sustained-release preparations has a large interindividual variability, for this reason, dosage must be changed to suit the individual patient. Theophylline is mainly eliminated by hepatic metabolism (less than 15% is excreted in the urine unchanged). There is wide variation in the rate of elimination of theophylline. The half-life of elimination is on average 8 to 9 hours in adults and about 3.5 hours in children. The half-life is increased in heart or liver failure, viral infections, in the elderly and with concomitant administration of some drugs such as cimetidine, ciprofloxacin, erythromycin, fluvoxamine, and oral contraceptives. The half-life of elimination of theophylline is decreased in smokers and in chronic alcoholics, and with concomitant administration of drugs such as phenytoin, carbamazepine, rifampicin, and barbiturates. In addition to bronchodilation, theophylline may increase cardiac contractility, have a psychostimulant or diuretic effect, and increase diaphragmic contractility. A possible therapeutic importance for COPD has been attributed to this last effect. However, theophylline has some disadvantages including its low therapeutic index which limits its administration. For this reason, and because of the large interindividual variability in its bioavailability, therapeutic monitoring of plasma theophylline concentrations is required. This involves taking regular blood samples after the theophylline concentrations reach a steady-state to ensure that the plasma theophylline concentration is within the therapeutic range for plasma theophylline concentrations for which the majority of patients obtain therapeutic effects without toxic effects, even though side effects are found with therapeutic concentrations. The therapeutic range for theophylline is between 10–20 μg/ml. Toxic side effects are associated with theophylline concentrations of more than 25 μg/ml. The risk of serious toxic effects, such as arrhythmias and convulsions, is high with theophylline concentrations of more than 40 μg/ml. At therapeutic plasma concentrations the main side effects of theophylline include anorexia, nausea, vomiting, insomnia, agitation, palpitation, and hypotension.

Glucocorticoids

Inhaled glucocorticoids currently available include beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate and triamcinolone acetonide. There are no significant differences between these drugs in terms of their efficacy and tolerability. Mometasone and ciclesonide, two new glucocorticoids in advanced clinical trials, seem to have a longer duration of action with the possibility of once a day administration. Ciclesonide is a prodrug which is activated by a pulmonary esterase, with the possibility of increased selectivity of action and reduced systemic side effects resulting from glucocorticoid absorption. Glucocorticoids do not cause relaxation of the airway smooth muscle and therefore have no effect on acute bronchoconstriction. Glucocorticoids bind to specific cytoplasmic receptor proteins, which, in turn bind to regulatory proteins such as heat shock proteins and an immunophyllin. The glucocorticoid–receptor interaction causes a receptor conformational change which leads to regulatory protein detachment, dimerization of the glucocorticoid receptor complexes and translocation to the nucleus where the drug-receptor complex binds to specific regulatory DNA sequences (glucocorticoid response elements, GRE), which modulate the expression of the adjacent genes. The time required for gene expression and protein synthesis explains the delayed effect of glucocorticoids which generally occurs several hours after administration. The anti-inflammatory mechanisms of action of glucocorticoids are largely due to the inhibition of gene expression which encodes for proinflammatory cytokines in the airway inflammatory cells. Part of the anti-inflammatory effect of glucocorticoids may be due to the induction of lipocortin. Lipocortin is a protein which inhibits phospholipase A_2. Phospholipase A_2 enzymes cause cleavage of arachidonic acid from phospholipids in the plasma membrane. The arachidonic acid is the substrate for the synthesis of leukotrienes, prostaglandins, and thromboxane A_2, which are important inflammatory mediators. Although glucocorticoids are generally effective in asthma, the anti-inflammatory effect of glucocorticoids in COPD patients remains controversial and seems to be very limited. This seems to reflect a pathophysiological difference between COPD and asthma. It has been suggested, on the basis of in vitro studies, that oxidative stress and cigarette smoke, which both play an important role in the pathophysiology of COPD, induce resistance to the action of glucocorticoids through mechanisms which involve the acetylation of histones. Histones are nucleic proteins that are important regulators in gene expressio. Furthermore, the variable effects of glucocorticoids on airway inflammation may be due to the heterogeneity of the disease and the limited reproducibility of markers of inflammation. What is certain is that glucocorticoids do not modify the natural history of COPD, as measured by the rate of decline in FEV_1 (Figure 1). Four large randomized placebo-controlled multicenter clinical trials

(European Respiratory Society study on chronic obstructive pulmonary disease [EUROSCOP], Copenhagen City Lung Study, Inhaled Steroids in Obstructive Lung Disease in Europe [ISOLDE], and Lung Health Study all found that inhaled glucocorticoids had no significant effects on the progressive decline in FEV_1 in patients with mild and moderate to severe COPD. One of these studies in patients with more severe COPD showed a reduction in the frequency of exacerbations (from 1.33 to 0.99 per year, a reduction of 25%). Other clinical trials with both fluticasone and budesonide showed that inhaled glucocorticoids reduce COPD exacerbation rate, although the mechanism for this effect is currently unknown. However, an earlier study on a smaller sample showed a reduction in severity, but not in the frequency of exacerbations with inhaled glucocorticoids. From these clinical trials it is concluded that inhaled glucocorticoids should only be administered to patients with severe to very severe COPD (post-bronchodilator $FEV_1 \leq 50\%$ of the predicted value) with frequent exacerbations requiring treatment with antibiotics or oral glucocorticoids. The dose of glucocorticoids required to reduce the frequency of exacerbations in these patients with COPD is not known.

DEMULCENTS AND EXPECTORANTS

Pharyngeal demulcents sooth 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.

Mucolytics

Bromhexine A derivative of the alkaloid vasicine obtained from Adhatoda vasica (Vasaka), is a potent mucolytic and mucokinetic, capable of inducing thin copious bronchial secretion.

ANTITUSSIVES Antitussives act centrally by suppressing the neurons located in the brainstem's cough center. Antitussives are often used with tracheitis, tracheobronchitis. When coughing worsens the inflammation that is already present and stimulates more coughing, it needs to be suppressed.

DEMULCENTS AND EXPECTORANTS

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- 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 rarely used now. Guaiphenesin, vasaka, tolu balsum are plant products which are supposed to enhance bronchialsecretion and mucociliary function while being secreted by tracheobronchial glands.

Opioids

Codeine: An opium alkaloid similar to but less potent than morphine

It is more selective for cough centre and is treated as the standard antitussive; suppresses cough for about 6 hours.

Non Opioids

Noscapine (Narcotine) An opium alkaloid of the benzoisoquinoline series. It depresses cough but has no narcotic, analgesic or dependence inducing properties.

Mucolytics

Bromhexine: A derivative of the alkaloid Hysosicine obtained from (Vasaka), is a potent mucolytic and mucokinetic, capable of inducing thin copious bronchial secretion. It depolymerises mucopolvsaccharides directly as well as by liberating lysosomal enzymesnetwork of fibres in tenacious sputum is broken. It is particularly useful if mucus plugs are present.

Side effects are rhinorrhoea and lacrimation, gastric irritation, hypersensitivity.

NASAL DECONGESTANTS

These are an agonists which on topical application as dilute solution (0.05-0.1%) produce local vasoconstriction. The imidazoline compoundsnaphazoline, xylometazoline and oxymetazoline are relatively selective a2 agonist (like clonidine).

They have a longer duration of action (12 hours) than ephedrine. After-congestion is claimed to be less than that with ephedrine or phenylephrine. They may cause initial stinging sensation (especially naphazoline). Regular use of these agents for long periods should be avoided because mucosal ciliary function is impaired: atrophic rhinitis and anosmia can occur due to persistent vasoconstriction. They can be absorbed from the nose and produce systemic effects-CNS depression and rise in BP. These drugs should be used cautiously in hypertensives and in those receiving MAO inhibitors.

Pseudophedrine A stereoisomer of ephedrine; causes vasoconstriction, especially in mucosae and skin, but has fewer CNS and cardiac effect and is a poor bronchodilator (little 2 agonistic activity). It has been used orally as a decongestant of upper respiratory tract, nose and Eustachian tubes.

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Pharyngeal demulcents sooth 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 balsum are plant products which are supposedto 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 these 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 potent mucolytic and mucokinetic, capable of inducing thin copious bronchial secretion. It depolymerises

mucopolysaccharides directly as well as by liberating lysosomal enzymes—networkof 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.

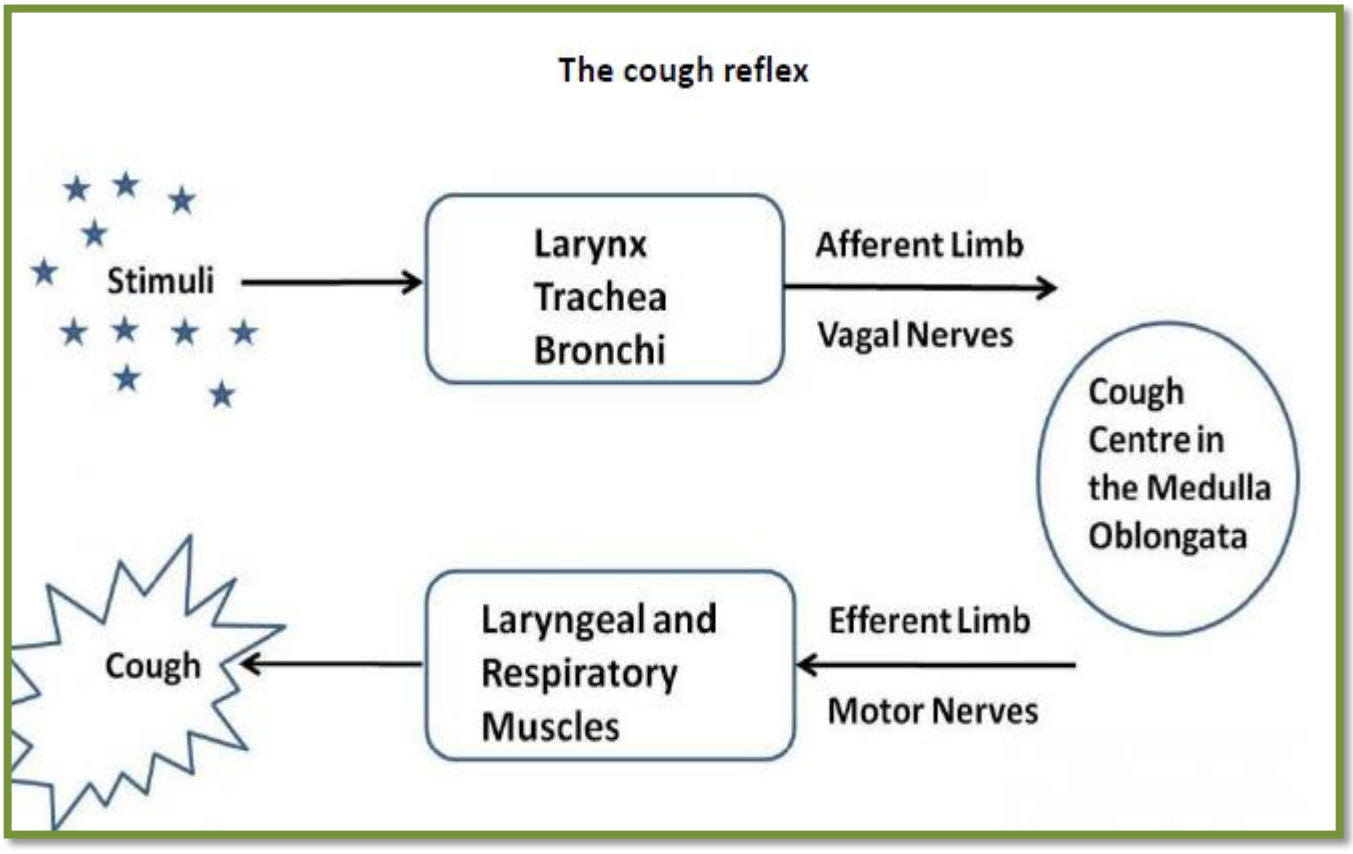
BROMHEXINE 8 mg tablet, 4 mg/5 ml elixir.

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

Acetylcysteine It opens disulfide bonds in mucoproteins present in sputum—makes it less viscid, but has to be administered directly into the respiratory tract.

MUCOMIX 200 mg/ml inj in 1,2,5 ml amps; injectable solution may be nebulized/instilled through trachiostomy tube.

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 gastric mucosal barrier; is contraindicated in peptic ulcer patients. Side effects are gastric discomfort and rashes.



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, antitussives should be used only for dry nonproductive cough or if cough is unduly tiring, disturbs sleep or is hazardous (hernia, piles, cardiac disease, ocular surgery).

Opioids

Codeine 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. 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: 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.

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.

Pholcodeine 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.

Nonopioids

Noscapine (Narcotine) An opium alkaloid of the benzoisoquinoline series (*see* Ch. 34). It 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.

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. The antitussive action of dextromethorphan has been rated equivalent to codeine, but some clinical studies have found it to be no better than placebo.

Side effect: Dizziness, nausea, drowsiness; at high doses hallucinations and ataxia may occur.

Dose: 10–20 mg, children 2–6 years 2.5–5 mg, 6–12 years 5–10 mg. It is a common ingredient of many proprietary cough formulations.

Chlophedianol It is a centrally acting antitussive with slow onset and longer duration of action.

Side effect: Dryness of mouth, vertigo, irritability.

Antihistamines

Many H1 antihistamines have been conventionally added to antitussive/expectorant formulations. 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.

Peripherally acting antitussives

Prenoxdiazine In contrast to other antitussives, it acts peripherally; desensitizes the pulmonary stretch receptors and reduces tussal impulses originating in the lungs. It is indicated in cough of bronchial origin. Efficacy, however, is not impressive. Though an old drug developed in Hungary, it has been introduced recently in India.

Bronchodilators Bronchospasm can induce or aggravate cough. Stimulation of pulmonary receptors can trigger both cough and bronchoconstriction, especially in individuals withbronchial 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.

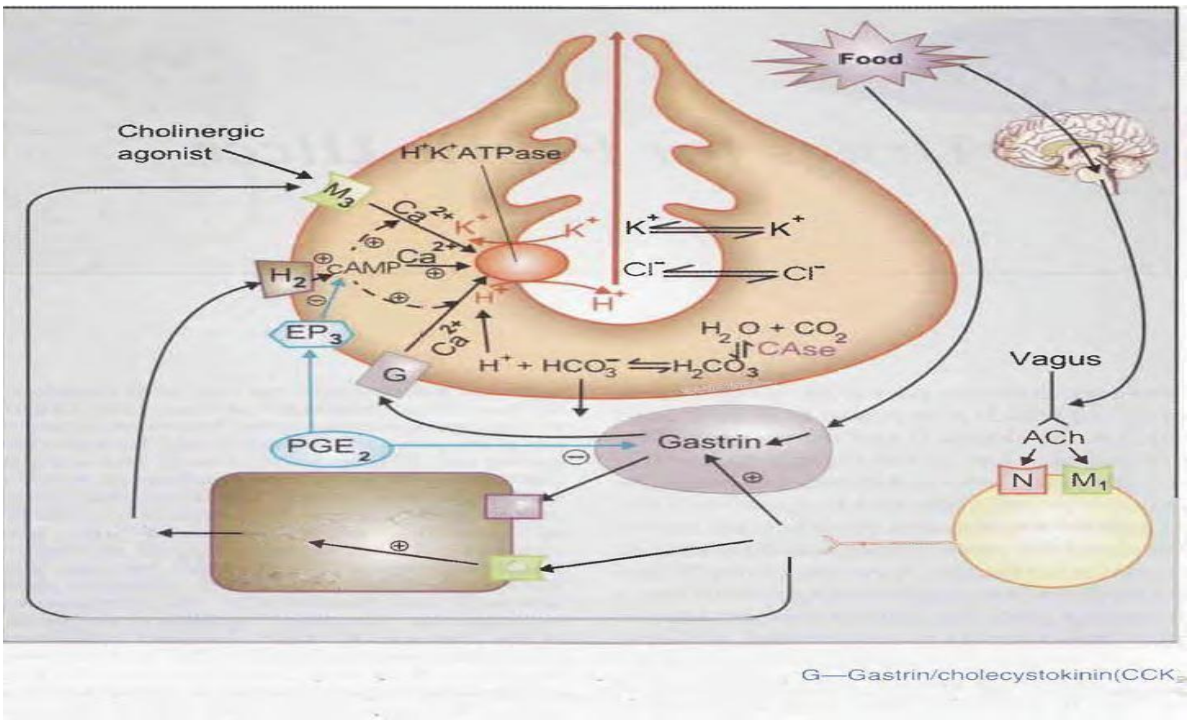
Aeromatic chest rub is widely advertized as a cough remedy. Though it has been shown to reduce experimentally induced cough in healthy volunteers, there is no evidence of benefit in pathological cough.

Pharmacology of Drugs Acting on the Gastrointestinal Tract

Anti Ulcer Drugs

Peptic ulcer occurs in that part of the gastrointestinal tract (g.i.t.) which is exposed to gastric acid and pepsin, i.e. the stomach and duodenum. The etiology of peptic ulcer is not clearly known. It results probably due to an imbalance between the aggressive (acid, pepsin, bile and H. pylori) and the defensive (gastric mucus and bicarbonate secretion, prostaglandins, nitric oxide, innate resistance of the mucosal cells) factors.

Regulation of gastric acid secretion



1. Reduction of gastric acid secretion

(a) H2 antihistamines: Cimetidine, Ranitidine, Famotidine, Roxatidine

(b) Proton pump inhibitors: Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Esomeprazole

(c) Anticholinergics: Pirenzepine, Propantheline, Oxyphenonium

(d) Prostaglandin analogue: Misoprostol

1. Neutralization of gastric acid (Antacids

(a) Systemic: Sodium bicarbonate, Sodium citrate

(b) Nonsystemic: Magnesium hydroxide, Mag. trisilicate, Aluminiumhydroxide gel, Calcium carbonate

3 . Ulcer protectives: Sucralfate, , bismuth subcitrate (CBS)

4Anti-H. pylori drugs: Amoxicillin,Clarithromycin, Metronidazole, Tinidazole, Tetracyclin

H2 ANTAGONISTS

These are the first class of highly effective drugs for acid-peptic disease. Four H2 antagonists cimetidine, ranitidine, famotidine and roxatidine are available in India; many others are marketed elsewhere. Their interaction with Hz receptors has been found to be competitive in case of cimetidine, ranitidine and roxatidine, but competitive noncompetitive in case of famotidine.

- H2 blockade Cimetidine and all other Hz antagonists block histamine-induced gastric secretion
- Gastric secretion the only significant in vivo action of Hz blockers is marked inhibition of gastric secretion

PROTON PUMP INHIBITORS (PPis)

Omeprazole It is the prototype member of substituted benzimidazoles which inhibit the final common step in gastric acid secretion and have overtaken H2 blockers for acid-peptic disorders. The only significant pharmacological action of omeprazole is dose dependent suppression of gastric acid secretion; without anticholinergic or H2 blocking action. It is a powerful inhibitor of gastric acid: can totally abolish HCl secretion, both resting as well as that stimulated by food or any of the secretagogues, without much effect on pepsin, intrinsic

factor, juice volume and gastric motility.

Zollinger-EIIison syndrome It is a gastric hypersecretory state due to a rare tumour secreting gastrin. H2 blockers in high doses control hyperacidity and symptoms in many patients, but relief is often incomplete and side effects frequent. PPis are the drugs of choice.

ANTICHOLINERGICS

A tropinic drug reduce the volume of gastric juice without raising its pH unless there is food in stomach to dilute the secreted acid. Stimulated gastric secretion is less completely inhibited. Effective doses (for ulcer healing) of nonselective antimuscarinics (atropine, propantheline, oxyphenonium) invariably produce intolerable side effects.

PROSTAGLANDIN ANALOGUE

PGE2 and PGI2 are produced in the gastric mucosa and appear to serve a protective role by inhibiting acid secretion and promoting mucus secretion. In addition, PGs inhibit gastrin production, increase mucosal blood flow and probably have an ill-defined "cytoprotective" action.

ANTI-HELICOBACTER PYLORI DRUGS

H. pylori are a gram negative bacillus uniquely adapted to survival in the hostile environment of stomach. It attaches to the surface epithelium beneath the mucus, has high urease activity produces ammonia which maintains a neutral microenvironment around the bacteria, and promotes back diffusion of H + ions.

DRUGS FOR CONSTIPATION AND DIARRHEA

Anti-diarrhoeal agents

Diarrhoea: frequent passage of liquid or semisolid stools is called diarrhoea.

Causes: enteric infection, food toxins, malnutrition, inflammation, drugs like reserpine, prostaglandins, metoclopramide, domperidome, cholinergic drugs, quinidine and purgatives.

Dysentery: abdominal pain and passage of bloody stools and mucous due to infection or inflammation.

Management of diarrhea

1. Non-specific therapy:

a) Oral and parenteral rehydration

b) Anti-motility and anti-secretory agents:

i) Opioids: codeine, diphenoxylate, loperaminde

ii) α-adrenergic receptor agonist: clonidine

iii) Octreotide.

2. **Specific therapy**: Antimicrobial agents

3. **Antispasmodics:** Atropine & oxyphenonium (antrenyl)

4. **Adsorbants:** Kaolin, pectin and chalk, bismuth subsalicylate

Non-specific therapy

Oral rehydration solution (ORS): 2.6 g NaCl, 1.5 g KCl, 2.9 g sodium citrate, 13.5 g glucose dissolved in 1 liter of water.

Super ORS: (boiled rice powder used instead of glucose)-also decreases frequency of diarrhoea along with rehydration.

Antimotility and antisecretory agents

- **Codeine**: opium alkaloid, reduces GI motility, also have antisecretory effects.
- **Diphenoxylate:** structurally related to pethidine, combined with small doses with atropine,

side effects are constipation, paralytic ileus, banned in many countries.

- **Loperamide:** opiate analogue and importantant antidiarroeal than morphine.
- Interact with μ-receptor in the gut, reduces GI motility and increase anal sphincter tone.

DRUGS FOR CONSTIPATION

LAXATIVES

(Aperients, Purgatives, Cathartics)

These are drugs that promote evacuation of bowels. A distinction is sometimes made according to the intensity of action.

(a) Laxative or aperient: milder action, elimination of soft but formed stools.

(b) Purgative or cathartic: stronger action resulting in more fluid evacuation.

Many drugs in low doses act as laxative and in larger doses as purgative.

CLASSI FICATION

1. Bulk forming:Dietary fibre: Bran, Psyllium (Plantago) Ispaghula, Methylcellulose

2. Stool softener :Docusates (DOSS), Liquid paraffin

3. Stimulant purgatives (a) Diphenylmethanes, Phenolphthalein, Bisacodyt Sodiumpicosulfate

(b) Anthraquinones (Emodins) Senna, Cascara sagrada

(c) 5-HT4 agonist Tegaserod (d) Fixed oil, Castor oil

4. Osmotic purgatives Magnesium salts: sulfate, hydroxide , Sodium salts: sulfate, phosphate Sod. pot. Tartrate Lactulose

M ECHANISM OF ACTION

All purgatives increase the water content of faeces by:

(a) A hydrophilic or osmotic action, retaining water and electrolytes in the intestinal lumen-increase volume of colonic content and make it easily propelled.

(b) Acting on intestinal mucosa, decrease net absorption of water and electrolyte; intestinal

transit is enhanced indirectly by the fluid bulk.

(c) Increasing propulsive activity as primary action-allowing less time for absorption of salt and water as a secondary effect.

Laxatives modify the fluid dynamics of the mucosal cell and may cause fluid accumulation in gut lumen by one or more of following mechanisms:

(a) Inhibiting Na+K+ATPase of villous cellsimpairing electrolyte and water absorption.

(b) Stimulating adenylyl cyclase in crypt cellsincreasing water and electrolyte secretion.

(c) Enhancing PG synthesis in mucosa which increases secretion.Structural injury to the absorbing intestinal mucosal cells

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APPETITE STIMULANTS AND SUPPRESSANTS

Appetite Stimulants : May help promote appetite and weight gain in elderly with unintentional weight loss or poor P.O. intake Drugs should not be considered as first-line treatment Even if successful in inducing weight gain, long-term effects on quality of life are unknown The following appetite stimulants Dronabionol (Marinol) Mirtazapine (Remeron) Megestrol Acetate (Megace) Metoclopraminde (Reglan) Cyproheptadine (Periactin) Anabolic Steroids (Oxandrolone; Oxandrin) Ghrelin Recombinant Human Growth Hormone (Serostim) Testosterone

Dronabinol Drug name: Marinol. A tetrahydrocannabinol Use: Weight gain in cancer-related anorexia patients Side Effects: Lightheadedness Sleepiness Blurred vision Can't think clearly Dizziness Sedation Fatigue Hallucinations

Mirtazapine • Drug Name: Remeron. A serotonergic norepinephrine uptake inhibitor used to treat depression in older adults

Use:

Appetite stimulant for cachexia and treats underlying depression in older adults

Side Effects:

- Sedation
- Dry mouth
- Constipation
- Fatigue
- Weight gain
- Dizziness
- Other studies show causes hepatotoxicity, bone marrow suppression, restless legs syndrome, arthralgia, and coagulopathy

Megestrol Acetate Drug Name: Megace. A progestational agent Use: Weight gain in Anorexia, AIDS, Cachexia, and Cancer patients Side Effects: Edema Constipation & delirium

Diarrhea Flatulence Rash Hypertension Fluid retention Glucose intolerance Nausea Insomnia • Gastrointestinal upset • Impotence •

Metoclopramide Drug Name: Reglan. Prokinetic agent Use: Relieves nausea-induced anorexia (Hoffman, 2002) Side Effects: Dystonia & Parkinsonian symptoms in elderly Many drug interactions such as B12, D3, Lipitor, Fish oils, Aspirin, Crestor Can cause GI obstruction.

perforation or hemorrhage Causes GI obstruction, perforation or hemorrhage; pheochromocytoma; history of seizures or concomitant use of other agents likely to increase movement disorder reactions May increase risk of seizures and movement disorders (extrapyramidal reactions)

Cyproheptadine Drug name: Periactin. Antihistaminic and serotonin-blocking drug Use: Weight gain in children with anorexia nervosa & cancer Elderly in nursing homes Side Effects: Blurred vision Dry mouth Urinary retention Constipation Tachycardia and delirium in older patients **Anabolic Steroids** Drug Name: Oxandrolone (Oxandrin), Ornithine What it is: Synthetic anabolic steroids Use: Treats wasting in AIDS & Cachexia in Cancer Side Effects Carpal tunnel syndrome Headache Arthralgias Myalgias, & gynecomastia Risk of prostate hyperplasia, fluid retention, and transaminase elevations

Ghrelin • Drug Name: None .Growth hormone produced from the fundus of the stomach increases food intake by stimulating nitric oxide in the hypothalamus • Use: Appetite stimulant in oncology patients and older adults

Recombinant Human Growth Hormone Drug Name: Serostim Anabolic Growth Hormone Use: Increase lean body mass in HIV patients with wasting or cachexia Side Effects: Carpal Tunnel Syndrome Headache Arthralgia Myalgias Gynecomastia Edema Arthralgia Impaired fasting glucose

Testosterone • Drug name: None • A steroid hormone from the androgen group and is found in mammals, reptiles, birds, and other vertebrates • Use: Treat cachexia and weight loss in HIV Patients • Side Effects: • Higher hematocrit • Leg edema • Prostate events (exacerbation of prostate cancer) • Lower HDL levels • Possible metabolic syndrome in men.

APPETITE SUPPRESSANT

An **anorectic** or **anorexic** is a drug which reduces appetite, resulting in lower food consumption, leading to weight loss. By contrast, an appetite stimulant is referred to as orexigenic. The term is (from the Greek *ἀν-* (an-) = "without" and (órexis) = "appetite"), and such drugs are also known as **anorexigenic**, **anorexiant**, or **appetite suppressant**.

Amfepramone, Bupropion and naltrexone (combination), Dexfenfluramine, Fenfluramine,Mazindol, Phentermine, Sibutramine, Topiramate, Benfluorex, Butenolide, Diethylpropion, Phenmetrazine' Phentermine, Phenylpropanolamine, Sibutramine, Lorcaserin

Sibutramine is a monoamine reuptake inhibitor (MRI) that, in humans, reduces the reuptake of norepinephrine (by ~73%), serotonin (by ~54%), and dopamine (by ~16%),[21] thereby increasing the levels of these substances in synaptic clefts and helping enhance satiety; the serotonergic action, in particular, is thought to influence appetite

Phentermine (phenyl-tertiary-butylamine), sold under the brand name **Ionamin** among others, is a medication used together with diet and exercise to treat obesity. The primary mechanism of phentermine's action in treating obesity is the reduction of hunger perception, which is a cognitive process mediated primarily through several nuclei within the hypothalamus

Orlistat is a drug designed to treat obesity. It is marketed as a prescription drug under the trade name **Xenical.** Orlistat is the saturated derivative of lipstatin, a potent natural inhibitor of pancreatic lipases isolated from the bacterium *Streptomyces toxytricini*. However, due to its relative simplicity and stability, orlistat was chosen over lipstatin for development as an anti- obesity drug.

CARMINATIVES

These are drugs which promote the expulsion of gases from the g.i.t. and give a feeling of warmth and comfort the epigastrium.

Commonly used drugs are:

Sodium bicarbonate 0.6--1.5 g

Oil Peppermint 0.06--0.1 ml

Tincture Cardamom Co. 1-2 ml

Oil of dil 0.06--0.2 ml

Tincture ginger 0.6--1 ml

Sodium bicarbonate reacts with gastric HCl, which rapidly distends stomach, relaxes

The others are condiments and spices, contain volatile oils, which by their mild irritant action and flavour and increase g.i.t. motility. They give a feeling of warmth and comfort in the abdomen.

DIGESTANTS

These arc substances intended to promote digestion of food. A number of proteolytic, amylolytic and lipolytic enzvmes are marketed in combination formulations and more vigorously promoted for dyspeptic symptoms, and appetite stimulants or health tonics.. Their routine use in tonics and appetite improving mixtures is irrational.

Hydrochloric acid It may be used in achlorhydria;10 ml of dilute HCl (10%) should be further diluted to 100-200 ml with water and sipped with a straw (to prevent contact with teeth) during meals.

Pepsin May be used along with HCl due to atrophic gastritis, gastric carcinoma, pernicious anaemia, etc.

Papain It is a proteolytic enzyme obtained from raw papaya. Its efficacy after oral ingestion is doubtful

Pancreatin It is a mixture of pancreatic enzymes obtained from hog and pig pancreas. It contains amylase, trypsin and lipase; indicated in chronic pancreatitis and other exocrine pancreatic deficiency states. Fat and nitrogen content of stools may be reduced and diarrhoea/ steatorrhoea may be prevented. It has to be used as enteric coated tablets or capsules to protect the enzymes from being themselves digested in stomach by pepsin. Nausea, diarrhoea and hypen:ricaernia are the occasional side effects.

Diastase and Takadiastase These are amylolytic enzymes obtained from the fungus Aspergillus. They have been used in pancreatic insufficiency.

EMETICS AND ANTI-EMETICS

Emesis Vomiting occurs due to stimulation of the emetic (vomiting) centre situated in the medulla oblongata. Multiple pathways can elicit vomitingThe chemoreceptor trigger zone (CTZ) located in the area postrema and the nucleus tractus solitarius (NTS) are the most important relay areas for afferent impulses arising in the g.i.t, throat and other viscera. The CTZ is also accessible to blood-borne drugs, mediators, hormones, toxins, etc. because it is unprotected by the blood-brain barrier.

EMETICS

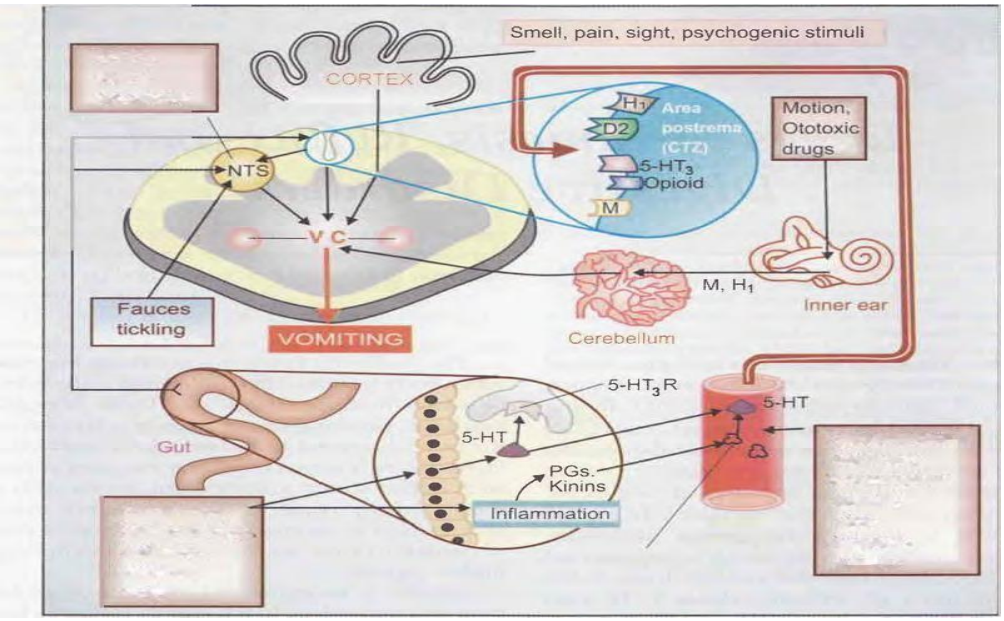
These are drugs used to evoke vomiting.

1 . Act on CTZ : Apomorphine

2 . Act reflexly and on CTZ : Ipecacuanha

Vomiting needs to be induced only when an undesirable substance (poison) has been ingested. Powdered mustard suspension or strong salts solution may be used in emergency. They act reflexly by irritating the stomach.

Apomorphine It is a semisynthetic derivative of morphine; acts as a dopaminergic agonist on the CTZ. Injected i.m./s.c. in a dose of 6 mg, it promptly (within 5 min) induces vomiting. Ipecacuanha The dried root of Cephne/is ipecncunnha contains emetine and is used as surup ipecac (15-30 ml in adults, 10-15 ml in children, 5 ml in infants) for inducing vomiting.



ANTI EMETICS

These are drugs used to prevent or suppress vomiting.

CLASSIFICATION

1. Anticholinergics Hyoscine, Dicyclomine
2. H1 antihistaminics: Promethazine, Diphenhydramine, Dimenhydrinate, Doxylamine, Cyclizine, Meclozine, Cinnarizine.
3. Neuroleptics Chlorpromazine,Prochlorperazine, Haloperidol, etc
4. Prokinetic drugs Metoclopramide, Domperidone, Cisapride, Mosapride, Tegaserod
5. 5-HT3 antagonists Ondansetron, Granisetron
6. Adjuvant antiemetics Dexamethasone, Benzodiazepines, Cannabinoids.

ANTICHOLINERGICS

Hyoscine (0.2-0.4 mg oral, i.m.) is the most effective drug for motion sickness. However, it is a brief duration of action; produces sedation and other anticholinergic side effects; suitable for short brisk journies. It acts probably by blocking conduction of nerve impulses across cholinergic link in the pathway leading from the vestibular apparatus to the vomiting centre and is not effective in vomiting of other etiologies.

H1 ANTI HISTAMINICS

Some antihistaminics are antiemetic. They are useful mainly in motion sickness and to a lesser extent in morning sickness, postoperative and some other forms of vomiting. Their antiemetic effect appears to be based on anticholinergic, antihistaminic and sedative properties. Promethazine, diphenhydramine, dimenhydrinate These drugs afford protection of motion sickness by their central anticholinergic action they block the extrapyramidal side effects
of metoclopramide while supplementing its antiemetic action. Their combination is used in chemotherapy induced vomiting.

NEUROLEPTICS

These are potent antiemetics; act by blocking D2 receptors in the CTZ; antagonize apomorphine induced vomiting and have additional antimuscarinic as well as H1 antihistaminic property.

PROKINETIC DRUGS

These are drugs which promote gastrointestinal transit and speed gastric emptying by enhancing coordinated propulsive motility.

Metoclopramide

Metoclopramide is chemically related to procainamide, but has no pharmacological similarity with it. Introduced in early 1970s as a 'gastric hurrying' agent, it is now a widely used antiemetic. Metoclopramide blocks D2 receptors and has an opposite effect fasting gastric emptying.

5-HT3 ANTAGONISTS

Ondansetron It is the prototype of a new class of antiemetic drugs developed to control cancer chemotherapy I radiotherapy induced vomiting and later found to be highly effective in postoperative nausea and vomiting as well. It blocks the depolarizing action of 5-HT through 5-HT3 receptors on vagal afferents in the g.i.t. as well as in NTS and CTZ.

ADJUVANT ANTIEMETICS

Cannabinoids Tetrahydrocannabinol (D. THC) is the active principle of the hallucinogen Cannabis indica. It possesses antiemetic activity against moderately emetogenic chemotherapy. It probably acts at higher centres or at vomiting centre itself by activating CB1 subtype of cannabinoid receptors. The disorienting and other central effects of THC limit its clinical utility.

Very Short Answer Questions (2 Marks)

1. Define asthma and its types.
2. Classification of drugs used in asthma.
3. Define bronchodialators.
4. What are mucolytics?
5. Define antitussive and expectorants.
6. What are nasal decongestants?
7. Define respiratory stimulants.
8. Define status asthmatics.
9. Define emetic and antiemetics
10. How does vomiting occur?
11. What are prokinetics drugs?
12. Why vomiting is necessary to produce?
13. Define cough and its types.
14. Define demulcents.
15. Define COPD.

Drugs acting on GIT

1. What is peptic ulcer?
2. Define acidifiers
3. What are digestant?
4. What are the precautions taken while taking haloperidol?
5. Define laxatives and purgatives.
6. What is constipation?
7. Define ispaghula.
8. Define gastric and duodenal ulcers
9. Define antacids and its types.
10. What are mast cells?
11. What is diarrhea?
12. Define Zollinger Ellision syndrome.
13. Define GERD.

14. Define H Pylori
15. Define triple therapy.
16. Define ORS and super ORS
17. What are appetite stimulants and suppressants? Examples
18. Define orlistat.
19. What are CTZ and NTS?
20. Write the M.OA of misoprostol
21. What are PPIs?
22. What are H2 antagonists?
23. Define ant secretary drugs.
24. Write the MOA of methyl xanthenes
25. Write the adverse effects of corticosteroids
26. Write the MOA of prednisolone
27. Examples of anti diarrheal and anti emetics
28. Define Productive and non productive cough.
29. Define laxative and purgatives.
30. Write the MOA of sucralfate.
31. Give the MAO of omalizumab.
32. Write the treatment for motion sickness.
33. What is histamine and where it is present?
34. Define astringents.
35. How do antiulcer acts?

Short Answer Question 5 Marks

1. Classify antiulcer drugs and discuss their pharmacology.
2. Give pharmacological detail of PPIs.
3. Write pharmacology of anti diarrheal agents.
4. Write note on appetite suppressant and stimulants.
5. Write note on carminatives and digestants.
6. Write note on emesis physiology.
7. Short note on triple Therapy used for H. Pylori.

8. Write note on ORS therapy.
9. Write note on laxative and purgatives.
10. Describe the MAO, AEs, indication and uses of ondansetron.
11. Write a short note on expectorants with their pharmacological actions.
12. Outline the drugs used in COPD.
13. Explain the pharmacological drugs of corticosteroids used in asthma.
14. Discuss the pharmacology of omalizumab.
15. Explain the pharmacology of drugs of opoids in cough.
16. Outline the mechanism of action, side effects and uses of terbutline and salbutamol.

C.Long Answer Question (10 Marks)

1. Classify anti emetics drugs and give pharmacological actions of metoclorpropamide.
2. Discuss the pharmacology of anti tussive drugs with mechanism of action, uses and adverse effects.
3. Discuss about respiratory stimulants with their pharmacological actions and therapeutic uses.
4. Classify anti asthmatic drugs and explain the pharmacology of bronchodialators.
5. Discuss the drugs used as nasal decongestants in detail.