PHARMACOLOGY 3

Unit one Content..

Topic 1.1: Autacoids (Introduction, definition and classification and Amine Autacoids)

An organic substance, such as a hormone, produced in one part of organism and transported by the blood or lymph to another part of the organism where it exerts a physiologic effect on that part.

**Types of Autacoids;**

1. Amines : Histamine,5-Hydroxytryptamine.
2. Lipids  : Prostaglandins, Leukotriens,
3. Platelet activating factor.
4. Peptide : Bradykinin , angiotensin.

**5-HYDROXYTRYPTAMINE: Serotonin;**

**SYNTHESIS, STORAGE AND DESTRUCTION**

5-HT is **β-aminoethyl-5-hydroxyindole**. It is synthesized from the amino acid **tryptophan** and degraded primarily by **MAO** and to a small extent by a **dehydrogenase**

The decarboxylase is non-specific, acts on DOPA as well as 5-hydroxytryptophan (5-HTP) to produce DA and 5-HT respectively.

Like NA, 5-HT is actively taken up by an amine pump serotonin transporter **(SERT),** a Na+ dependent carrier, which operates at the membrane of **platelets** (therefore, 5-HT does not circulate in free form in plasma) and serotonergic nerve endings.

This pump is inhibited by **selective serotonin reuptake inhibitors (SSRIs) and tricyclic** **antidepressants (TCAs).**

**Platelets do not synthesize 5-HT but acquire it by uptake during passage through intestinal blood vessels.**

Again like CAs, 5-HT is stored within storage vesicles, and its uptake at the vesicular membrane by vesicular monoamine transporter (VMAT-2) is inhibited by reserpine, which causes depletion of CAs as well as 5-HT. The degrading enzyme

MAO is also common for both. **The isoenzyme MAO-A preferentially metabolizes 5-HT**

**RECEPTORS**

Four families of 5-HT receptors

1. 5-HT1,
2. 5- HT2,
3. 5-HT3,
4. 5-HT4-7
* Comprising of 14 receptor subtypes have so far been recognized.

All 5-HT receptors (except 5-HT3) are G protein coupled receptors which function through decreasing (5-HT1) or increasing (5-HT4, 5-HT6, 5-HT7) cAMP production or by generating IP3/ DAG (5-HT2) as second messengers.

**The 5-HT3 is a ligand gated cation (Na+,K+) channel which on activation elicits fast depolarization.**

**5-HT1 Receptors**

Five subtypes (5-HT1 A, B, D, E, F) have been identified. All subtypes of 5-HT1 receptor couple with **Gi/Go**protein and inhibit adenylyl cyclase;

**5-HT2 Receptors**

There are 3 subtypes of 5-HT2 receptor; all are coupled to Gq protein→activate phospholipase C and function through generation of IP3/DAG. 5-HT2A receptor also inhibits K+ channels resulting is slow depolarization of neurones.

**α-methyl 5-HT**is a selective agonist for all 3 subtypes.

**5-HT3 Receptor**

This is the **neuronal 5-HT receptor** which rapidly depolarizes nerve endings by opening the cation channel located within it and corresponds to the original M type receptor. It mediates the indirect and reflex effects of 5-HT

**5-HT4–7 Receptors**

The 5-HT4 receptor couples to Gs protein, activates adenylyl cyclase and has been demonstrated in the mucosa, plexuses and smooth muscle of the gut → probably involved in augmenting intestinal secretion and peristalsis.

**Cisapride and renzapride are selective 5-HT4 agonists.**

The recently cloned **5-HT5, 5-HT6 and 5-HT7 receptors** are closely related to the 5-HT4 receptor. These are mainly located in specific brain areas, but their functional role is not known.

An interesting finding is that **clozapine** (atypical antipsychotic) has **high affinity for 5-HT6 and 5-HT7** **receptors**in addition to being a**5-HT2A/2C antagonist.**

**Actions of Serotonin on different organs.**

**1.    CVS**

Arteries are **constricted** (by direct action on vascular smooth muscle) as well as **dilated** (through EDRF release) by 5-HT, depending on the vascular bed and the basal tone. Larger arteries and veins are characteristically constricted.

In the microcirculation 5-HT dilates arterioles and constricts venules: capillary pressure rises and fluid escapes. The direct action to increase capillary permeability is feeble.

 **2. Visceral smooth muscles**

5-HT is a potent stimulator of g.i.t., both by direct action as well as through enteric plexuses. **Peristalsis** is increased and diarrhoea can occur (also due to increased secretion). **It constricts bronchi, but is less** **potent than histamine and leukotrienes.**

**3. Glands**

5-HT inhibits **gastric secretion** (both acid and pepsin), but **increases mucus production.** It thus has ulcer protective property.

**4. Nerve endings and adrenal medulla**

Afferent nerve endings are activated causing tingling and pricking sensation, as well as pain.

Depolarization of visceral afferents elicits respiratory and cardiovascular reflexes, nausea and vomiting.

**5. Respiration**

A brief stimulation of respiration (mostly reflex from bronchial afferents) and hyperventilation are the usual response, but large doses can cause transient apnoea through coronary chemoreflex.

**6. Platelets**

By acting on **5-HT2A receptors** 5-HT causes changes in **shape of platelets, but is a weak aggregator.**

**7. CNS**

Injected i.v., 5-HT does not produce central effects because of poor entry across bloodbrain barrier.

**PATHOPHYSIOLOGICAL ROLES OF SEROTONIN**

 1.       **Neurotransmitter**

 5-HT is a confirmed neurotransmitter in the brain; brain 5-HT has a fast turnover rate.

Cells containing 5-HT are present in the raphe nuclei of brainstem, substantia nigra and few other sites—send axons rostrally (to limbic system, cortex and neostriatum) as well as caudally to spinal cord.

5-HT appears to beinvolved in sleep, temperature regulation, thought, cognitive function, behaviour and mood, appetite, vomiting and pain perception.

**2.**    **Precursor of melatonin**

5-HT is theprecursor of melatonin in pineal gland. It is believed to regulate the biological clock and maintain circadian rhythm.

**3.**    **Neuroendocrine function**

The hypothalamic neurones that control release of anterior pituitary hormones are probably regulated by serotonergic mechanism.

**4.    Nausea and vomiting**

Especially thatevoked by cytotoxic drugs or radiotherapy ismediated by release of 5-HT and its action on 5-HT3 receptors in the gut, area postrema andnucleus tractus solitarious.

**5.**    **Migraine**

5-HT is said to initiate the vasoconstrictor phase of migraine and to participate in neurogenic inflammation of the affected blood vessels.

**Methysergide (5-HT antagonist)**is an effective prophylactic and**sumatriptan (5-HT1B/1Dagonist)**cancontrol an attack.

**Haemostasis**

Platelets release 5-HT during aggregation at the site of injury to blood vessel.

Acting in concert with collagen and other mediators, this 5-HT accelerates platelet aggregation and clot formation. Thus, it serves to amplify the response. Its contractile action appears to promote retraction of the injured vessel.

Both the above actions contribute to haemostasis.

**6.       Raynaud’s phenomenon**

Release of 5-HT from platelets may trigger acute vasospastic episodes of larger arteries involved in Raynaud’s phenomena. **Ketanserin has prophylactic value.**

**7.    Variant angina**

Along with **thromboxane-A2**, 5-HT released from platelets has been implicated in causing coronary spasm and variant angina.

However, the inefficacy of anti 5-HT drugs inthis condition points to the involvement of other mediators.

**8.    Hypertension**

Increased responsiveness to 5-HT as well as its reduced uptake and clearance by platelets has been demonstrated in hypertensive patients.

**Ketanserin**has antihypertensive property.

**5-HT has been held responsible for pre-eclampticrise in BP.**

**9.    Intestinal motility**

Enterochromaffin cells and 5-HT containing neurones may regulate peristalsis and local reflexes in the gut.

This system appears to be activated by intestinal distension and vagal efferent activity.

**10. Carcinoid syndrome**

**The carcinoid tumours produce massive quantities of 5-HT.**

Bowel hypermotility and bronchoconstriction incarcinoid is due to 5-HT but flushing and hypotension are probably due to other mediators.

Pellagra may occur due to diversion of tryptophanfor synthesizing 5-HT.

**Use**

Due to widespread and variable actions,

5-HT has no therapeutic use.

**DRUGS AFFECTING 5-HT SYSTEM**

 **1.    5-HT precursor**

 Tryptophan increases brain 5-HT and produces behavioural effects

 **2.**    **Synthesis inhibitor**

 p-Chlorophenylalanine (PCPA) selectively inhibits tryptophan hydroxylase (rate limiting step) and reduces 5-HT level in tissues.

 **It is not used clinically due to high toxicity.**

 **3.**    **Uptake inhibitor**

**Tricyclic antidepressants**inhibit 5-HT uptake along with that of NA.

The **selective serotonin reuptake inhibitors (**SSRI) like fluoxetine, sertraline, etc. inhibit only 5-HT reuptake and have **anti depressant and antianxiety property**.

**4.**    **Storage inhibitor**

 **Reserpine**blocks 5-HT (as well as NA) uptake into storage vesicles by inhibiting VMAT-2, and causesdepletion of all monoamines.

**Fenfluramine**selectively releases 5-HT by promoting its reverse transport at serotonergic nerve endingsin the brain, followed by its prolonged depletion, and has **anorectic property.**

**5.    Degradation inhibitor**

**Nonselective MAO inhibitor (tranylcypromine) and selective MAO-A inhibitor (chlorgyline)**increase 5-HT content by preventing its degradation.

**6.**    **Neuronal degeneration**

**5, 6-dihydroxytryptamine**selectively destroys 5-HT neurones.

**7.**    **5-HT receptor agonists**

A diverse range of compounds producing a variety of actions have been found to activate one or more subtypes of 5-HT receptors.

Notable among these are:

1. D-Lysergic acid diethyl amide **(LSD)**
2. **Azapirones**(like**buspirone, gepirone and ipsapirone**) are a novel class of antianxiety drugswhich do not produce sedation. They act as **partial agonists of 5-HT1A receptors** in the brain.
3. **Sumatriptan and other triptans**are selective**5-HT1D/1B agonists,**constrict cerebral bloodvessels and have emerged as the **most effective treatment of acute migraine attacks.**
4. **Cisapride**This prokinetic drug which increases gastrointestinal motility is a selective**5-HT4 agonist**.**Renzapride**is still more selective for**5-HT4 receptors.**

**8.       5-HT receptor antagonists**

 A variety of drugs block serotonergic receptors; many are nonselective, but some newer ones are highly subtype selective.

**5-HT ANTAGONISTS**

**1.**    **Cyproheptadine**

It primarily **blocks 5-HT2A receptors** and has **additional H1 antihistaminic, anticholinergic and sedative** **properties**.

The anti 5-HT activity of cyproheptadine has been utilized in controlling intestinal manifestations of carcinoid and postgastrectomy dumping syndromes as well as in antagonizing priapism/orgasmic delay caused by 5-HT uptake inhibitors like fluoxetine and trazodone.

**Side effects drowsiness, dry mouth, confusion,ataxia, weight gain**

**2.**    **Methysergide**

It is chemically related to ergotalkaloids; **antagonizes action of 5-HT** on smooth musclesincluding that of blood vessels, without producing other ergotlike effects: **does not interact with** **α** **adrenergic or** **dopamine receptors.**

Methysergide is a **potent 5-HT2A/2C antagonist** with some tissue specific agonistic actions as well; but is **nonselective—acts on 5-HT1 receptors also**.

It has been used for migraine prophylaxis, carcinoid and postgastrectomy dumping syndrome.

**Prolonged use has caused abdominal, pulmonaryand endocardial fibrosis**

**3.**    **Ketanserin**

It has selective **5-HT2 receptor blocking property** with negligible action on 5-HT1, 5-HT3 and 5-HT4 receptors and no partial agonistic activity.

Among 5-HT2receptors, **blockade of 5-HT2A is stronger than 5-HT2Cblockade.**

5-HT induced vasoconstriction, platelet aggregationand contraction of airway smooth muscle are antagonized.

**4.  Ritanserin**

**5.**    **Clozapine**

 Atypical antipsychotic is a **5-HT2A/2C blocker**.

Clozapine may also exert **inverse agonist activity at cerebral5-HT2A/2C** receptors which may account for its efficacy in resistant cases of schizophrenia

 **6.**    **Ondansetron**

 It is the prototype of the new class of selective 5-HT3 antagonists that have shown remarkable efficacy in controlling nausea and vomiting following administration of highly emetic anticancer drugs and radiotherapy.

 **Granisetron and Tropisetron are the other selective 5-HT3 antagonists**

 **ERGOT ALKALOIDS**

 **1.  Ergotamine**

 It acts as a **partial agonist and antagonist at** **α** **adrenergic and all subtypes of 5-HT1 and 5-HT2** **receptors**, but does not**interact with 5-HT3 or dopamine receptors:**produces sustainedvasoconstriction, visceral smooth muscle contraction, vasomotor centre depression and  **antagonizes the action of NA and 5-HT on smooth muscles.**

 **It is a potent emetic (through CTZ and vomiting centre) and moderately potent oxytocic.**

 **2.   Dihydroergotamine (DHE)**

 Hydrogenation of ergotamine reduces serotonergic and α-adrenergic agonistic actions, but enhances α-receptor blocking property.

 Consequently DHE is a less potent vasoconstrictor; primarily constricts capacitance vessels and causes less intimal damage.

 **It is a weaker emetic and oxytocic, but has some antidopaminergic action as well.**

 **3.  Dihydroergotoxine (Codergocrine)**

This hydrogenated mixture of ergotoxine group of alkaloids is a more potent α blocker and a very weak vasoconstrictor.

**It has been advocated for treatment of dementia**

#### Bromocriptine

The 2 bromo derivative of ergocryptine is a relatively selective dopamine D2 agonist on pituitary lactotropes (**inhibits prolactin release**), in striatum (**antiparkinsonian**) and in CTZ (**emetic—but** **less than ergotamine**).

 It has very weak anti 5-HT or α blocking actions and **is not an oxytocic.**

 **Ergometrine (Ergonovine)**

 This amine ergot alkaloid has very weak agonistic and practically no antagonistic action on α adrenergic receptors: vasoconstriction is not significant.

 Partial agonistic action on 5-HT receptors has been demonstrated in uterus, placental and umbilical blood vessels and in certain brain areas.

 It is a moderately potent 5-HT2 antagonist in g.i. smooth muscle and a weak dopaminergic agonist on the pituitary lactotropes as well as CTZ; emetic potential is low.

 The most prominent action is contraction of myometrium; used exclusively in obstetrics

**Adverse effects of Ergometrin;**

 Nausea, vomiting, abdominal pain, muscle cramps, weakness, paresthesias, coronary and other vascular spasm, chest pain (due to coronary vasoconstriction) are the frequent side effects. These drugs are contraindicated in presence of sepsis, ischaemic heart disease, peripheral vascular disease, hypertension, pregnancy, liver and kidney disease.

**PROSTAGLANDINS AND LEUKOTRIENES (Eicosanoids)**

**Prostaglandins (PGs)**and**Leukotrienes (LTs)**are biologically active derivatives of 20 carbonatom polyunsaturated essential fatty acids that are released from **cell membrane** **phospholipids**.

They are the major lipid derived **autacoids**.

Also known as **Eicosanoids.**

**CHEMISTRY, BIOSYNTHESIS AND DEGRADATION**

PG has a five membered ring and two side chains projecting in opposite directions at right angle to the plane of the ring.

There are many series of **PGs** and **thromboxanes (TXs)** designated A, B, C....I, depending on the ring structure and the substituents on it. Each series has members with subscript 1, 2, 3 indicating the number of double bonds in the side chains.

Leukotrienes are so named because they were first obtained from leukocytes (leuko) and have 3 conjugated double bonds (triene). They have also been similarly designated A, B, C.....F and given subscripts 1, 2, 3, 4.

**In the body PGs, TXs and LTs are all derived from eicosa (referring to 20 C atoms) tri/tetra/ penta enoic acids. Therefore, they can be collectively called eicosanoids.**

In human tissues, the fatty acid released from membrane lipids in largest quantity is 5,8,11,14 eicosa tetraenoic acid (**arachidonic acid**).

**During PG, TX and prostacyclin synthesis**,**2 of the 4 double bonds of arachidonic acid get saturated in the process of cyclization, leaving 2 double bonds in the side chain**. Thus,subscript 2 PGs are the most important in man**, e.g. PGE2, PGF2α, PGI2, TXA2.**

**During LT synthesis**No cyclization or reduction of double bonds occurs—the LTs of biologicalimportance are **LTB4, LTC4, LTD4.**

Eicosanoids are the most universally distributed autacoids in the body. Practically every cell and tissue is capable of synthesizing one or more types of PGs or LTs.

**There are no preformed stores of PGs and LTs**.

 They are synthesized locally and the rate of synthesis is governed by the rate of release of arachidonic acid from membrane lipids in response to appropriate stimuli. These stimuli activate hydrolases, including phospholipase A, probably through increased intracellular Ca2+.

 **The cyclooxygenase (COX) pathway generates eicosanoids with a ring structure (PGs, TXs, prostacyclin) while lipoxygenase (LOX) produces open chain compounds (LTs).**

 **All tissues have COX—can form cyclic endoperoxides PGG2 and PGH2 which are unstable compounds**.

 **Lung and spleen can synthesize the whole range of COX products.**

 **Platelets primarily synthesize TXA2**which is—chemically unstable, spontaneously changes to TXB2.

 **Endothelium**mainly generates**prostacyclin (PGI2)**which is also chemically unstable and rapidlyconverts to **6-keto PGF1α.**

 **Cyclooxygenase**is known to exist in two**isoforms COX-1 and COX-2**, both isoforms catalyse the samereactions

**COX-1**

It is a constitutive enzyme in most cells—it is synthesized and is active in the basal state; the level of COX-1 activity is not much changed once the cell is fully grown.

 Eicosanoids produced by COX-1 participate in physiological (house keeping) functions such as secretion of mucus for protection of gastric mucosa, haemostasis and maintenance of renal function

**COX-2**

Normally present in insignificant amounts, is inducible by cytokines, growth factors and other stimuli during the inflammatory response.

Eicosanoids those produced by COX-2 lead to inflammatory and other pathological changes.

 However, certain sites in kidney, brain and the foetus constitutively express COX-2 which may play physiological role.

 **Lipoxygenase pathway appears to operate mainly in the lung, WBC and platelets.**

 Its most important products are the LTs, (generated by 5- LOX) particularly **LTB4 (potent chemotactic)** and **LTC4**,

 **LTD4**which together constitute the**‘slow reacting substance of anaphylaxis’ (SRS-A)**

 A membrane associated transfer protein called **FLAP (five lipoxygenase activating protein)** carrys arachidonic acid to 5-LOX, and is essential for the synthesis of LTs.

 **Platelets have only 12-LOX.**

 **HPETEs**produced by LOX can also be converted to**hepoxilins, trioxilins and lipoxins**.

#### Inhibition of synthesis (Eicosanoids)

1. **Synthesis of COX products can be inhibited by nonsteroidal antiinflammatory drugs (NSAIDs).**
2. **Aspirin**:**acetylates COX**at a**serine residue**and causes**irreversible**inhibition while other NSAIDsare **competitive and reversible inhibitors.(BINDS AT ARGININE RESIDUE)**
3. Most NSAIDs are nonselective COX-1 and COX-2 inhibitors, but some later ones like celecoxib, etoricoxib are selective for COX-2.
4. The sensitivity of COX in different tissues to inhibition by these drugs varies; selective inhibition of formation of certain products may be possible at lower doses.
5. **NSAIDs do not inhibit the production of LTs: this may even be increased since all the arachidonic acid becomes available to the LOX pathway.**
6. **Zileuton: inhibits LOX**and decreases the production of LTs.
7. **Glucocorticosteroids**inhibit the release of arachidonic acid from membrane lipids (bystimulating production of proteins called annexins which inhibit phospholipase A2)—indirectly reduce production of all eicosanoids—PGs, TXs and LTs. Moreover, they inhibit the induction of COX-2 by cytokines at the site of inflammation.

**Degradation**

 Biotransformation of arachidonates occurs rapidly in most tissues, but **fastest in the lungs.**

 Most **PGs, TXA2 and prostacyclin** have plasma t½ of a few seconds to a few minutes.

 **PGI2 is catabolized mainly in the kidney.**

**ACTIONS AND PATHOPHYSIOLOGICAL ROLES**

**(Prostaglandins, thromboxanes and Prostacyclin)**

**1.       CVS**

**PGE2 and PGF2α cause vasodilatation in most, but not all, vascular beds.**

**PGF2α cause vasoconstriction jn many larger veins including pulmonary vein and artery.**

**PGI2**is uniformly**vasodilatory**and is more potent hypotensive than PGE2.

**TXA2**consistently produces**vasoconstriction**.

**PG endoperoxides (G2 and H2)**are inherently**vasoconstrictor**, but often produce**vasodilatation**or a biphasic response due to rapid conversion to other PGs, especially**PGI2**inthe blood vessels themselves.

**PGE2 and F2α**stimulate heart by weak direct but more prominent reflex action due to fall in BP.The cardiac output increases.

**Roles of Prostaglandins;**

1. PGs do not circulate in blood and have no role in regulating systemic vascular resistance. However, PGI2 generated in the vascular endothelium, mainly by COX-2, appears to be involved in the regulation of local vascular tone as a dilator.
2. PGE2 is continuously produced locally in the ductus arteriosus by COX-2 during foetal life—keeps it patent; at birth its synthesis stops and closure occurs. Aspirin and indomethacin induce closure when it fails to occur spontaneously. These PGs may also be important in maintaining placental blood flow.
3. PGs, generated mainly by COX-2, along with LTs and other autacoids may mediate vasodilatation and exudation at the site of inflammation.

 **2.       Platelets**

**TXA2,**which can be produced locally by platelets, is a**potent inducer of aggregation and release reaction**.

**The endoperoxides PGG2 and PGH2 are also proaggregatory.**

**PGI2**(generated by vascular endothelium) is a**potent inhibitor of platelet aggregation**.

**PGD2**has**antiaggregatory action**, but much less potent than**PGI2**.

**PGE2**has**dose dependent and inconsistent effects**.

**Role**

 TXA2 produced by platelets and PGI2 produced by vascular endothelium probably constitute a mutually antagonistic system: preventing aggregation of platelets while in circulation and inducing aggregation on injury, when plugging and thrombosis are needed.

 Aspirin interferes with haemostasis by inhibiting platelet aggregation.

 TXA2 produced by platelet COX-1 plays an important role in amplifying aggregation. Before it is deacetylated in liver, aspirin acetylates COX-1 in platelets while they are in portal circulation. Further, platelets are unable to regenerate fresh COX-1 (lack nucleus: do not synthesize protein), while vessel wall is able to do so (fresh enzyme is synthesized within hours). Thus, in low doses, aspirin selectively inhibits TXA2 production and has antithrombotic effect lasting > 3 days.

 **3.    Uterus**

 **PGE2 and PGF2α uniformly contract human uterus, in vivo, both pregnant as well as nonpregnant.**

 The sensitivity is higher during pregnancy and there is progressive modest increase with the advance of pregnancy. However, even during early stages, uterus is quite sensitive to PGs though not to oxytocin.

 **PGs increase basal tone as well as amplitude of uterine contractions. At term, PGs soften the cervix at low doses and make it more compliant.**

 Role

1. Foetal tissues produce PGs: At term PGF2α has been detected in maternal blood. It is postulated that PGs mediate initiation and progression of labour.  **Aspirin has been found to delay the initiation of labour and also prolong its duration.**
2. Dysmenorrhoea in many women is associated with increased PG synthesis by the endometrium. This apparently induces uncoordinated uterine contractions which compress blood vessels →uterine ischaemia →pain. **Aspirin group of drugs are highly effective in relieving dysmenorrhoea in most women.**

 **4.       Bronchial muscle**

**PGF2α, PGD2 and TXA2**are potent**bronchoconstrictors**(**more potent than histamine**)

**PGE2**-powerful**bronchodilator**.**PGI2**-milddilatation. (PGE2 and PGI2 also inhibit histaminerelease and are effective by aerosol)

**Asthmatics are more sensitive to constrictor as well as dilator effects of PGs.**

**Role**

1. Asthma may be due to an imbalance between constrictor PGs (F2 , PGD2, TXA2) and LTs on one hand and dilator ones (PGE2, PGI2) on the other.
2. In allergic human asthma, LTs play a more important role, and COX inhibitors are without any effect in most patients.

**5.**    **GIT**

 Propulsive activity is enhanced in man, especially by **PGE2** →colic and watery **diarrhoea** are important side effects. PGE2 acts directly on the intestinal mucosa and increases water, electrolyte and mucus secretion.

 **Role:**PGs may be involved in mediating toxin induced increased fluid movement in secretorydiarrhoeas. In certain diarrhoeas, aspirin can reduce stool volume, but is not uniformly effective.

 PGE2 markedly **reduces acid secretion** in the stomach. **Volume of juice and pepsin content are also** **decreased.**It inhibits fasting as well as stimulated secretion (by feeding, histamine, gastrin). Releaseof **gastrin is suppressed**. The gastric **pH may rise upto 7.0**. PGI2 also inhibits gastric secretion, but is less potent. **Secretion of mucus and HCO3¯ by gastric** mucosal epithelial cells as well as mucosal blood flow are increased. Thus, PGs are **antiulcerogenic.**

**Role in PUD protection;**

1. PGs (especially PGI2) appear to be involved in the regulation of gastric mucosal blood flow. They may be functioning as natural ulcer protectives by enhancing gastric mucus and HCO3 ¯ production, as well as by improving mucosal circulation and health. The ulcerogenic action of NSAIDs may be due to loss of this protective influence. Normally, gastric mucosal PGs are produced by COX-1. Selective COX-2 inhibitors are less ulcerogenic.
2. However, COX-2 gets induced during ulcer healing, and COX-2 inhibitors have the potential to delay healing.

**6.**    **Kidney**

1. **PGE2 and PGI2**increase water, Na+ and K+ excretion and have a diuretic effect. They cause renal**vasodilatation**and inhibit tubular reabsorption. PGE2 antagonizes ADH action, and this adds to thediuretic effect.
2. In contrast, **TXA2** causes renal **vasoconstriction**.
3. PGI2, PGE2 and PGD2 evoke release of renin.

 **Role**

1. PGE2 and PGI2 produced mainly by COX-2 in the kidney appear to function as intrarenal regulators of blood flow as well as tubular reabsorption in kidney. Accordingly, the NSAIDs, including selective COX-2 inhibitors, tend to retain salt and water.
2. Renin release in response to sympathetic stimulation and other influences may be facilitated by PGs.
3. **Bartter’s syndrome**, characterized by decreased sensitivity to angiotensin II is associated with increased PG production; **improved by prolonged use of NSAIDs.**

 **7.       CNS**

**Role**

PGE2 may mediate pyrogen induced fever and malaise. Aspirin and other inhibitors of PG synthesis are antipyretic. Pyrogens, including cytokines released during bacterial infection, trigger synthesis of PGE2 in the hypothalamus, which resets the thermostat to cause fever. COX-2 is the major isoenzyme involved; selective COX-2 inhibitors are equally efficacious antipyretics. A role of COX-3 has also been proposed.

PGs may be functioning as neuromodulators in the brain by regulating neuronal excitability. A role in pain perception, sleep and some other functions has been suggested.

**8.       AUTONOMIC NERVOUS SYSTEM**

 Depending on the PG, species and tissue, both **inhibition as well as augmentation of NA release from** **adrenergic nerve endings**has been observed. Role PGs may modulate sympathetic neurotransmission inthe periphery.

**9.**    **Peripheral nerves**

**PGs (especially E2 and I2)**sensitize afferent nerve endings to pain inducing chemical and mechanicalstimuli.

**Role**

PGs appear to serve as **algesic agents** during inflammation. They cause tenderness and amplify the action of other algesics. **Inhibition of PG synthesis is a major antiinflammatory mechanism.**

**10. Eye:**

PGF2α induces ocular inflammation and lowers i.o.t by enhancing uveoscleral and trabecular outflow.

**Role**

Locally produced PGs appear to facilitate aqueous humor drainage. The finding that COX-2 expression in the ciliary body is deficient in **wide angle glaucoma** patients supports this cotention.

**11. Endocrine system**

**PGE2**facilitates the release of anterior pituitary hormones—growth hormone, prolactin, ACTH, FSH andLH as well as that of insulin and adrenal steroids.

**12. Metabolism**

**PGEs**are antilipolytic, exert an insulin like effect on carbohydrate metabolism and mobilize Ca2+ frombone. They may mediate hypercalcaemia due to bony metastasis.

**LEUKOTRIENS**

The straight chain lipoxygenase products of arachidonic acid are produced by a more limited number of tissues but probably they are pathophysiologically as important as PGs.

 (**LTB4 mainly by neutrophils; LTC4 and LTD4—the cysteinyl LTs—mainly by macrophages**),

 **1.**    **CVS and blood**

 **LTC4 and LTD4**injected i.v. evoke a brief rise in BP followed by a more prolonged fall. The fall in BP is notdue to vasodilatation because no relaxant action has been seen on blood vessels.

 It is probably a result of coronary constriction induced decrease in cardiac output and reduction in circulating volume due to increased capillary permeability.

 These LTs markedly increase capillary permeability and are more potent than histamine in causing local edema formation.

 **LTB4**is highly chemotactic for**neutrophils and monocytes**; Migration of neutrophils through capillariesand their clumping at sites of inflammation in tissues is also promoted by LTB4.

 The **cysteinyl LTs (C4, D4)** are chemotactic for **eosinophils**.

 **Role**

1. LTs are important mediators of inflammation. They are produced (along with PGs) locally at the site of injury.
2. While LTC4 and D4 cause exudation of plasma, LTB4 attracts the inflammatory cells which reinforce the reaction.
3. 5-HPETE and 5-HETE may facilitate local release of histamine from mast cells.

**Leukotriens effects on Smooth muscle;**

 **LTC4 and D4**contract most smooth muscles. They are potent**bronchoconstrictors**and induce spasticcontraction of g.i.t. at low concentrations. They also increase mucus secretion in the airways.

**Role**

**The cysteinyl LTs (C4 and D4) are the most important mediators of human allergic asthma.**

They are released along with PGs and other autacoids during AG: AB reaction in the lungs.

In comparison to other mediators, they are more potent and are metabolized slowly in the lungs, exert a long lasting action.

LTs may also be responsible for abdominal colics during systemic anaphylaxis.

**2.**    **Afferent nerves**

Like PGE2 and I2, the LTB4 also sensitizes afferents carrying pain impulses—contributes to pain and tenderness of inflammation.

**USES OF PGs**

Clinical application of PGs and their analogues is rather restricted because of limited availability, short lasting action, cost and frequent side effects. However, their use in glaucoma and in obstetrics is now common place. Their indications are:

**1. Abortion;**

1. Abortion During the first trimester, termination of pregnancy by transcervical suction is the procedure of choice. Intravaginal PGE2 pessary inserted 3 hours before attempting dilatation can minimise trauma to the cervix by reducing resistance to dilatation.
2. Medical termination of pregnancy of upto 7 weeks has been achieved with high success rate by administering mifepristone (antiprogestin) 600 mg orally 2 days before a single oral dose of misoprostol 400 g.
3. Ectopic pregnancy should be ruled out beforehand and complete expulsion should be confirmed afterwards. Uterine cramps, vaginal bleeding, nausea, vomiting and diarrhoea are the common side effects.
4. Methotrexate administered along with misoprostol is also highly successful for inducing abortion in the first few weeks of pregnancy.
5. PGs have a place in midterm abortion, missed abortion and molar gestation, though delayed and erratic action and incomplete abortion are a problem.
* **2. Induction/Augementation of labour;**
* Induction/augmentation of labour PGs do not offer any advantage over oxytocin for induction of labour at term. They are less reliable and show wider individual variation in action. PGE2 and PGF2α  (rarely) have been used in place of oxytocin in toxaemic and renal failure patients, because PGs do not cause fluid retention that is possible with oxytocin. PGE2 may also be used to augment labour, if it is slow, in primipara. Intravaginal route is preferred now: side effects care milder; extra/intra amniotic route is infrequently used.

**3. Cervical ripening**

Cervical priming (ripening) Applied intravaginally or in the cervical canal, low doses of PGE2 which do not affect uterine motility make the cervix soft and compliant. This procedure has yielded good results in cases with unfavourable cervix. If needed labour may be induced 12 hours later with oxytocin: chances of failure are reduced.

**4. PPH-Post Partum Haemorrhage management;**

Postpartum haemorrhage (PPH) Carboprost (15-methyl PGF2 ) injected i.m. is an alternative drug for control of PPH due to uterine atony, especially in patients unresponsive to ergometrine and oxytocin. PGE2 (Dinoprostone) PROSTIN-E2 for induction/augmentation of labour, midterm abortion. Gemeprost for softening of cervix in first trimester—1 mg 3 hr before attempting dilatation; for 2nd trimester abortion/molar gestation— PGF2     (Dinoprost) for midterm abortion/induction of labour (rarely used).

 15-methyl PGF2    (Carboprost) PPH, midterm abortion, missed abortion.

**5.  PUD treatment;**

Peptic ulcer Stable analogue of PGE1 (misoprostol) is occasionally used for healing peptic ulcer, especially in patients who need continued NSAID therapy or who continue to smoke

**6.  Glaucoma/increased intra ocular pressure;**

Glaucoma Topical PGF2 analogues like latanoprost, travoprost, bimatoprost that are FP receptor agonists are the first choice drugs in wide angle glaucoma.

**7. Management of congenital heart disease**

To maintain patency of ductus arteriosus in neonates with congenital heart defects, till surgery is undertaken. PGE1 (Alprostadil) is used; apnoea occurs in few cases.

**8.  Prophylaxis during haemodialysis;**

To avoid platelet damage PGI2 (Epoprostenol) can be used to prevent platelet aggregation and damage during haemodialysis or cardiopulmonary bypass. It also improves harvest of platelets for transfusion. Few cases of primary pulmonary hypertension have been successfully maintained on epoprostenol infusion

SIDE EFFECTS These are: nausea, vomiting, watery diarrhoea, uterine cramps, unduly forceful uterine contractions, vaginal bleeding, flushing, shivering, fever, malaise, fall in BP, tachycardia, chest pain.

 **PLATELET ACTIVATING FACTOR (PAF)**

 Like eicosanoids, platelet activating factor (PAF) is a cell membrane derived polar lipid with intense biological activity.

 PAF is **acetyl-glyceryl ether-phosphoryl choline**. The ether-linked alkyl chain in human PAF is mostly 16 or 18 C long.

 **Synthesis and degradation**

 PAF is synthesized from precursor phospholipids present in cell membrane by the following reactions:

 The second step is rate limiting. Antigen-antibody reaction and a variety of mediators stimulate PAF synthesis in a Ca2+ dependent manner on demand: there are no preformed stores of PAF. In contrast to eicosanoids, the types of cells which synthesize PAF is quite limited—mainly WBC, platelets, vascular endothelium and kidney cells.

PAF is degraded in the following manner:

**Actions**

PAF has potent actions on many tissues/ organs.

**1. Platelets**

**Aggregation**and release reaction; also releases**TXA2**; i.v. injection of PAF results in intravascularthrombosis.

**2.  WBC**

**PAF is a potent chemotactic for neutrophils, eosinophils and monocytes**. It stimulates neutrophils toaggregate, to stick to vascular endothelium and migrate across it to the site of infection. It also prompts release of lysosomal enzymes and LTs as well as generation of superoxide radical by the polymorphs. The chemotactic action may be mediated through release of **LTB4**. It induces degranulation of eosinophils.

**3.  Blood vessels**

 **Vasodilatation**mediated by release of**EDRF**occurs fall in BP on i.v. injection. Decreased coronaryblood flow has been observed on intracoronary injection, probably due to formation of platelet aggregates and release of TXA2. PAF is the most potent agent known to increase vascular permeability. Wheal and flare occur at the site of intradermal injection. Injected into the renal artery PAF reduces renal blood flow and Na+ excretion by direct vasoconstrictor action, but this is partly counteracted by local PG release.

**4.  Visceral smooth muscle**

**Contraction**occurs by direct action as well as through release of**LTC4, TXA2 and PGs**.

**Aerosolized PAF is a potent bronchoconstrictor.**

In addition, it produces mucosal edema, secretion and a delayed and long-lasting bronchial hyper-responsiveness. It also stimulates intestinal and uterine smooth muscle.

**5. Stomach**

 PAF is highly **ulcerogenic**: erosions and mucosal bleeding occur shortly after i.v. injection of PAF. The gastric smooth muscle contracts.

 **Mechanism of action**

 Membrane bound specific PAF receptors have been identified. The PAF receptor is a G-protein coupled receptor which exerts most of the actions by coupling with Gq protein and generating intracellular messengers IP3/DAG Ca2+ release. It can also inhibit adenylyl cyclase by coupling with Gi protein. As mentioned above**, many actions of PAF are mediated/ augmented by PGs, TXA2 and LTs which may be considered its extracellular messengers.**PAF also acts intracellularly, especially in the endothelial cells;rise in PAF concentration within the endothelial cells is associated with exposure of neutrophil binding sites on their surface. Similarly, its proaggregatory action involves unmasking of fibrinogen binding sites on the surface of platelets.

 **PAF antagonists**

 A number of natural and synthetic PAF receptor antagonists have been investigated. Important among these are;

**Ginkgolide B** (from a Chinese plant), and some structural analogues of PAF. The PAF antagonists have manyfold therapeutic potentials like treatment of stroke, intermittent claudication, sepsis, myocardial infarction, shock, g.i. ulceration, asthma and as contraceptive. Some of them have been tried clinically but none has been found worth marketing.

 **Alprazolam and triazolam antagonize some actions of PAF.**

 **Pathophysiological roles**

PAF has been implicated in many pathological states and some physiological processes by mediating cell-to-cell interaction. These are:

**1.  Inflammation**: Generated by leukocytes at the site of inflammation PAF appears to participate in thecausation of vasodilatation, exudation, cellular infiltration and hyperalgesia.

**2.    Bronchial asthma**: Along with LTC4 and LTD4, PAF appears to play a major role by causingbronchoconstriction, mucosal edema, recruiting eosinophils and provoking secretions. It is unique in producing prolonged airway hyperreactivity, so typical of bronchial asthma patient.

**3.  Anaphylactic (and other) shock conditions**: are associated with high circulating PAF levels.

**4.  Haemostasis and thrombosis:**PAF may participate by promoting platelet aggregation.

 **5. Rupture of mature graafian follicle and implantation**: Early embryos which produce PAF have greater chance of implanting. However, PAF is not essential for reproduction.

Ischaemic states of brain, heart and g.i.t., including g.i. ulceration.

## Unit Two Content..

### Topic 1.1: Management of Peptic Ulcer Disease (PUD), EMETICIS, ANTI EMETICSand ANTIBLOATING (Carminatives)

**PEPTIC ULCER DISEASE AND MANAGEMENT**

  Gastric acidity

•Secretion of gastric acid occur in three ways:

**1. Primary secretion**

1. Also called narrow phase/cephalic/primary phase
2. Gastric acid secretion is due to reflex excitation of centers in the medulla oblongata and the efferent pathway in the vagus nerve
3. This phase can be stimulated/initiated by either site of food, smell of food or even thought of food.
4. Other thoughts that may stimulate it : anger, anxiety, apprehension
5. The main transmitter for the phase is acetylcholine

**2. Secondary phase**

1. Mainly involve local reflexes and local hormones in the GIT especially gastrin
2. The phase is initiated by the actual presence of food in the stomach which induces mechanical distension of pyloric antrum
3. The presence of food stimulate local reflexes by virtue of presence of stimulatory chemical substances in the food like amino acids, peptones, caffeine, ethanol etc
4. The local reflexes results in secretion of gastric juice that is rich in HCL
5. The chemical transmitter is acetylcholine. Acetylcholine can also cause direct release of gastrin
6. Maximum gastric acid secretion requires intact cholinergic nerves and also presence of gastrin

**3. Intestinal phase**

1. Involves release of enterogastrin from duodenum
2. Also involves release of substances such as cholescystokinin and enteroxyntin
3. The mechanisms is not clear
4. Serotonin inhibits intestinal phase and its absence induces formation of ulcers
5. Substances that cause depletion of serotonin have been known to be ulcerogenic for example reserpine , adrenergic neurone blocker depletes catecholamines and serotonin

   **Ulcerogenic agents**

1. Anti-inflammatory drugs e.g. NSAIDs which inhibit prostaglandins that are important for maintenance of integrity of intestinal membrane
2. Methylxanthines e.g. xanthines, caffeine, theophiline and theobromide
3. Glucocorticoids-cause peptic ulcers after prolonged use
4. Prolonged use of vasodilators such as alpha adrenergic blockers e.g. phentolamine, prazosin
5. Reserpine-increases gastric acid secretion and vagal activity. Causes depletion of serotonin which is supposed to block or terminate the intestinal phase
6. Betahistine-has histamine like effects. Act by inhibiting metabolism of histamine. It’s a vestibular sedative used in management of vertigo and meniers disease.

**PEPTIC ULCER DISEASE**

**Factors that predispose to PUD**

1. Lifestyle-stress
2. Excessive alcohol consumption
3. Drugs e.g prolonged used of ASA.
4. Blood group O+ is at higher risk
* **First signs of PUD**
1. Epigastric pain-pain referred to upper abdomen
2. Burning sensation to esophagus
3. Blood in stool
4. Haematemesis
5. Severe generalized abdominal pain in severe cases

    **Diagnosis of PUD;**

1. History of epigastric pain
2. Endoscopy/gastroscopy
3. Barium meal test
4. Rapid urease test for H pylori
5. Cultures for H pylori detection

**Peptic Ulcer Disease management;**

**Drugs for PUD**

1. Antacids
2. Anti-secrotory agents
3. H2-receptor blockers
4. Anti-cholinergic agents
5. Proton pump inhibitors
6. Prostaglandins

###     1.  Antacids

•They react with HCL in the GIT through neutralization or potentially neutralize gastric acidity

•They increase PH thus relieving pain and discomfort

•They abolish muscle spasm by adjusting the muscle tone

•Are also used in hyperchlorhydria and Zollinger Ellison syndrome

•They are salts of magnesium, aluminium, potassium and even sodium

•They have varying levels of buffering/neutralizing capacity and quantity of actions e.g K+ salts have rapid onset of action and short duration of action while Al3+ salts have long onset of action and longer duration of action

•Should not raise the stomach PH above 6 to prevent deactivation of pepsin which may interfere with digestion.

**Classification of antacids**

1. Systemic alkaline antacids
2. Non-systemic colloidal antacids

#### 1. Systemic alkaline antacids

•Consists of salts that are absorbed in the GIT and are capable of producing metabolic alkalosis thus disturbing acid-base balance

•Are preferred when rapid onset of action is required though not commonly used

•Should be avoided in hypertensive patients

 Examples of systemic antacids

1. NA2HCO3 ( Sodium bicarbonate), used in many effervescent mixtures e.g Eno, Andrews.

**2.  Non-systemic colloidal antacids**

•Consists of antacid with cationic moiety that are not absorbed or little absorbed from the GIT

•Neutralize gastric acid, not associated with systemic alkalosis

•Minimal systemic effects

Examples of non systemic antacids:

1. Ca(OH)2,
2. CaCO3,
3. Al(OH)3,
4. MgCO3 and
5. Magnesium trisilicate

**Calcium carbonate, caco3**

1. More effective than aluminium hydroxide
2. Very good for the treatment of heartburn, reflux esophagitis and flatulence
3. Neutralizing activity maintains PH between 3.7-5.8, thus do not deactivate pepsin
4. Less expensive and rapid onset of action
5. May be absorbed in large doses leading to formation of calcific renal stones

**Magnesium salts**

1. Magnesium trisilicate is commonly used
2. Has slow onset of action and longer duration of action
3. Its neutralizing capacity may raise PH of GIT to 7
4. Can absorb pepsin
5. Have a laxative effect  and thus are combined with Al(OH)3 or caco3 neutralize this effect
6. May cause renal toxicity if used for a long time, CVS impairement, neurological disturbance and death.

 **Aluminium hydroxide, Al(OH)3**

1. Most popular antacid
2. Have acid neutalizing capacity and buffering capacity, thus potent antacid
3. Neutralize gastric acidity to PH 4-6 do not deactivate pepsin
4. They coat ulcerated cells and potent against direct contact with acid
5. Minimally absorbed from the GIT and cause less systemic effects

### 2.  Anti-secretory agents

#### 1).  H2-Receptor blockers

1. Are competitive reversible blockers of histamine at H2-receptors
2. Decrease gastric acid and pepsin secretion
3. May decrease release of intrinsic factor if used for a long time
4. Their efficacy can be compared to those of antacids and have lower incidence of relapses
5. Metiamide and burimamide were first members to be synthesized but lacked potency and selectivity
6. Newer drugs in this group include:
	1. Cimetidine,
	2. Ranitidine,
	3. Famotidine,
	4. Nizatidine,
	5. Roxatidine and
	6. Niperotidine

**1. Cimetidine**

•It is as 10x as effective as burimamide

•Formulated in form of tabs or injections 200-800 mg

•Dose : 200 mg tds or 400 mg od

  Adverse effects of Cimetidine

1. Acute pancreotitis
2. Acute interstitial nephritis
3. Induce anti-androgenic effects and decrease libido after long term use
4. Endocrine disturbance e.g. can cause plasma increase in prolactins and parathyroid hormone
5. May potentiate effects of beta blockers e.g propranolol
6. May potentiate the effects of benzodiazepines
7. May cause reversible mental confusion especially in very ill and elderly patients
8. Can reduce tetracycline absorption by raising gastric PH  and interfering with dissolution of tetracycline
9. Inhibits liver microsomal enzymes and can potentiate the effects of drugs metabolized by the liver
10. Interact with phenytoin,theophiline and chlordiazepoxide and reduce their effects
11. By raising gastric PH cimetidine favours the growth of bacteria including the nitrate producing bacteria in the stomach and duodenum and their presence cimetidine is metabolised to nitrosocimetidine which is a potential carcinogenic agent.
12. Reduces the rate of hair growth and used in treatment of hirsutism

**2. Ranitidine**

•Formulated as**tablets and injectables, dose: 150 mg bd for less severe cases and 300 mg od for severe cases**

•Have fewer side effects

•More expensive

•Incidence of gastric cancers is lower due to structural differences

**3. Famotidine**

•It is given at **dose of 20-40 mg od at bed time**

•10x as potent as cimetidine

•It is given after major surgery and patients who are likely to be bed ridden for a very long time since they will get PUD

•H2-receptor blockers are generally well tolerated

•Has anti-androgenic effects

•Duration of treatment with H2-receptor blockers is a minimum of 6 weeks

•Treatment can be continued for 6 months in chronic conditions

#### Uses of H2-receptor blockers

1. Management of gastric ulcers
2. Management of duodenal ulcers
3. Reflux esophagitis
4. Zollinger Ellison syndrome
5. Tumour of pancrease associated with increased levels of pepsin/HCL.

**2)  Proton Pump Inhibitors (PPIs)**

•Gastric acid secretion is driven by enzyme in the secretory membrane in the parietal cell

•It is involved in the exchange of H+ from the cytosol of the parietal cells with K+ from the secretory canaliculi.

•This process is preceded by a passive movement of K+ and CL- out of the cell cytoplasm into the secretory canaliculi upon stimulation of parietal cell.

•The net effect is the formation of HCL.

•The proton pump inhibitors inhibits H+/K+ ATpase hence inhibiting acid production

•Are very effective especially when used as triple therapy in situations where H pylori is implicated

•Are superior to H2-receptor blockers

•Provide symptomatic relief

•Healing rates are higher

•Are cost effective

•Better adherence because dose regimen is OD

•Very effective in management of stress ulcers and can also be used prophylactically

**Typical examples of PPIs**

1. Omeprazole,
2. Lanzoprazole,
3. Pentoprazole,
4. Rabeprazole and
5. Esomeprazole.

•Esomeprazole is enantiomer of omeprazole

**Pharmacokinetics of PPIs;**

1. Have similarity in absorption rates, distribution, metabolism and excretion
2. All PPIs are extensively metabolised in the liver cytochrome P450 mixed function oxidases especially CYP2C19 and CYP3A4.
3. Are well tolerated and excellent safety profile.

**Clinical uses of PPIs.**

1. Management of gastrinomas
2. Management of H pylori associated ulcers, typical combination therapies include:
	1. PPI +Clarithromycin 500 mg + amoxycillin 1g
	2. PPI +  Clarithromycin 500 mg + metronidazole 400 mg
	3. PPI + Clarithromycin 500 mg + amoxiclav 625 mg

•The above combination has cure rate of 88-95%

Bismuth salts

1. Potentiate the effect of metronidazole and also reduce the rate of development of resistance to metronidazole
2. H2  blockers are combined with bismuth e.g. ranitidine + bismuth salts + metronidazole
3. Other antibiotics include: tetracyclines, erythromycin and azithromycin

**3) Anticholinergics;**

•Are selective M1 receptor blockers

•Duration of treatment is 1-2 weeks

•Inhibits primary and secondary phase of acid production

•Are antispamodics

•Used in combination with other antiulcer drugs e.g. H2 receptor blockers

•Are effective and well tolerated

  Examples of anticholinergics: Pirenzepine, Benzotropine

  Side effects of Anticholinergics;

1. •Constipation
2. •Acute headaches

 **Other anti ulcers agents**

 **1.  Prostaglandins-PGE2**

1. Inhibits gastric acid secretion via cAMP system
2. Mainly used in management of NSAID induced ulcers
3. Also as abortifacient and management of postpartum haemorrhages

Example include Misoprostol (Cytotek)

**2.  Carbenoxolone sodium**

1. Increases rate of mucous secretion
2. Prolongs lifespan of mucous cells
3. Inhibits action of pepsin
4. Can cause Na+ retention and increases K+ excretion and therefore should be used with caution in hypertension

**3.  Liquorice (glycyrrhiza)**

1. Promotes ulcer healing by increasing rate of mucous secretion
2. Can cause sodium retention due to presence of glycyrrhiza

 **4.   Local anaesthetics**

1. Useful in PUD
2. Used in combination with antacids
3. Used in management of pain associated with peptic ulcers
* Examples: Oxythazine and Benzocaine

**5.  Algnic acid derivatives**

1. Commonly used in PUD
2. Have mucoprotective properties

 **Antibiotics in PUD**;

1. Only indicated in duodenal ulcers where H pylori is implicated

#### Other anti Ulcer agents;

**1)  Sucralfate**

1. Contains sulphated polysaccharide plus aluminium complexes
2. Have mucoprotective effects and inhibits diffusion of H+ and also potentially inhibits pepsin
3. Neutralizes gastric acid locally in the GIT without affecting intra-gastric PH
4. Binds bile acids and salts
5. Equipotent to H2 antagonists but with minimal side effects
6. Form of satchets e.g. 1 g satchets
* Dose: **1 satchet half hour before food tds**

**2)  Garfanate**

1. Found in white cabbage promotes healing by cytoprotective effects
2. In USA used as tabs 100-200 mg bd

**3)  Sedatives**

1. Alleviates anxiety and stress associated with increased acid production
2. Examples: benzodiazepines such as diazepam, barbiturates

### EMETICS

•Used to induce vomiting

1. Centrally acting emetics
2. Reflex emetics

**1. Centrally acting emetics**

•Act by stimulating chemo trigger zones which in turn stimulates vomiting centre e.g. apomorphine

•Others are:

1. Increased intra occular pressure causes centrally mediated vomiting
2. Excessive pain
3. Motion sickness
4. Feeling of disgust
5. Cardiac glycosides and ergot alkaloids

**2.  Reflex emetics**

•Act locally and cause local irritation of pharyngeal or GIT tract to induce reflex vomiting by irritant effects

•Examples-

1. Copper sulphate,
2. Zinc sulphate,
3. Mercuric salts,
4. Antimony salts,
5. Emetine from ipecacuanha and
6. High concentration of sodium chloride, warm.

•Are not effective parenterally

**Other drugs with emetic effects**

1. Tetracycline
2. Colchicine
3. Antineoplastic drugs
4. NSAIDs
5. Chlorohydrate

•Emetics do not have wide chemical applications

•Indicated for management of some types of poisoning

•Excessive emesis of CL- and K+ leads to dehydration

 **Chlorpiricin ( vomiting gas )**

•Product of misuse during wartime

### ANTIEMETICS;

Drugs used to prevent vomiting e.g. in

1. Pregnancy
2. Motion sickness
3. Excessive alcohol
4. Chemotherapy
5. Anti-migraine drugs
6. Radiation therapy
7. Disease induced emetics
8. Post operative nausea and vomiting

•Common anti emetics have weak sedative effects, atropine like effects, antihistamine and neuroleptic effects

**Examples of anti emetics:**

1. Phenothiazines
2. Antihistamines
3. Anticholinergics
4. Serotonin antagonists
5. Dopamine antagonists
6. Steroids
7. Vitamin B6
8. Benzodiazepines
9. Cannabinoids and benzamide derivatives

**ANTI EMETICS**

**1.  Phenothiazines**

Example:

1. Chlorpromazine,
2. Perphenazine,
3. Thioperazine,
4. Trifluoroperazine ethylperazine and
5. Prochlorperazine.

•Prolonged use leads to toxicity e.g. jaundice

•Useful in prevention of nausea and vomiting in pregnancy except chlorpromazine

•Also useful in radiation induced nausea and vomiting, uraemia, drug induced emesis and post anesthetic emesis.

•However are not effective in motion sickness or in cardiac glycoside induced emesis.

•They acting by blocking chemotrigerzone.

**2.  Antihistamine**

•Block not only HI receptors, but also have antimuscarinic and antiserotonin effects

Examples:

1. Dimenhydrinate,
2. Cyclizine,
3. Ceclizine,
4. Diphenhydramine,
5. Phenothiazine and
6. Hydroxyzine.

•Are mainly indicated in  motion sickness

**3. Anticholinergics**

•Antimuscarinics are commonly used-

1. Hyoscine (Buscopan) and
2. scopolamine

•Indicated for motion sickness when they are used prophylactically

**4. Serotonin antagonists**

•5 HT3 receptor antagonists

Examples:

1. Ondasetron,
2. Granisetron,
3. Tropisetron,
4. Dolasetron and
5. Romasetron
6. Metochlorpramide ( plasil) block dopamine and 5 HT.

•Mainly indicated for management of post operative nausea and vomiting, radiation and anti cancer agents induced nausea and vomiting.

**5. Steroids**

•Mainly used prophylactically in prevention of nausea and vomiting induced by general anesthesia.

•Also effective in management of post operative nausea and vomiting

Examples:

1. Dexamethasone,
2. Betamethasone and
3. Methylprednisolone

**6. Vitamin B6 (pyridoxine)**

•Used in management of nausea and vomiting in pregnancy

**7. Benzodiazepines**

•Controlling nausea and vomiting

Example:

1. Alprazolam and
2. Prolazepam

**8. Cannabinoids**

•Include:

1. Tetrahydrocannabinoid,
2. Dronabidol and
3. Nabilone

•Used to control nausea and vomiting

**9. Benzamide derivatives**

* Examples:
1. Cisapride,
2. Clebopride,
3. Alizapride

•Have serotonin and dopamine blocking properties

•Also directly antagonise the effect of chlorpromazine and can potentiate the effect of sedatives.

### CARMINATIVES

•Are substances that assist in repelling gas from the intestine/stomach

•Causes relaxation of esophageal and anal sphincters

•**Are also flavouring agents**

•Examples:

1. Ginger,
2. Cadamon,
3. Fennel,
4. Coriander,
5. Cloves,
6. Cinnamon and
7. Nutmeg

•**Woodwards and beta health care gripe water decreases retention of gas in young children**

**BITTERS AND APPETITE BOOSTERS**

1. Are products taken before meals to improve appetite
2. Stimulate taste buds and cause reflex secretion of saliva
3. When taken orally increases gastric acid secretion and rate of digestion of food

Examples:

1. Tonic mixtures and alcoholic beverages
2. Ginseng
3. Strychnine pure form/tincture of Nux vomica
4. Products with liver extracts
5. Preperations with glycerol phosphate
6. Cyproheptadine-stimulates appetite
7. Chlorpromazine
8. Anabolic steroids
9. Clonidine
10. Amitryptylline
11. Gentian root.

Topic 1.2: ANTIDIARRHOEALS

**DIARRHEA**

•Usually viewed and treated as symptom of underlying condition, e.g.

1. Kidney disease
2. Liver disease
3. Thyroid disease
4. Lung disease
5. Heart disease

**Acute diarrhea**

1. Characterised by sudden onset or frequent liquid stools
2. Patients may also complain of joint pain, weaknesses, fever and vomiting
3. It can be due to bacterial infection or often due to bacteria toxins or use of chemicals
4. They may lead to inflammation in the GIT mucosa, increased mucous secretion and increased GIT motility
5. Bacteria include: clostridium, salmonella
6. Chemicals include: lead, mercury, cadmium
7. Allergic reactions by food e.g. eggs, milk, wheat

**Chronic diarrhea**

•It is due to etiological factors

•Characterised by persistent concurrent passing of loose stools

•Diagnosis is difficult

**CAUSES OF DIARRHEA**

1. Food-food poisoning, change in diet can cause diarrhea
2. Emotional disturbance-characterised by psychological disturbance such as anxiety can lead to severe diarrhea
3. Infections:
	1. Parasitic infections especially with Giardia lamblia
	2. Amoebic dysentery-has two phases, intestinal and hepatic phase
	3. Bacillary dysentery especially shigella dysentery, Rx amoxicillin and cotrimoxazole
	4. Typhoid fever caused by Salmonella typhi, Rx ciprofloxacine, amoxiclav and chloramphenical.
	5. Balantidium dysentery, Rx  tetracycline and clioquinol
4. Ulcerative colitis
5. Neoplasia of colon
6. Malabsorption
7. Thyrotoxicosis
8. Neurotic disorders
9. Carcinoid syndrome
10. Drugs e.g carthatics, broad spectrum antibiotics

**Management of diarrhoea;**

Drugs used in management of diarrhea act in two ways:

1. Increasing viscocity of GIT contents by their direct action
2. Delaying passage of GIT contents so that there is more time for water to be reabsorbed

**NB**: management of diarrhea below 5 year patients should not include use of drugs that delay passage of GIT contents. Main intervention is oral rehydration therapy and zinc sulphate tabs

**Drugs that act by increasing viscocity of GIT contents**

1. They acts adsorbents and also demulcents i.e. provide a protective coating on GIT mucosa
2. Adsorb toxins responsible for diarrhea
3. Add solid to the colon improving cosistency of faeces
4. Adsorbents are not specicific in function, they can adsorb nutrients and even co administered drugs

 **Examples of drugs that increase viscosity of GIT Contents:**

1. Kaolin
2. Arrow root
3. Chalk
4. Attapulgite
5. Bismuth subgallate
6. Aluminium hydroxide
7. Activated charcoal
8. Synthetic resins

**Drugs delaying passage of GIT contents**

•They have antispasmodic effects e.g.

1. Morphine and derivatives,
2. Atropine and its derivative.

 **Atropine and its derivatives**

•Include;

1. Hyoscine,
2. Hyoscyamine,
3. Propanthine,
4. Mebeverine

•Can either be used a lone or in combination with adsorbents

•Act by inhibiting / decreasing muscle crumps and also by reducing intestinal GIT motility

•Are basically antispasmodic agents

•Delay GIT emptying time allowing for time for more water to be reasorbed

**Morphine and derivatives**

1. Act by decreasing the propulsive movements of the GIT
2. Prolong or increase transit time of GIT content
3. They increase water absorption hence leading to better formed stool
4. They have risk of dependence and therefore used with care
* **Examples of Morphine and its derivatives**
1. Morphine
2. Camphorated tincture of opium
3. Diphenoxylate sodium
4. Codeine phosphate tabs
5. Loperamide
6. Fluperamide

Topic 1.3: CONSTIPATION, HAEMORRHOIDS AND THEIR MANAGEMENT

**CONSTIPATION**

•It is abnormally slow movement of stool a long the colon and rectum

•It is associated with distention of the rectum, feeling of malaise, headache and hard dry stool.

**Factors that affect bowel movement**

1. Nature  of diet
2. Relative proportion of indigestible fibres
3. Previous straining habits
4. Psychological status
5. Physical disturbances e.g. trauma
6. Drugs used to treat constipation are referred to us carthatics/laxatives/purgatives/evacuants/aperiants.

**Causes of constipation**

1. Drugs e.g.
	1. Morphine,
	2. Atropine,
	3. Sympathomimetics,
	4. Ganglion blockers,
	5. General anesthetics,
	6. Tricyclic antidepressants and
	7. Sedatives
2. Illness
3. Reduced food intake
4. Psychosomatic disorders
5. Atony of colon and or rectum
6. Organic causes such as;
	1. Hyperthyroidism,
	2. Vasoconstriction,
	3. Oral lesions and
	4. Prolonged use of irritant carthatics

**MANAGEMENT OF CONSTIPATION**

**1. CARTHATICS**

**Classification of Carthatics;**

1. Bulk carthatics-saline and hydrophilic carthatics
2. Irritant/stimulant carthatics
3. Lubricant carthatics
4. Emollients/faecal softeners/surfactants
5. Miscelleneous

**1) Bulk carthatics;**

 Mechanism of action

•They absorb water, increasing volume, lower viscocity of non-absorbable intestinal content

•Cause reflex distention of the colon and initiate defacation reflex

•Useful for constipation associated with rock hard bulky stool

**Examples of bulk carthatics**

1. Saline carthatics-consists of inorganic salts that are insoluble either anion or cation such as;
	1. Magnesium sulphate,
	2. Magnesium carbonate,
	3. Sodium sulphate,
	4. Sodium-patassium tartarate,
	5. Tartaric acid and
	6. Sodium phosphat
* Examples of saline carthatics:**rochelle salts, milk of magnesia, glaubers salt, epsom salts** .
* **2. Hydrophillic carthatics**-consists of natural polysaccharides or cellulose derivatives
* •They absorb water, swell, decrease in bulk and cause reflex stimulation of peristalisis.
* Examples of hydrophillic carthatics:
1. Bran,
2. Methylcellulose,
3. Konsyl,
4. Metamucil,
5. Plant gums e.g acacia, sodium alginate,lactulose

**3. Irritant/Stimulant Carthatics;**

•They stimulate  peristalisis by irritating the sensory nerve endings in the GIT mucosa thus increasing the GIT motility.

•They reduce the passage time of GIT material and reduce water absorption

•They act either in small intestine or colon

**Examples of Irritant carthatics;**

1. Emodin type carthatics e.g aloe, senna, cascara, rhubarb and frangular
2. Castor oil- obtained from Ricinus communis, very potent and can induce labour
3. Croton oil-withdrawn from clinical use due to toxicity, causes GIT perforation in PUD, severe nausea, gastro enteritis, prolapse and protraction
4. Resinous irritant carthatics- e.g. jalap, podophyllin, colocynth, ipomoea, cambogia
5. Miscelleneous irritant carthatics:
	1. Glycerin-used in form of supposotories for children and adults
	2. Mercuric chloride- potent, causes kidney damage
	3. Bisacodyl- potent, has slow onset of effects between 6-8 hours. Mainly taken at night so that maximum effects is observed in the morning.
	4. Phenolphthalein-rarely used alone. Its incorporated in some consumer products due to its laxative effects. Found in chewing gums

**4. Lubricant Carthatics;**

•Act by softening the stool, also retards water absorption . Forms a coating on the surface of hard stool and therefore eases defacation by lubricating process.

•The product can be taken orally either in the form of neat oil or can be formulated in form of oil emulsion

**1) Liquid paraffin**

It is tasteles, indigestible in the GIT, chemically inert and absorbed only to a limited extend.

**2) Faecal softeners/emollients/surfactants**

•Consist mainly of surface active agents especially ionic and cationic surfactants.

•They act by softening the stool i.e by lowering its surface tension and therefor facilitate admixture of the lipophile and hydrophilic component of fecal material.

•They therefore leads to formation of soft emollients

Examples of stool softeners;

1. Dioctyl sodium sulphosuccinate.
2. Polloxakol.

They are not significantly absorbed in the GIT, are virtually non toxic. However they can cause an increase in absorption of liquid paraffin if used concurrently and therefore should not be used together

Clinical uses of stool softeners

1. Management of spastic constipation since they do not retard absorption of nutrients from intestine
2. Management of constipation of hard stool and post surgical paralytic ileus

**Indication of cathartics**

1. Prevent undue straining of stool especially after surgery because it can lead to rapture of operated area
2. To relieve constipation
3. To prepare patients for anaesthesia and general surgery especially abdominal surgery
4. To prepare patients for radiological process e.g. X-rays of the abdomen
5. To promote elimination of toxic materials from the GIT
6. Promote elimination of intestinal parasites like worms
7. To induce labor in full term pregnancy
8. Management of hepatic coma;**magnesium sulphate is used** , the hepatic portal vein is usually congested, magnesium sulphate causes relaxation of hepatic portal vein.

**Contraindication of Carthatics**

1. Advanced pregnancy
2. In case of mechanical obstruction and inflammation of the GIT
3. Chronic constipation
4. Patients with abdominal muscle cramps, colic pain, nausea and vomiting

**General side effects of Carthatics;**

1. Excessive water and electrolytes loss leading to hypokalemia, hyponatremia and hypocalcemia
2. Steatorrhea
3. Peritonitis in case of perforation of the GIT mucosa

**HAEMMORROIDS**

•A condition where the veins become swollen due to increased pressure within them

•In mild form they cause distention only during defacation process

•In severe form they maybe so distended that they prolapse (protrude) through the anus during the process of defacation

•Thrombosis may occur which may worsen pain associated with haemmorrhoids

•The veins are fragile, breaking and bleeding

**Signs and symptoms of haemorrhoids;**

1. Blood stool
2. Pain
3. Inflammation of veins
4. Prolapse

**Management of Haemorrhoids;**

**1. Sclerosing agents**

•Act on venous membrane to decrease the fragility and hence reduce bleeding tendencies

 Examples of sclerosing agents:

1. Sodium tetradecyl sulphate
2. Quinine/ urea injections
3. Morrhuate injections
4. Phenol in almond oil

**2. Vasoconstrictors**

•Include; phenyephrine, ephedrine

**3. Local anaesthetics**

•They minimize the pain

•The preferred one with topical local anaesthetic effects include;

1. Tetracaine,
2. Benzocaine,
3. Mepivacaine,
4. Pramoxine,
5. Cyclomethacaine,
6. Cinchocaine

**4. Anti inflammatory agents**

•Corticosteroids e.g.

1. Hydrocortisone,
2. Betamethasone,
3. Prednisolone and
4. Fluticasone

Are mainly used topically

**5. Antibacterial agents**

•The ones effective when used topically are preferred

1. Neomycin,
2. Gramicidin,
3. Bacitracin,
4. Fusidic acid,
5. Antiseptics

**6. Astringents**

•Have ability to reduce/minimize  the fragility of veins e.g.

1. Phenol in almond oil
2. Zinc oxide
3. Tannic acid
4. Aluminium sub acetate
5. Bismuth sub gallate

Unit Three Content..

Topic 1.1: OVERVIEW AND CLASSIFICATION OF RESPIRATORY PHARMACOLOGY

**Overview**

1. Asthma,
2. Chronic obstructive pulmonary disease (COPD), and
3. Allergic rhinitis
* Are commonly encountered respiratory diseases.
* Each of these conditions may be associated with a troublesome cough, which may be the patient's only presenting complaint.
*
* Asthma is a chronic disease characterized by hyperresponsive airways, affecting 10 million patients (four to five percent of the U.S. population), and resulting annually in 2 million emergency room visits, 500,000 hospitalizations, and 5,000 deaths.
*
* COPD, also called emphysema or chronic bronchitis, affects approximately 30 million Americans and is currently the fourth most common cause of preventable deaths in the United States. Allergic rhinitis, characterized by itchy, watery eyes, runny nose, and a nonproductive cough, is an extremely common condition that significantly decreases patient-reported quality of life.
* Allergic rhinitis affects approximately 20 percent of the population. Coughing is an important defensive respiratory response to irritants and has been cited as the number-one reason why patients seek medical care. A troublesome cough may represent several etiologies, such as the common cold, sinusitis, and/or an underlying chronic respiratory disease

Each of these respiratory conditions can be adequately controlled through a combined approach of appropriate;

1. Lifestyle changes/Modification. and
2. Medication management.

 **Drugs used to treat respiratory conditions can be delivered;**

1. Topically to the nasal mucosa,
2. Inhaled into the lungs, or
3. Given orally or parenterally for systemic absorption.

Topical delivery methods, such as nasal sprays or inhalers, are preferred so as to target affected tissues while minimizing systemic side effects. Clinically useful drugs mitigate the specific pathology, such as by relaxing bronchial smooth muscle or modulating the inflammatory response.



ASTHMA MANAGEMENT

Asthma is an inflammatory disease of the airways characterized by episodes of **acute bronchoconstriction** causing;

1. Shortness of breath,
2. Cough,
3. Chest tightness,
4. Wheezing, and
5. Rapid respiration.

These acute symptoms may resolve spontaneously, with;

1. Nonpharmacologic relaxation exercises,
2. Quick relief medications, such as a short-acting -adrenergic agonist

Unlike chronic bronchitis, cystic fibrosis, or bronchiectasis, **asthma is usually not a progressive disease**; that is, it does not inevitably lead to crippled airways.

Asthma is a chronic disease with an underlying inflammatory pathophysiology that, if untreated, may incur **airway**, resulting in increased severity and incidence of exacerbations and/or death.

Deaths due to asthma are relatively infrequent, but significant morbidity results in;

1. High outpatient costs,
2. Numerous hospitalizations, and
3. Decreased quality of life

**Goals of therapy in Asthma;**

1. **Reducing impairment:**
	1. Prevent chronic and troublesome symptoms.
	2. Require infrequent use (2 days a week) of inhaled short-acting  agonist for quick relief of symptoms.
	3. Maintain (near) normal pulmonary function.
	4. Maintain normal activity levels (including exercise and other physical activity and attendance at work or school).
	5. Meet patients' and family expectations of and satisfaction with asthma care.
2. **Reducing risk:**
	1. Prevent recurrent exacerbations of asthma, and minimize the need for emergency department visits or hospitalizations.
	2. Prevent progressive loss of lung function; for children, prevent reduced lung growth.
	3. Provide optimal pharmacotherapy with minimal or no adverse effects

**TX OF ASTHMA;**

**1. ADRENERGIC AGONISTS**

Inhaled adrenergic agonists with activity are the drugs of choice for **mild asthma** that is, in patients showing only occasional, intermittent symptoms .

**Quick relief;**

1. Direct-acting  agonists are potent bronchodilators that relax airway smooth muscle.
2. Most clinically useful  agonists have a rapid onset of action (5-30 minutes) and provide relief for 4 to 6 hours. They are used for symptomatic treatment of bronchospasm, providing quick relief of acute bronchoconstriction. **[Epinephrine is the drug of choice for treatment of acute anaphylaxis]**
3. Agonists have no anti-inflammatory effects, and they should never be used as the sole therapeutic agents for patients with persistent asthma. Monotherapy with short-acting  agonists may be appropriate only for patients identified as having mild intermittent asthma, such as exercise-induced asthma.
4. The direct-acting -selective agonists, such as
	1. **Pirbuterol** [peer-BYOO-ter-ole],
	2. **Terbutaline** [ter-BYOO-ta-leen], and
	3. **Albuterol** [al-BYOO-teh-rall], offer the advantage of providing maximally attainable bronchodilation with little of the undesired effect of stimulation.
	4. The  agonists are not catecholamines and, thus, are not inactivated by catechol-O-methyltransferase. Adverse effects, such as tachycardia, hyperglycemia, hypokalemia, and hypomagnesemia are minimized with dosing via inhalation versus systemic routes.
	5. Although tolerance to the effects of  agonists on nonairway tissues occurs, it is uncommon with normal dosages. All patients with asthma should be prescribed a quick-relief inhaler and regularly assessed for appropriate inhaler technique.

**Long-term control:**

1. Salmeterol [sal-ME-te-rol]
2. Xinafoate and
3. Formoterol [for-MOH-ter-ol] are long-acting  agonists bronchodilators. They are chemical analogs of albuterol but differ by having a lipophilic side chain, increasing the affinity of the drug for the -adrenoceptor.
4. **Salmeterol and formoterol**have a long duration of action, providing bronchodilation for at least 12 hours. Both salmeterol and formoterol have slower onsets of action and should not be used for quick relief of an acute asthma attack. long-acting agonists should be prescribed for routine administration.
5. Whereas**inhaled corticosteroids remain the long-term control drugs of choice in asthma**, long-acting  agonists are considered to be useful adjunctive therapy for attaining asthma control. Adverse effects of the long-acting  agonists are similar to quick-relief agonists. Appropriate inhaler technique with long-acting  agonists is critical to the success of therapy, may differ from the patient's other inhalers (metered-dose inhaler versus dry powder inhaler), and should be reassessed regularly

**2. CORTICOSTEROIDS;**

Inhaled corticosteroids (ICS) are the drugs of first choice in patients with any degree of persistent asthma (mild, moderate, or severe).

Severe persistent asthma may require the addition of a short course of oral glucocorticoid treatment. **No other medications are as effective as ICS in the long-term control of asthma in children and adults**. If appropriately prescribed and used, ICS therapy may reduce or eliminate the need for oral glucocorticoids in patients with severe asthma.

**To be effective in controlling inflammation, glucocorticoids must be taken continuously**. Current guidelines recommend selecting ICS therapy for a newly diagnosed patient with asthma at dosing equivalent to the patient's asthma classification  Patients achieving 3 to 6 consecutive months of improved asthma control may be considered for a reduction in ICS dosing  as clinically indicated

**Actions of corticosteroids on lung:**

ICS do not directly affect the airway smooth muscle.

Instead, ICS therapy directly targets underlying airway inflammation by ;

1. Decreasing the inflammatory cascade (eosinophils, macrophages, and T lymphocytes),
2. Reversing mucosal edema,
3. Ddecreasing the permeability of capillaries, and
4. Inhibiting the release of leukotrienes.

After several months of regular use, ICS reduce the hyperresponsiveness of the airway smooth muscle to a variety of bronchoconstrictor stimuli, such as allergens, irritants, cold air, and exercise.

**Route of administration of Corticosteroids;**

1. **Inhalation:** The development of ICS has markedly reduced the need for systemic corticosteroid treatment to achieve asthma control. Appropriate inhalation technique is critical to the success of therapy.
	* Metered-dose inhalers have propellants that eject the active medication from the canister. Patients should be instructed to SLOWLY and DEEPLY inhale upon activation of these inhalers to avoid impaction of the medication onto the laryngeal mucosa rather than the bronchial smooth muscle.
	*
	* Improper use of a metered-dose inhaler can result in a large fraction (typically 80-90 percent) of inhaled glucocorticoids to be deposited in the mouth, pharynx, and/or swallowed. The 10 to 20 percent of the metered dose of inhaled glucocorticoids that is not swallowed is deposited in the airway. If ICS are inappropriately inhaled, systemic absorption and adverse effects are much more likely. ICS delivered by dry powder inhalers require a different inhaler technique. Patients should be instructed to inhale QUICKLY and DEEPLY to optimize drug delivery to the lungs. Even properly administered, corticosteroid deposition on the oral and laryngeal mucosa can cause adverse effects such as oropharyngeal candidiasis and hoarseness. Patient counseling incorporating a rinsing of these tissues via the swish and spit method should avoid these adverse events.
* **2. Oral/systemic**: Patients with severe exacerbation of asthma (status asthmaticus) may require**intravenous administration** of**methylprednisolone or oral prednisone.** Once the patient has improved, the dose of drug is gradually reduced, leading to discontinuance in 1 to 2 weeks. In most cases, suppression of the hypothalamic-pituitary axis will not occur during the short course of oral prednisone typically prescribed for an asthma exacerbation; therefore, dose reduction is not necessary.

**Spacers;**

A spacer is a large-volume chamber attached to a metered-dose inhaler. Spacers decrease the deposition of drug in the mouth caused by improper inhaler technique .

The chamber reduces the velocity of the injected aerosol before entering the mouth, allowing large drug particles to be deposited in the device. The smaller, higher-velocity drug particles are less likely to be deposited in the mouth and more likely to reach the target airway tissue.

Spacers minimize the problem of adrenal suppression by reducing the amount of glucocorticoid deposited in the oropharynx. Spacers improve delivery of inhaled glucocorticoids and are advised for virtually all patients, especially children less than 5 years old and elderly patients who may have difficulty coordinating actuation with inhalation.

Patients should be counseled about regular washing and/or rinsing of spacers to reduce the risk of bacterial, mold, or mildew growth inducing an asthma attack.

**Adverse effects of steroids;**

Oral or parenteral glucocorticoids have a variety of potentially serious side effects ; inhaled glucocorticoids, particularly if used with a spacer, have few systemic effects.

Studies have demonstrated the effect of ICS on vertical bone growth in children to be negligible, whereas the retardation of vertical bone growth secondary to low oxygenated blood levels from uncontrolled asthma can occur in more severe cases.

**OTHER ALTERNATIVE DRUGS USED TO TREAT ASTHMA;**

These drugs are useful for treatment of moderate to severe allergic asthma in patients who are poorly controlled by conventional therapy or experience adverse effects secondary to high-dose or prolonged corticosteroid treatment.

**These drugs should be used in conjunction with ICS therapy, not as sole therapies**.

**1. Leukotriene antagonists**

Leukotriene (LT) B4 and the cysteinyl leukotrienes, LTC4, LTD4, and LTE4, are products of the 5-lipoxygenase pathway of arachidonic acid metabolism and part of the inflammatory cascade.

5-Lipoxygenase is found in cells of myeloid origin, such as mast cells, basophils, eosinophils, and neutrophils. LTB4 is a potent chemoattractant for neutrophils and eosinophils, whereas the cysteinyl leukotrienes constrict bronchiolar smooth muscle, increase endothelial permeability, and promote mucous secretion.

**Examples of Leukotrein antagonists**

1. Zileuton [zye-LOO-ton] is a selective and specific inhibitor of 5-lipoxygenase, preventing the formation of both LTB4 and the cysteinyl leukotrienes.
2. Zafirlukast [za-FIR-loo-kast] and
3. Montelukast [mon-tee-LOO-kast] are selective, reversible inhibitors of the cysteinyl leukotriene-1 receptor, thereby blocking the effects of cysteinyl leukotrienes .

Montelukast, the market leader in this pharmacologic class, claims two primary advantages: dosing recommendations for children 1 year of age and older as well as being available in chewable tablets and granule formulations. All three drugs are approved for the prophylaxis of asthma but are not effective in situations where immediate bronchodilation is required.

Modest reductions in the doses of -adrenergic agonists and corticosteroids, as well as improved respiratory function, are among the therapeutic benefits.

**Pharmacokinetics of Leukotrein Antagonists;**

1. All three drugs are orally active, although food impairs the absorption of zafirlukast.
2. Greater than 90 percent of each drug is bound to plasma protein.
3. The drugs are extensively metabolized.
4. Zileuton and its metabolites are excreted in the urine, whereas zafirlukast and montelukast and their metabolites undergo biliary excretion.

**Adverse effects of Leukotrein antagonists:**

1. Elevations in serum hepatic enzymes have occurred with all three agents, requiring periodic monitoring and discontinuation when enzymes exceed three to five times the upper limit of normal.
2. Although rare, eosinophilic vasculitis (Churg-Strauss syndrome) has been reported with all agents, particularly when the dose of concurrent glucocorticoids is reduced. Other effects include headache and dyspepsia.
3. Both zafirlukast and zileuton are inhibitors of cytochrome P450. Both drugs can increase serum levels of warfarin.

**2. Cromolyn and nedocromil**

1. Cromolyn [KROE-moe-lin] and
2. Nnedocromil [ne-doe-KROE-mil]

Are effective prophylactic anti-inflammatory agents. However, they are not useful in managing an acute asthma attack, because they are not direct bronchodilators.

These agents can block the initiation of immediate and delayed asthmatic reactions. For use in asthma, cromolyn is administered either by inhalation of a microfine powder or as an aerosolized solution. Because it is poorly absorbed, only minor adverse effects are associated with it. Pretreatment with cromolyn blocks allergen- and exercise-induced bronchoconstriction.

Cromolyn is also useful in reducing the symptoms of allergic rhinitis. A 4 to 6-week trial is required to determine efficacy. Given its safety, an initial trial of cromolyn is often recommended, particularly in children and pregnant women. Toxic reactions are mild and include a bitter taste and irritation of the pharynx and larynx.

Due to short duration of action, these agents require frequent daily dosing, which has been shown to affect adherence and, therefore, therapeutic efficacy. Neither cromolyn nor nedocromil should replace ICS or quick-relief  agonists as the mainstay of asthma therapy.

**3. Cholinergic antagonists;**

Anticholinergic agents are generally less effective than-adrenergic agonists. They block the vagally mediated contraction of airway smooth muscle and mucus secretion.

Inhaled ipratropium [i-pra-TROE-pee-um], a quaternary derivative of atropine, is useful in patients who are unable to tolerate adrenergic agonists. Ipratropium is slow in onset and nearly free of side effects.

These agents are not traditionally effective for patients with asthma unless COPD is also present

**4. Theophylline**

Theophylline [thee-OFF-i-lin] is a bronchodilator that relieves airflow obstruction in chronic asthma and decreases its symptoms. Theophylline is well absorbed by the gastrointestinal tract, and several sustained-release preparations are available.

Previously the mainstay of asthma therapy, theophylline has been largely replaced with agonists and corticosteroids due to a narrow therapeutic window, high side-effect profile, and potential for drug interactions. Overdose may cause seizures or potentially fatal arrhythmias.

Theophylline is metabolized in the liver, is a CYP1A2 and 3A4 substrate, and interacts adversely with many drugs.

**5. Omalizumab**

Omalizumab [oh-mah-lye-ZOO-mab] is a **recombinant DNA monoclonal antibody** that selectively binds to human immunoglobulin E (IgE). This leads to decreased binding of IgE to the high-affinity IgE receptor on the surface of mast cells and basophils. Reduction in surface-bound IgE limits the degree of release of mediators of the allergic response.

Omalizumab may be particularly useful for treatment of moderate to severe allergic asthma in patients who are poorly controlled with conventional therapy. Due to the high cost of the drug  limitations on dosage, and available clinical trial data, it is not presently used as first-line therapy

TREATMENT OF COPD, ALLERGIC RHINITIS AND COUGH

**COPD**

Chronic obstructive pulmonary disease is a chronic, irreversible obstruction of airflow.

Smoking is the greatest risk factor for COPD and is directly linked to the progressive decline of lung function as demonstrated by forced expiratory volume (FEV). Smoking cessation and/or continued avoidance should be recommended regardless of stage/severity of COPD and age of patient.

**Drugs used for treatment of COPD;**

1. Inhaled bronchodilators, such as anticholinergic agents (ipratropium and tiotropium) and
2. Adrenergic agonists, are the foundation of therapy for COPD .

These drugs increase airflow, alleviate symptoms, and decrease exacerbation of disease.

Combinations of an anticholinergic plus adrenergic agonist may be helpful in patients for whom a single inhaled bronchodilator has failed to provide an adequate response.

For example, the combination of albuterol and ipratropium provides greater bronchodilation than with either drug alone.

Longer-acting drugs, such as salmeterol and tiotropium [tee-oh-TROE-pee-um], have the advantage of less frequent dosing. ICS should be restricted to patients with an FEV in 1 second (FEV1) of less than 50 percent of predicted and three or more exacerbations in the last 3 years (Stage III or IV). Whereas the addition of ICS may provide symptomatic relief, the progressive decline in FEV1 is not impacted. Addition of a long-acting adrenergic agonists such as salmeterol, improves lung function compared to either a short-acting adrenergic agonist or steroid alone.

**ALLERGIC RHINITIS;**

**Drugs Used to Treat Allergic Rhinitis**

Rhinitis is an inflammation of the mucous membranes of the nose and is characterized by sneezing, itchy nose/eyes, watery rhinorrhea, and nasal congestion. An attack may be precipitated by inhalation of an allergen (such as dust, pollen, or animal dander). The foreign material interacts with mast cells coated with IgE generated in response to a previous allergen exposure.

The mast cells release mediators, such as histamine, leukotrienes, and chemotactic factors, that promote bronchiolar spasm and mucosal thickening from edema and cellular infiltration. Combinations of oral antihistamines with decongestants are the first-line therapies for allergic rhinitis.

Systemic effects associated with these oral preparations (sedation, insomnia, and, rarely, cardiac arrhythmias) have prompted interest in topical intranasal delivery of drugs.

**1. Antihistamines (H1-receptor blockers)**

Antihistamines are the most frequently used agents in the treatment of sneezing and watery rhinorrhea associated with allergic rhinitis. H1-histamine receptor blockers, such as;

1. Diphenhydramine,
2. Chlorpheniramine,
3. Loratadine, and
4. Fexofenadine, are useful in treating the symptoms of allergic rhinitis caused by histamine release.

Ocular and nasal antihistamine delivery devices are available over-the-counter for more targeted tissue delivery. Combinations of antihistamines with decongestants (see below) are effective when congestion is a feature of rhinitis.

Antihistamines differ in their ability to cause sedation and in their duration of action. In general, anticholinergic side effects of the first-generation antihistamines (dry eyes/mouth, difficulty urinating and/or defecating) are transient and may resolve in 7 to 10 days.

Constipation associated with chronic use of the first-generation antihistamines is not transient and may require treatment with a stool softener, especially in more susceptible patients.

**2. Adrenergic agonists**

1. Short-acting  adrenergic agonists (nasal decongestants), such as **phenylephrine**, constrict dilated arterioles in the nasal mucosa and reduce airway resistance.
2. Longer-acting **oxymetazoline** [ok-see-met-AZ-oh-leen] is also available. When administered as an aerosol, these drugs have a rapid onset of action and show few systemic effects. Oral administration results in longer duration of action but also increased systemic effects. Combinations of these agents with antihistamines are frequently used.

The adrenergic agonists should be used no longer than several days due to the risk of rebound nasal congestion (rhinitis medicamentosa).Adrenergic agents have no place in the long-term treatment of allergic rhinitis.

**3. Corticosteroids**

Corticosteroids, such as

1. Beclomethasone,
2. Budesonide,
3. Fluticasone,
4. Flunisolide, and
5. Triamcinolone, are effective when administered as nasal sprays. [Note: Systemic absorption is minimal, and side effects of intranasal corticosteroid treatment are localized.

Side effects of corticosteroids (intranasal)

1. Nasal irritation,
2. Nosebleed,
3. Sore throat, and rarely,
4. Candidiasis.

To avoid systemic absorption, patient counseling should emphasize the importance of topical deposition of the drug (tell patients NOT to deeply inhale while administering these drugs because the target tissue is in the nose, not in the lungs or the throat).

Topical steroids may be more effective than systemic antihistamines in relieving the nasal symptoms of both allergic and nonallergic rhinitis. The effects of long-term usage are unknown, but these agents are considered to be generally safe. Periodic assessment of the patient is advised. Treatment of chronic rhinitis may not result in improvement until 1 to 2 weeks after starting therapy.

**4. Cromolyn**

Intranasal cromolyn may be useful, particularly when administered before contact with an allergen.

To optimize the therapeutic effect of cromolyn, dosing should occur at least 1 to 2 weeks prior to allergen exposure. Due to a short duration of action, cromolyn requires multiple daily dosing, which may deleteriously impact adherence and, therefore, therapeutic efficacy

**COUGH TREATMENT;**

**1. Cough suppresants/antitusives;**

1. Codeine [KOE-deen] is the gold-standard treatment for cough suppression due to its long history of availability and use.
* Codeine decreases the sensitivity of cough centers in the central nervous system to peripheral stimuli and decreases mucosal secretion. These therapeutic effects occur at doses lower than those required for analgesia but still incur common sides effects like constipation, dysphoria, and fatigue, in addition to its addictive potential. (See p. 159 for a more complete discussion of the opiates.)

2. Dextromethorphan [dek-stroe-METH-or-fan] is a synthetic derivative of morphine that suppresses the response of the central cough center. It has no analgesic effects, has a low addictive profile, but may cause dysphoria at high doses, which may explain its status as a potential drug of abuse. Dextromethorphan has a significantly better side effect profile than codeine and has been demonstrated to be equally effective for cough suppression.

3. Chlorpheniramine.

**2. Expectorants;**

1. Guaifenesin (Glyceryl guaicolate)- It acts by thinning the mucus and making expectoration of mucus easier.
2. Carbocystein- A mucolytic.
3. Ammonium chloride