Friday, October 05, 2007

Introduction to Drug Action and Biological Response

Health is defined as a state of optimal physical, mental and social well being and not merely the absence of disease; whereas disease is any deviation from or interruption of the normal structure or function of any organ or system of the body manifested by characteristic sign and symptoms whose etiology, pathology and prognosis, may be known or unknown.

What is a Drug?

- A drug is any substance that affects physiological function in a specific way.

- It can be any substance used in the diagnosis, prevention or treatment of disease.

Mode of Action of Drugs

1. Interaction with receptors

2. Inhibition or Activation of enzyme function.

3. Alteration of cytosolic ion concentration by promoting or inhibiting ion entry through membrane ion channels.

The Efficacy of a Drug

The efficacy of a drug is determined by **the mutual relationship** between:

What the drug dose to the body = pharmacodynamics.

What the body dose to the drug = pharmacokinetics.

Pharmacodynamics

A study of what the drug does to the body. Describe where and how a drug acts on the body.

In order to produce a physiological response by binding to:

1. A particular site (Receptor or Ion channel) of cell.

2. Tissues

3. Target protein (Enzyme or Enzyme system)

e.g. When adrenaline binds to its receptor in the heart, the heart beats faster. The receptor produces an effect only when adrenaline is bound; otherwise it is functionally silent.

Receptors

1. Specific protein molecules at cell membrane.

2. Possess a binding site for a specific substance

3. Occupation of the binding-site can induce a biological response.

Biological Response

Excitation

e.g. Acetylcholine (Ach) activates the cholinergic receptors at the gastro-intestinal (GI) tract produce muscle contraction.

Inhibition

e.g. Anti-cholinergic drugs block cholinergic receptors causing muscle relaxation of the gut.

Highly specific

Receptor only bind with certain types of ligand

Certain types of ligand	**Binds with**
Acetylcholine	cholinergic receptor
Adrenaline	Adrenergic receptor
Morphine	Opioid receptor
Histamine	Histamine receptor

To produce a physiological response

	Full agonist	**Partial agonist**	**Antagonists**
Receptor	bind with a receptor	bind with a receptor	bind with a receptor
Activates	activates the receptor system	activates the receptor system	fail to activate
Response	maximum response	No maximum response	block the receptor
Efficacy	High efficacy	Intermediate efficacy	No efficacy at all

Efficacy

Describes **the strength** of a single drug-receptor complex in producing a biological response

Potency

A comparative measure of the different doses of two drugs A and B that can produce the same effect.

If drug A can produce the same effect as drug B at lower doses, then drug A is said to have a higher potency than drug B.

Depends on Reception Affinity and Efficacy

Enzyme

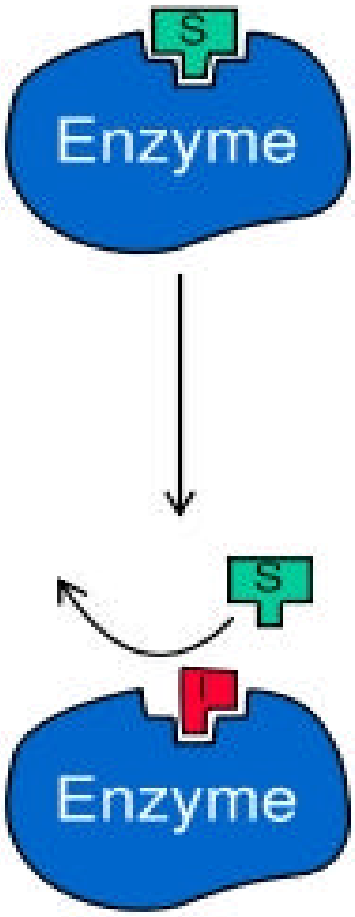
Another important target for drug action:

Catalyzes biological reactions

Activates metabolic processes

Produces vital substances in the cell

Drugs targeted at enzyme are called **activators** or **inhibitors**.



Pharmacokinetics

A study of what the body does to the drug. Administered drug will come across a series of events in the human body depending on the various routes of administration of the drug.

A study of the Absorption, Distribution, Metabolism and Excretion of drug in the body (ADME).

Drug Absorption

Affected by the nature and Route of Administration of the drug:

Oral, Sublingual, Parenteral, Rectal, Cutaneous/ Transdermal, Inhalation

Oral route

Advantage: Convenient, Safest and Least expensive

Affected by:

1. Drug solubility
2. Gastro-intestinal (GI) motility
3. Particle size and formulation e.g. micronised particle enteric-coating, Sustained released tablets
4. Chemical interaction with gut contents e.g. Gastric pH, Food Milk, Alcohol
5. Drug interaction e.g. Tetracycline and Calcium
6. Drug action via the oral route is slow
7. Liver metabolism (First-pass Metabolism)

First-pass Metabolism/ First-pass Effect

Most drugs are metabolized by the liver so that the amount reaching the systemic circulation is less than the amount absorbed after oral administration.

This is a detoxification mechanism of our body.

Sublingual route

1. Absorbed directly from Oral cavity into Systemic circulation without entering Portal system
2. Escape first-pass metabolism
3. Produce a faster effect
4. Suitable for drugs unstable at gastric pH e.g. insulin
5. Rapidly metabolized by the liver e.g. Nitroglycerine

Rectal route

1. Useful to a patient who is unconscious or vomiting
2. Useful for drugs required to produce a local effect e.g. Glycerine suppository
3. Absorption from the rectal mucosa is less predictable than from the small intestine

Transdermal route

1. Drugs applied to the skin surface may be absorbed slowly
2. Allow lipid-soluble drugs to be delivered lowly and continuously over many hours and days
3. May develop local irritation at the site of application
4. Only suitable for drugs given in small daily dose

Parenteral route

1. Intravenous (iv) injection is the fastest and most certain route, subcutaneous (sc) and intramuscular (im) injections also produce a faster effect than oral administration
2. Given directly into the blood stream
3. Bypasses many biological barriers
4. Can be used for drugs unstable to gastric juices e.g. Insulin, Vaccines and Gamma globulin
5. The rate of absorption depends on the site of administration and local blood flow

Inhalation route

1. Used for volatile substances and gaseous anesthetics
2. Drugs used for their effects on the lungs and bronchial tree
3. Achieve higher drug concentration
4. Minimize side effects
5. Fast onset of action
6. Bypass the liver
7. Proper use of the aerosol is important e.g. bronchodilator

Drug Distribution

After entry into the system circulation a drug will distribute between the circulating plasma and various body compartments

To be able to enter cells, a drug must cross an epithelial barrier (biological barrier) e.g. the blood brain, placenta

The equilibrium pattern of distribution between the various compartments depends on the physico-chemical properties of the drug

1. Lipophilic drugs can cross the biological barrier more readily than hydrophilic drug
2. Drugs that are strongly protein-bound stay mainly in the plasma e. g. Diazepam, Aspirin
3. Water soluble drugs are readily excreted from the body
4. Lipid-soluble drugs reach all compartments and accumulate in fat

Some drugs tend to accumulate in certain tissues and organs causing adverse effects

Drug Metabolism

The Process by which a drug is chemically altered by the body to from readily excretable products

The liver enzyme system, such as cytochrome P-450 plays a key role

The metabolites, which may be active or inactive, toxic or nontoxic, are excreted from the body.

The liver enzyme may be regarded as a detoxification system of foreign substances

The elderly people have reduced enzymatic activity, therefore require less drugs than young adults do

Drug Excretion

Drugs are eliminated from the body either unchanged or as metabolites

The kidney is the main excretory organ and most drugs leave the body in the urine

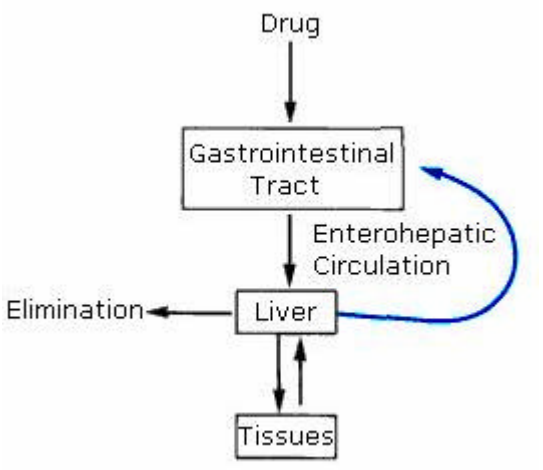
Certain drugs (e.g. aluminum) excreted from the kidney cause toxicity in patient with renal disease

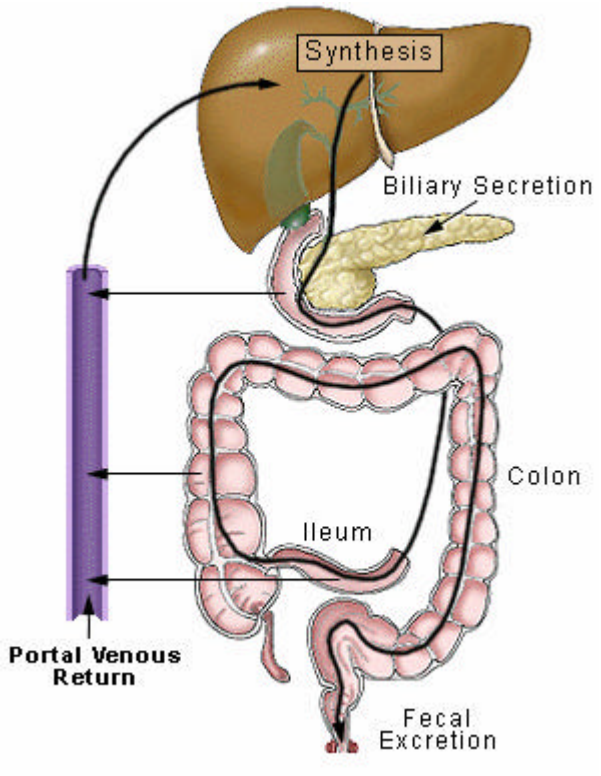
Drugs may also be excreted in breast milk, sweat, tear and genital secretions

Highly volatile agents (e.g. anaesthetic) are excreted via the lungs

Entero-hepatic circulation

Some drugs (e.g. oral contraceptives) are excreted into the bile via the liver, but in most cases reabsorbed from the intestine, prolong drug action





The Parasympathetic nervous system

The Autonomic Nervous system

The ANS is the part of the nervous system that regulates the activity of:

1. Visceral and vascular smooth muscles
2. Glandular secretions
3. Heart beat and force of contraction of the heart
4. It is regulated by centers in the brain

The ANS consists of two divisions: The sympathetic system & The parasympathetic system

They have opposing actions in some situations.

Many organs receive neurons from both the sympathetic and the parasympathetic system.

The Parasympathetic System (Cholinergic System)

The parasympathetic system is also called cholinergic system because when it is activated all parasympathetic nerves release Acetylcholine (ACh)⋯ Cholinergic

ACh then reacts with its receptors, known as muscarinic receptors found on all visceral tissues to produce biological responses.

The gastrointestinal Tract (GI tract)

The GI tract is innervated by both the sympathetic and parasympathetic nerves to regulate its functions:

1. Activation of the parasympathetic system in the GI tract leads to contraction of GI smooth muscles and increased gastric acid secretions
2. Inhibition of the parasympathetic system in the GI tract (by drugs that block ACh access to its receptors) causes reduced GI motility and secretion

Therefore, drugs that enhance/ antagonize the effect of ACh can alter GI functions.

Antispasmodic Agent

Antispasmodic agents are drugs that antagonize the effect of ACh and inhibit parasympathetic activities leading to: GI smooth muscle relaxation & Reduced gastric acid secretion

They are also called Anticholinergics or Antimuscarinics since they antagonize the effect of ACh by blocking the muscarinics receptors.

A. Atropine and Related Alkaloids

Atropine (hyoscyamine, Belladonna) Related alkaloids (Hyoscine)

Plant alkaloids with similar activities

Lipid soluble and can penetrate the blood-brain barrier

Clinical Uses

1. GI hyper motility
2. To dilate pupil for eye examination
3. Motion sickness
4. Anaesthetic premedication
5. Parkinson ś disease
6. Management of asthma
7. Urinary frequency (incontinence)

Side Effects

CNS effect: Excitation, confusion, anti-emetic and anti-Parkinsonian effect

Common Side Effects: Thirst, arrhythmias, palpitation, constipation, flushing, pupilary dilatation, relaxation of gut, bronchial, biliary tract and bladder smooth, inhibition of gastric acid and respiratory secretions

B. Synthetic Antimuscarinics

Synthetic Drugs with action similar activities to atropine but have **fewer side effects**

Clinical Uses

They are widely used for hypermotility and hyperacidity of the of GI tract

1. Gut, Biliary tract and bladder
2. Excessive gastric acid secretion
3. Ulcerative colitis, peptic ulcer
4. Adjunctive treatment for non-ulcer dyspepsia

Tertiary amines

Name: Dicyclomine HCI

Less marked antimuscarinics action than atropine

Some direct antispasmodic action on smooth muscle

Side effects: Not recommended for infant under 6 months of age

Quaternary ammonium compounds

1. Represent a number of drugs

2. Less lipid-soluble than atropine

3. Less likely to cross the blood brain barrier

4. Widely used

Side effects:

Anti-cholinergic effect: Dry month, blurred vision, hesitant micturition and constipation

The elderly are particularly susceptible

Contraindicated in patients with glaucoma and urinary retention

Name: Hyoscine butylbromide (Buscopan, Dhacopan)

Recommended for GI spasm

Useful in endoscopy

Name: Scopolamine methylbromide (Holopon), Oxyphencyclimine HCI (Daricon), Pipenzolate bromide, Propantheline bromide, Robinul, Cospanon

M1-selective antimuscarinic

Name: Pirenzepine (Bisvanil)

1. Inhibits gastric acid and pepsin secretions

2. Useful in gastric and duodenal ulcers

Side effects: fewer, agranulocytosis and thrombocytopenia may occur

C. Other Drugs Altering GI Motility

Clinical Uses

1. Direct relaxants of intestinal smooth muscle

2. May relieve pain in the irritable bowel syndrome and GI spasm

3. No serious adverse effects but should be avoided in paralytic ileus (distension, vomiting)

Name: Averine citrate (Spasmonal)

Antispasmodic activity similar to Buscopan with fewer cholinergic side effects

Name: Piper mint oil

Produces local antispasmodic effect on the gut wall

Name: Mebeverine HCI (Duspatalin)

The antispasmodic action is not CNS medicated or cholinergic adverse effects are few

Relieves spasm without affecting gut motility

Can be used for patient with Benign Prostatic Hyperplasia (BPH) and glaucoma

Diarrhoea

Diarrhoea = Increased frequency of bowels evacuation + watery fasces + gripping pain

Diarrhoea is a defense mechanism of the human body to expel toxin, bacteria and harmful substances from the intestine

Most cases of diarrhoea will be acute and self-limiting

The basis of treatment is fluid and electrolyte replacement especially for infants and elderly patients

Antidiarrhoeals may be used in adults and older children

Antibiotics are not recommended for uncomplicated gastroenteritis

They are given only for some severe cases of food poisoning

Causes of Diarrhoea

A. Viral Infections

Viruses often cause gastroenteritis esp. in children < 2 years old

Associated symptoms are those of cold, such as fever and vomiting

The acute phase is usually over within 2-3 days

The infection is usually self-limiting

B. Parasitic/ Protozoan Infections

These infections may occur in travelers, who acquire the infection and return with the organism, e.g. amoeba, worm

Diagnosis is made by sending stool sample to the laboratory and appropriate treatment is necessary

C. Bacterial Infections

1. Cause of food poisoning

2. When poultry is undercooked

3. Contaminated food reheated insufficiently

Salmonella is one of the bacteria responsible for food poisoning, whose symptoms may arise 12-48 hours after ingesting the infected food

An abrupt onset of frequent diarrhoea, occasionally with abdominal pain and vomiting

Antibiotics for Salmonella are best avoided, except in extreme situations

The main stay of treatment is fluid replacement

The bacteria are eliminated quickly from the bowel

D. Chronic Diarrhoea

Recurrent or persistent diarrhoea due to irritable bowel syndrome, e.g. stress, anxiety, bowel tumor or an inflammation, e.g. ulcerative colitis or Crohn ś disease

Antidiarrhoeals, bulk-forming agents and sometimes corticosteroids are required

E. Change of Diet

1. Lactose intolerance may result in osmotic diarrhoea

2. Changing from breast milk to cow ś milk in infant

Bottle-fed babies may suffer from osmotic diarrhoea resulting from insufficient dilution of milk

F. Drug-induced Diarrhoea

Certain drug may cause diarrhoea, e.g. Antibiotics, Magnesium antacids, Metformin

Management of Diarrhoea

Diet Intake

1. The food must be well done and personal hygiene is important

2. Bland diet is recommended while milk products should be avoided

3. For children changing from breast milk to cow ŝ milk, small and frequent meal should be given

4. World Health Organization (WHO) recommends that

   4.1. Breast-fed babies should continue feeding and increase the frequency of breast-feeding to at least every 3 hours in order to increase the nutrient and fluid intake

   4.2. For bottle-fed babies milk powder should be diluted with twice the usual amount of water and be given every 3 hours for children over 6 months

Oral Rehydration Therapy

1. The standard treatment for acute diarrhoea in babies and young children

2. Contain sodium as chloride and bicarbonate, glucose and potassium

3. The absorption of sodium is facilitated in the presence of glucose

Preparation Available of Diarrhoea

GES 45 (KCI 380mg, NaCI 230mg, NaHCo3 420mg, Glucose 5.77g)

Pedialyte solution (sodium, potassium, chloride, citrate, glucose)

When to refer of Diarrhoea

If there are any signs of dehydration, the child should be referred to the physician

A. Signs of Dehydration

1. Dry mouth and thirst
2. No urine
3. Crying with no tears

B. Later Signs

1. Sunken eyes
2. Drowsiness
3. Rapid breathing
4. Coma

Occur of Conditions

1. Duration
    1.1. < 1 year with diarrhoea > 1 day
    1.2. < 3 years and elderly with diarrhoea > 2 days
    1.3. Older children and adults with diarrhoea of 3 days
2. The presence of blood or mucus in the stools
3. Diarrhoea with severe vomiting and high fever (cholera)
4. Chronic diarrhoea (more than three week ś duration) may be caused by bowel conditions such as Crohn ś disease, irritable bowel syndrome or ulcerative colitis
5. Diarrhoea in a patient who has recently traveled abroad
6. Suspected drug-induced reaction to prescribed medicine

Antidiarhoeal Agent

Adsorbents

Name: Kaolin Pectin Mixture (Kaopectate)

Kaolin would absorb water in the GI tract and adsorb toxins and bacteria onto its surface

Name: Smecta

For acute and chronic diarrhoea, especially in children

Name: Activated Charcoal

Use as a GI adsorbent in acute poisonings

Reduce gut motility

Name: Morphine and Codeine

Narcotic drugs, Can slow the motility of the GI tract, indeed constipation is a well-recognized side effect of such drugs

Name: Lomotil (Diphenoxylate 2.5mg/ Atropine 25mcg)

Reduces gut motility and secretion and can be used in acute and chronic diarrhoea. Usually given one tablet q4h until diarrhoea stops

Not more than two days

Not recommended for children < 4 years old

Name: Loperamide (Imodium)

A synthetic agent chemically resembles and the activities similar to morphine but with fewer

side effect

It reduces gut motility by blocking acetylcholine receptors in the gut

Not recommended for children < 12 years old

Constipation

Constipation = decreased frequency of defecation + hard dry stool + abdominal discomfort

Sometimes can obstruct the bowel

Obstruction of the bowel occurs as colicky abdominal pain , abdominal distension and vomiting

When these symptoms of obstruction are present, urgent referral is necessary because constipation is only one of the possible causes of obstruction and there are others such as bowel tumour

Reference

The following signs and symptoms require medical advice:

1. Sudden change of bowel habit, which has lasted for 2 weeks or longer
2. The presence of blood in the stool
3. Presence of abdominal pain, vomiting and distension
4. Drug-induced constipation
5. Failure to OTC medication

Cause of constipation

1. Insufficient dietary fiber is a common cause of constipation
2. Change in diet and lifestyle, e.g. following a job change, travel and inadequate intake of food and fluids may be responsible
3. Drug induced, e.g. morphine, calcium channel antagonist, etc

Management of Constipation

1. Increasing the amount of dietary
2. Drinking more fluids
3. Taking regular exercise
4. In the short term, a laxative may be recommended to ease the immediate problem

Laxatives

Clinical Uses

Laxatives may be required for the following conditions:

1. In cardio-vascular disease
2. In patients with hemorrhoids
3. Following surgery
4. To clear the gut before surgery or for diagnosis
5. Hormonal change in pregnancy
6. Drug induced

Preparations available of Laxatives

A. Bulk Laxatives

1. Most of them are prepared from natural substances, such as wheat, in form of granules or powder intended to be mixed with fluid before taking
2. They absorb fluid in the gut, swell and increase faecal mass, which exert pressure to the gut wall and stimulates bowel movement
3. The laxative effect will take 3 days to develop
4. Increase fluid intake in order to avoid faecal impaction and obstruction in the oesophagus
5. Bulk laxatives are recommended in pregnancy and cannot have enough fiber intakes

Preparation

Ispahula husk (Fybogel, Isogel)

Psyllium (Metamucil)

Sterculia (Normacol)

1. Methylcellulose (Celevac)

B. Stimulant Laxatives

1. Stimulate nerve endings in the gut wall and increase intestinal movement

2. They work within 6-12 hours

3. Stimulant laxatives should not be used for more than one week

4. Produce gripping pain

5. Can cause tolerance, smooth muscle atony in the colon and potassium loss

Preparation

Senna glycosides (e.g. Senokot tablets, granules)

Anthraquinones are the active compound liberated into the colon by gut and increase intestinal movement

Aloes, Cascara and Rhubarb belongs to the anthraquinone group and has similar properties

Bisacodyl (Dulcolax tablets, suppositories)

Often used for evacuation of colon before endoscopies or after surgical operation

Taken orally it acts within 6-10 hours

Given as a suppository, the effect usually occurs with one hour

Dulcolax tablets are enteric coated; antacids should be avoided within one hour of administration

C. Osmotic Laxatives

Osmotic laxatives act by retaining fluid in the gut by osmosis

The increase pressure in the gut then stimulates bowel movement

Produce a rapid bowel evacuation within a few hours

Preparation

1. Magnesium Salt (Saline Purgatives)

Magnesium sulphate (Epsom salt)

Should not be used regularly, especially in patients with renal impairment, because it may be absorbed causing unconsciousness

It should also be used with care in the elderly and patients with cardiac problems

Magnesium hydroxide (Milk of Magnesia)

Commonly abused but is safe for occasional use

Golytely

Polythene glycol 3350 (an emulsifying agent) 118 g + Potassium chloride 1.5 g + Sodium chloride 2.9 g + Sodium bicarbonate 3.36 g + Sodium sulphate 11.36 g = [137 g per packet]

Dissolve whole pack in 2 liters of water and drink at the rate of 1 liter/hour

This preparation is used for whole bowel irrigation in preparation of GI examination, X-ray procedure and colonic surgery

Fleet Enema

Sodium bi-phosphate 19 g + Sodium phosphate 7 g = [in bottle of 4.5 fl.oz]

This is a saline laxative with rapid onset of action

It is used for constipation and bowel cleansing before rectal examination

2. Lactulose (Dusphalac)

Non-absorbable disaccharide, which retains water in the bowel by an osmotic action

Gut bacteria degrade Lactulose to acetic and lactic acids, which stimulate colon motility

It has a slow onset of action of 1-2 days, but is safe and effective for children and the elderly

Usual dose: 15ml bd for 3 days, For hepatic encephalopathy 30-50 ml tds

Glycerin suppositories/ Glycerin bulb enema

Have both osmotic and irritant effects and usually act within an hour

May cause rectal discomfort

Moistening the suppository before use will make insertion easier

D. Faecal Softeners

Docusate Sodium/ Dioctyl Sodium Sulphosuccinate (Colace, Softon) 1-2 Caps daily

Emulsifying agents, which reduce the surface tension of hard stool and allow water to penetrate into the faecal mass and soften the faeces

They work rather slowly (in 1-2 days), but are safe for the elderly and those who had a stroke or myocardial infarction

Useful as an adjunct to stimulant laxatives in the treatment of Opioid-induced constipation

E. Lubricant Laxatives

Liquid Paraffin, Agarol

Liquid paraffin works by coating and softening the faeces and prevents further absorption of water into the colon

Long-term use can result in impaired absorption of fat-soluble vitamins and leakage of liquid paraffin through the anus may occur

Choice of Laxatives

Constipation in Children

Change in diet and emotional causes

A single glycerin suppository and dietary advice

Constipation in Pregnancy

Hormonal changes and oral iron

In take of plenty of high fiber foods and fluids can help

Bulk laxatives are preferred when necessary

Constipation in the Elderly

Less physically active and poor natural teeth

Bulk laxative is recommended

Laxative Abuse

1. Those with chronic constipation get into the vicious cycle by using stimulant laxatives repeatedly
2. This damages the nerve plexus in the colon leading to smooth muscle atony in the colon
3. Prolonged use of laxatives to control weight may form a habit and may result from water and electrolyte loss
4. Especially sodium and potassium leading to postural hypotension (Orthostatic hypotension) general weakness and arterial fibrillation

Gastric Acid Secretion

Control of Gastric Acid and Secretion

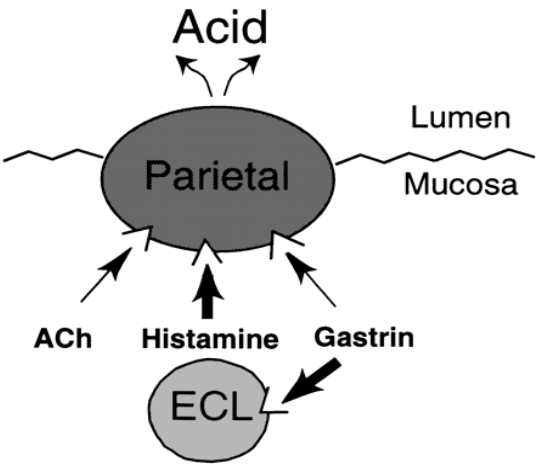
Gastric acid is secreted from the gastric parietal cell by a proton-pump H+/K+ ATPase located at the membrane of the parietal cell

The proton-pump H+/K+ ATPase is a Hydrogen-Potassium Adenosine Triphosphatase Enzyme System, which can be activated by 3 endogenous substances (Neurotransmitters)

1. Acetylcholine (ACh)
2. Histamine [EnteroChromaffin-Like Cell (ECL)]

Gastrin (G Cell)

Pathways in the Control of Gastric Acid and Secretion



Secretion of these substances is controlled centrally by the medulla, and locally by the stomach wall

The taste, smell and distension of food in the stomach stimulate the medulla to release acetylcholine (ACh), which acts on appropriate receptors at:

1. The parietal cell on the stomach wall to secrete gastric acid
2. Histamine storage cells (similar to mast cells) to release histamine, which in turn acts on H2 receptors at the parietal cell to release gastric acid
3. Gastrin cells to release gastrin, which directly stimulates the parietal cell and indirectly induces the histamine storage cells to release histamine and so repeats the process in 2

Peptic Ulcer Diseases

Ulcer that develop in areas of the gastrointestinal (GI) tract exposed to gastric acid are peptic ulcers

Peptic ulcer developed in the stomach are called gastric ulcers

Developed in the duodenum are called duodenal ulcers

Peptic ulcers tend to relapse and most peptic ulcers are duodenal

Gastric ulcers are characterized by epigastric pain precipitated by eating

Duodenal ulcers are characterized by pain relieved by food and often disturbs at night

The most common complication of peptic ulcers is bleeding and another is perforation erosion of the ulcer

Causes of Peptic Ulcer Formation

1. Hyper-secretion of gastric acid (hydrochloric acid) seems to be the immediate cause of duodenal ulcer
2. Hypo-secretion of protective mucus may be the cause of peptic ulcer since the stomach wall is highly adapted to resist gastric acid through the secretion of protective mucus
3. Hyper-secretion of pepsin. Normally, the mucous membrane lining the stomach and duodenal walls can resist acid and pepsin, however, in some people, this resistance breaks down and an ulcer develops
4. Other factors believed to stimulate an increase in acid secretion are emotions, cigarette smoking, certain food medication (e.g. alcohol, coffee, aspirin)
5. Helicobacter pylori (H. pylori) are microorganism found in the gastric mucosa and have been implicated as a cause of relapse after initial ulcer healer ulcer healing. Eradication of the organism has successfully reduce relapse rate and prevent gastric carcinoma

Ulcer Healing Drugs

A. Antacids

Antacids are basic compounds which neutralize hydrochloric acid in the stomach

Management of dyspepsia, Gastro-Oesophageal Reflux Disease (GORD) and peptic ulcer disease

Normally given between meals and at bedtime, the tablets should be chewed

Suspensions are more effective than tablets, but for neutralizing gastric acidity, large doses are required

Treatment should be maintained for 8 weeks to heal up an ulcer

Antacids should not be taken at the same time with other drugs, especially with tetracycline. It may impair their absorption

Antacids may damage enteric coatings designed to prevent dissolution in the stomach

Antacids may cause rebound acid secretion, especially Calcium carbonate

Preparations available

1. Sodium Bicarbonate (Soda Mint) neutralizes HCI rapidly but produces CO2 in the stomach, so belching and distension often follow its use

Sodium can be absorbed and is not suitable for patients with hypertension

Bicarbonates ion can affect the acid-base balance of the body

It is rarely used as antacid

2. Calcium carbonate (Titralac) neutralizes HCI rapidly but produces CO2 as does sodium bicarbonate, but tends to produce constipation and acid rebound

It is mainly used as calcium supplement for renal failure

3. Magnesium salts (Magnesium Trisilicate and Magnesium Hydroxide) (Mylanta, Triact, Diovol-plus, Maalox-plus, Gelusil-plus etc) react with HCI producing Magnesium chloride, which cause Osmotic Diarrhoea

Contraindication: renal disease patients. Magnesium can be absorbed causing hyper-magnesaemia, which may cause CNS and Cardiac depression

4. Combination of preparations

Aluminum hydroxide gel has a slow and sustained effect on the stomach and may form a protective coat over the ulcer

The main side effect is constipation, which may be counteracted by combining Aluminum hydroxide with Magnesium salt

Magnesium hydroxide cause diarrhoea. Aluminum hydroxide cause constipation

Simethicone is an oral anti-foaming agent used to reduce bloating, discomfort and pain caused by excess gas in the stomach or intestinal tract

Gasteel is used for flatulence.

Prolong administration of Aluminum is contraindicated to patient with renal impairment, because aluminum can be absorbed causing neurotoxicity

B. Mucosal protectant (Cytoprotectants)

Mucosal protectants are anti-secretory and protective substances used in the prevention and treatment of peptic ulcer diseases

They mimic the effect of endogenous e.g. the postaglandins (PGs), which protect the mucosa by inhibiting gastric acid secretion and by enhancing protective mucus secretion

Preparations available

1. Misoprostol (Cytotec) is a synthetic analogue of (prostaglandin E2) PGE2

Used of prevention of Non-Steroid Anti-Inflammatory Drug-induced gastric damage

The major side effects of this compound are contraction of GI smooth muscle causing abdominal cramps, diarrhea and uterine contraction

Contraindicated in pregnancy

Sucralfate (Ulsanic)

Stimulates PGE2 production and enhances mucosal protection

In acid environment it binds to the ulcer surface and forms a barrier, which protects the ulcer from further attack by acid and pepsin

Concomitant administration of sucralfate with antacid and anti-secretory agents reduce its efficacy

It should be taken on empty stomach because the presence of food in the stomach will block the bond to the ulcer surface

It is contraindicated to patients with renal impairment due to Aluminum intoxication

2. Bismuth Subcitrate (Denol)

Acts in a similar manner as Sucralfate

Stimulate PG formation

Bismuth Subcitrate + Metronidazole + Tetracycline or Amoxycillin or other Antibiotics, for the eradication of Helicobacter pylori.

Bismuth has a number of toxicities and neurotoxicity, include headache, GI disturbances, blackening of stool and tongue and neurotoxicity

Cannot be given for prolong period

Usually 120mg qid for 28 days with a washout period of 2 months

Concomitant administration with milk, antacid and H2-receptor antagonists increases its toxicities and reduces its efficacy, because bismuth can be absorbed in raised pH to toxicity

Should be taken at least 30 minutes before meals or two hours after

Cannot be given to patients with renal impairment

C. H2-receptor Antagonists

Block histamine receptors (known as H2-receptors) in gastric parietal cells and so inhibit gastric acid secretion

Significant effect in relieving peptic ulcers and reflux oesophagitis

May relapse following cessation of treatment

Maintenance treatment is best given in courses of 4-8 weeks

Preparations available

1. Cimetidine (Tagamet)

Has some anti-androgenic activity with occasional gynaecomastia

Inhibits cytochrome P-450 and prolongs half-life of some drugs, e.g. Warfarin, Theophylline

2. Ranitidine (Zantac)

3. Famotidine (Pepcid, Famox)

4. Nizatidine (Axid) are newer H2-receptor antagonists with minimal side effect

D. Proton-pump Inhibitors

The gastric proton-pump is an enzyme system (H+/K+ ATPase) situated in the secretory membrane of the gastric parietal cell responsible for gastric acid secretion

The proton-pump inhibitors inactivate the proton-pump process by binding selectively and irreversibly to the enzyme system

Effectively inhibit gastric acid secretion

Produce long-lasting and complete achlorhydria (no gastric acid production) in therapeutic doses

1. In patient not respond satisfactorily to other treatment

Erosive oesophagitis

Zollinger-Ellison Syndrome

2. Triple Therapy : Omeprazole (Losec) + Klacid + Amoxycillin for the eradication of Helicobacter pylori regimen for 7 days

Long period of achlorhydria may precipitate infection

May cause tumour formation (found in rats)

Also cause liver enzyme changes, headache, skin reactions, diarrhoea, nausea, constipation and GI disturbances

Preparations available

1. Omeprazole (Losec) used for Duodenal ulcer : 20mg qd for 2-4 weeks
2. Pantoloc and Takepron have similar activities and uses as Losec
3. Nexium is a second-generation proton-pump inhibitors claimed to have fewer side effects with higher efficacies

E. Anti-muscarinics (Anti-cholinergics)

Mode of Action

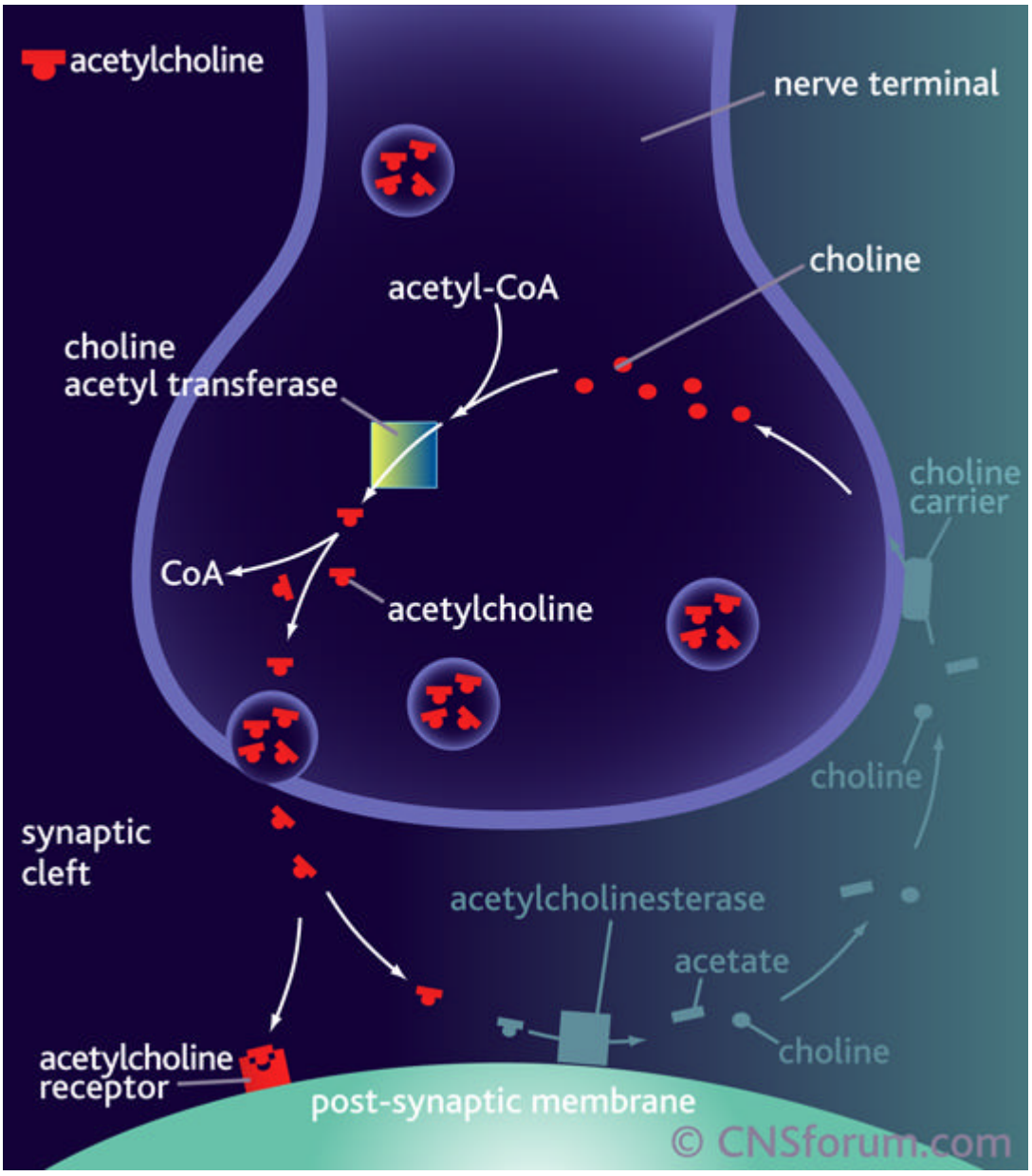
Reduce gastric motility, inhibit gastric acid secretion and therefore reduce pain

Clinical uses

Gastric ulceration

GI spasm

Excessive gastric acid secretion



Histamines

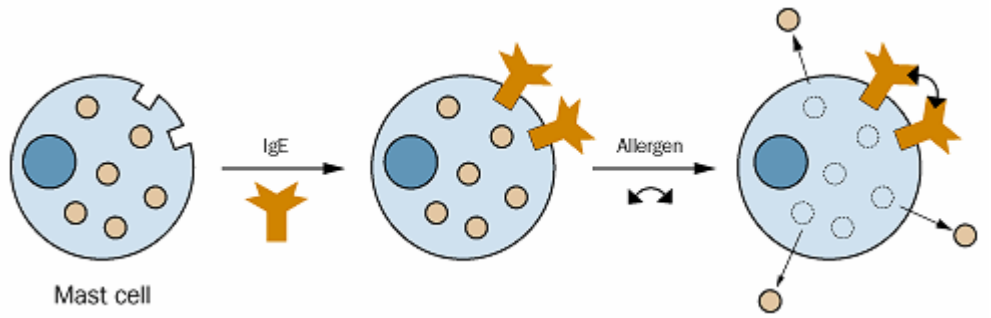
Histamine is a biologically active amine found in many tissues of the body, e.g. in the lungs, skin and GI tract

It is an important mediator of allergic and inflammatory reactions

It is stored in a bound form in granules in mast cells and is biologically inactive

Many stimuli can trigger the release of mast cell histamine from its bound form, allowing the free histamine to exert its actions on surrounding tissues causing allergic reaction

For example, when antigen-antibody reactions take place on the surface membrane of the mast cell, histamine is released causing allergic reactions (Immunoglobulin Ig E)



Biological Effect

Pharmacological Properties

Histamine binds to specific histamine receptors to produce biological effects

H1-receptors

1. found in bronchial smooth muscle, ileum and uterus

2. stimulation causes an increase in contraction of these muscles

H2-receptors

1. found in acid secreting cells in the stomach

2. stimulation causes an increase in gastric acid secretion

Cardiovascular effects

1. Histamine relaxes blood vessel and reduce peripheral resistance leading to oedema
2. Intense reaction may cause rapid fall in blood pressure, bronchoconstriction and circulatory collapse (Histamine Shock or Anaphylactic Shock), which is fatal
3. Increase heart rate and force of contraction leading to arrhythmia, flush and headache

Skin Reaction

Histamine cause a characteristic Wheal-and-Flare Response (triple response) to the skin

1. A reddening appears on the site of infection owning to dilation of blood vessel
2. An oedematous wheal and a red irregular flare surrounding the wheal
3. The sensation of itch or pain

Effect of smooth muscle

1. Contraction of intestinal smooth muscle
2. Bronchoconstriction
3. Contraction of uterus of pregnant women leading to abortion

Gastric Acid Secretion

Histamine increase gastric acid secretion by acting on H2-receptors and is blocked by H2 antagonists

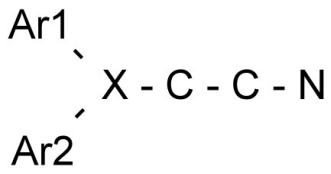
Nerve Ending

Histamine is a powerful stimulant of sensory nerve endings, especially those nerves mediating pain and itching, e.g. insect stings

Antihistamines

Characteristics

1. Compounds structurally similar to histamine possessing a substituted ethyl-amino group



2. Conventionally divided into six groups based on X and its relation to Ar1 and Ar2

3. All of lipid soluble and all are reversible competitive blockers of histamine at H1-receptor

Pharmacokinetics

1. Well absorbed after administration

2. Maintain their pharmacological action for 4-6 hours

3. Metabolized in the liver and excreted through the kidney

4. Widely distributed through the body, including the central nervous

Pharmacological Properties

1. Relax GI and bronchial smooth muscle

2. Inhibit vasodilation caused by histamine (e.g. decongestion)

3. Antagonize capillary permeability and so reduce oedema

4. Antagonize the triple reaction and itching

5. Both stimulate at high dose and depress the CNS

6. Possess anti-cholinergic or atropine-like effects

7. Mepyramine (contained in Anthisan cream) possesses local anaesthetic effect at high concentrations and is used to relieve itching caused by insert bites, sunburn and prickly heat

Preparations and Therapeutic Uses of Classical Antihistamines

1. Block H1-receptor

Symptomatic treatment of allergic disease due to histamine release

Eczema, urticaria, hay fever, allergic rhinitis, cough and cold

The widely used antihistamines

Chlorpheniramine (Piriton), Cyproheptadine (Periactin)

2. Motion Sickness, Nausea, Vomiting, Vertigo

Dimenhydrinate (Gravol), Cyclizine (Marzine)

Vestibular Disturbances (Meniere ś disease)

Cinnarizine (Stugeron), Betahistine (Meris lon)

3. Use as Hypnotics

Diphenhydramine (Benadryl, Bendrol)

4. Nausea and Vomiting of pregnancy

May be temporarily alleviated by an antihistamine or Promethazine (Phenergan)

Adverse Reactions

1. Sedation interfere with patient ś day time activities

2. Concurrent administration of sedative and alcohol enhance this effect

3. Dizziness, fatigue, nervousness, tremor, GI disturbance and dry mouth

4. Drug allergy

5. Acute poisoning

Hallucination, excitement, incoordination, convulsion

Atropine-like poisoning: fixed dilated pupils with flushed face, tachycardia, urinary retention, dry mouth and fever

Non-Sedative Antihistamines

Non-sedative antihistamine have similar therapeutic efficacy to the older agents but are less sedating

They are much more expensive and are mainly used for the treatment of allergic rhinitis and chronic urticaria

Pharmacological Properties

1. Hydrophilic structure, cannot cross the blood-brain-barrier, less sedating
2. Do not potentiate the effect of alcohol and diazepam
3. Psychomotor skill or alertness is not affected
4. No anti-cholinergic activities
5. Long-lasting
6. Have similar therapeutic efficacy to the older agent
7. Mainly used for the treatment of allergic rhinitis and chronic urticaria

Preparation

Preparations available of Non-Sedative antihistamine

Terfenadine

Contraindication to patients with: Significant hepatic dysfunction and On Erythromycin or oral antifungal (e.g. Nizoral, Lamisil)

Co-administration with these drugs may cause cardiac fibrillation

Astemizole (Hismanal)

Acrivastine (Semeprex)

Cetirizine (Zyrtec)

Loratadine (Clarityne)

1. Aerius is a new generation Loratadine

Fenoxofenadine (Telfast)

Ebastine (Kestine)

Colds and Influenza (Flu)

The common cold comprises of a mixture of Upper Respiratory Tract Infections (URTI) and 90% is caused by Rhinoviruses. They are self-limiting

Common Signs and Symptoms of Colds and Flu

1. Runny nose
2. Sneezing or Coughing
3. Headache or Aches
4. Sore throat
5. Earache

This is due to blockage of the Eustachian Tube

The air pressure in the ear cannot be equalized with the atmospheric pressure

When the middle ear fills up with fluid, a secondary bacterial infection occurs and the ear becomes acutely painful

This is called Otitis Media, a serious complication of common cold in children

6. Fever

The presence of fever may be an indication for flu rather than cold

Flu often starts with low-grade fever and chill, muscular aches and pain in the limbs

Sore throat and cough may present and there is often a period of generalized weakness

The symptoms may resolve over 3-5days

Management of Colds and Flu

1. Self-limiting
2. Adequate fluid intake, bed rest, humidification of room
3. Symptomatic treatment

Preparations available of Colds and Flu

A. Decongestants

Sympathomimetcs (Decongestants): Ephedrine, Pseudoephedrine, Phenylpropanolamine (PPA) and Phenylephrine

Constrict the dilated blood vessels in the nasal mucosa and improve drainage of mucus

These medicines can be given orally or applied topically

Oral administration stimulating effects on the CNS and the heart, increase in blood pressure and may affect diabetic control

Not suitable for diabetes, heart disease or hypertension

Topical administration < 7 days because rebound congestion may occur

The most widely used nasal drops and sprays for nasal congestion:

1. Oxymetazoline 0.05% (Afrin)

Naphazoline (Privine)

2. Xylometazoline (Otrivin) long lasting decongestant lasts up to 6 hours

B. Antihistamine

Antihistamine (Chlorpheniramine, Promethazine, Diphenhydramine, etc) help to reduce sneezing and runny nose

Cause drowsiness

Not for anyone who drives or operate machinery at work

Have anti-cholinergic effect: dry mouth, blurred vision, constipation, increase intra-ocular pressure and urinary retention

Not for patients with glaucoma and prostatic hypertrophy

Non-sedating antihistamines (Clarityne, Clarinase and Telfast, etc)

C. Analgesics

Paracetamol, Caffeine, Salicylamide and Aspirin are employed for symptomatic relief of sore throat or fever

Also contained in preparations for colds and flu

D. Preparations Containing Multiple Ingredients for Colds and Flu

Neozep, Dimetapp, Panadol, Dristan

PPA has been linked with increased risk of stroke with chronic use

Not suitable for those with high blood pressure and heart disease

E. Lozenges

Dequadin, Strepsils, Cepacol help to sooth and moisten the throat

F. Cough Mixtures

These drugs can be used alone or in combinations as required

Antibiotics are generally not recommended

G. Immunization

Flu vaccine is indicated for the elderly (> 65 years old)

Residents of nursing homes and patient with chronic illness

An immunization can cover a period of protection for up to 6 months

H. Selective Drugs Treatment for Flu

Relenza

An inhaled anti-influenza agent effective for both influenza A and B

Tamiflu

This is the first oral anti-influenza effective for both influenza A and B

Sore Throat

Most sore throat is caused by viral infection and is self-limiting, only a few are caused by bacteria

Sore throats are often associated with other symptoms of a cold or influenza

Antibiotics are of no value

Viral of Sore Throat

A. Laryngitis

Laryngitis is typically a viral infection usually associated with sore throat and a hoarse, diminished voice

Usually settles within a few days

If hoarse occurs for more than 3 weeks referral is necessary

B. Glandular Fever

Glandular Fever (Infectious Mononucleosis), is another form of vial sore throat

Often produces marked discomfort

May cause dysphagia (difficulty in swallowing)

Typically occurs in teenagers and young adults

A serious sore throat may follow a week or two with general malaise

The throat may become very inflamed with creamy exudates present

Glands (lymph nodes) in the neck and axilla (armpit) may be enlarged and tender

The diagnosis may be confirmed with blood test

If Ampicillin is given during the infection, a measles type rash is likely to develop

Treatment is aimed at symptomatic relief

Bacterial Infections of Sore Throat

A. Tonsillitis

Tonsillitis is a Bacterial infection of the tonsils

Severe throat infection and dysphagia

Abscess develop in the region of the tonsils

Hospital admission to drain the abscess

Antibiotic therapy is required

B. Streptococcal Pharyngitis

Streptococcal Pharyngitis is also known as Strep throat

Infection caused by Group A beta-hemolytic Streptococcus (GAS or Pyogenes Bacteria)

The bacteria damaged the heart valves

Resulting in an inflammation of the heart

The condition is called rheumatic fever and is a complication of streptococcal sore throat

The symptoms of rheumatic fever include arthritis, carditis, fever, subcutaneous nodules, skin rash and malaise

Due to an immunogenic reaction localized in the joints, heart valves and other tissues involved

C. Glomerulonephritis

Glomerulonephritis (GN) is an inflammation of the kidney due to an immunological reaction to the toxin given off by Streptococci bacteria that have recently infected another part of the body, especially the throat

The toxin deposits on the glomeruli and the antibodies attack the tissue causing inflammation

The glomeruli may be permanently damaged leading to acute or chronic renal failure

When to refer

1. Sore throats > a week (= secondary infection may occur)
2. Hoarseness > 3 weeks (= severe infection, e.g. cancer may present)
3. Difficulty in swallowing (always associated with severe throat infection)
4. Recurrent bouts of infection (tonsillitis)
5. Any patient taking Carbimazole and presenting with a sore throat should be referred at once, can be the first sign of a life-threatening adverse drug reaction

Management of Sore Throat

1. Most sore throats are caused by viral infections and are self-limiting
2. Providing symptomatic relief from discomfort and pain until the infection subsides
3. Increasing fluid intake and mild analgesics for short period are helpful

Preparation Available for Symptomatic Relief of Viral Sore Throat

A. Lozenges and Pastilles

Sooth and moisten the throat and reduce soreness rather than to get rid of the infection

1. Antiseptic lozenges –Cetylpyridinium CI (Cepacol)

2. Antifungal lozenges –Dequalinium CI (Dequadin)

3. Local anaesthetic –Benzocaine lozenge

4. Local anaesthetic and Antiseptic lozenges –Phenol-based lozenge (Strepsils, Cepastat)

5. Anti-inflammatory lozenges –Benzdamine (Difflam)

Benzdamine absorbed through the skin and mucous membrane and has been shown to be effective in reducing pain and inflammation in sore throat; Side effects are numbness and stinging of the mouth and throat

B. Mouthwashes and Sprays

These preparation contain antiseptic and anti-inflammatory properties

Unlikely to have anti-viral activities

Useful of bacterial involvement

Chlorhexidine (Corsodyl)

Hexetidine (Bactidol)

C. Analgesics

Analgesics: Paracetamol, Caffeine, Salicylamide and Aspirin (Acetyl Salicylate) can alleviate pain

Cough

Reflex action due to irritation of the airway

Protective mechanism to clear the airway so that breathing can continue normally

Mainly due to viral infection of the Upper Respiratory Tract (URT) and is self-limiting

Refer if cough persists > 2 weeks duration

Smoking can exacerbate a cough

Nature of Cough

A. Unproductive Cough (Dry cough)

Dry and tight cough; no sputum is produced

Usually caused by viral infection

Self-limiting

Dry Cough: Phensedyl, Fendil, Cosyr syrup, Codoplex, Benylin CD syrup, Actifed Co syrup,

Actifed DM syrup, Promethazine + Ephedrine + Codeine = PEC syrup

B. Productive Cough

Chesty or loose coughs which produce sputum

May indicate a chest infection such as bronchitis, General Practitioner (GP) referral is required

If sputum is green, yellow or rusty-coloured thick mucus

Productive Cough: Mist expect Stim, Cocillana Co syrup, Benylin, Robitussin, Polaramine Exp

C. Whooping Cough (pertussis)

The whoop is the sound produced when breathing and is caused by narrowing of the

bronchioles

The bouts of coughing prevent normal breathing and the whoop represents the desperate

attempt to get a breath in GP referral is necessary for whooping cough (pertussis)

When to refer of Cough

1. Cough > 2 weeks
2. Sputum yellow, green or rusty or blood stained
3. Chest pain (caused by heart disease?)
4. Shortness of breath or recurrent nocturnal cough (asthma?)
5. Wheezing
6. Suspected adverse drug reaction (taking ACE inhibitor)

Management of Cough

1. Cough suppressants for dry cough
2. Expectorants for productive cough
3. Demulcents for young children and pregnant women

The effectiveness of cough remedies remains unproven

The use of combinations with apparently contradictory ingredients has been cited (both codeine and expectorants are used in the same formula)

Increase fluid takes (6-8 glasses/ day)

Maintaining humidity of inspired air by steam inhalation can help to hydrate the lungs and airway

Hot drinks can have a soothing effect

Preparations available of Cough

A. Cough Suppressants

Reduce the intensity and frequency of cough by acting centrally at the cough center

They are narcotics or synthetic narcotic derivatives and are effective is unproductive coughs

Codeine and Pholcodeine

Cough suppressant, mild sedative, analgesic and anti-cholinergic effects

Dependence may occur on prolonged use

Liable to abuse

Not suitable for asthmatics

Codeine is best avoided in the treatment of children ṡ cough

Should not be used in children < 1 year old, due to respiratory depression

Dextromethorphan (DM)

Synthetic codeine substitute with similar activities

Non-sedative and fewer side effects

Also liable to abuse

Can be given to children > 2 years old

Adult dose 15-30 mg up to qid

Noscapine and Cofrel

Synthetic anti-tussives with milder activities and fewer side effects than DM

Sometimes used for cough but effectiveness is uncertain

Available in cough and cold preparations

B. Expectorants

Expectorants work by stimulating bronchial secretion, increasing the amount of respiratory fluid and so reducing the viscosity of tenacious mucus

Ipecacuanha (Ipecac)

Has been used as expectorant for many years in clinics and hospitals

Usually as an ingredient in formulary preparations, Ammonia and Ipecac Mixture (Mist Exp Stim)

Ammonia Salts (Ammonium Chloride/ Bicarbonate)

Used as expectorants in formulary mixture such as Mist Exp Stim and Benylin Syrup

Have an unpleasant smell of ammonia not acceptable by some patient especially children

Guaiphenesin (Glyceryl Guaiacolate)

Can be used alone or in combinations with other antitussives in cough mixtures

Safe and has a pleasant taste suitable for children

Usual adult dose: 100-200 mg qid

1. Other Expectorants

Squill Linctus, Tolu Linctus and Anise, Lemon Tincture (certain volatile oil)

Also used in some formulary preparations as expectorants

C. Steam Inhalation

Can humidify the airway

Reduce viscosity of bronchial secretions

Pro duce soothing effect in patients with airway disease

Had been used in bronchitis and asthma

D. Mucolytic Agents

Mucolytic agents work by breaking down the disulphide bonds of mucus structure

Reducing the viscosity of bronchial mucus and increasing this flow properties

Used in the management of bronchitis, asthma and pneumonia

However, the benefits are not proven

Available in various dosage forms, and some are included in cough and cold preparations

Preparation: Acetylcystein (Flumucil), Carbocystein (Mucodyne), Bromhexine (Bisolvon), Ambroxol (Mucosolvon)

In forms of tablets, effervescent tablets, granules, capsules, syrups and even injections

E. Antihistamines

Antihistamine are often included in cough and cold remedies for the treatment of cough and associated symptoms, such as sneezing

F. Sympathomimetics (Decongestants)

Sympathomimetics (Decongestants) are commonly included in cough and cold remedies for their bronchial dilator and decongestant properties

G. Demulcent

Demulcents: Lemon and Honey, Glycerin and Simple syrup linctus

Soothing effect on the throat

No active ingredient

Safe for children and pregnant women

High syrup content is unsuitable for diabetic patient

Allergic Rhinitis

A common problem of the nose caused by allergen deposited on the nasal mucosa

Seasonal Allergic Rhinitis (Hey Fever)

Caused by grass and tree pollens or fungal mould spores

Peaks between the months of May and July

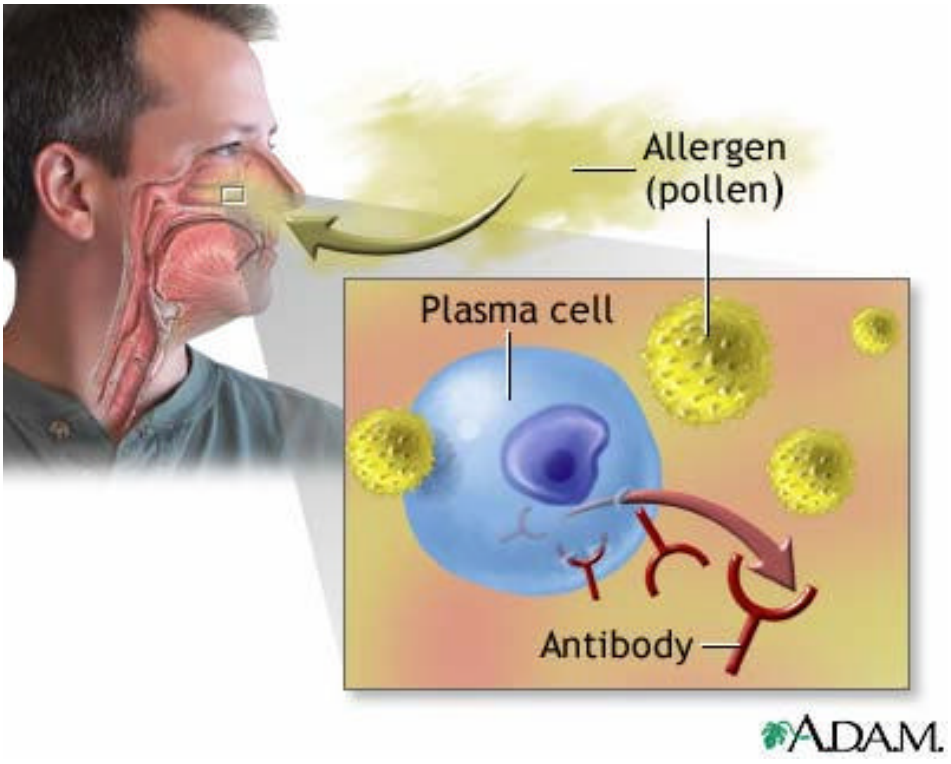
Perennial Allergic Rhinitis

Occurs all year round

Commonly caused by the house dust mite, animal dander and feathers

May start at any age

Frequently has a family history of atopy (asthma, eczema)



http://adam.about.com/reports/Allergies.htm

Symptoms of Allergic Rhinitis

A. Sneezing

Starts with symptoms of sneezing, then rhinorrhoea progressing to nasal congestion

More severe in the morning and in the evening

B. Rhinorrhoea

Thin, clear and watery discharge progress to thick, coloured purulent one, suggesting a secondary infection

No need for antibiotic treatment

C. Nasal Congestion

Inflammation of the nasal mucosa produces vasodilatation

Headache

Earache

Otitis media

Sinusitis

D. Eye Symptoms

In hey fever, the eyes may be itchy and watery

A local inflammation response called allergic conjunctivitis

E. Danger Symptoms

Wheezing

Tightness of the chest

Shortness of breath

Immediate referral to physician is recommended

Management of Allergic Rhinitis

A. Antihistamines

Effective in reducing sneezing and rhinorrhoea

Non-sedating antihistamines can be used for if drowsiness is a problem

B. Decongestants

Oral or topical decongestants in combination with an antihistamine to reduce congestion

C. Sodium Cromoglycate

Sodium Cromoglycate is used as a prophylactic for hey fever and allergic rhinitis

Start 2 - 3 weeks before the hey fever season and use through the reason

Cromoglycate eye drops are also available

D. Topical Corticosteroid

For severe case of allergic rhinitis

Old preparations (Beconase) may cause systemic effect

Newer preparations (Rhinocort spray, Flixonase spray) have fewer systemic side effects

E. Specific Allergen Immunotherapy

Specific allergen immunotherapy is presently the only disease-modifying treatment for allergic rhinitis

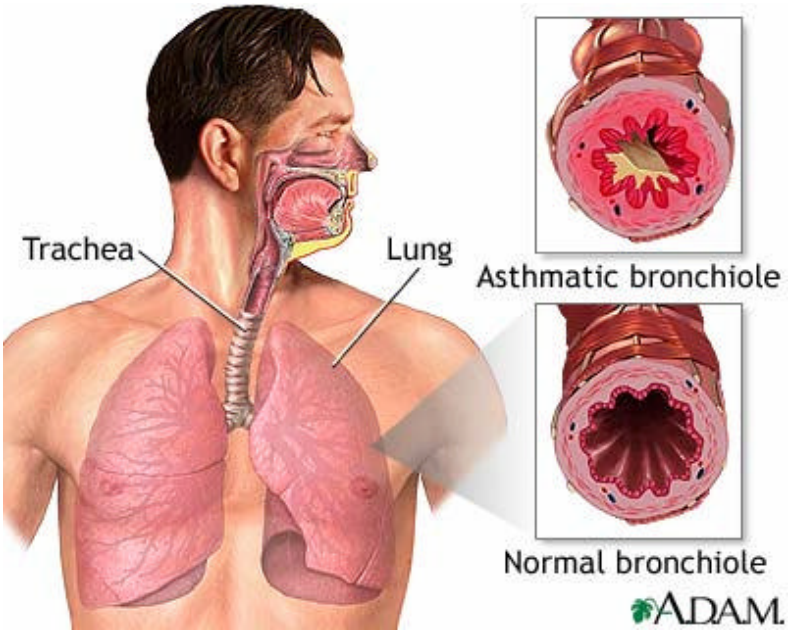
Subcutaneous injections of increasing doses of allergens, such as pollen to desensitize the patient

Asthma

A Common airways disease affecting all age groups

In asthma, the airways are more sensitive

An asthma attack happens when the airways (bronchial tube) narrow



As exposed to **Trigger Factor**

The airways overreact with trigger factor and become inflamed

Inflammation causes the airways to constrict, due to

1. Swelling of the mucous membrane

2. Spasm of smooth muscles in the bronchial wall

3. Increased mucus secretion

Signs and Symptoms of Asthma

1. Coughing, especially at night

2. Wheezing (the characteristic noisy breathing)

3. Tightness in the chest

4. Shortness of breath

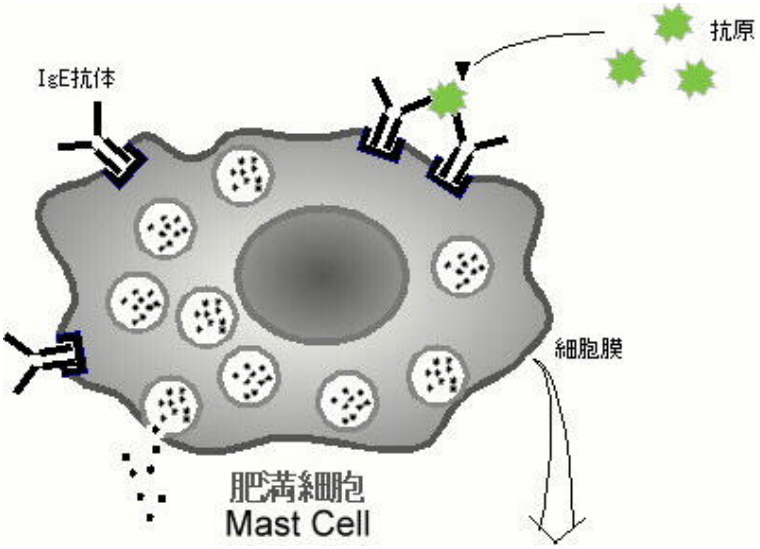
Symptoms are often worse in the morning and on waking up

Trigger Factor

1. Allergy to house dust mite, pollens mould or animal dander
2. Viral infection
3. Cold air or sudden temperature change
4. Irritants; dust, smoke, fume
5. Certain medicine; Aspirin
6. Exercise
7. Emotional stress or excitement
8. Some food additives

Pathophysiology

Asthma is caused by chronic inflammation of the airway initiated by the release of chemical substances from the mast cells



When the cell membrane is injured by antigen, infection or by physiological changes due to stress, excitement or exertion

The masts cells then release mediators (e.g. prostaglandin, heparin, histamine, leukotriene and other pro-inflammatory substance), which cause inflammation, swelling and constriction of the airways

This situation is made worse by an excessive secretion of mucus leading to obstruction of the airways

Treatment of Asthma

Objectives

1. Identify and eliminate causative Triggers, or try to stay to stay away from them

2. Restore normal airway function by doing regular exercises

3. Treat chronic symptoms by using preventive medicine

4. Prevent acute asthma attack by using medicine

5. Educate patient

Route of administration

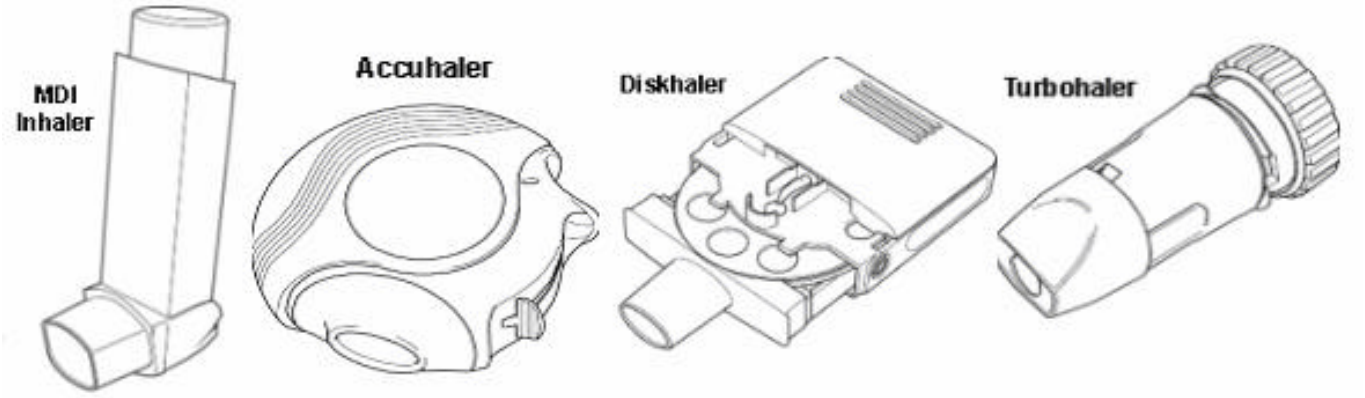
Treatment of asthma depends on the frequency of attacks and the severity of symptoms

For severe cases, preventive therapy with an inhaled corticosteroid is requires to avoid an acute attack

The preferred Route of administration for asthma is inhalation, which allows drugs to be delivered directly to the airway

Inhalation is enable a faster onset of action and requires smaller doses and therefore has fewer systemic side effects

Inhalation of a beta-2 agonist, e.g. salbutamol is the first line treatment of an acute asthma attack



Anti-Asthma

A. Beta-2 Adrenergic Agonists

Beta-2 Adrenergic Agonists (Bronchodilators) act directly on beta-2 receptors, relaxing the bronchial smooth muscles and dilating the airways

Side Effects

Palpitation (increased heart rate), tremor and tolerance

Administration of beta-blocker may cause wheezing and precipitate an asthma attack

Short-Acting Beta2 Agonists

Salbutamol (Ventolin, Volmax)

Terbutaline (Bricanyl)

Fenoterol (berotec)

Long-Acting Beta2 Agonists (not for acute attacks)

Salmeterol (Serevent Inhaler)

Bambuterol (Bambec)

B. Corticosteroids

They work by suppressing the production of mediators or pro-inflammatory substance

Side effect

Oral thrush and hoarseness

Can be reduced by mouth rinsing or by using spacer

Large doses can produce adrenal suppression, especially in children

Corticosteroids can be absorbed into blood circulation

Inhaled corticosteroid Therapy

Used for the prevention of an asthma attack

For patient requiring inhaled bronchodilator (aerosol) > once daily, Not effective in acute attack

Oral Corticosteroid Therapy

For acute and severe case, a short course of oral steroid (Prednisolone, Dexamethasone)

For emergency, an injection of steroid (hydrocortisone) is given followed by oral preparation

The dosage must be reduced gradually in order to prevent recurrence

Combination Preparations

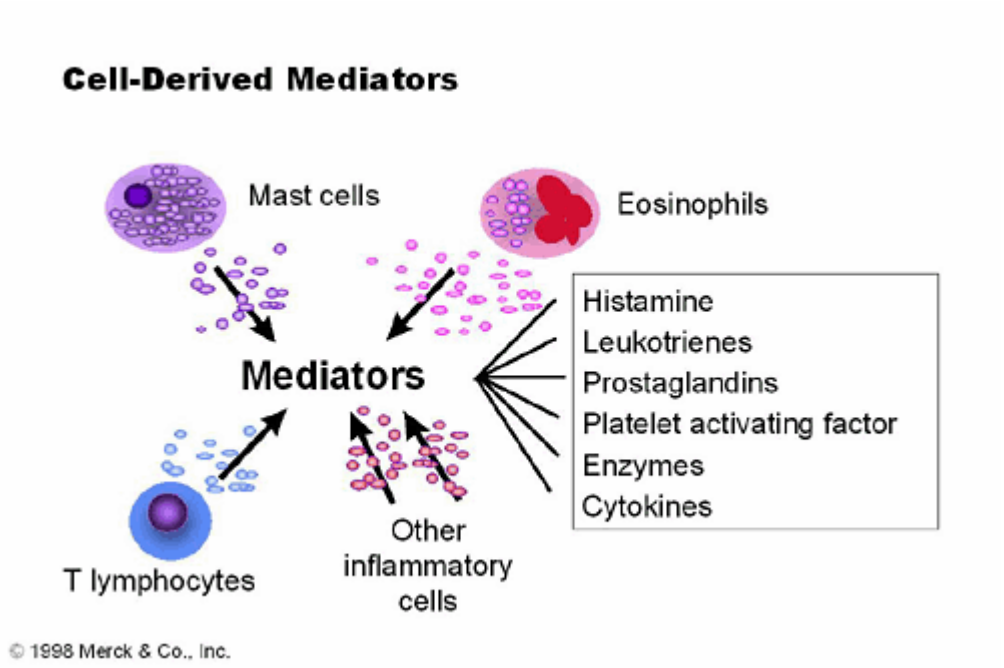
Salbutamol + Beclomethasone (Ventide Inhaler)

Salmeterol + Fluticasone (Seretide Accuhaler)

Salbutamol + Ipratropium (Combivent Inhaler)

C. Mast Cell Stabilizers

Stabilizing mast cell membrane and inhibit the release of **mediators** that cause inflammation and constrict the airway



Not bronchodilators

No direct effect on bronchial smooth muscles

Used for the prevention of asthma, especially in children

Sodium Cromoglycate (Intal)

Nedorcromil Sodium (Tilade)

They are usually administered by inhalation due to poor oral absorption

Side effects are mild

Ketotifen (Zaditen tablets, syrup)

D. Muscarinic-receptor antagonists

Atrovent inhaler is relax bronchial smooth muscles and inhibit mucus secretion

Usually given by inhalation and in combination with bronchodilator

Useful in chronic asthma and bronchitis

E. Theophylline and its derivatives

Theophylline is a powerful bronchial relaxant

Relaxes bronchial smooth muscles and reduces mucus secretion

A week diuretic

A cardiac muscle stimulant

A week CNS stimulant

Narrow therapeutic index

Its hepatic metabolism varies from person to person

Side effects

GI irritation, nausea and vomiting, increase heart rate, headache, nervousness and convulsion on overdose

F. Leukotriene Receptor Antagonists

Leukotriene is one of the mediators released from mast cells causing bronchial spasm

Leukotriene receptor antagonists block leukotrienes and therefore can prevent an asthma attack

Side effect

Include abdominal pain, headache and not for pregnancy and breast-feeding

Inhibit liver enzyme cytochrome P-450 so have a lot of drug interaction

Preparation

Montelukast Sodium (Singulair)

Zafirlukast (Accolate)

G. Others of Preparation

Antihistamines to reduce secretion; Cetirizine (Zyrtec)

Mucolytic agent to dissolve sputum (Mucosolvon, Flumucil)

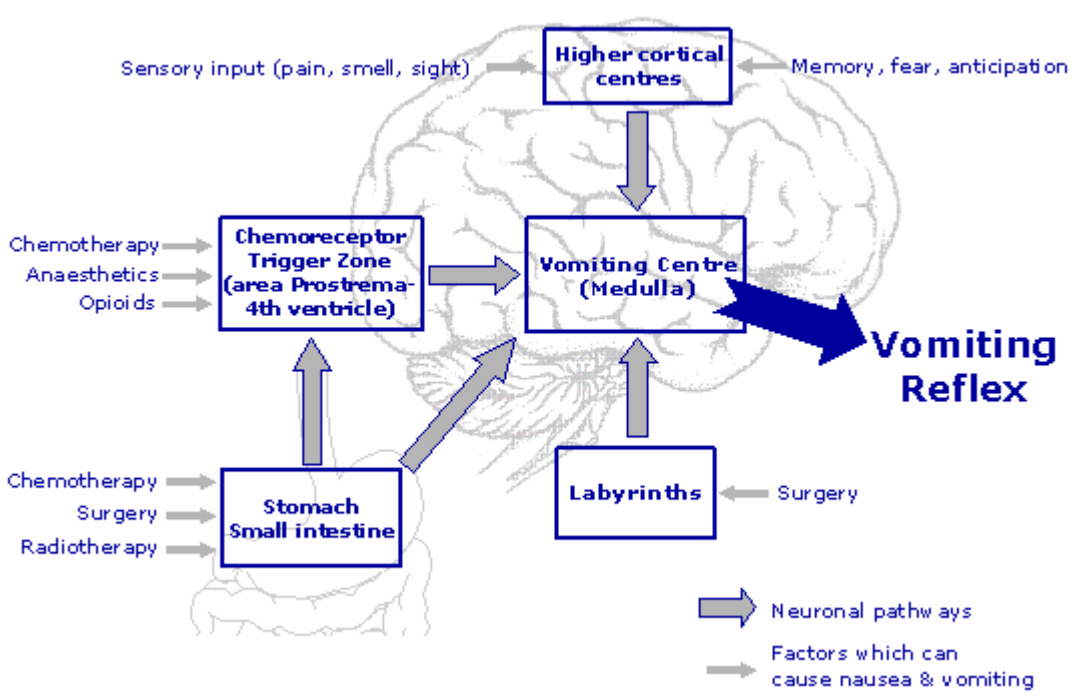
Emesis (Vomiting)

The Reflex Pathways of Emesis

Vomiting is a reflex process

The vomiting center area of the brain responsible for vomiting

The vomiting center receives stimuli from various areas in the brain and induces the process of vomiting by downloading signals to the stomach



Stimuli for vomiting

1. Irritation and distension of the stomach

2. Unpleasant sights, smell, dizziness psychogenic cause

3. Drugs such as Morphine

Areas involved in relaying stimuli to the vomiting center

1. Chemoreceptor Trigger Zone (CTZ) - detest toxic agents in the blood

2. Higher Cortical Centers - reflect unpleasant stimuli from the environment

3. Vestibular Apparatus - input disturbances of balance (motion sickness, inner ear disease)

4. Direct input of irritation and distension in stomach (gastritis, radiotherapy)

Neurotransmitters Responsible of Emesis

When these areas are stimulated, certain neurotransmitters are release:

5-hydroxytryptamine (5-HT)

1. Acetylcholine

Dopamine

2. Histamine

5-hydroxytryptamine (5-HT)

5-HT appears to be the principal transmitter responsible for vomiting

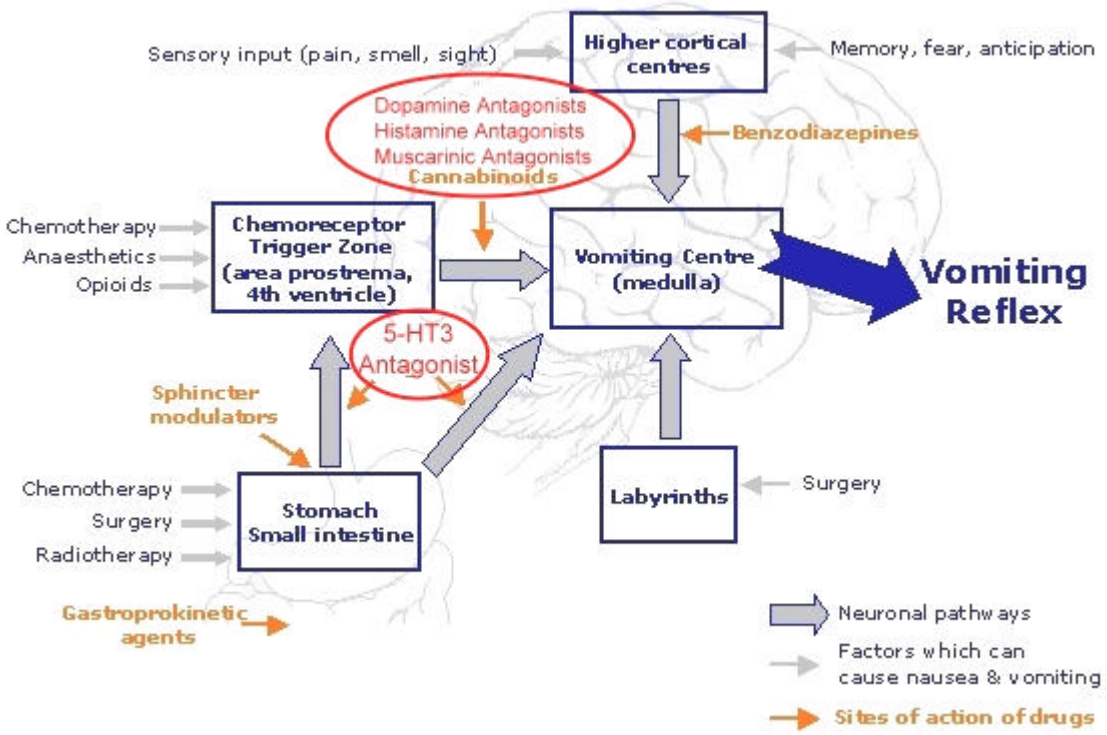
5-HT reacts with its receptors in the gut and CTZ, and activates the CTZ

The CTZ stimulates the vomiting center to send signals to the stomach to induce the act of vomiting

Therefore, drugs antagonizing the effect of 5-HT and those transmitters are used for vomiting

Anti-emetics

Anti-emetics inhibit the binding of those neurotransmitters with their receptors in the CTZ and/ or in the stomach responsible for vomiting, therefore prevent and inhibit vomiting



A. 5-HT3 Antagonists

They are selective 5-hydroxytryptamine3 (5-HT3) antagonists

Effective in the management of nausea and vomiting caused by cytotoxic chemotherapy and radiotherapy

Not effective in motion sickness

Side effect: constipation, headache and flushing

Ondansetron (Zofran)

Granisetron (Kytril)

Tropisetron (Navoban)

B. Dopamine Antagonists

1. Phenothiazines

Phenothiazines are block dopamine receptors in the CTZ/ gut and inhibit vomiting

Also inhibit muscarinic and H1-receptor

They are non-selective anti-emetics

Side effects

Extrapyramidal disturbances, dyskinesia, dry mouth, constipation and hypotension

Used for the treatment of various kinds of vomiting

Produce sedative effects

Also used as anti-psychotic drugs

1. Prochlorperazine (Stemetil) –for vomiting and dizziness

2. Chlorpromazine (Largactil) –mainly used as Antipsychotic

3. Sulpiride (Dogmatil) –antipsychotic drug occasionally used as anti-emetic

2. Metoclopramide

Metoclopramide (Maxolon) are block D2 receptors in the CTZ/ gut

Increase gastric emptying

Used for vomiting caused by GI irritation, radiation sickness and chemotherapy

Side effects

Mild sedation, rarely extrapyramidal reactions and tardive dyskinesia

3. Domperidone

Domperidone (Motilium) is used for nausea and vomiting caused by cytotoxic drug therapy

Less sedating than Metoclopramide and the Phenothiazines

Not effective in motion sickness and vestibular disorders

C. Antihistamines

Block H1-receptor at the CTZ

Used in motion sickness, vertigo and nausea in pregnancy

For motion sickness they are administered 1/2 –1 hour before trip

Side effects: drowsiness and dry mouth

Cyclizine (Marzine), Meclizine, Dimenhydrinate (Gravol), Promethazine theoclate, Cinnarizine

(Stugeron); Cinnarizine is mainly used for Meniere ś disease

D. Anticholinergic

Block acetylcholine in the CTZ and so inhibit vomiting

Used in the prevention and treatment of motion sickness

Side effects: Dry mouth, blurred vision, constipation, dilation of pupils

Contraindication: glaucoma, prostatic hyper-trophy, pregnancy and breast-feeding

Scopolamine TTS (Transdermal Therapeutic System)

Useful in single dose for the prevention of motion sickness for long journeys

Should be applied on area behind ear 5-6 hours before trip; avoid press; can last 72 hours

E. Others of Anti-emetic Drugs

1. Betahistine (Serc, Merislon)

Used in the treatment of vertigo and Meniere ś disease

Cisapride (Prepulsid)

Stimulates Ach release in the gut wall and enhances gut motility

Used for oesophageal reflux, gastric stasis and anti-emetic

Side effects

Occasionally abdominal cramps, diarrhoea, headache, vertigo and extrapyramidal effects

The Sympathetic Nervous System

Most sympathetic nerve fibers release noradrenaline (NA) to elicit sympathetic stimulation

Release NA then stimulate the adrenal glands to release both NA and adrenaline

Since noradrenaline (NA) and adrenaline (ADR) are release upon sympathetic stimulation

The Physiological effects produced are determined by the type of adrenergic receptors with which they interact

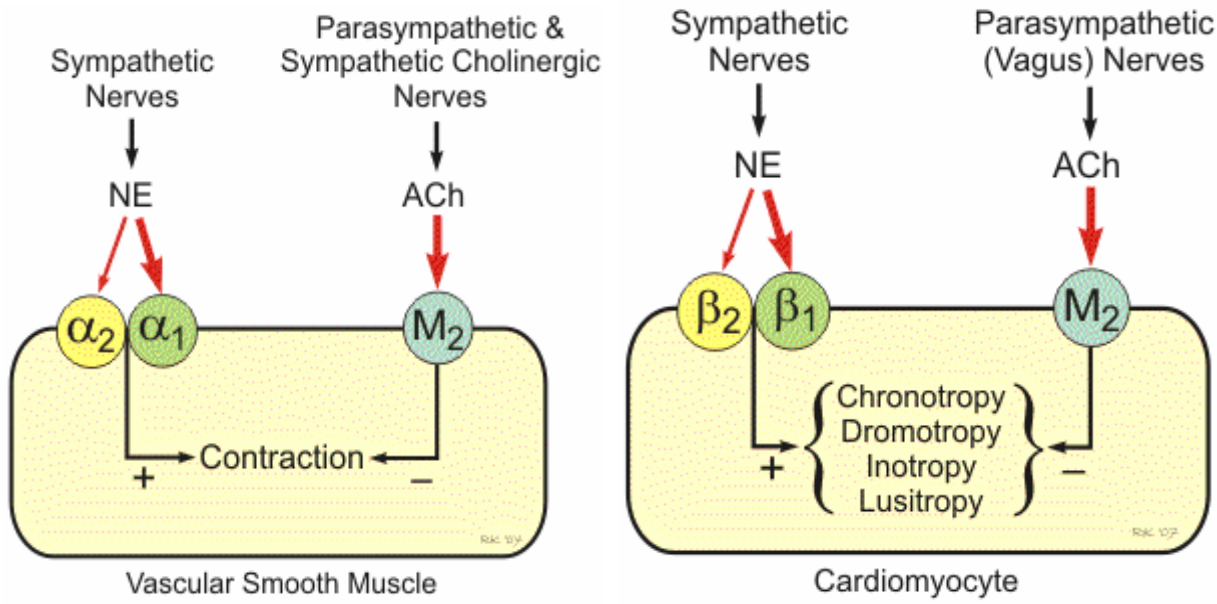
Adrenoceptors

The sympathetic system is adrenergic; adrenergic receptors also called Adrenoceptors

They are found on various visceral tissues; Blood vessels, Heart, Bronchiole

Referred to as alpha-receptors (a1, a2) and beta-receptors (b1, b2)

	Location of receptor	**Activated to produce Biological effect**
Alpha-1	mainly at vascular beds	Contraction of blood vessel, raises BP
Alpha-2	on adrenergic nerve terminal	Reduce NA release, lowers BP
Beta-1	heart muscle	increase heart rate/ contractility
Beta-2	Bronchiole	Relaxation of bronchioles



Biological Effect

Noradrenaline

NA is the most powerful agonist at alpha-1 and alpha-2 receptors

Activation of alpha-1 receptors causes contraction of blood vessels and raised blood pressure

Inhibition of alpha-1 receptors results in relaxation of blood vessels and lowered blood pressure

Adrenaline

Adrenaline is the most powerful agonist at beta-1 and beta-2 receptors

Activation of beta-1 receptors causes the heart muscles to more forcibly and beat faster

Inhibition of beta-receptors reduces heart rate and contractility

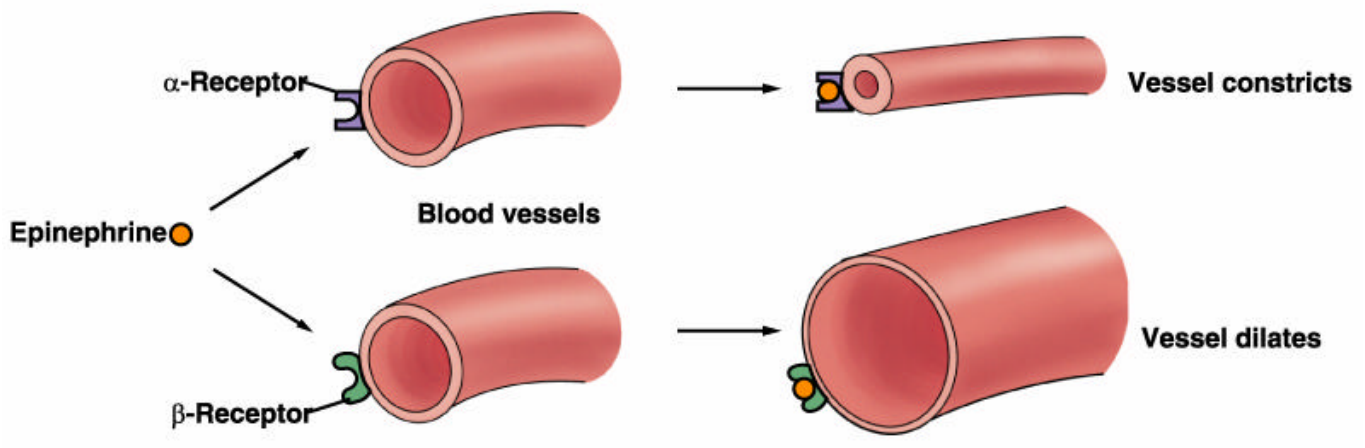
Activation of beta-2 receptors produce relaxation of bronchial smooth muscles leading to bronchodilation

Beta-2 agonists are effective for the treatment of asthma

Adrenaline also acts on alpha-receptors leading to vasoconstriction and raised blood pressure

These properties make Adrenaline useful for emergency treatment of heart arrest (cessation of an effective heart beat)

It is added in local anaesthetic injections to prolong drug action



Drugs Action on the Sympathetic Nervous System

Adrenoceptor Agonists

A. Selective alpha-1 Agonists

NA is the most powerful and selective alpha-1 agonist

Synthetic alpha-1 agonists are used to relieve nasal congestion and red eye syndrome

Phenylephrine, Oxymetazoline (Afrin) and Xylometazoline (Otrivin)

Phenylephrine can be used orally in cough and cold remedies to relieve nasal congestion

It is also used to dilate pupil for examination of the retina

It is contra-indicated in pregnancy when it may cause foetal hypoxia

B. Selective alpha-2 Agonists

Clonidine can selectively activate alpha-2 adrenoceptors on the adrenergic nerve terminal

leading to reduction of NA release

Reduced NA release causes vasodilatation leading to lower blood pressure

It is also used in the prevention of migraine headache

C. Selective beta-2 agonists

Salbutamol is the first selective bet-2 agonist

It is used to dilate the airways and relieve asthma

Terbutaline and Fenoterol have similar activities to salbutamol

Salmeterol is a long acting beta-2 agonist

It is used as aerosol spray for maintenance and prophylaxis of asthma

Adrenoceptor Antagonist

A. Selective alpha-1 Antagonists

Prazosin and Terazosin are alpha-1 antagonist effect of NA on blood vessels

Cause vasodilatation leading to lowered arterial blood pressure

They are used to treat hypertension

B. Beta Antagonists (Beta-blocker)

Beta adrenoceptor antagonists (beta-blocker) block beta-receptors and so inhibit adrenergic stimulation to the heart

Used to treat hypertension, cardiac dysrhymthmias, angina pectoris and myocardial infarction

Side effect: Bronchoconstriction, bradycardia and cardiac failure

1. Non-Selective Beta-blocker

Propranolol (Inderal) is the first beta-blocker

It has an equal blocking effect on beta-1 and beta-2 receptors

2. Cardio-selective beta-blockers

Atenolol (Tenormin) and Metoprolol (Betaloc) have considerably higher affinity for beta1 than beta 2

They reduce heart rate and contractility more effectively than contract bronchial smooth muscles

Receptor Specificity of Adrenoceptors				
Agonists	***Receptors Subtypes***			
	alpha-1	**alpha-2**	**beta-1**	**beta-2**
Noradrenaline	+++	+++	++	+
Adrenaline	++	++	+++	+++
Isoprenaline	-	-	+++	+++
Phenylephrine	++	-	-	-
Clonidine	-	+++	-	-
Salbutamol	-	-	+	+++
Terbutaline	-	-	+	+++

Receptor Type	***alpha-1***	***alpha-2***	***beta-1***	***beta-2***
Selective Agonist	Phenylephrine Oxymetazoline	Clonidine	Dobutamine	Salbutamol Salmeterol
Selective Antagonist	Prazosin	Idazoxan	Atenolol Metoprolol	Butoxamine
Physiological Effect	Smooth muscle Contraction	Inhibit transmitter release Hypotension vasoconstriction	Increase heart rate and force	Vasodilatation Bronchodilation

Hypertension

Blood pressure (BP) is the pressure generated by heart to circulate blood all around the body

When this pressure stays higher than needed, it is high blood pressure or Hypertension

Blood press is expressed in the following equation:

BP = Cardiac Output (CO) x Peripheral Vascular Resistance (PVR)

The most common disease affecting the heart and blood vessels:

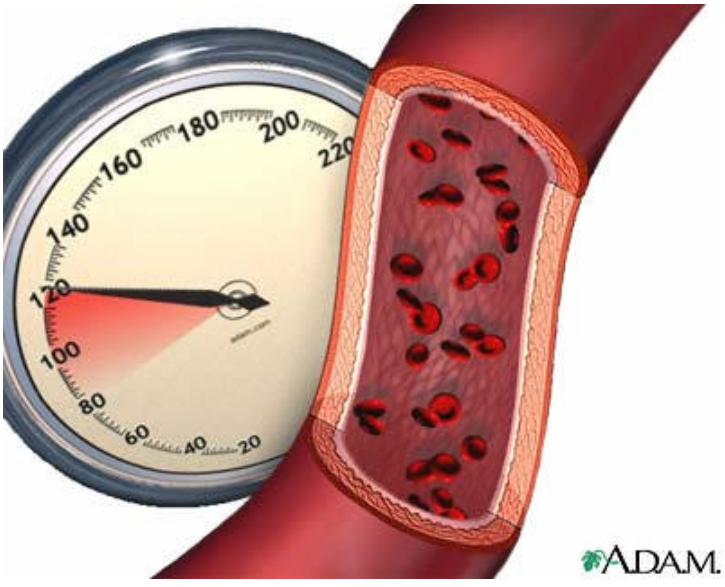
Coronary heart disease, Stroke, Renal failure

There is no symptom until the elevated pressure damages certain organs

It is important to measure BP regularly before the damage is done

Risk Factor of Hypertension

1. Smoking (increase cardiac workload)
2. Drinking too much wine (increase heart rate and blood cholesterol)
3. Obesity
4. Hyperlipidaemia
5. Family history of vascular disease
6. Taking oral contraceptive pills



Categories for Blood Pressure Levels in Adults (in mmHg, millimeters of mercury)

Category	Systolic	Diastolic
Normal	< 120	< 80
Pre-hypertension	120 –139	80 –89
Hypertension Stage 1	140 –159	90 –99
Hypertension Stage 2	160 >	100 >

Systole is the pressure of ventricular contraction

Diastole is the pressure of arteries when the heart relax

Increase diastolic pressure = increase risk of stroke

Treatment of Hypertension

High blood pressure must be controlled, if BP < 140/100, Drugs is not necessary

A healthy lifestyle means

1. Keep slim
2. Eat low fat, low salt and high fiber diet (vegetable, wholegrain, cereals)
3. Avoid or limit alcohol drinks and be a non-smoker
4. Exercise regular
5. Blood pressure checked regular

Take Medicine

If cannot bring BP down by changing lifestyle

1. ACE inhibitors
2. Calcium-channel blockers
3. Beta-adrenoceptor antagonists (Beta-blockers)
4. Diuretics- for mild to moderate hypertension

The Kidneys

1. Regulate the composition and volume of blood

2. Remove waste from the blood

3. Form Erythropoietic factors

4. Control pH

5. Activate vitamin D

6. Regulate blood pressure

The Nephron

The functional unit of the kidney, Consists of the renal tubule and the glomerular capsule

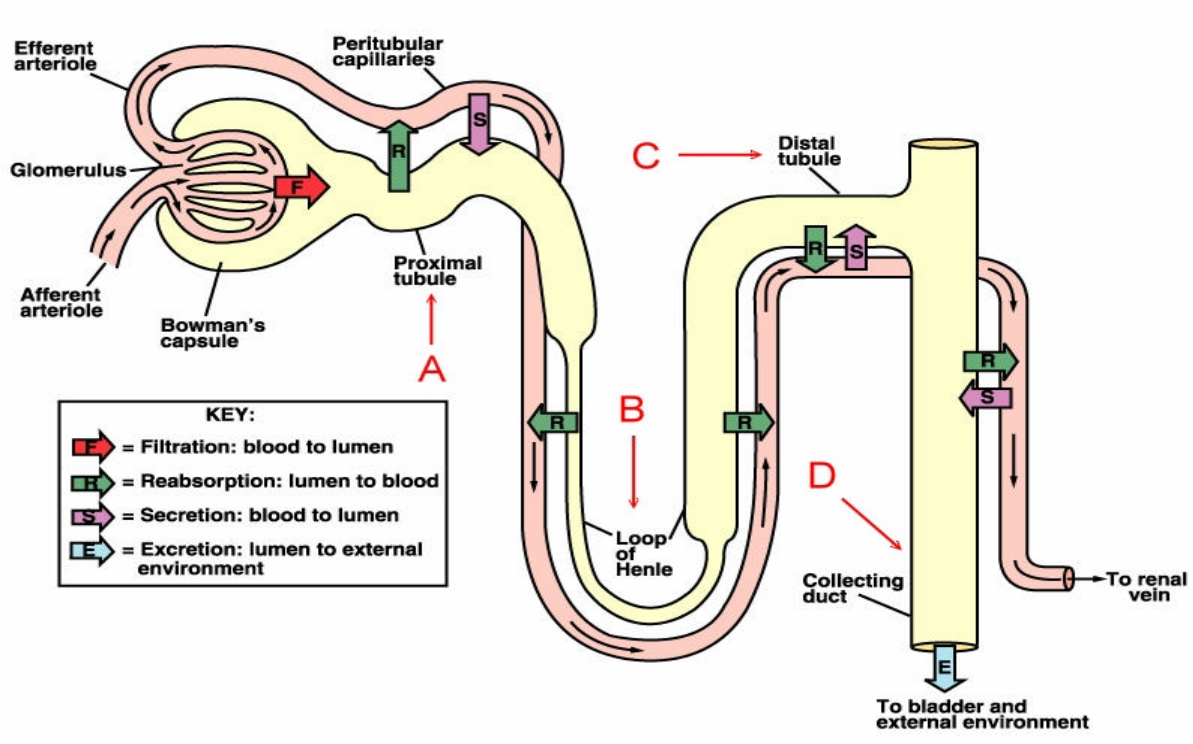
The Renal Tubule

A. the first part of the renal opens into called the proximal convoluted (coiled) tubule

B. The tubule bends into a U-shaped structure called Loop of Henle

C. The last part of renal tubule called distal convoluted tubule

D. The distal convoluted tubule empties into the collecting tubule



Water and electrolytes are reabsorbed throughout the renal tubule at various sites

1. The proximal convoluted tubule

Sodium (Na) is reabsorbed into cell and water is reabsorbed as a result of osmotic pressure

2. The loop of Henle

Active reabsorbed of Sodium Chloride (NaCI) occurs in the ascending limb

3. The distal convoluted tubule

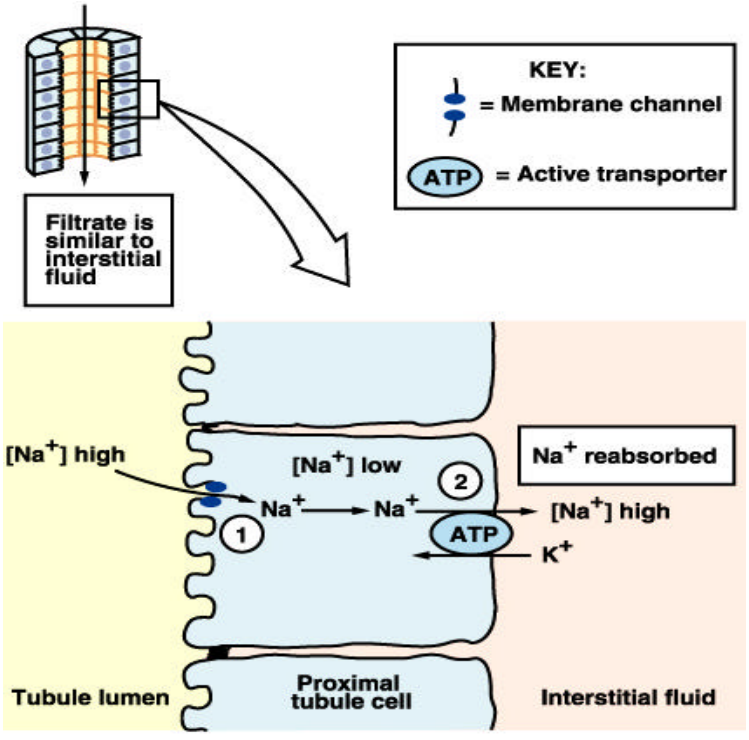
There is a moderate absorption of Na+ and CI-

Potassium (K) is excreted into lumen

4. The collecting tubules

Low permeability to salt and water

Sodium is absorbed by the action of aldosterone and the process is inhibited by potassium sparing diuretics



Diuretic

A. Thiazides

1. Inhibit the active Na/K exchange mechanism of the distal tubule into the blood circulation; enhance potassium excretion
2. Thiazides have moderate diuretic action, which will be saturated; further increases in drug dosages have no additional effect
3. Thiazides have vasodilator effect and reduce blood volume
4. Decrease glomerular filtration rate; may affect patient with impaired renal function and hypertension
5. Increase serum uric acid

Side effects

Large therapeutic index

Decrease plasma potassium

Increase plasma uric acid (may precipitate gout)

Hypersensitivity reactions (dermatitis, acute pancreatitis, acute pulmonary oedema, hyponatremi)

Short-acting Thiazides (8-12 hours)

Hydrochlorthiazide 25-50mg

Cyclopenthiazide 0.5-1mg

Long-acting Thiazides

Indapamide (Natrilix) 2.5mg qd

Methyclothiazide (Enduron) 5mg

Chlortalidone (Hygroton) 50-100mg (last for 2-3 days)

B. Loop Diuretic

Inhibit active transport of Na+, K+, and 2CI- from loop of Henle in the luminal membrane

The most powerful diuretics, capable of causing 15-25% of the sodium in the filtrate to be excreted

They are termed High-Ceiling diuretics

They have shorter duration of action of about 6 hours and can be given bd prn

The degree of diuresis is dose related

In patients with impaired renal function, very large doses may be needed; in such doses these drugs may cause deafness

Properties of Loop Diuretic

1. Have a venodilator action, through the release of a renal factor (e.g. PGE2), useful to patients with acute heart failure
2. Increase renal blood flow, leading to increased solute and water excretion
3. Given orally, they act within one hour and lasts for 4-6 hours
4. They cause potassium loss
5. Increase calcium and magnesium excretion
6. They decrease uric acid excretion

Clinical uses

1. Acute pulmonary oedema
2. Oedema due to heart failure, liver disease and renal oedema

Electrolyte disturbances (e.g. hyperkalaemia)

3. Moderate hypertension
4. Oliguria due to renal failure

Side effects

Potassium, magnesium and Calcium loss

Hypovolaemia and hypotension due to sudden loss of extracellular fluid

Pancreatitis and allergic skin reaction maybe seen with Frusemide (Lasix) and Bumetanide (Burinex) and is more likely to occur in patients allergic to Sulphonamides

Kidney damage produced by Cephalosporin antibiotic is exacerbated by Frusemide

Ototoxicity and hearing loss; concomitant use of an aminoglycoside antibiotic will compound the problem

C. Potassium (K+) Sparing Diuretics

They act on distal tubules by inhibiting the Na+/K+ exchange mechanism

They inhibit sodium reabsorption and retain potassium

1. Aldosterone Antagonist

Spironolactone (Aldactone), and so inhibit sodium absorption and retain potassium in cells

Water is excrete as result of higher osmotic pressure in the lumen

Spironolactone potentiates the effect of Thiazides and loop diuretics

Used in the treatment of cirrhosis of the liver and congestive; more effective than loop diuretics in cirrhosis, commonly given with the potassium-losing diuretics to prevent potassium loss

Side effect: GI upset, hyperkalaemia, gynaecomastia, menstrual disorders and peptic ulceration

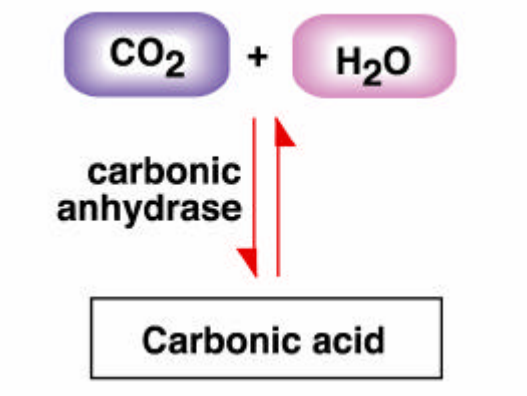
2. Triamterene and Amiloride

Triamterene and Amiloride have a limited diuretic efficacy causing excretion of about 5% of the sodium, Because of their potassium-sparing ability they are used as alternative to giving K+ supplement with Thiazide or Loop diuretics in order to maintain Potassium balance

Moduretic, Navispare, Dyazide

D. Carbonic Anhydrase Inhibitors

Carbonic anhydrase is an enzyme, which converts carbon dioxide to carbonic acid:



1. CO2 + H2O ←----------→H2CO3

2. H2CO3 --------→ HCO3 + H

3. H is secreted into the lumen in exchange for sodium

If carbonic anhydrase is inhibited, less H will be secreted into the lumen in exchange for sodium

More sodium will be excreted

Acetazolamide (Diamox) has a rapid onset of action and short duration

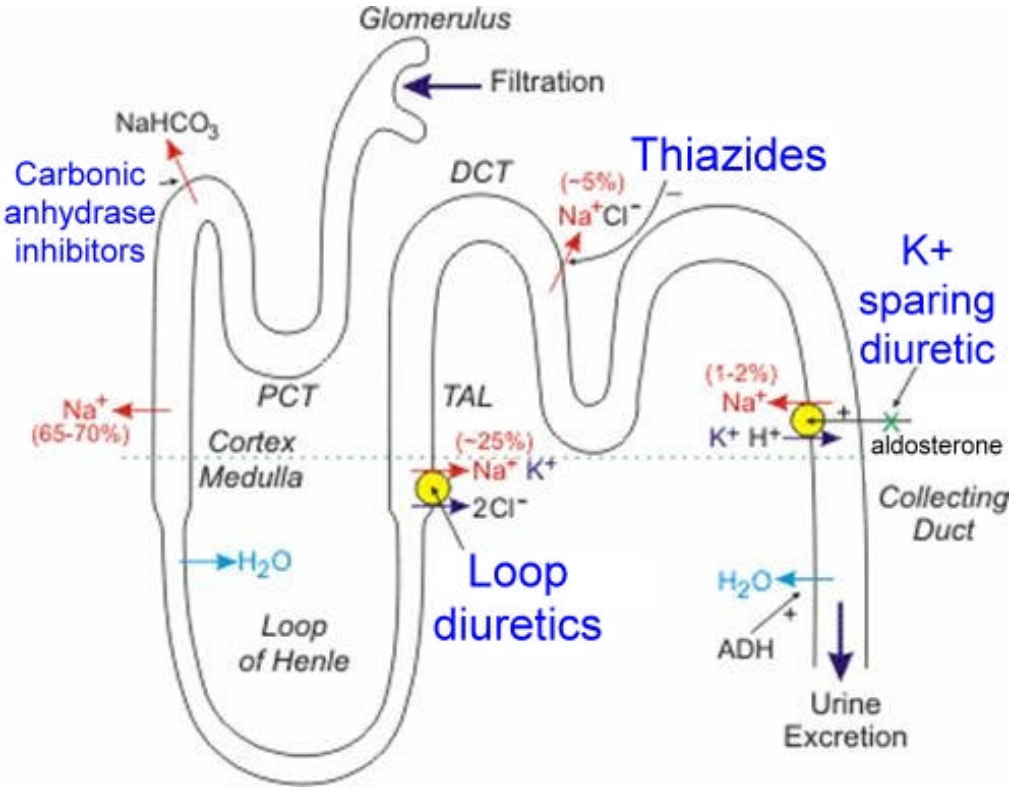
Repeated use will lose the diuretic action

This limits its use in the treatment of mild oedema

Clinical uses

Used to reduce raise intra-ocular pressure in glaucoma

Sometime in mountain sickness (dosage: 250mg bd)



Calcium-Channel Blockers

Smooth muscle contraction is produced by a rise in intracellular calcium

Calcium channel blocker inhibit calcium entry into cell by preventing opening of calcium channel

Inhibit myocardial contractility

Inhibit smooth muscle constriction

Cause dilation of peripheral and coronary arteries

Types of Calcium-Channel Blockers:

1. Verapamil is relatively cardio-selective; heartbeat

2. Diltiazem is intermediate

3. Nifedipine is relatively smooth-muscle-selective; blood vessel

Action on the heart: 1 > 2 > 3

Action on blood vessel and smooth muscle varies: 3 > 2 > 1

Should not be used with beta-blockers

Clinical uses

1. Dysrhythmia (types 1 and 2)

2. Angina (mainly type 2)

3. Hypertension (types 1, 2 and 3)

Side effect:

Constipation, headache and flushing are most common

A. Verapamil

Verapamil increases the supply of blood and oxygen to the heart to control chest pain (angina).

It is used in the treatment of hypertension, angina pectoris, and some types of arrhythmia.

May precipitate heart failure; exacerbate (make worse) conduction disorders

Cause hypotension at high dose

B. Diltiazem

Diltiazem is a potent vasodilator, increasing blood flow and variably decreasing the heart rate via strong depression of A-V node conduction.

Used in the treatment of hypertension, angina pectoris, and some types of arrhythmia

Side effect: bradycardia, headache, flushing, hypotension, ankle oedema, GI disturbances

C. Nifedipine

1. Nifedipine (Adalat) relaxes smooth muscle dilates coronary and peripheral arteries

Its main uses are in angina pectoris (especially Prinzmetal's angina) and hypertension,

Nifedipine rapidly lowers the blood pressure and patients are commonly warned they may feel dizzy or faint after taking the first few doses.

More influence on vessels than the myocardium

No effect on arrhythmia; rarely precipitates heart failure

2. Nicardipine and Zanidip resembles Nifedipine

3. Amlodipine (Norvasc) and Felodipine (Plendil)

Can be used with beta-blockers for severe symptoms

Side effect: flushing, headache and ankle swelling

Beta-adrenoceptor Antagonist (Beta-Blocker)

1. Block Beta-receptors in heart, bronchi and peripheral blood vessels
2. Reduce external stimuli to the cardiovascular system
3. Reduce cardiac output
4. Block peripheral adrenoceptors
5. Suppress plasma renin secretion

Properties of Beta-blockers

1. All beta blockers slow heart rate may depress the heart and precipitate heart failure
2. Beta blockers may precipitate asthma; dangerous to asthmatics
3. Beta blockers reduce blood glucose; dose adjustment in diabetic patients is necessary
4. Beta blockers produce fatigue and coldness of extremities (hands and feet)
5. Increase serum triglycerides and reduce HDL cholesterol
6. Rebound hypertension may occur within hours to 2 days, if therapy be stopped suddenly

Signs and symptoms of rebound hypertension are nervousness, sweating and tachycardia

7. Some beta-blockers have more effect on the heart than bronchioles, called cardio-selective beta-blockers Metoprolol (Betaloc) and Atenolol (Tenormin)
8. Some beta-blockers are less likely to enter the brain, and may cause less sleep disturbances and nightmares, e.g. Atenolol, Nadolol and Sotalol
9. Some beta-blockers have Intrinsic Sympathomimetic Activity (partial agonist activity), e.g. Pindolol (Visken) and Acebutolol (Sectral)

Can stimulates as well as block adrenergic receptors

Tend to cause less bradycardia and less coldness of extremities

Angiotensin-Converting Enzyme Inhibitors (ACEIs)

The Renin Angiotensin Aldosterone System

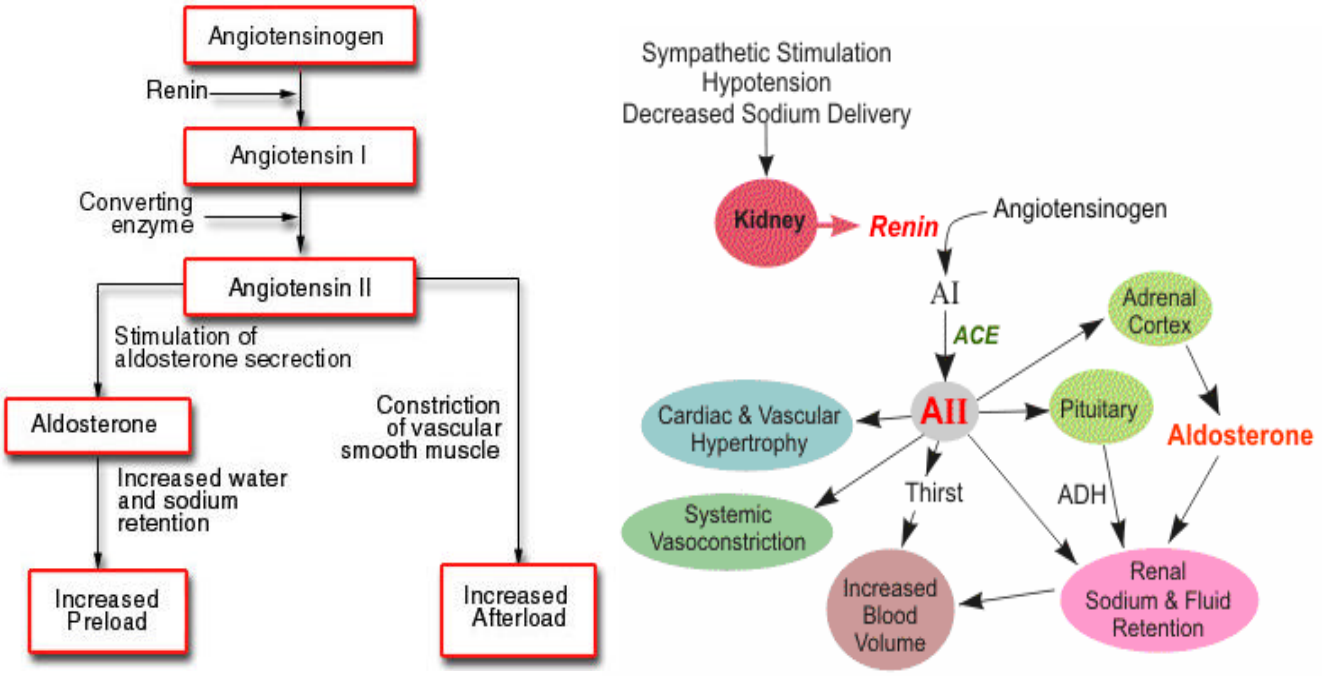
Renin Angiotensin Aldosterone is a hormonal system of the body that maintains blood pressure

When plasma sodium concentration or blood volume is low, the kidneys secrete renin (a proteolytic enzyme), which converts angiotensinogen (present in blood) to angiotensinogen I

Angiotensinogen I (Ang I) is inactive but is converted to Ang II by an enzyme in blood:

Angiotensin-converting enzyme

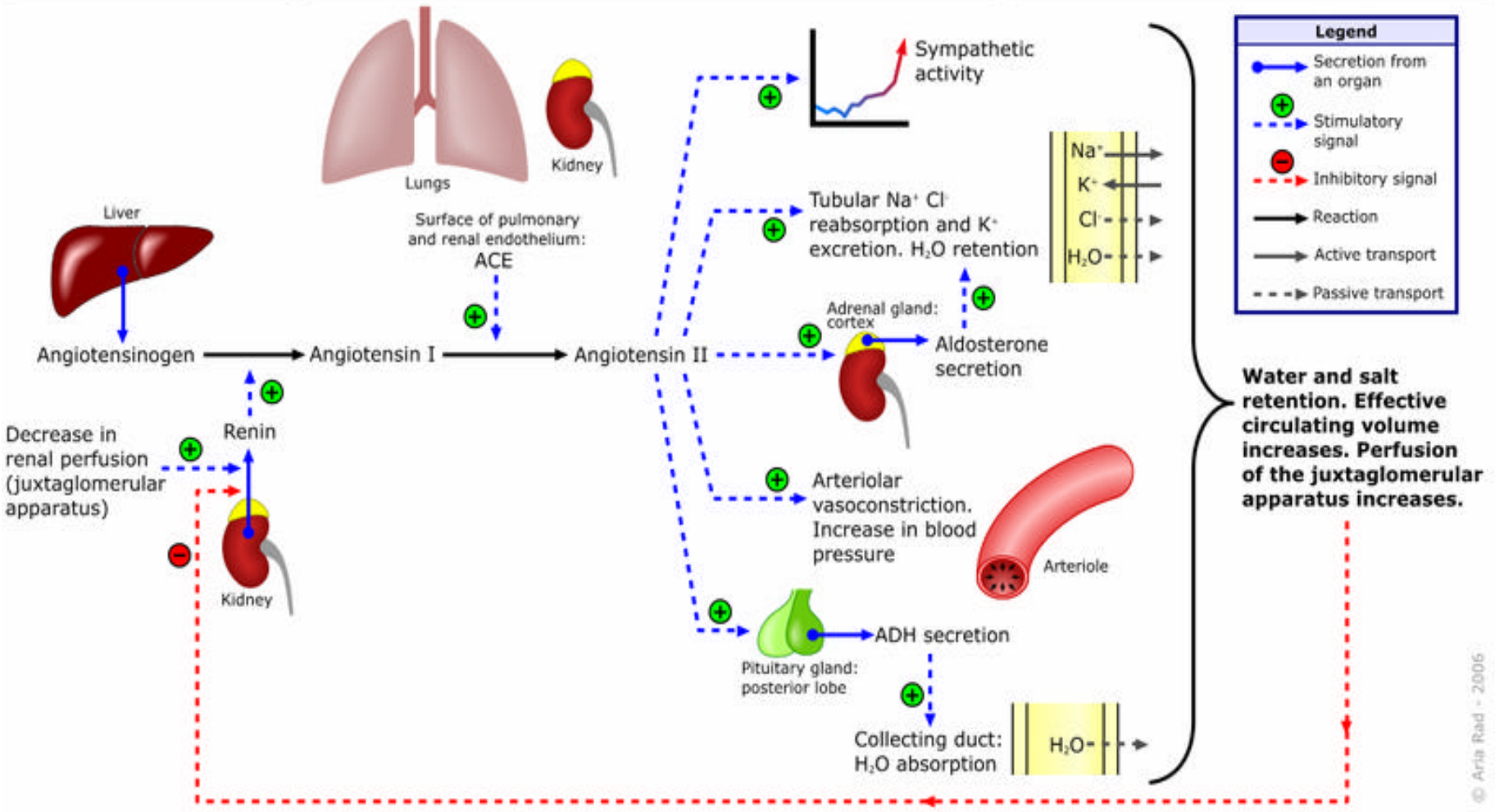
Ang II cause vasoconstriction and induces secretion of aldosterone leading to sodium and fluid retention and rise in blood pressure



The pathway is import in the pathogenesis of hypertension

Can be corrected by Angiotensin-Converting Enzyme Inhibitions (ACEIs)

Renin-angiotensin-aldosterone system



The ACE inhibitors

Drugs that inhibit the conversion of Ang I to its active form Ang II

Inhibit the renin-angiotensin system and to low blood pressure

General Properties and Precaution

1. Potent anti-hypertensive, and may cause very rapid fall of BP

Diuretic therapy should be stopped before starting ACEIs

2. First dose hypotension

The first should be given at bedtime, and be started at very low dose

3. Combination products should be reserved for those who has not responded to ACEI alone

Contraindications

1. Tend to retain potassium

Avid potassium sparing diuretics

2. May cause renal impairment

Avoid concomitant treatment with NSAIDs (e.g. Aspirin)

3. Contraindicated in pregnancy

Clinical uses of the ACE inhibitors

Used for hypertension when Thiazides and Beta-blockers are not adequate to control BP

Used as an adjunct to diuretic therapy for heart failure

Side effect

Persistent dry cough, dizziness, fatigue, change of taste and voice, sore throat, hypotension, nausea, rash, renal impairment

Preparation of the ACE inhibitors: Captopril (capoten), Enalapril (Renitec), Quinalapril (Accupril), Lisinopril (Zestril), Acertil

Angiotensin II Receptor Antagonists

Angiotensin II receptor antagonists block ANG II receptors, depleting the hormone and lowering blood pressure

Their therapeutic effects and uses are similar to ACEIs

Advantages over ACEIs

4. Do not inhibits ACE and therefore do not produce dry cough

5. Can be used in patients with renal and hepatic insufficiency

6. Have no notable effect on total cholesterol

7. Abrupt withdrawal has not been associated with rebound hypertension

8. No significant drug interactions

Contraindications

Not be used together with potassium-sparing diuretics or potassium supplement

Not in pregnancy and lactation

Side effect

Headache and dizziness

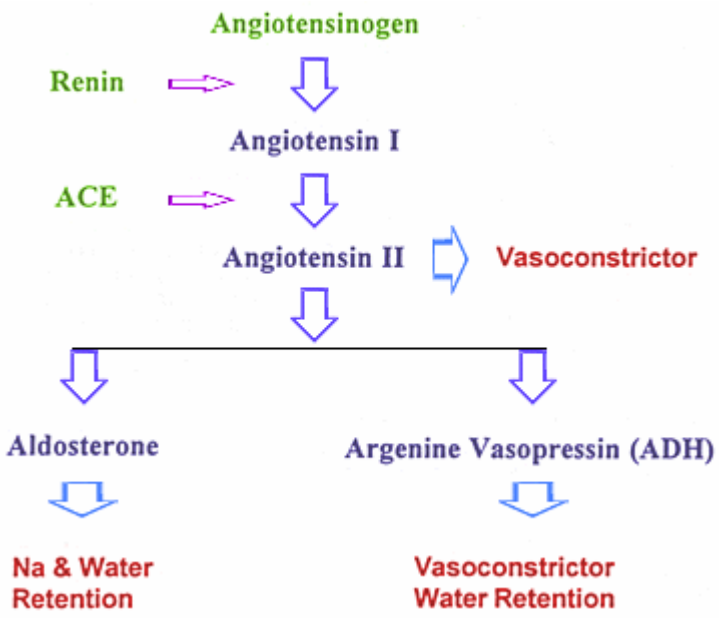
Preparation Available

Losartan Potassium (Cozaar),

Valsartan (Diovan),

Irbsartan (Aprovel),

Telmisartan (Micardis)



E. Other Antihypertension Drugs

1. Alpha Adrenoceptor Antagonist

These substances block alpha-1 receptors leading to vasodilatation and reduction of Bp

Favorable effect on serum lipids

Manifest first dose hypotension

Start at low dose

Relax smooth muscle of the prostate and bladder neck

Effective for the treatment of benign prostatic hypertrophy (BPH)

Preparations: Prazosin (Minipress), Terazosin (Hytrin), Doxasozin (Cadura)

Side effect: dizziness, headache, and fatigue

2. Central-acting Adrenergic Agonists

a. Clonidine (Dixarit, Catapress)

Alpha-2 agonists; stimulation inhibits NA release leading to vasodilation

Used for the prevention of migraine

Side effect: dry mouth, fatigue and dizziness; Contraindicated to bradycardia

b. Methyldopa (Aldomet)

Known as False transmitters of Noradrenaline (NA)

NA is biosynthesized from dopamine

Methyldopa structurally resembles dopamine and is able to complete with dopamine for biosynthesis of NA

The product formed from methyldopa is a weaker agonist than NA and does not function as NA

Side effect: sedation, headache, asthenia, oedema

Contraindication: active hepatic disease

3. Vasodilators

Direct relaxation on arteriolar smooth muscle and decrease peripheral resistance

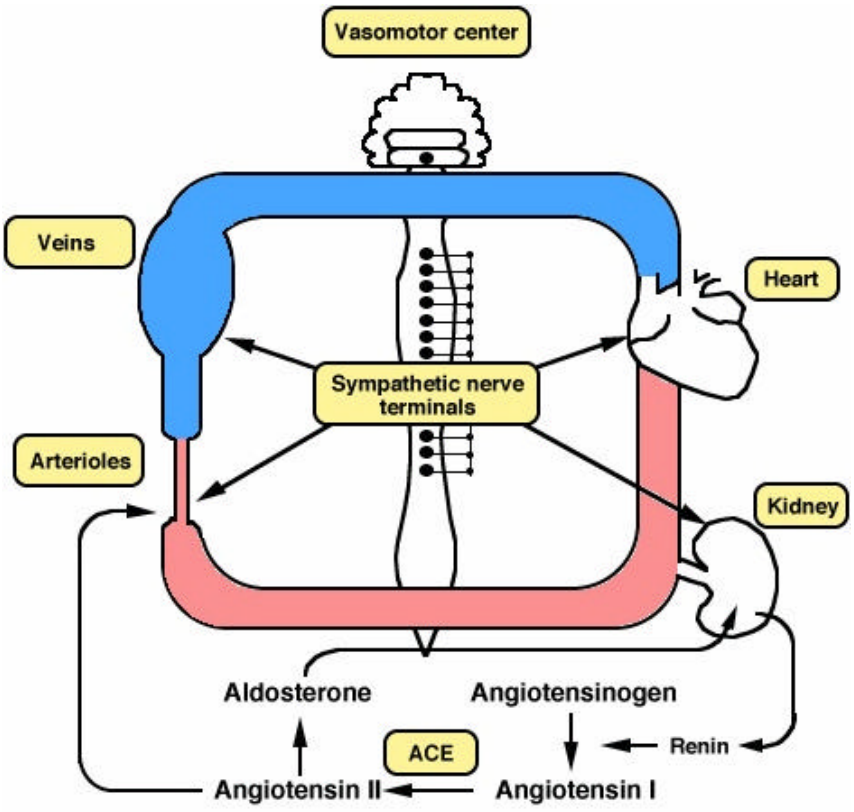
a. Hydrallazine (Apresoline 25mg)

Side effect: joint swelling, arthralgia, fever, tachycardia, hypotension, headache and GI disturbances

b. Minoxidil (Loniten)

Available in oral tablets of 5mg and 10mg for the hypertension

It is also available in topical solutions of 2% and 5% for the treatment of male pattern baldness (e.g. Regaine paint)



Physiology of the Heart

In a normal heartbeat, the two atria contract while the two ventricles relax

A complete heartbeat comprises a systole and diastole of both ventricles

Cardiac Output

Cardiac Output (CO) is the amount of blood ejected from the left ventricle into the aorta per minute; Cardiac output is determined by:

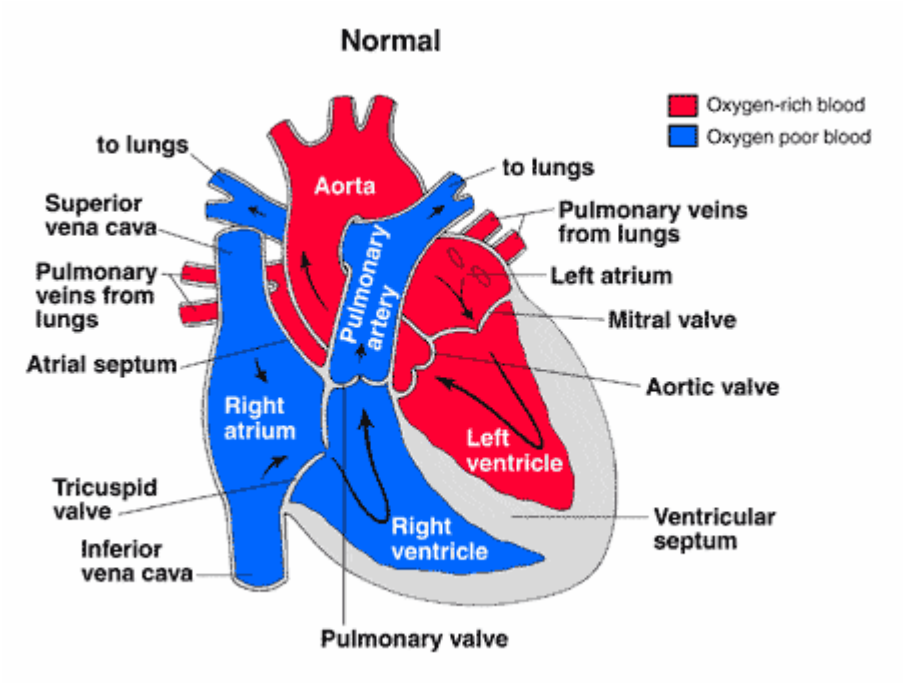
1. Stroke Volume

2. The number of heartbeats per minute

The amount of the blood ejected by a ventricle during each systole (contraction) is called the Stroke Volume

In a resting adult, stroke volume averages 70ml and heart rate is about 75 beats per minute.

CO = stroke volume x heart beat per minute = 70ml x 75/min = 5.25L/min



Contractility

The Force of contraction of the heart is determined by Intrinsic and Extrinsic Factors

Intrinsic Contractility

The availability of calcium ion in the heart cells.

1. The ability of calcium entry across the cell membrane

2. Those people who acquire chronic heart failure because they have got problem with this intrinsic factor hence, the force of contraction of the heart is weak

Extrinsic Circulatory Factors

1. Central Venous Pressure

The pressure created by blood flowing into the heart, if this pressure increased by blood flowing into the ventricle, and the heart will contract more forcibly in order to cope with the increased blood volume

2. Peripheral Resistance

Resistance of the peripheral arterial wall that blood experiences when it is pumped out of the ventricles

Peripheral resistance increases if arterial constrict

3. Heart Rate

If the heart is weak, stroke volume will be reduced and more blood is dumped in the heart leading to congestion

In order to pump out the blood, the heart beats faster

This is a compensatory mechanism to maintain CO

Coronary Heart Diseases (CHD)

The Coronary Circulation

1. The flow of blood through the numerous vessels that pierce the myocardium

2. Delivers nutrients and oxygen to the heart

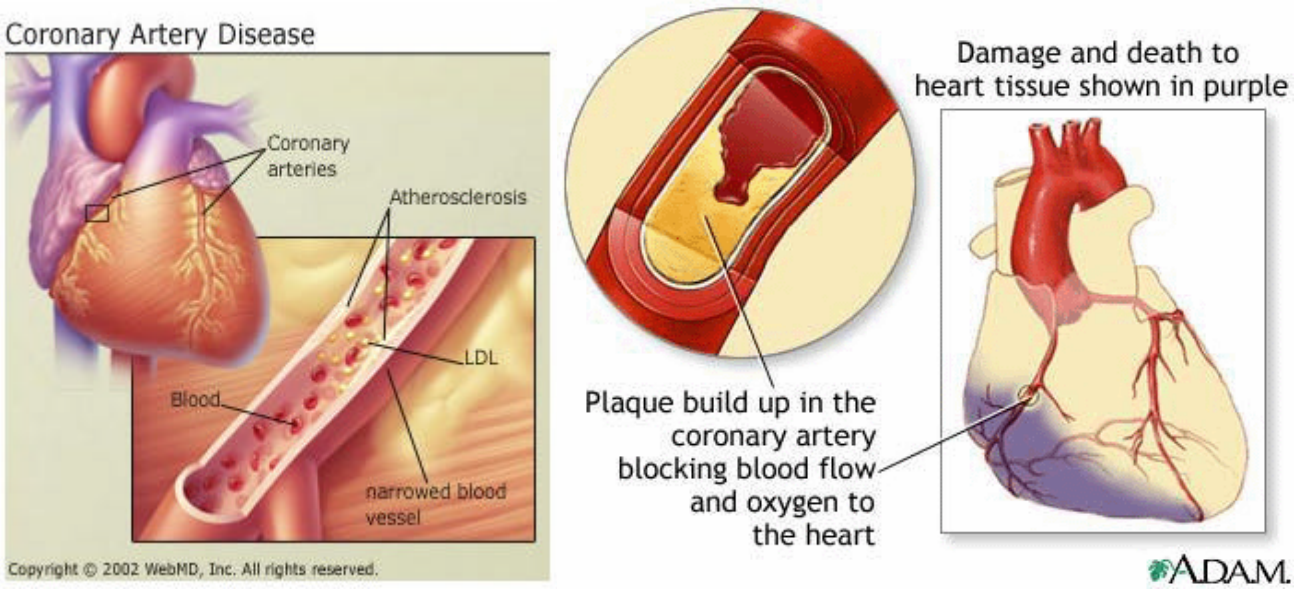
3. Collects carbon dioxide and waste

4. It is important for the heart

Extracts approximately 75% of the available oxygen under condition of no stress

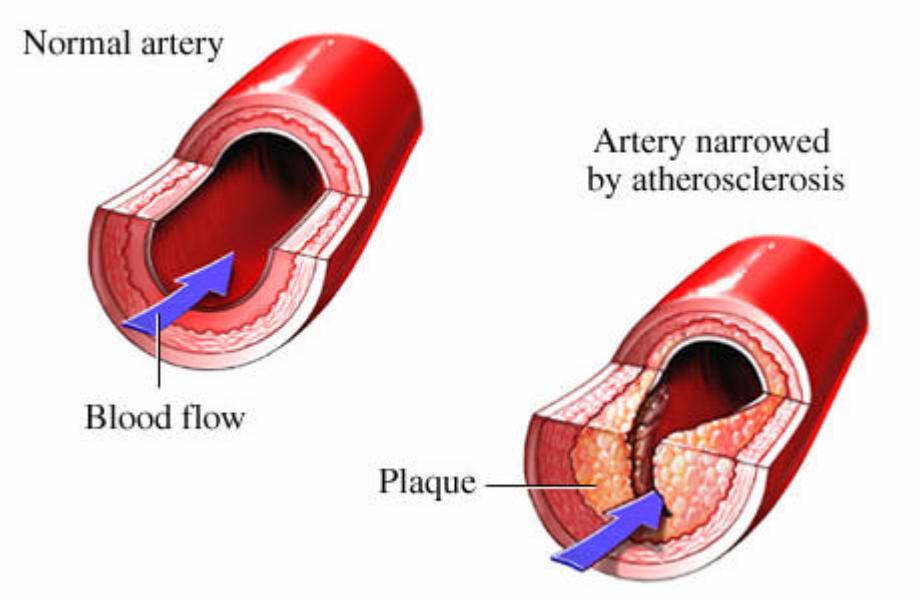
Oxygen requirement increases when there is an increase in heart rate, contractility, arterial pressure and ventricular volume

Most coronary heart diseases result from faulty coronary circulation that is inadequate oxygen supply to the myocardium, resulting from, Angina Pectoris and Myocardial Infarction (MI)



Angina Pectoris

A condition caused by transient ischaemia of the myocardium, due to narrowing of the coronary arteries; this occurs as, Atheromatous plaques, Atherosclerosis or coronary artery spasm



In all cases the myocardial

O2 consumption > O2 supply

Therefore, the myocardium is short of oxygen to support its metabolic needs

Stable angina

The most common type of angina, which is precipitated by exercise and relieved by rest and by sublingual Glyceryl Trinitrate

Unstable angina

Angina pain, which occurs at rest and may last for longer than 15 min, the pain may be nocturnal

The pain is no longer relieved by sublingual nitrates

Valiant angina

This is a rare type of angina whish occurs at rest and is associated with coronary artery spasm

Risk Factors for Developing Angina

Major Risk Factors

1. Age

Incidence of CHD increases with age

2. Sex

Males are more at risk of CHD than females

3. Family history

Hypertension and hyperlipidaemia can be hereditary, which may increase the risk of CHD

4. Smoking

Smoking accelerates arteriosclerosis by damaging the endothelium of blood vessels and increase platelet aggregability

5. Serum cholesterol

Risk of CHD is directly proportional to the level of total cholesterol in blood

6. Hypertension

Minor Risk Factors

1. Social class

2. Diabetes increases the risk of CHD due to arteriosclerosis

3. Obesity increase the risk of CHD

4. Oral contraceptives increase lipid profiles and risk of hypertension

Signs and Symptoms of Anginal Diseases

1. Typically presents with chest pain

2. Pain with no fixed location in the chest but affects a small area over the sternum

3. The pain may radiate to the left arm and shoulder, the back, neck and jaw

4. Patients describe the chest pain as heavy, dull, gripping, pressing and choking

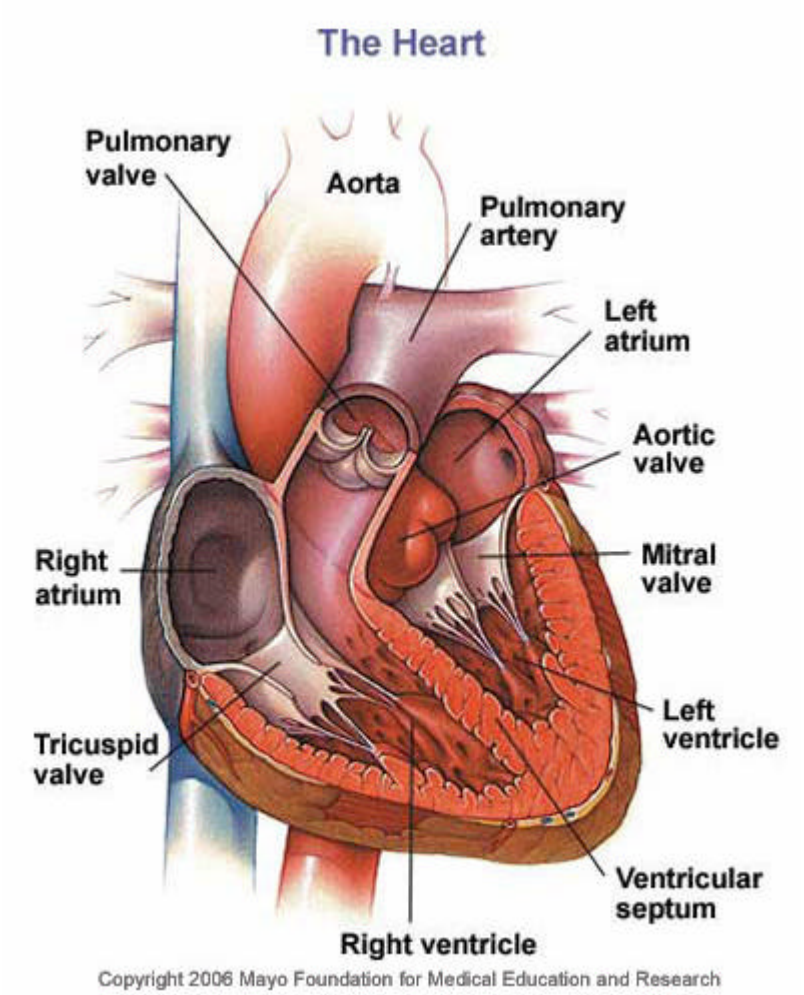
5. It may be described as discomfort rather than pain

6. Pain may be accompanied by breathlessness and fear

7. During an attack, the patient is often sweaty, uneasy and wants to remain still

8. The frequency of attack varies from several attacks per day to occasional episodes separated by symptom-free periods

9. Angina is made worse by cold weather or heavy meal



Management of Angina

Aim of Treatment of Angina

Reduction of myocardial O2 demand

1. Reduction of heart rate by beta-blockers

2. Reduction of arterial pressure by beta-blockers and calcium-channel blockers

3. Reduction of ventricular pressure by nitrates

Increase coronary blood flow and O2 supply

1. Use coronary vasodilators, Calcium blocker and Nitrates

2. Promote growth of collaterals by exercise

3. Perform coronary artery bypass surgery or angioplasty

A. Nitrates

Mechanisms of action

Reduces cardiac output and hence myocardial O2 consumption

1. Nitrates dilate coronary arteries and therefore increase O2 supply

2. Nitrates also dilate veins and allow pooling of blood there

3. Less blood is return to the heart

Clinical uses

A. Short-acting nitrates

1. For prophylactic use before exertion and for chest pain occurred at rest

2. Provide rapid symptomatic relief of angina but their effects only last for 20-30 minutes

B. Long-acting nitrates are used for maintenance

Side Effects

1. Common side effects: flushing, headache, postural hypotension, dizziness, palpitation

2. Nitrate Tolerance: Long-acting or Transdermal nitrates produce nitrate tolerance

3. Remove Transdermal patch for several hours in each 24hours may maintain effectiveness

Preparation of Nitrates

1. Nitroglycerine (Glyceryl Trinitrate): Angised (Sublingual) 0.5mg

Nitradisc (Transdermal) 5mg/ 24hrs or 10mg/ 24hrs, Nitroderm TTS-5 or TTS-10

2. Isosorbide dinitrate 5, 10, 20mg

3. Isosorbide mononitrate (Elantan) oral tablets 20mg, 40mg

4. Isosorbide-5-mononitrate (Imdur) oral tables 60mg

Isosorbide mononitrate is the active metabolite of Isosorbide dinitrate

B. Beta-adrenoceptor Antagonists

1. Reduce heart rate and contractility and thus reduce myocardial O2 consumption

2. They improve exercise tolerance and reduce the severity and frequency of angina caused by exertion

C. Calcium-Channel Blocker

Verapamil, Diltiazem and Nifedipine

Myocardial Infarction (MI)

1. A much more serious CHD

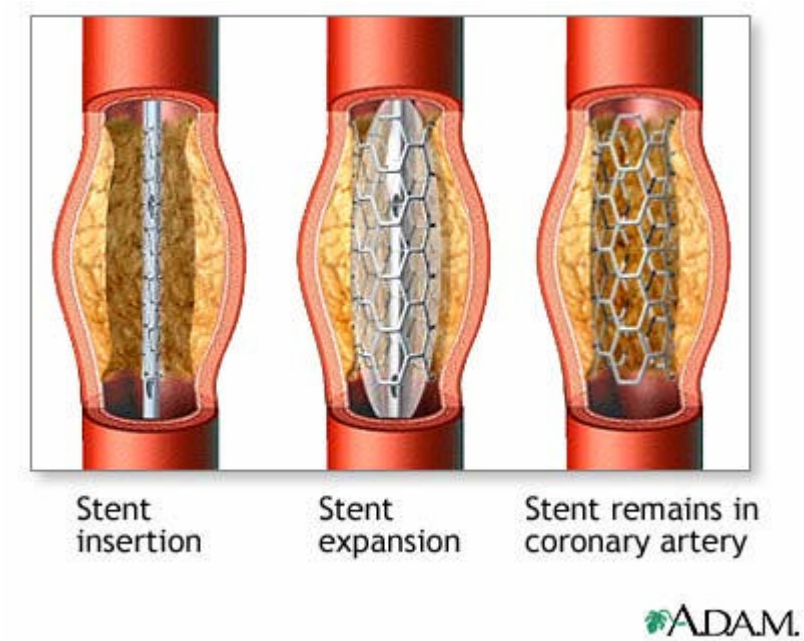
2. Infarction means the death of an area of tissue because of an interrupted blood supply

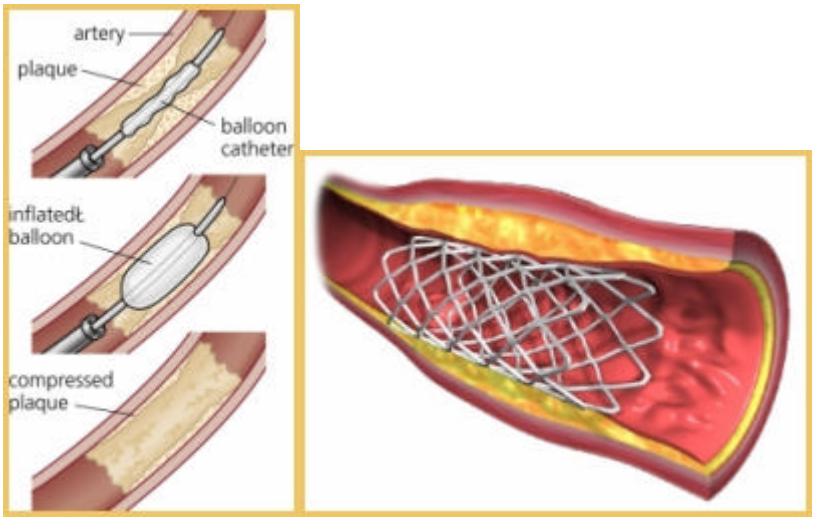
3. The non-contractile scar tissue weakens the strength of the heart muscle

4. May disturb the conducting system of the heart leading to arrhythmia

5. Ventricular fibrillation is one form of arrhythmia which may cause sudden death

6. The most modern treatment for a MI is to perform coronary angiographies and inject a thrombolytic agent or to do coronary angioplasty such as Coronary Artery Bypass Grafting (CABG)





Blood Coagulation

Haemostasis

Mechanisms for sealing the damaged vessels to prevent blood loss, three basic mechanisms:

1. Vascular Contraction

When a blood vessel is damaged, the vascular smooth muscle contracts immediately and reduces blood loss for several minutes to several hours, during which time

Other hemostatic mechanisms can go into operation

2. Adhesion and Activation of Platelets (Platelet plug formation)

Platelets come into contact with parts of a damaged vessel such as collagen and begin to enlarge and become irregularly shaped with numerous projections

Platelets to come into contact with each other forming a plug

The platelets secrete prostaglandin and other substances called coagulation factors that help to reduce bleeding

3. Blood Coagulation

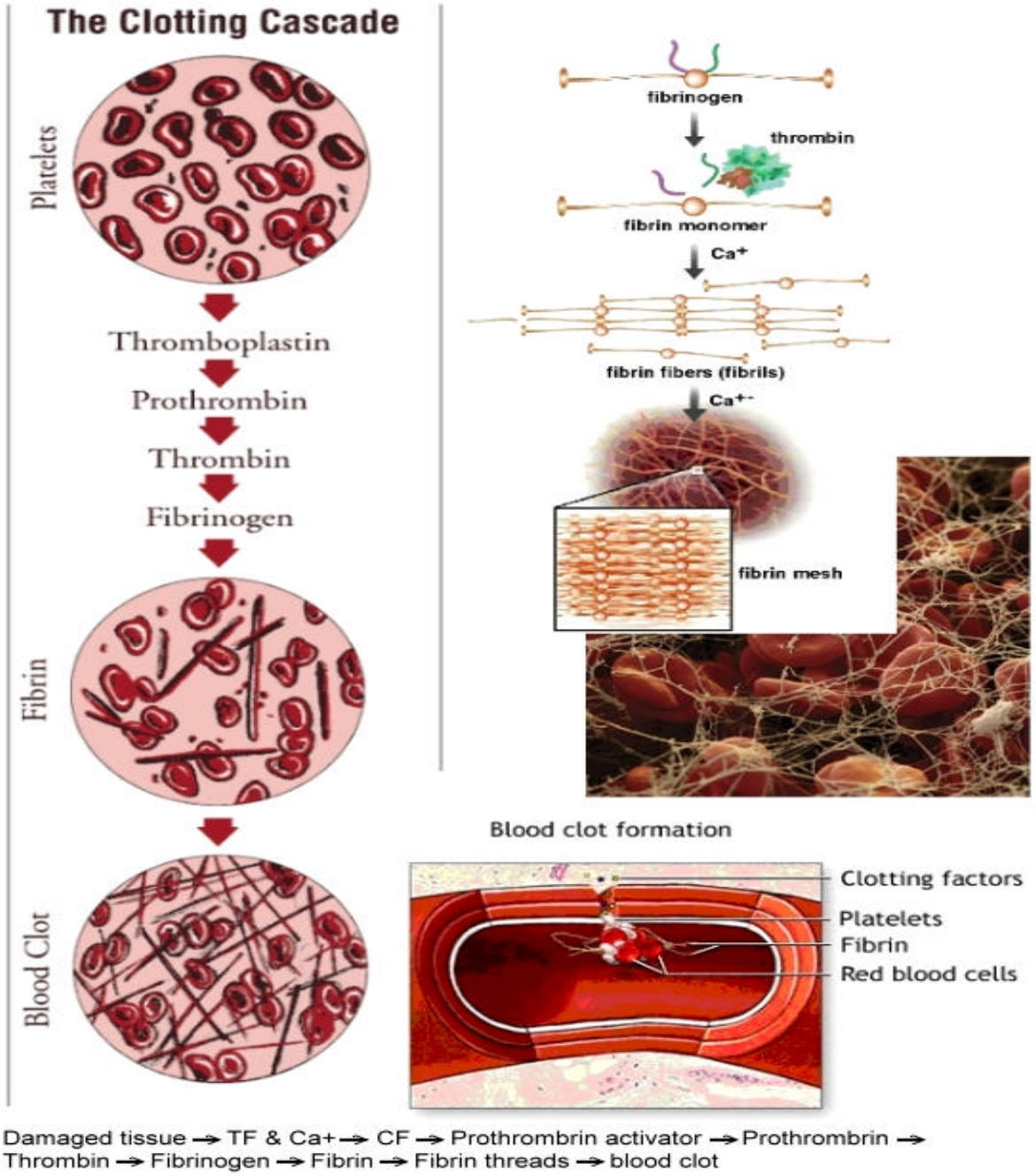
Blood coagulation is the conversion of fluid blood to a solid gel or clot

A complex process and involves various chemicals known as Coagulation Factors (CF) present in blood

The damaged blood vessel first releases chemical substance called Tissue Factor (TF) to initiate the process of coagulation. (To activate the first CF)

Once the process is initiated, the activated form of one CF catalyzes the next factor in the clotting sequence and this goes on until the whole coagulation process is complete

Finally, fibrin forms the threads of the clot, plugs the ruptured area of the blood vessel and prevents bleeding



Damaged tissue → TF & Ca+ → CF → Prothrombrin activator → Prothrombrin → Thrombin → Fibrinogen → Fibrin → Fibrin threads → blood clot

Thrombosis

Thrombosis is the unwanted formation of a plug (thrombus) in a vessel

The thrombus in a vessel retards blood flow leading to ischaemia or infarction of the tissue beyond

Furthermore, when part of a venous thrombus detaches, it can block the pulmonary arteries or vessels in the brain leading to cerebrovascular diseases

Inhibition of blood Coagulation (Anticoagulants)

In a normal subject, blood coagulation is controlled and balanced by a series of inhibitors in the plasma

Anti-thrombin III is one of the most important inhibitors, which inhibits the formation of thrombin (an enzyme which catalyzes the formation of fibrin leading to a blood clot) and therefore inhibits the coagulation process

Besides, other substances in blood (e.g. Heparin) can also inhibit coagulation, called Anticoagulants

They are used clinically to dissolve blood clots (thrombus) associated with cardiovascular and cerebral vascular diseases

FIG. 1A

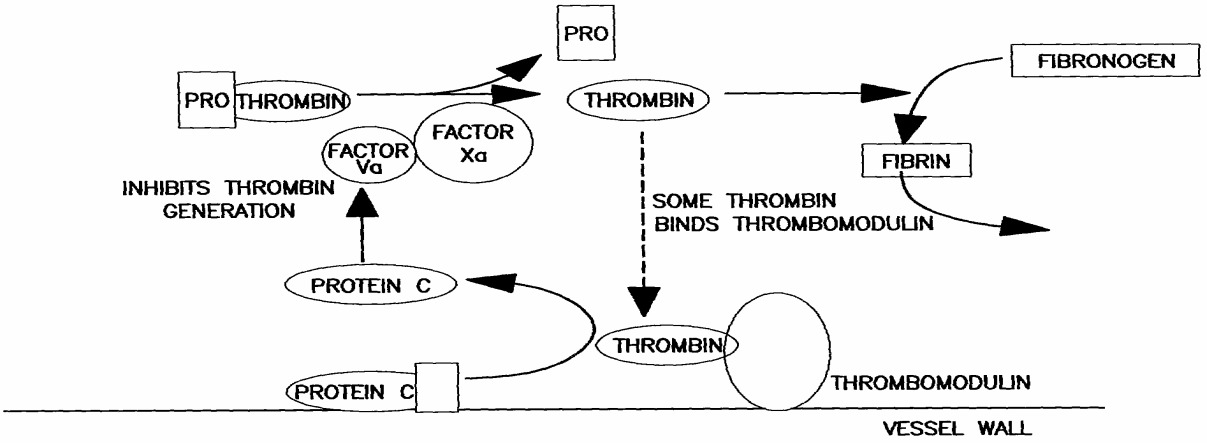
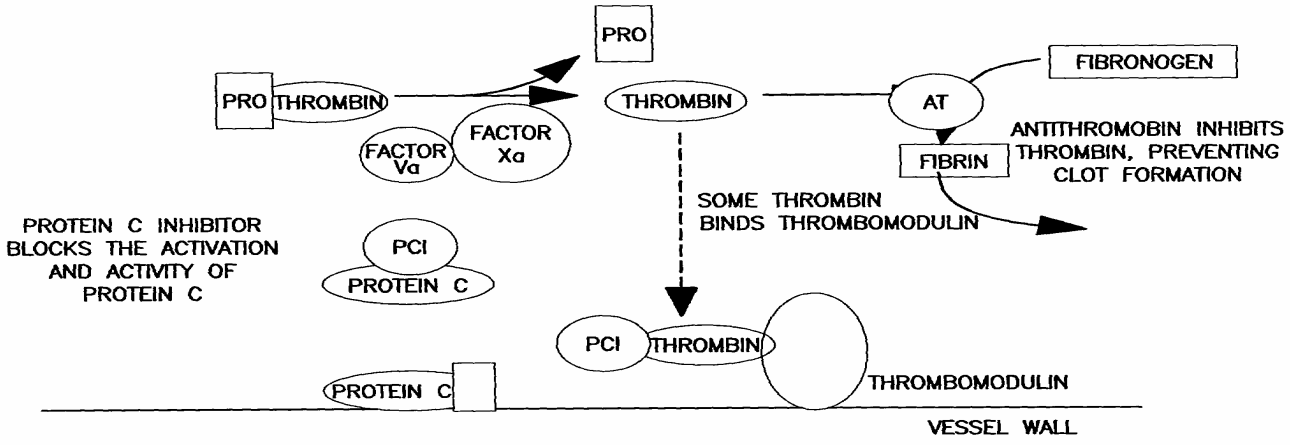


FIG. 1B



Anticoagulants may affect Haemostasis and Thrombosis in various ways

1. By inhibiting fibrin formation

2. By modifying platelet adhesion and activation

A. Inhibit fibrin formation

1. Injectable Anticoagulants

Heparin is a potent anticoagulant

It enhances the activities of anti-thrombin III and inhibits blood coagulation

Large molecule with many negative charges, not absorbed by the gut, Can be given i.v. or s.c.

Mainly used for cerebrovascular diseases and angina

The main adverse effect: Hemorrhage which is treated by stopping therapy or by Giving

Protamine Sulfate, a heparin antagonist which inactivates complex with heparin

2. Oral Anticoagulants

Warfarin antagonize the effect of vitamin K which is required to activate the coagulant factor in the coagulation cascade

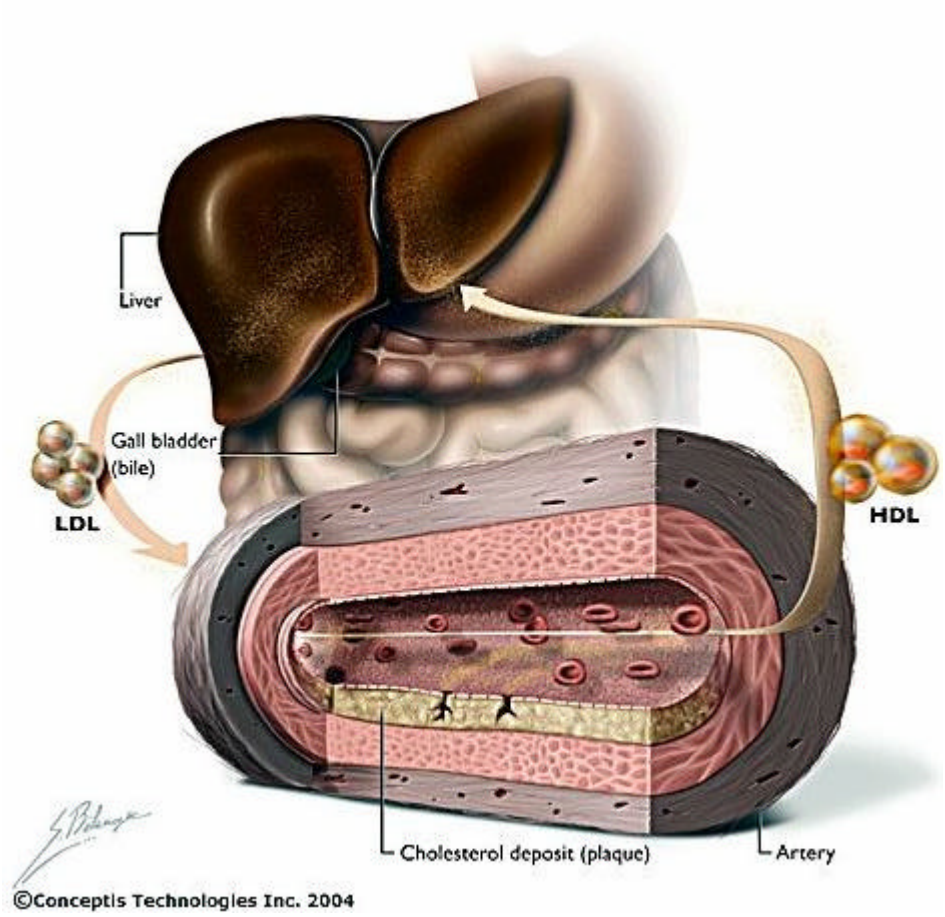
Take at least 48-72 hours for the anticoagulant effect to develop

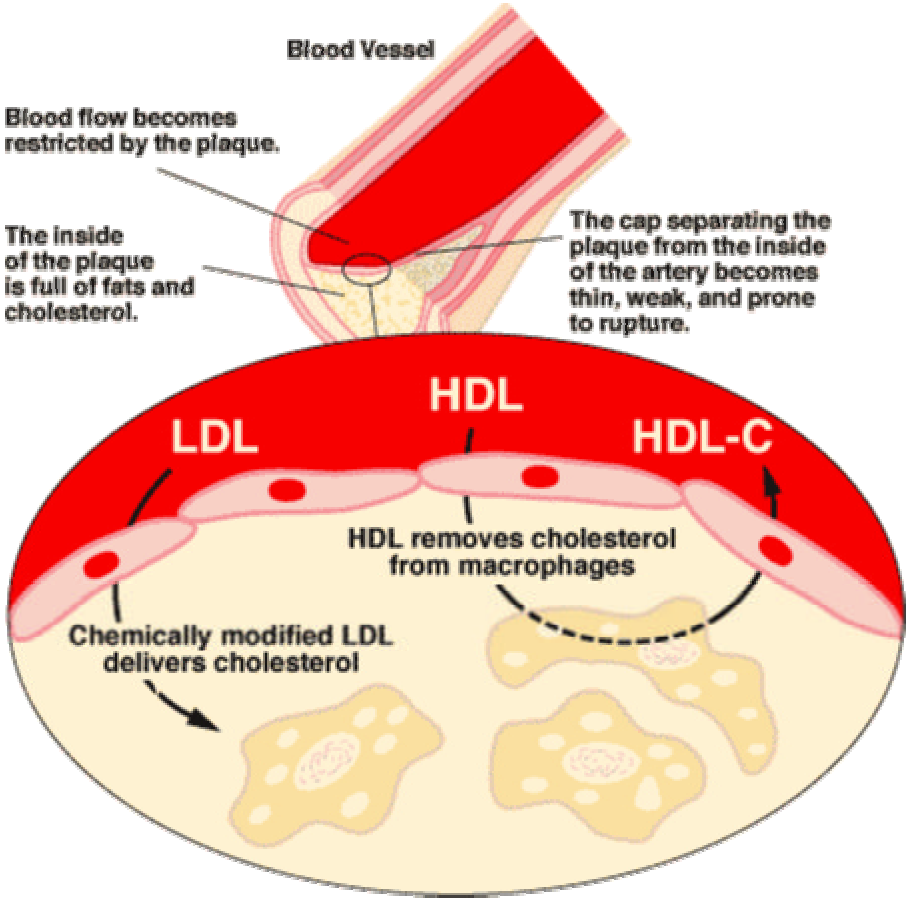
Warfarin is the most widely used oral anticoagulant

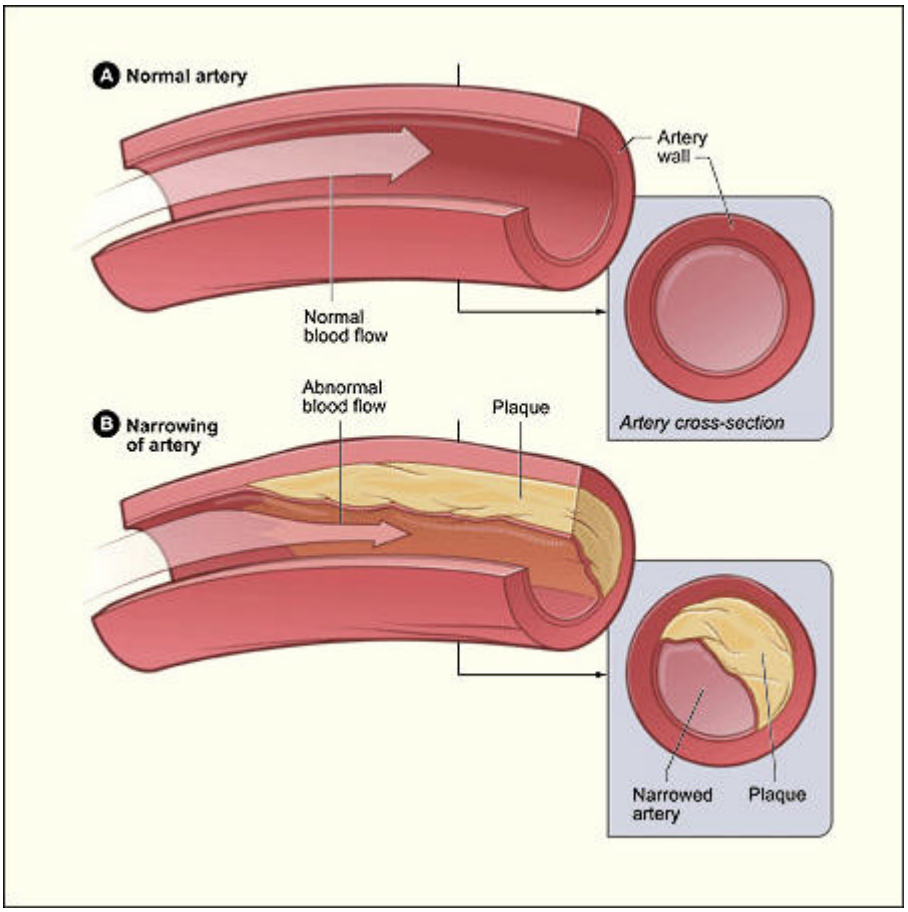
It inhibits the function of vitamin K and therefore inhibits the forming of blood clot

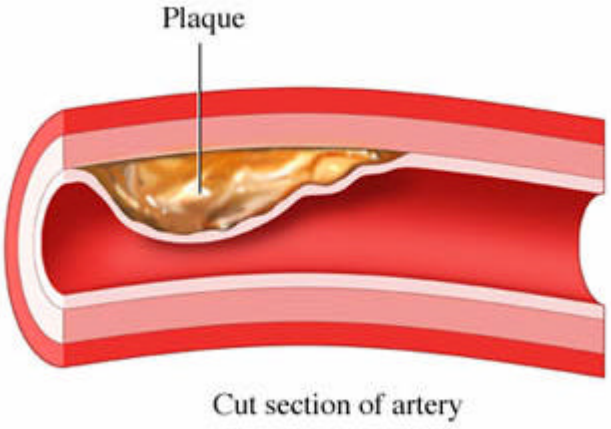
Indicated for deep-vein thrombosis, pulmonary embolism and heart diseases

$HCl + NaHCO_3 \rightarrow NaCl + H_2CO_3$









Cut section of artery