Introduction

Edition by

Dr.Firas Alaasam

M.Sc Pharmacology & Toxicology

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Definitions:

1-Pharmacology: science dealing with → interactions between chemicals (drugs) and living systems.

2. Drug: chemical substances, when introduced into the body, alters the body's function, producing → biological effects . Can be:

* Stimulatory. * Inhibitory.

3. Prodrug: chemical, is readily absorbed and distributed and then converted to → active drug by → biologic process inside the body.

4. Medical pharmacology: science of materials used to:

- Prevent.
- Diagnose.
- Treat.

5. Toxicology: deals with the → undesirable effects of chemicals in biological system.

6. Pharmacogenomics (pharmacogenetics): study the → genetic variations that cause individual differences in drug response. Aren't found in general population (allergies), but due to→ an inherited trait that produces a diminished or enhanced response to a drug.

General concept of Pharmacology:

1. Pharmaceutical Phase: when medications → enters the body in one form and changes into another form.
2. Pharmacokinetics: what the body does to the drug.

- Absorption.
- Distribution.
- Metabolism.
- Elimination.

General concept of Pharmacology:

3. Pharmacodynamics: what the drug does to the body.

Interaction of drugs with → cellular proteins(receptors/enzymes), to → control changes in physiological function of particular organs:

- Drug receptor interaction → binding.
- Dose-response → effect.
- Signal transduction → mechanism of action.

Routes of administration

its determined by:

- Properties of the drug (water/lipid soluble).
- Therapeutic objective (desirability of a rapid onset of action).

1. Enteral (GI route) → systemic:

- Oral: by the → mouth (most common).
- Sublingual: drugs subject to → high degree of first-pass metabolism.
- Rectal (high vascular): excellent site of → absorption (it's also used to → administer antiemetic agents)

Routes of administration

2. Parenteral (Injections) route → local: they're three:

- Intravascular (I.V.).
- Intramuscular (I.M.).
- Subcutaneous (S.C.).

3. Others:

- Inhalation.
- Intrathecal/Intraventricular.
- Topical (skin and mucous membrane).
- Trans-dermal.
- Intranasal.

1.Pharmacokinetic Phase (What does the body to the drug)

1-Absorption: the movement of drug from its site of application into the blood / lymphatic system without being chemically altered.

- Rate of absorption depend on → route of administration.
- I.V. route → absorption is complete, that's mean; the total dose of drug reaches the systemic circulation.
- Other routes → absorption is partial → lower bioavailability.

Mechanisms of drug transport across membranes (absorption):

1. Passive (simple)diffusion (Glomerular filtration)	? The drug moves from a region of ↑ conc. to one of ↓ conc. ? Doesn't involve a carrier. ? Not saturable. ? Rapid for → lipophilic, non-ionic and small molecules. *Lipid-soluble drugs: moves across most biological membrane *Water-soluble drugs:penetrate the cell membrane through aqueous channels.	No energy.

Mechanisms of drug transport across membranes (absorption):

2. Pore transport (aqueous channels)	Small hydrophilic drugs (water-soluble): diffuse by → passing through pores (aqueous channels).	No energy.
3- Facilitateddiffusion	Bind to carrier → non-covalently.	No energy.
4. Active transport	Identical to facilitated diffusion. The drug moves from a region of ↓ conc. to one of ↑ conc. (against conc. gradient)..	Energy is needed (ATP). .
5. Pinocytosis and phagocytosis	Engulfing of drug for large substance to → enter the cells (iron). Appropriate binding proteins.	

Factors affecting drug absorption:

1. Effect of pH on drug absorption:

- Most drugs are → week acidic / weak bases:

*Acidic drugs (HA) release H+ , producing a charged ion A-

[HA ↔ H+ + A-] HA: can penetrate.

*Basic drug (BH+) release H+, producing an uncharged ion B

[HB+ ↔ H+ + B] B: can penetrate.

Passage of uncharged drug through a membrane:

- Drug passes through membrane more readily if it's uncharged.
- The effective conc. of permeable form is determined by → the relative conc. of the charged and uncharged forms.
- The ratio between the two forms (charged and uncharged) is determined by → pH at the site of absorption. → pKa: the strength of weak acid/base.
- Lower pKa → stronger acid. Higher pKa → stronger base.

Factors affecting drug absorption:

2- Physical factors influencing absorption:

1. Blood flow to the absorption site:

- Decrease in blood flow → decrease in absorption.
- Blood flow in the intestine is much greater than the flow of stomach.

2. Total surface area available for absorption:

- Absorption in the intestine is more efficient, because it has a surface rich in microvilli.

3. Contact time at the absorption surface:

- If drug moves through GIT very quickly (diarrhea), it's not well absorbed.
- Anything that delays the transport of drug from the stomach to the intestine, delays the retention of drug.
- Presence of food in stomach → dilutes the drug. → shows gastric emptying.
- Drugs taken with meal is generally absorbed more slowly.

2. Distribution: when the drug leaves the blood and enters the interstitium and/or the cells of the tissue.

1-Blood flow: rate of B.F varies widely

- B.F. to the brain, liver and kidney is → greater than B.F. to skeletal muscle.
- Adipose tissue has a → low rate of B.F.

2. Capillary permeability: is determined by:

A- Capillary structure: varies widely, due to → the fraction of the basement membrane that's exposed by → slit (tight) junctions between endothelial cells.

- In the brain: the capillary structure is continuous → there are no slit junctions.
- In contrast, the liver and spleen: large part of their basement membrane it's exposed, due to → large discontinuous capillaries, through which plasma proteins can pass.

b. Drug structure (chemical nature of the drug):

1. Hydrophobic drug	2. Hydrophilic drug
Uniform distribution of electrons.	Non-uniform distribution of electrons.
No charge.	Positive/negative charge.
Readily penetrate most biological membranes.	Don't readily penetrate biological membranes, must go through the slit junctions
Can dissolve in the lipid membranes.	-

3. Binding to proteins:

 Plasma protein:

1-Sequesters drugs in a non-diffusible form.

2. Slows their transfer out of the vascular compartment.

 Binding is → non selective, takes place at → sites on the protein to which endogenous compounds attach (bilirubin).

***Plasma albumin:** is the major drug binding protein, and may act as drug reservoir.

 As the conc. of free drug ↓, due to → elimination by metabolism/excretion, the bound drug dissociates from the protien.

 This maintain the free drug conc. as a constant fraction.

***Binding of drugs to plasma proteins:**

 Bound drug are pharmacologically inactive.

 Only the free unbound drug can:

1-Act on target sites in the tissue

2. Elicit a biological response.

 By binding to plasma proteins, drugs become → trapped, and, in effect, → inactive.


Thank you

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3. Drug metabolism:

- Drugs are eliminated by:
  1. Biotransformation.
  2. Excretion into the urine/bile.
- Liver → major site of drug metabolism.
- Specific drugs may undergo → biotransformation in other tissues
- Kidney → cannot eliminate lipophilic drugs, that readily cross cell membranes and are reabsorbed in the distal tubules.

*__Lipid-soluble agents__: must be first metabolized in the liver, using

two phases:

1. Phase I: convert lipophilic molecule into → more polar molecules, by introducing → polar functional group.

- May ↑, ↓ or leave unaltered the drugs pharmacologic activity.
- Are catalyzed by → Cytochrome P-450 system.
- Smooth microsomes are rich in enzymes responsible for oxidative drugs metabolism.
- The activity of these enzymes require:
  1. Reducing agent.
  2. NADPH.
  3. Molecular O2.

Phase I:

This involves microsomal oxidation , non microsomal oxidation , reduction and hydrolysis . Phase I reaction convert lipophilic molecules into more polar molecules by introducing or unmasking a polar function group , such as – OH OR – NH_2. Phase I metabolism may increase , decrease or uncharged the pharmacologic activity of the drug

*__Cytochrome P-450:__ iso-enzymes located in → cells of liver and intestinal tract.

1. Cytochrome P-450 enzyme induction: stimulation of hepatic drug metabolism.

Some → stimulate their own metabolism.

→ accelerate the metabolism of other drugs.

E.g. → Pheno-barbital.

2. Cytochrome P-450 enzyme inhibition: ↓ the stimulation of hepatic drug metabolism enzyme, which lead to → ↑ levels of active drug in the body. E.g. → Alcohol.

2. Phase II: 2.

This phase consists of conjugation reactions. If the metabolite from Phase I metabolism sufficiently polar, it can be excreted by the kidneys. However, many Phase I metabolites are too lipophilic, so they are retained in the kidney tubules.

A subsequent conjugation reaction with an endogenous substrate, such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid results in polar, usually more water-soluble compounds that are most often therapeutically inactive. These conjugated drugs are highly polar and may be excreted by the kidney or in bile

4. Drug elimination

(excretion): removal of drug from the body.

1. **Major organs:**
   - Kidney: into the urine.
   - Liver.
   - GIT and lung.

2. **Minor organs:**
   - Milk: nursing mothers.
   - Salivary glands.
   - Sweat.

*Mechanism of renal elimination of a drug:

1.Glomerular filtration (passive diffusion):

- Drugs enter the kidney through → renal arteries, which divide to form → glomerular capillary plexus.
- Lipid solubility and pH don't influence the passage of drugs.
- Small molecules, water soluble and free drugs → pass more rapidly.
- Drugs bound to plasma protein → don't pass through G.F.

2.Tubular secretion:

- Drugs bind to carriers are → transported.
- Drugs was not transferred into G.F., leaves the → glomeruli, through → efferent arteriole, which divide to form → capillary plexus surrounding the → nephric lumen in the proximal tubule.

3.Tubular reabsorption:

- If the drug is → uncharged, may diffuse out of → the nephric lumen, and back into → systemic circulation.
- Manipulating the pH of urine to:
  - ↑ the ionized form of the drug in the lumen, to →
  - ↓ the amount of back diffusion, and to →
  - ↑ the clearance of an undesirable drug.
- Small non-ionic drugs → pass more rapidly.

-if the drug was acidic and the urine was acidic too the drug become ionize this is lead to reabsorption

- But if the drug become noionize this is lead to readily excretion

2.Pharmacodynamic Phase

(What does the drug to the body)

 Occurs when medication reaches the → target cell, tissue, organ and a therapeutic effect occurs.

Mechanism of drug action:

1. Physical action: alter the environment of the cell through physical action (Kaolin adsorbs toxins in → diarrhea).

2. Chemical action: alter the environment of the cell through chemical action ($NaHCO_3$ in → hyperacidity).

3. Cytotoxic action: stop cell division (anti-cancer drugs)

4. Interfere with selective passage of ions (Ca^{+2} and Na^{+} entry → local anesthetics drugs)

5. Interference with normal metabolic pathway (Sulphon-amides competes with PABA → essential for bacterial growth).

2.Pharmacodynamic Phase

(What does the drug to the body)

6. Action on enzyme stimulation/inhibition: enzyme inhibition could be:

- **Reversible:** short-term (Neostigmine → Cholin-esterase inhibitor).
- **Irreversible:** long-term for new enzyme synthesis (irreversible Anti-cholin-esterase).

7. Action on specific receptors (drug receptor interaction):

- Receptors: are macromolecular protein structures, present on → cell membrane / within the cell.
- React with a ligand (drug, hormone or neurotransmitter) to → produce a biological response.
- Receptors translate the signal from → ligand, to → several subcellular elements (enzymes), to produce a biological response.

Drugs can be categorized into:

Agonists	**Drugs which → stimulate receptors: initiate changes in cell function producing effects.** **Potency depends on:** **1. Affinity.** **2. Efficacy.** **E.g → Diazepam**	**Affinity: tendency to bind receptors.**	**Efficacy: ability to initiate changes, which lead → effect.**	**Rapid Dissociatin rate.**
Antagonists	Drugs which → block receptors; they bind to receptors without initiating change in receptors. Have no effect in the absence of agonist. Prevent the action of agonists. E.g → Flumazenil.	Affinity.	No efficacy.	Slow dissociation rate.

Drugs can be categorized into:

Partial agonists	**timulate and block receptors. .g →Buprenorphine.**	**Affinity.**	**Efficacy.**	**Moderate dissociation rate..**
Inverse agonists	Produce effects opposite to agonist. E.g → Carbolines.	Affinity.	efficacy.	Rapid dissociation rate.

Types of antagonists:

1-Pharmacological Antagonists:

A. Competitive	B. Non-Competitive
Compete for the binding site.	Bind anywhere in the receptor.
Reversible	Irreversible.
Surmountable.	Un-surmountable.
The effect can be overcome by more agonist (drug). Higher the conc. of antagonis used → more drug you need to get the same effect.	The effect cannot be overcome by more agonist (drug).
	Inactivates the receptors

2. Functional Antagonists:

2. Functional Antagonists:

1. Physiologic antagonist:

- Binds to → non-related receptor.
- Opposite effect to that produced by the drug.
- Intrinsic activity = 1.

  * Glucocorticoid hormones → ↑ blood sugar.

  * Insulin → ↓ blood sugar.

2. Chemical antagonist:

- It's a chelator (sequester).
- Interacts directly with the drug, being → antagonized, to remove it / prevent it from binding to its receptor.
- Doesn't depend on → interaction with agonists receptors.

* Heparin (anti-coagulant, acidic): if there's → too much bleeding and hemorrhage.

*Prot-amine sulfate (base): form a → stable inactive complex with heparin, and inactivates it.

Receptors and signal transduction mechanism:

-binding of agonist to receptors → activates effectors/signaling mechanism.

1. Ion-channel linked receptors (Ligand-gated ion channel):

- Ach + nicotinic receptors → Na+ influx → depolarization.
- GABA + GABAA receptors → Cl influx → hyper-depolarization.

These responses takes → milliseconds.

2. G-protein linked receptors (glucagon):

- Time elapsed between binding to receptor and cellular response takes → seconds.
- These receptors has → a seven trans-membrane, because → receptor polypeptide across cell membrane 7 times.
- When agonist bind to → the domain, G-protein will be → activated, to transduce agonist-induced signal to a variety of effectors elements located intracellular / in the cell membrane.
- Effector element change → the conc. of an intracellular second messenger.

Receptors and signal transduction mechanism:

*__Second messenger__ → include:

1. cAMP (cyclic Adenosine Mono-Phosphate).
2. Ca +2 ion.
3. Phospho-ino-sitides.
4. cGMP (cyclic Guanosine Mono-Phosphate).

3. Membrane-tyrosinase kinase linked receptors (insulin):

 Receptors for → insulin, act on → membrane receptors, which can

phosphorilate → signal transducers and activators of transcription, which → dimerize, and then → dissociate from the receptor to:

1. Cross the nuclear membrane.
2. Modulate gene transcription.

Receptors and signal transduction mechanism:

4. DNA-linked receptors (intracellular receptor):

- When agonist bind to → the domain, hsp90 domain is → released

leaving the DNA binding domain, which regulates:

1. Gene transcription.
2. Translation.
3. Protein synthesis.

- Has a slow onset → long duration.

Variation in drug responsiveness

- **Idio-syncratic drug response:** unusual individual reaction, caused

by: 1. Genetic differences in metabolism.

2. Hyper-sensitivity.

3. Tolerance.

- **Hypo-reactive**: intensity of effect is ↓.
- **Hyper-reactive:** intensity of effect is ↑.
- **Hyper-sensitivity:** allergic / immunological response to drug.
- Tolerance: responsiveness usually ↓ as a consequence of → continuous drug administration. Need → greater doses / substitute different drug.
- **Tachy-phylaxis:** responsiveness ↓ rapidly, after administration of a drug.

Variation in drug responsiveness

Four general mechanisms:

1. Patients may differ in the rate of:

- Absorption of drug.
- Distribution of drug through the body.
- Elimination of drug from the body.

These will → alter the conc. of drug that reaches receptor.

Can be due to → age, weight, sex, disease state, liver and kidney disease, genetic differences.

2. Patients may vary in their:

- Conc. of endogenous receptor ligand.
- Response to pharmacologic antagonist.

Variation in drug responsiveness

3. Patients may have differences in the:

- Number of receptors sites.
- Function of receptors.

Due to → efficiency of coupling receptor to effectors.

Antagonist	Agonist
When discontinued, elevated number of receptors can produce an exaggerated response to physiologic conc. Of agonist.	When discontinued, elevated number of receptors have bee down-regulation, is too low for endogenous agonist to produce effective stimulation.

E.g. → Clonidine (α-agonist):

1. ↓ blood pressure.
2. Produce → hyper-tensive crisis.

Variation in drug responsiveness

4. Patients vary in:

- Functional integrity of biochemical processes in the responding cell.
- Physiologic regulation by → interacting organ systems.

Caused by → age, general health, severity and patho-physiologic mechanism of the disease.

Drug therapy:

1. Correct diagnoses.
2. Accurately directed.


Thank you

DRUGS ACTING ON THE AUTONOMIC NERVOUS SYSTEM (AUTONOMIC DRUGS)

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M.Sc. Pharmacology & Toxicology

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1. Drugs acting on the sympathetic nervous system

a) Sympathomimetics or adrenergic drugs: are drugs that mimic the effects of sympathetic nerve stimulation.

b) Sympatholytics: are drugs that inhibit the activity of sympathetic nerve or that of sympathomimetics.

2. Drugs acting on the parasympathetic nervous system

a) Parasympathomimetics or cholinergic drugs: are drugs which mimic acetylcholine or the effects of parasympathetic nerve stimulation.

b) Parasympatholytics: are drugs that inhibit parasympathetic nervous system activity or that of cholinergic drugs.

CHOLINERGIC DRUGS

CHOLINERGIC DRUGS

There are two groups of cholinergic drugs:

1. Direct-acting: bind to and activate muscarinic or nicotinic receptors (mostly both) and include the following subgroups:

a. Esters of choline: methacholine, carbachol, betanechol

b. Cholinergic alkaloids: pilocarpine, muscarine, arecoline, nicotine

2. Indirect-acting: inhibit the action of acetylcholinesterase enzyme

a. Reversible: neostigmine, physostigmine, edrophonium

b. Irreversible: Organophosphate compounds; echothiophate

The actions of acetylcholine may be divided into two main groups: -

1. Nicotinic actions- those produced by stimulation of all autonomic ganglia and the neuromuscular junction
2. 2. Muscarinic actions- those produced at postganglionic cholinergic nerve endings

ESTERS OF CHOLINE

It has two types of actions: nicotinic and muscarinic; the muscarinic actions are of main interest and are discussed below.

Cardiovascular system

Heart slow heart rate

Blood vessels: vasodilator

Blood pressure: falls because of the effect on the heart and blood revels

1. Gastrointestinal tract

It stimulates the tone and motility of the Gl tract but the sphincters will be relaxed

2.Urinary tract

It stimulates the detrusor muscle and relaxes the internal urethral sphincter resulting in evacuation of bladder

3. Bronchioles

It increase bronchial secretion and brings about bronchoconstriction

4) Eye- It has two effects-miosis and accommodation for near objects because of stimulation of the constrictor pupillae and ciliary muscles respectively.

5) Exocrine glands- it stimulates salivary, gastric, bronchial, lachrymal and sweat gland secretions

SYNTHETIC CHOLINE ESTERS.

These are synthetic derivatives of choline and include metacholine, carbachol and betanechol. These drugs have the following advantages over acetylcholine:

- They have longer duration of action,
- They are effective orally as well as parenterally, and
- They are relatively more selective in their actions.

CARBACHOL

It has similar actions to those of acetylcholine with pronounced effects on the gastro intestinal tract and the urinary bladder

Indications

- Glaucoma
- Retention of urine (postoperative)
- Paralytic ileus

BETANECHOL

This drug is similar to carbachol in all parameters

CHOLINERGIC ALKALOIDS

1. Those with chiefly nicotinic actions include nicotine
2. Those with chiefly muscarinic actions include muscarine, pilocarpine

PILOCARPINE

The drug directly stimulates the muscarinic receptors to bring about all the muscarinic effects of acetylcholine.

Indications

- Glaucoma

ANTICHOLINESTERASE DRUGS:

The commonly used cholinesterase inhibitors fall into three chemical groups:

1. Simple alcohols bearing quaternary amines, e.g., edrophonium
2. Carbamate and related quaternary or tertiary amines, e.g., neostigmine, physostigmine
3. Organic derivatives of phosphates, e.g., isofluorophate,

PHYSOSTIGMINE

Inhibits the enzyme cholinesterase; therefore, it increases and prolongs the effect of Endogenous acetylcholine at the different sites.It has no direct effect on cholinergic receptors.

Indications

- Glaucoma

NEOSTIGMINE

Just like physostigmine, it inhibits cholinesterase enzyme; but unlike physostigmine, it has a direct nicotinic action on skeletal muscles.

Indications

- Myasthenia gravis
- Reversal of effect of muscle relaxants, e.g. tubocurarine
- Post operative urine retention

Organophosphates:

Such as echothiophate, isofluorophate, etc. combine with cholinesterase irreversibly and thus hydrolysis is very slow.

They may be used in glaucoma. Other organophosphates like parathion and malathion are used as insecticides.

ANTICHOLINERGICS

ANTICHOLINERGICS

Anticholinergics fall into two major families:

1. Antinicotinics which include ganglion blockers such as hexamethonium, trimethaphan, etc.,and neuromuscular blockers such as gallamine, tubocurarine, pancuronium.

2. Antimuscarinics include tertiary amines such as atropine, scopolamine, tropicamide, etc, andquaternary amines such as propantheline, ipratropium, benztropine.

ATROPINE

Atropine is found in the plant Atropa belladonna and it is the prototype of muscarinic antagonists.

Atropine antagonizes the effect of acetylcholine by competing for the muscarinic receptors peripherally and in the CNS; therefore the effects of atropine are opposite to the acetylcholine effects.

Organ-system Effects:

CNS: - lower doses produce sedation

- higher doses produce excitation, agitation and hallucination

Eyes: - relaxation of constrictor pupillae (mydriasis)

-relaxation or weakening of ciliary muscle (cycloplegia-loss of the ability to accommodate)

CVS: - blocks vagal parasympathetic stimulation (tachycardia)

- vasoconstriction

Respiratory: - bronchodilatation and reduction of secretion

GIT: - decreased motility and secretions

GUS: - Relaxes smooth muscle of ureter and bladder wall; voiding is slowed.

Sweat Glands: - suppresses sweating

Clinical Indications

Pre anesthetic medication -to reduce the amount of secretion and to prevent excessive

vagal tone due to anesthesia.

As antispasmodic in cases of intestinal, biliary, and renal colic

Heart block

Hyperhidrosis

Side effects;

- Dryness of the mouth, tachycardia and blurred vision
- Retention of urine

HYOSCINE (SCOPOLAMINE)

This drug has the same effect as atropine except for some differences which includes:-

- It has shorter duration of action

- It is more depressant to the CNS.

- All other properties are similar to atropine. It has certain advantage over atropine.

These include:

1- Better for preanesthetic medication because of strong antisecretory and antiemetic action and also brings about amnesia

2- Can be used for short- travel motion sickness

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ADRENERGIC DRUGS

they may be divided into two groups on the basics of their chemical structure.

1. Catecholamines: -these are compounds which have the catechol nucleus.

Catecholamines have a direct action on sympathetic effectors cells through interactions with receptor sites on the cell membrane.

The group includes adrenaline, noradrenaline, dopamine, isoprenaline, and dobutamine.

2-Noncatecholmines: - lack the catechol nucleus. They may directly act on the receptorsor may indirectly release the physiologic

catecholaminese. e.g. ephedrine, phenylephrine, amphetamine

1. Adrenergic Agonists

Direct	Indirect	Mixed
Epi-nephrine	Amphet-amine	Ephidrine
Nor-epi-nephrine	Tyr-amine	Pseudo-ephedrine
Iso-proterenol	Cocaine	Metar-aminol
Dop-amine		
Dobut-amine		
Oxy-metazoline Phenyl-ephrine Methox-amine Clo-nidine Meta-proterenol		

Mechanism of action of adrenergic agonists:

1. Direct-acting:	2. Indirect-acting:	3. Mixed-acting:
Act directly on α or β adrenergic receptors, producing → effects similar to those that occur following: 1. Stimulation of sympathetic nerves 2. Release of the hormone epinephrine from the adrenal medulla.	May block the uptake of nor-epinephrine or are taken up into the pre-synaptic neuron, and cause → the release of nor-epinephrine from the adrenergic neuron. As in neuronal stimulation: the nor-epinephrine traverses the synapse and binds to the α or β receptors.	Act directly on α or β receptors (adrenergic receptors) and release of nor-epinephrine from the adrenergic neuron.

1. Direct-acting:

1. Epinephrine	Therapeutic uses	Adverse effects
One or four catechol-amines. • Stimulate α and β adrenergic receptors. • Low dose: β effects → vasodilatation. • High dose: α effects → vasoconstriction.	1. Treatment of → asthma and anaphylactic shock, few minutes after S.C. administration. 2. Glaucoma: • 2% topically, to ↓ IOP in open-angle glaucoma. • ↓ the production of aqueous humor by → vasoconstriction of the ciliary body b.v. 3. treatment of → type I hyper-sensitivity reactions in response to → allergens. 4.Cardiac arrest: restore cardiac rhythm in patients with cardiac arrest. 5. Anesthetics: L.A. sol.	• CNS disturbances: anxiety, fear, tension, headache, tremor. • Hemorrhage (cerebral): due to marked→ elevation of B.P. • Cardiac arrhythmias: if the patient is receiving digitalis. • Pulmonary edema.

2- Dop-amine	Therapeutic uses	Adverse effects
▯ Immediate metabolic precursor of → Nor-epin-ephrine. ▯ Occurs → naturally in the CNS in the basal ganglia, where it act as a → neurotransmitter, like in the adrenal medulla. ▯ Stimulate → α and β adrenergic receptors. ▯ Low dose: activating β1 cardiac receptors. ▯ High dose: activating α1 receptor → vasoconstriction.	▯ Drug of choice for → shock, is given by → continuous infusion. ▯ ↑ B.P. by: 1. Stimulation β-receptors on the heart to ↑ COP 2. Stimulation α-receptors on blood vessels to ↑ peripheral resistance. ▯ Enhance perfusion to the kidney and splanchnic areas. ▯ An ↑ blood flow to the kidney enhances → the GFR and causes → sodium dieresis.	▯ An overdose produce → same effect as sympathetic stimulation. ▯ Rapidly metabolized to → Homovanillic acid by MAO or COMT. ▯ It's adverse effects are → short-lived (nausea, hyper-tension, arrhythmia).

*MAO: Mono-Amine Oxidase.
*COMT: Catechol-O-Methyl Transferase.

2. Indirect-acting:

1. Amphet-amine

- Cause → nor-epinephrine (NE) release only.
- CNS stimulant effects: have lead to their use for → treating hyperactivity in children, narcolepsy and appetite control.
- ↑ B.P by → α effect on vasculature.
  → β effect on heat.
- It's use in pregnancy should be → avoided, because has adverse effects on the development of the fetus.

2. Cocaine

- Local anesthetic having the ability to → block Na+ / K+- activated ATPase, required for → cellular uptake of NE on the cell membrane of the adrenergic neuron.
- Cause → NE accumulates in the synaptic space.
- Magnified effects of NE and epinephrine (E).
- ↑ duration of action of NE and E.
- Can ↑ B.P → α agonist actions, and β stimulatory effects.
- CNS stimulant.
- Drug of abuse (cause addiction).

3. Mixed-acting:

1. Ephedrine

- Causes → NE release and stimulates receptor.
- α and β stimulant.
- Use → asthma as nasal sprays.
- Slower action.
- Is eliminated largely unchanged in the urine.
- ↑ systolic and diastolic B.P. by → vasoconstriction and cardiac stimulation.
- Produces → broncho-dilation.
- Produce → mild stimulation of CNS, this ↑ alertness, ↓ fatigue and prevents sleep.
- Improve → athletic performance.
- Used to → treat chronic asthma (rather than acute asthma, to prevent attacks), as a nasal decongestant, due to its' → local vasoconstrictor action.

2. Pseudo-ephedrine

- Used to → treat nasal and sinus congestion or congestion of the Eustachian tubes.
- Clinical use: is declining, due to → the availability of better and more potent agents that cause fewer adverse effects. It containing → herbal supplements (ephedra) were prohibited by → the US food and drug administration, because of → life-threatening cardiovascular reactions.
- Has been illegally converted to → metha-amphetamine.
- Thus, products containing pseudo-ephedrine have certain restrictions and should be kept behind the sales counter.
- Fewer CNS effects.
- Undergoes → incomplete hepatic metabolism before elimination in the urine.

*Ephedrine and Pseudo-ephedrine

- Plant alkaloids (made synthetically).
- Non-catechols, are poor substrates for → COMT and MAO.
- Long duration of action.
- Excellent absorption orally.
- Penetrate into → CNS.

2.Adrenergic Antagonists (Blockers / Sympatholytic)

1. α-Adrenergic Blocking Agents	2. β-Adrenergic Blocking Agents
⍰ Blockade of these receptors ↓ the sympathetic tone of the blood vessels, resulting in ↓ peripheral vascular resistance, lowering B.P. ⍰ This induces a → reflex tachycardia resulting from the lowered B.P.	⍰ All the clinically available are → competitive antagonists. ⍰ Non-selective act at both: β1 and β2 receptors. ⍰ Cardiovascular-selective act at: β1. ⍰ ↓ B.P in hyper-tension, they don't induce postural hypo-tension, because → α-receptors remain functional.
Phenoxy-benzamina	Propranolol
Phen-tolamine	Timolol and Nadolol
Yohimbine	Labetalol and Carvedilol

1. α-Adrenergic Blocking Agents:

1. Phen-tolamine

- Competitive block of → α1 and α2 receptors.
- Last about 4h after a single administration.
- Produces → postural hypo-tension, and causes → epinephrine reversal.
- Induced → reflex cardiac stimulation and tachycardia which are mediated by:

1. The baroreceptor reflex.
2. Blocking the α2-receptors of the cardiac sympathetic nerves.

- Can trigger → arrhythmias and anginal pain, it's contraindicated in patients with ↓ coronary perfusion.
- Is used for → short-term management of pheo-chromo-cytoma.

2. Yohimbine

- Selective α2 competitive blocker.
- Found as a component of → the bark of the Yohimbine tree.
- Works at → the level of CNS, to ↑ sympathetic outflow to the periphery.
- Directly block α2-receptors, and has been used to → relieve vasoconstriction associated with Reynaud's disease.
- Is contraindicated in → CNS and cardiovascular conditions, because → it's a CNS and cardiovascular stimulant.

2. β-Adrenergic Blocking Agents:

1. Atenolol, Metoprolol, Bisoprolol, Betaxolol, Nebivolol and Acebutolol	Actions
? Preferentially block β1-receptor at doses 50-100 fold less than those required for block β2-receptor. ? Cardio-selective blockers (acebutolol, atenolol and metoprolol). ? Cardio-selectivity is → most pronounced at low doses, and is → lost at high doses.	? In hypertension: cardio-selective β-blockers are useful in → hypertensive patients with impaired pulmonary function. ? Cardio-selective β-blockers are useful in → diabetic hypertensive patients who are receiving insulin or oral hypoglycemic agents. ? ↑ exercise tolerance in angina.

2. Labetalol and Carvedilol	Therapeutic use (In hypertension)	Adverse effect
▯ Blocks α and β receptors. ▯ Reversible β-blockers with concurrent α1 blocking actions that produce → peripheral vasodilatation, then ↓ B.P. ▯ Contrast with the other β-blockers that produce → peripheral vasoconstriction, and they are therefore useful → in treating hypertensive patients for whom ↑ peripheral vascular resistance is undesirable. ▯ Don't alter → serum lipid or blood glucose levels. ▯ Carvedilol: ↓ lipid peroxidation and vascular wall thickening, effects are → benefit in heart failure	▯ Labetalol: useful for → treating the elderly or black hypertensive patient in whom ↑ peripheral vascular resistance is undesirable. ▯ Labetalol: can be employed as → alternative to methyldopa in the treatment of → pregnancy-induced hypertension. ▯ I.V. labetalol: used to treat → hypertensiemergencies, because it ve can rapidly ↓ B.P.	▯ Orthostatic hypotension. ▯ Dizziness. *(with α1-blockade)

Drugs acting on respiratory system

Edition by

Dr.Firas Alaasam

M.Sc. Pharmacology & Toxicology

L .N (5)

Drugs acting on respiratory system:

- Respiratory system is subjected to a lot of injurers and harms because it is nearly the only system which is in continuous contact with the external environment during the whole life of human being. As a result respiratory system is subjected to pollution smoke, chemicals dust, & microorganism which means it is subjected to everything in the environment.

- *Drugs that are used for treatment of respiratory problems include*

1. Drugs & air flow obstruction.
2. Oxygen.
3. Respiratory stimulants.
4. Expectorants & cough suppressant.

1-Drugs & air flow obstruction

The aim of treatment in air flow obstruction is to increase ventilation by reducing bronchial smooth m. tone with specific agonist & antagonist drugs, by blocking the mechanisms of allergic response.

Drugs used in the treatment of airways obstruction are:

1. ***B_2 - Adrenoceptors agonist or stimulants:*** The mechanism of action is by increasing cAMP in the bronchial smooth muscles and mast cell leading to bronchodilation.
2. ***Theophylline and other xanthine derivatives:*** they act by blocking the enzyme phosphodiesterase leading to increase intracellular cAMP.
3. ***Mast cell membrane stabilizers:*** as Na cromoglycate [cromolyn], they prevent the release of broncho constrictor mediators.

- ***4. Corticosteroids:*** they stabilize mast cell and improve the pulmonary function in asthma.

- ***5. Anti-cholinergic drugs:*** they act by decreasing muscarinic bronchoconstriction.

1) B2 - Adrenoceptors agonists or stimulants:

- **. Salbutamol:**
- *Mechanism of action:*

- Agents as salbutamol, terbutaline and fenoterol are selective stimulants of B_2 receptors; they act on these receptors in bronchi and small airways and on mast cells.
- They cause fewer side effects on heart than adrenaline or isoprenaline which are non-selective.

- ***Action:***

1. Relaxation of bronchial smooth muscles.

2. Stabilization of mast cells.

- Route of administration:

- Salbutamol is best given by inhalation because:

1. It permits direct delivery of the drug to the site of action.

2. It reduces the possibility of general systemic side effect.

3. The total dose administered is very small.

4. It provides large surface area for absorption.

5. Rapid onset of action.

- ***Side effect:***

1. Tremor due to Stimulation of B_2 receptors.

2. Other dose-dependent effects resulting from weak activation of B-receptor as tachycardia and hypokalemia.

- ***Clinical Uses:***
- ***1.*** In asthma.
- ***2.*** In chronic obstructive airways disease (COAD).

2) Theophylline,Aminophylline & other Xanthine derivatives:

- ***Mechanism of the action:***
- By inhibition of phosphodiesterase and thus increasing cAMP cone. by blocking the enzyme that breaks down the nucleotide.
- Increased cAMP reduce the tone in bronchial smooth m. and stabilizes mast cell membrane. Xanthine may have wide spread effect on smooth m. not only in bronchi but also in CVS.

****Adverse effect:***

Tachycardia and palpitation at therapeutic doses. Nausea. vomiting and diarrhea at high therapeutic doses and convulsions are associated with plasma level above 30µg/l.

Clinical Uses:

It is used orally in long term treatment of asthma & Chronic obstructive airways diseases (COAD) especially in patient who show response to it.

3) Mast cell membrane stabilizers:

- As **Na cromoglycate (cromolyn)** & **Ketotifen.**

***Na cromoglycate (cromolyn)**

- They are not bronchodilators but they prevent bronchoconstriction in patient with allergic asthma which is caused by pollen & allergic agents.
- They stabilize sensitized mast cell and inhibit the release bronchoconstrictor agent like: histamine, SHT (serotonin) & SRS-A (slow reacting substances for anaphylaxis) as leukotrines.
- Mast cell stabilizers are useful in extrinsic (Allergic) asthma particularly in children & young adults & can prevent exercise induced asthma.
- ***Clinical uses:***
- Na Cromoglycate is administered locally to the lung by inhalation or nebulizers.

Ketotifen:

- It is a histamine Hl - receptor blocker which may also has some antiasthmatic effect.
- Ketotifen is given orally as tablets or capsules.
- Side effect: sedation & dry mouth that result from additional antihistamine.

4) Corticosteroids:

- Their effect are the result of the following action:
- a. Anti-inflammatory (for any reason).
- b. Reduction of mucosal oedema → increase airflow.
- c. Modification of immune response & stabilization of mast cells.
- d. Increase B2 - receptor responsiveness to agonist

- In the management of airway obstruction they are given by inhalation, orally and IV according to the condition:

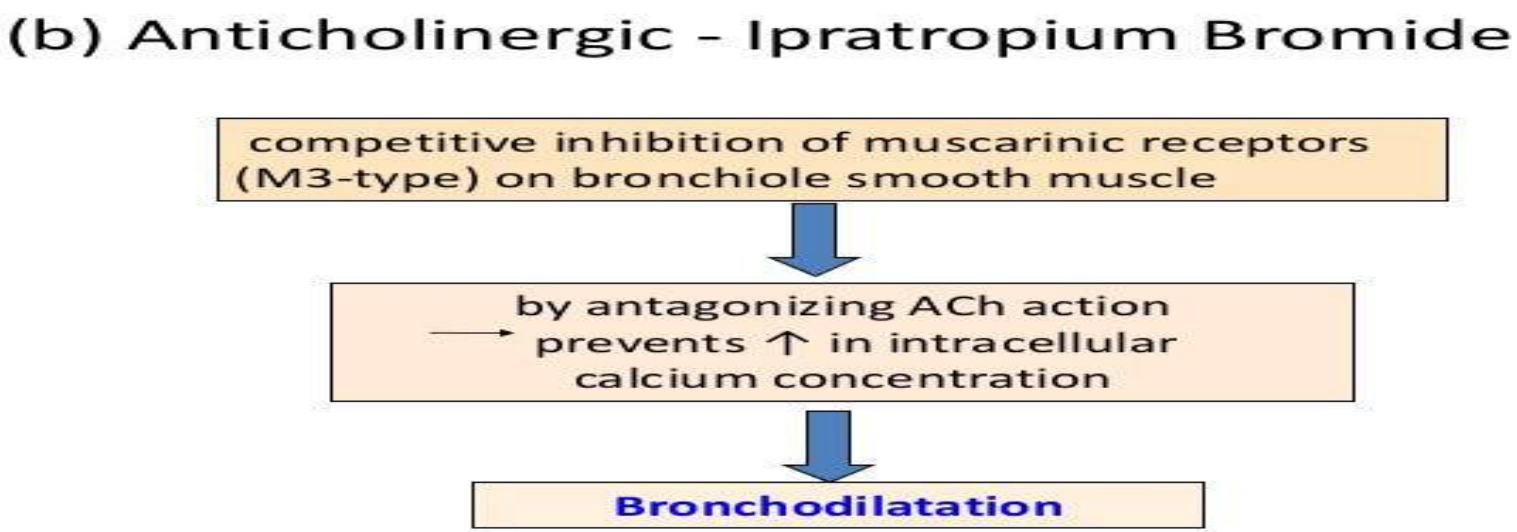
- ***A. Inhalation corticosteroids:***
- • **Beclomethasone & betamethasone & administered by aerosol inhalant**
- • **Adverse effects:** they are usually very much less than those of systemic agents.
- ***B. I.V corticosteroids:***
- When there is sever unresponsive asthma, especially when there is respiratory failure. Hydrocortisone (cortisol) is given I.V.

- ***C. oral corticosteroid:***

Patients with severe exacerbation of asthma require high doses of prednisolone by mouth after I.V hydrocortisone.

5) Anti-cholinergic drugs: Ipratropium:

Mechanism of action:



Adverse effect:

The anticholinergic adverse effects of synthetic derivativesipratropium bromide are much less than those of atropine itself, it is given by pressurized aerosols or from nebulizers.

2- Oxygen

- When O2 is given to supplement the amount normally present in the inspired airit should be regarded as drug.
- It is given in tow forms:

1. High cone. as possible

2. Low cone. (controlled) (24 %-28%)

- High O2 cone. :

It should be given to all hypoxic patients except those with established potential narcosis. Any apparatus which provide O2 flow to the oro-nasal area at a rate of 5 liters/min or more is effective in supplying a high cone. of O2 in the inspired gas.

Indications:

a. Pneumonia.

b. Acute pulmonary edema.

c. Pulmonary thrombo-embolism.

d. Fibrosing alveolitis.

e. Status asthmaticus.

f. respiratory failure or arrest due to drug over dose.

g. Acute circulatory failure.

h. Cyanide and CO poisoning.

3-Respiratory stimulant

Respiratory stimulant

A respiratory stimulant is a drug which acts to increase the action of the respiratory system.

Doxapram:

-It is given by continuous IV infusion

-It is used to stimulate respiration in patients who fail to ventilate spontaneously after general anesthesia or in chronic respiratory failure with CO_2 retention.

-doxapram stimulates an increase in tidal volume, and respiratory rate

4-Expectorants & cough suppressant

- These are two other classes of drugs commonly used in respiratory disease; but their Therapeutic value is doubtful.

Expectorants:

- Drugs that liquefy and dilute viscid secretions of respiratory tract thereby helping in evacuation of those secretions.
- • Agents with expectorant properties as **ammonium chloride & guaniphesin are often included in cough mixtures.**

- **Mucolytics**: such as Acetylcysteine: decrease the viscosity of respiratory secretions by altering the chemical composition of the mucus through breakdown of chemical disulfide bounds.

4-Expectorants & cough suppressant

Cough suppressant (Antitussive):

- Cough is a frequent complaint or secondary to an upper respiratory tractinfection. Chronic persistent cough is often caused by cigarette smoking.
- In acute respiratory infection, cough is a useful protective mechanism enabling the clearing the secretions from trachea and bronchi. Cough usually improves spontaneously with treatment of any underlying bacterial infection.
- Drugs used of cough suppression are usually given in the form of a sweet syrup or linctus, although oral or parental opiate will block cough reflexes justified as effective examples are: Diamorphine, Methadone, and Codeine phosphate.

- **Codeine :**

is the gold-standard treatment for cough suppression due to its long history of availability and use. ***Codeine*** decreases the sensitivity of cough centers in the central nervous system to peripheral stimuli and decreases mucosal secretion.

- **sides effects** like constipation, dysphoria, and fatigue, in addition to its addictive potential.

- **Dextromethorphan**

is a synthetic derivative of ***morphine*** that suppresses the response of the central cough center. It has no analgesic effects, has a low addictive profile, but may cause dysphoria at high doses.

DRUGS ACTING ON CARDIOVASCULAR SYSTEM

Edition by

Dr.Firas Alaasam

M.Sc. Pharmacology & Toxicology

L .N (6)

DRUGS ACTING ON CARDIOVASCULAR SYSTEM

I. Antihypertensive drugs :

Classified according to the principal regulatory site or mechanism on which they act. They include:

1- Diuretics, which lower blood pressure by depleting the body sodium and reducing blood volume, include:

1. Thiazides diuretics reduce blood pressure by reducing blood volume and cardiac out put as a result of a pronounced increase in urinary water and electrolyte particularly sodium excretion.

2. Loop diuretics, e.g. furosemide

3.Potassium sparing diuretics, e.g. spironolactone

2. Direct vasodilators.

• A)Arterial vasodilators, e.g. hydralazine

- Hydralazine: It dilates arterioles but not veins.

- adverse effects : headache, nausea, anorexia, palpitations, sweating and flushing

•B) Arteriovenous vasodilators, e.g. sodium nitroprusside

-Sodium nitroprussideIt dilates both arterial and venous vessels, The most serious toxicities include metabolic acidosis, arrhythmias, excessive hypotension and death.

3- Renin-angioteinsin enzyme inhibitors:

A) Angiotensin converting enzyme inhibitors:

e.g. captopril, enalapril. Captopril inhibits angiotensin converting enzyme that hydrolyzes angiotensin I (Inactive) to angiotensin II (Active), a potent vasoconstrictor, which additionally stimulates the secretion of aldosterone.

-adverse effects : maculopapular rash, angioedema, cough, granulocytopenia and diminished taste sensation.

B) Angiotensin –receptor blocker :

like candesartan ,losartan ,valsartan

4. Calcium channel blockers:

, e.g. verapamil . The mechanism of action in hypertension is inhibition of calcium influx in to arterial smooth muscle cells, resulting in a decrease in peripheral resistance. Verapamil has the

greatest cardiac depressant effect and may decrease heart rate and cardiac out put as well.

toxic effects : cardiac arrest, bradycardia, congestive heart failure.

II. Drug used in heart failure

Drugs used to treat heart failure divided into:

A. Drugs with positive inotropic effect.

B. Drugs without positive inotropic effect.

A. Drugs with positive inotropic effect:-

Drugs are increase the force of contraction of the heart muscle. include:

- Cardiac glycosides,
- Bipyridine derivatives
- Sympathomimetics
- Methylxanthines

1. Cardiac glycosides.

cardiac glycosides are digoxin and digitoxin.

Therapeutic uses:

- Congestive heart failure
- Atrial fibrillation,
- Atrial flutter, and
- Paroxysmal atrial tachycardia.

Toxicity:

- Gastrointestinal effects : anorexia, nausea, vomiting, diarrhoea
- Cardiac effects : bradycardia, heart block, arrhythmias
- CNS effects : headache, malaise, hallucinations, delirium, (yellow vision)

2. Bipyridine derivatives, e.g. amrinone, milrinone.

These drugs possess both positive inotropic effect and vasodilator effects.

The mechanism of action is inhibition of an enzyme known as phophodiesterase, which is responsible for the inactivation of cyclic AMP, result in an increase in cAMP. Bipyridine derivatives are used in cases of heart failure.

3. Beta - adrenergic stimulants e.g. dobutamine, dopamine

The positive inotropic effect of dobutamine is proportionally greater than its effect on heart rate.

4. Methylxanthines, e.g. theophylline (aminophylline)

Aminophylline has a positive inotropic effect, bronchodilating effect and a modest effect on renal blood flow.

B-Drugs without positive inotropic effect.

- Diuretics, e.g. furosemide
- Vasodilators, e.g. hydralazine, sodium nitroprusside
- Angiotensin converting enzyme inhibitors e.g. captopril

III.Drugs used in angina pectoris:

1. Organic nitrates e.g. nitro-glycerine.
2. Beta adrenergic blocking agents e.g. propranolol, atenolol, etc.
3. Calcium channel blocking agents e.g. verapamil.
4. Miscellaneous drugs e.g. aspirin, heparin .

1. Organic nitrates

The effects of nitrates are mediated through the direct relaxant action on smooth muscles.

Adverse effects : flushing, weakness, dizziness, tachycardia, palpitation, vertigo, sweating.

Therapeutic uses: prophylaxis and treatment of angina pectoris, post myocardial infarction, coronary insufficiency, acute LVF (left ventricle failure)

- **2. Adrenergic blocking agents**
- e.g. atenolol, propranolol.
- Adverse effects: Lethargy, fatigue, rash, cold hands and feet, nausea bronchospasm.
- Therapeutic uses other than angina include hypertension, Cardiac arrhythmias, post
- myocardial infarction and pheochromocytoma.

3. Calcium channel blockers: e.g. verapamil

Adverse effects: flushing nausea/vomiting, headache, Ankle swelling, dizziness, constipation .

4. Miscellaneous drugs,e.g. Acetylsalicylic acid

IV) Anti – arrhythmics

Drugs are traditionally classified into:

Class (I): Sodium channel blockers : quinidine, lidocaine

Class (II): Beta adrenergic blockers : propranolol, atenolol.

Class (III): Potassium channel blockers : amiodarone.

Class (IV): Calcium channel blockers: verapamil.

Class (V): Digitalis :digoxin.

DRUGS ACTING ON GASTROINTISTINAL TRACK

Edition by

Dr.Firas Alaasam

M.Sc. Pharmacology & Toxicology

L .N (7)

1- Peptic ulcer (P.U) and gastro esophageal reflux disease

2- Vomiting

3- Diarrhea

4- constipation

- **Drugs used to peptic ulcer are and gastro esophageal reflux disease:**
- Causative factors for peptic ulcer are

1- infection with gram-negative Helicobacter pylori

2- Use of non steroidal anti-inflammatory drugs (NDAIDs)

3- increase hydrochloride acid secretion

4- inadequate mucosal defense against gastric acid and tumors (rare)

-Treatment approaches :

- 1) Eradicating the H. pylori infection,

2) Reducing secretion of gastric acid with the use of H2-receptor antagonists or PPIs

3) Providing agents that protect the gastric mucosa from damage, such as *misoprostol* and *sucralfate.*

4) neutralizing gastric acid with non absorbable antacids, If patients are unable to tolerate the above therapies

1- Antimicrobial agents:

Eradication of H. pylori result in rapid healing of active peptic ulcers and low recurrence rate successful regiment is either :

a)- triple therapy consisting of

a PPI with either *metronidazole* or *amoxicillin* plus *clarithromycin*.

b)- quadruple therapy of *bismuth subsalicylate* (Pepto-Bismol) and *metronidazole* plus *tetracycline* plus a PPI

- there are administered for a 2-week course. This usually results in a 90 percent or greater eradication rate. -

2. H2-receptor antagonists:

Gastric acid secretion by parietal cells of the gastric mucosa is stimulated by histamine. **H2 blockers** are a group of medicines that reduce the amount of acid produced by the cells in the lining of the stomach. They are also called 'histamine **H2-receptor antagonists**' but are commonly called **H2 blockers**. There are four H2-receptor antagonists used; **cimetidine ranitidine, famotidine and nizatidine** and have various different brand names. which potently inhibit secretion of gastric acid.

Action: The histamine H-receptor antagonists act selectively on H receptors in the stomach, They are competitive antagonists of histamine and thus inhibit secretion of gastric acid.

Therapeutic uses:

All four agents are equally effectiye in promoting the healing of duodenal and gastric ulcers. However, recurrence is common after stopping the treatment with H2 antagonists. Patients with NSAID-induced ulcers should be treated with PPIs, because these agents heal and prevent future ulcers better than H2 antagonists.

a) Cimetidine:

is Ha-receptor antagonists, but it inhibits cytochrome P450 and potentiates the action of several drugs for example, warfarin, diazepam, phenytoin, quinidine, carbamazepine, theophylline, and imipramine resulting in serious adverse effects. So, its use is limited due to its adverse effect and drug-drug interactions

b)-Ranitidine:

as compared to cimetidine, ranitidine is loner acting, more tent (5-10 fold), has minimal side effects and does not produce the anti androgenic and prolactin stimulating effects of cimetidine. Unlike cimetidine, it does not inhibit cytochrome P450 and does not affect the concentrations of other drugs.

c). Famotidine:

Famotidine is similar to ranitidine in its pharmacalogic action, but it is more potent

d). Nizatidine:

Nizatidine is similar to ranitidine in its pharmacologic action and potency. In contrast to cimetidine, ranitidine and famotidine, which are metabolized by the liver, nizatidine is eliminated principally by the kidney

3. Inhibitors of the H'/K -ATPase proton pump (PPI):

Mechanism of action:

They bind to proton pump parietal cell and suppress the secretion of hydrogen ions into the gastric lumen and thus inhibit the secretion of gastric acid. Six PPls are now available: Omeprazole dexlansoprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole

-Adverse effects :

The PPls are generally well tolerated, possible increased risk of fractures of the hip, wrist, and spine are associated with patients taking the PPls for one year or greater because they interfere with absorption of calcium carbonate products. Omeprazole has been shown to inhibit the metabolism of warfarin, phenytoin, diazepam and cyclosporine, PPls and H2 antagonists, may result in low vitamin-BI2, because acid is required for its absorption in a complex with intrinsic factor.

4. Prostaglandins :

Prostaglandin E is produced by the gastric mucosa and it inhibits secretion of HCl and stimulates secretion of mucus and bicarbonate (cytoprotective effect)

Misoprostol:

a stable analog of prostaglandin E1 , as well as some PPIs are approved for the prevention of gastric ulcers induced by NSAIDs. It is less effective than H2 antagonists and the PPIs for treatment of acute peptic ulcers.

-Misoprostol produces uterine contraction and it is contraction during pregnancy . Dose –related diarrhea and nausea are the most common adverse effects and limit the use of this agent .

5. Antacids:

Antacids are weak bases that react with gastric acid to decrease the eastric acidity and resduce pepsin activity, because pepsin is inactive at a pH greater than 4. Commonly used antacids:

1. Aluminum salts (usually a mixture of Al(OH)3 and aluminum oxide
2. Magnesium hydroxide [Mg (OH)2], either alone or in combination.
3. Sodium bicarbonate which can produce transient metabolic alkalosis. hydrates) Calcium carbonate [CaCO3). Therefore, this antacid is not recommended for long-term use

Adverse effects:

Aluminum hydroxide tends to cause constipation and it binds with phosphate which can lead to hypophosphatemia while magnesium hydroxide tends to produce diarrhea. Sodium bicarbonate can causes systemic alkalosis and it liberates CO_2, causing belching and flatulence. Also, sodium content is a risk factor for patients with CHF in patients with renal impairment.

6. Mucosal protective agents:

1. Sucralfate This binds to positively charged groups in proteins of both normal and necrotic mucosa and forming complex gels with epithelial cells and thus creates a physical barrier that prevents degradation of mucus by pepsin and acid. Sucralfate effectively heals duodenal ulcers.

2. Bismuth subsalicylate: Preparations of this compound effectively heal peptic ulcers. In addition to their antimicrobial actions, they inhibit the activity of pepsin, increase secretion of mucus, and interact with glycoproteins in necrotic mucosal tissue to coat and protect the ulcer crater.

DRUGS ACTING ON GASTROINTISTINAL TRACK

Edition by

Dr.Firas Alaasam

M.Sc. Pharmacology & Toxicology

L .N (7)

Antiemetic drugs

Antiemetic drugs :

represent a variety of classes:

1. Anticholinergic (especially the muscarinic receptor antagonist like scopolamine)

2. Hi-receptor antagonists, likes dimenhydrinate, meclizine and cyclizine, are very useful in motion sickness but are ineffective against substances that directly on the chemoreceptor trigger zone

Antiemetic drugs are often present in combined forms to increase antiemetic activity or decrease toxicity. The major categories of drugs used to control chemotherapy-induced nausea and vomiting shown in the table .

1- Phenothiazines: acts by blocking dopamine receptors. It is effective against low or moderately emetogenic chemotherapeutic agents

Side effects: hypotension, sedation , restlessness and extrapyramidal symptoms

2. Metoclopramide: is effective antiemetic drug. Its side effects include sedation, diarrhea, and extrapyramidal symptoms which limit its use in high-dose

No	Chemical groups	Examples
1	Phenothiazine	**Prochlorperazine**
2	5-HT3 serotonin receptor blockers	**Dolasetron, Ondansetron , Palonosetron**
3	Substituted Benz amides	**Metoclopramide**
4	Butrophenones	**Droperidol , Halperidol**
5	Benzodiazepines	**Alprazolam , Lorazepam**
6	Corticosteroids	**Dexamethaxone ,Methyl Prednisolone**
7	Substance P/ neurokinin-1 receptor blocker	**Aprepitant**

Antidiarrheals

A-Antimotility agent

1-Diphenoxylate and loperamide : both have opioid –like action on the gut . they inhibit acetylcholine release and decrease peristalsis

Side effects: drowsiness, abdominal cramps and- dizziness. These drugs can contribute to toxic megacolon, so, they should not be used in young ,children or in patients with severe colitis.

B. Adsorbents:

Aluminum hydroxide and methylcellulose: act by adsorbing intestinal toxins or microorganisms and by coating or protecting the intestinal mucosa.

C. Agents that modify fluid and electrolyte transport :

Bismuth subsalicylate: used for traveler's diarrhea and it decreases fluid secretion in the bowel. Its action may be due to its salicylate component as well as its coating action. **Adverse effects** may include black tongue and black stools.

Laxatives

- Laxatives are commonly used for constipation to accelerate the movement of food through the gastrointestinal tract. All of these drugs, have a risk of dependency for the user, except lubiprostone which is chloride channel activator.

Classification according to their mechanism of action:

1. Irritants and stimulants

a. Senna: is a widely used stimulant laxative. It is useful in treating opioid-induced constipation.

b. Bisacodyl: is a potent stimulant of the colon. It acts directly on nerve fibers the mucosa.of the colon.

Adverse effects: abdominal cramps and atonic colon with prolonged use

c. castor oil: is very iritating to the stomach and promptly increases peristalsis. Pregnant patients should avoid castor oil because it may stimulate uterine contractions

2. Bulk laxatives

Methylcellulose, psyllium seeds and bran: form gels in the large causing water retention and intestinal distension, thereby increasing peristaltic activity. They should be used cautiously in patients who are immobile because of their potential for causing intestinal obstruction.

3. Saline and osmotic laxatives

a. Magnesium citrate, magnesium hydroxide and sodium phosphate are non- absorbable salts that hold water in the intestine by osmosis. This distends the bowel and increasing the intestinal activity and producing defecation in a few hours.

b. Electrolyte solutions containing polyethylene glycol (PEG): are used as colonic lavage solutions to prepare the gut for radiologic or endoscopic procedures. They cause less cramping and gas than other laxatives.

c. Lactulose: is a semisynthetic disaccharide sugar that also acts as an osmotic laxative that soft stools and defecation.

4. Stool softeners (emollient laxatives or surfactants):

Docusate sodium, docusate calcium, and docusate potassium: they emulsified with the stool and produce softer feces and ease passage. They may take days to become effective and are often used for prophylaxis rather than acute treatment.

5. Lubricant laxatives:

Mineral oil and glycerin suppositories are considered to be lubricants and act by facifitating the passage of hard stools

6. Chloride channel activators Lubiprostone:

currently the only agent in this class, works by activating chloride channels to increase fluid secretion in the intestinal lumen which facilitates the passage of stools and causes little change in electrolyte balances. It is used in the treatment of chronic constipation (produce no dependency), drug- drug interactions are minimal and nausea isa relatively common side effect with lubiprostone.

General Anesthesia

Edition by
Dr.Firas Alaasam
M.Sc. Pharmacology & Toxicology

L .N (9)

Anesthesia

-Anesthesia reversible state of CNS depression, resulting in loos of response to and perception of external stimuli. Anesthesia provides important benefits:

1. Sedation and reduction of anxiety
2. Lack of awareness and amnesia
3. Skeletal muscle relaxation
4. suppression of undesirable reflexes

5-Analgesia

- No single agent provides all desirable properties, so, several categories of drugs are used in combination to produce optimal anesthesia.

PREANESTHETIC MEDICATIONS

1. Antacids: (H2 blockers) prevent gastric acid secretion. (ranitidine)

2. Anticholinergic: prevent bradycardia and secretion of fluids into the respiratory tract (atropine)

3. Antiemetic's: prevent aspiration of stomach contents and postsurgical nausea and vomiting. (Plasil)

4. Antihistamines: prevent allergic reactions.

5. Benzodiazepines: relieve anxiety.

6. Opioids: Provide analgesia.

7. Neuromuscular blocking agents: facilitate intubation of the trachea and suppress muscle tone (relaxation).

Potent general anesthetics are delivered via inhalation and/or intravenous (IV) injection. With the exception of nitrous oxide, modern inhaled anesthetics are all volatile, halogenated hydrocarbons. IV anesthetic agents are used for the rapid induction of anesthesia.

PATIENT FACTORS IN SELECTION OF ANESTHESIA

1. Nature of the surgical or diagnostic procedure.
2. Patient's physiologic, pathologic, and pharmacologic state.

STAGES OF ANESTHESIA

inject General anesthesia can be divided into three stages:

1. Induction: The period of time from the onset of administration of the anesthetic to the development of effective surgical anesthesia

2- Maintenance: provides a sustained surgical anesthesia.

3. Recovery: is the time from discontinuation of administration of anesthesia until consciousness and physiologic reflexes are regained

. **A. Induction:**

General anesthesia in adults is normally induced with:

1. An IV anesthetic like propofol, which produces unconsciousness within 30-40 seconds

2. Additional inhalation and/or IV drugs (anesthetic combination) may be given to produce the desired depth of surgical anesthesia

3. Coad ministration of an IV skeletal muscle relaxant such as rocuronium, vecuronium, or succinylcholine to facilitate intubastion and muscle relaxation

B. Maintenance of anesthesia

The patient's vital signs and response to various stimuli are monitored continuously throughout the surgical procedure to balance the amount of drug inhaled and/or infused with the depth of anesthesia. Anesthesia is commonly maintained by the administration of:

1. Volatile anesthetics, which offer good control over the depth of anesthesia.

2. Opioids such as fentanyl are often used for pain relief, along with inhalation agents, because the latter are not good analgesics.

C. Recovery

Postoperatively, the anesthetic admixture is withdrawn, and the patient is monitored for the return of consciousness. If skeletal muscle relaxants have not been fully metabolized, reversal agents may be used. The patient should be monitored to ensure that he or she is fully recovered.

Depth of anesthesia

Stage I-Analgesia: Loss of pain sensation, the patient progresses from conscious to drowsy, amnesia and awareness of pain

2. Stage ll-Excitement: The patient experiences delirium, rise and irregularity in BP and respiration as well as a risk of laryngospasm. To shorten or eliminate this stage, a rapid acting agent, such as propofol, is given intravenously before inhalation anesthesia is administered.

3. Stage Ill-Surgical anesthesia: There is gradual loss of muscle tone and reflexes. Regular respiration and relaxation of skeletal muscles with loss of spontaneous movement occur in stage. Continuous careful monitoring is required to prevent undesired progression into Stage

4. Stage IV-Medullary paralysis: Severe depression of the respiratory and vasomotor centers occurs during this stage and death can rapidly occur unless measures are taken to maintain circulation and respiration.

GENERAL ANESTHETICS: INHALED

Modern inhalation anesthetics are nonflammable, nonexplosive agents that include the gas nitrous oxide and a number of volatile, halogenated hydrocarbons. These agents decrease cerebrovascular resistance, resulting in increased perfusion of the brain. They also cause bronchodilator and decrease volume of air per unit time moved into or out of the lungs.

Mechanism of action

No specific receptor has been identified as the site of general anesthetic action. The focus is now on interactions of the inhaled anesthetics with proteins comprising ion channels.

1. The general anesthetics increase the sensitivity of the y-aminobutyric acid (GABAA) receptors to the neurotransmitter, GABA. Postsynaptic neuronal excitability is, thus, diminished. Also, the activity of the inhibitory glycine receptors in the spinal motor neurons is increased

2. The inhalation anesthetics block the excitatory postsynaptic current of the nicotinic receptors. The mechanism by which the anesthetics perform these modulatory roles is not undserstood.

1. Halothane:

Halothane is a potent anesthetic but a relatively weak analgesic. So, it is usually Coad ministered with nitrous oxide, opioids, or local anesthetics. It is a potent bronchodilator, relaxes both skeletal and uterine muscle, and it can be used in obstetrics when uterine relaxation is indicated. Halothane is not hepatotoxic in pediatric patients and its pleasant odor makes it suitable in children for inhalation induction, although sevoflurane is now the agent of choice for inhalation induction if cost is not a factor

Adverse effects: Bradycardia, arrhythmias, hypotension

2-Isoflurane

Isoflurane (eye-soe-FLUR-ane) little metabolism, toxic to liver or kidney. It does not induce cardiac arrhythmias does not sensitize the heart to the action of catecholamines. However, produces dose-dependent hypotension due to peripheral vasodilation. has a pungent odor and stimulates respiratory reflexes (breath-holding, salivation, coughing, and laryngospasm) and is, therefore, not used for inhalation induction

3-Desflurane

Desflurane [DES-flure-ane] provides very rapid onset and recovery due to its low blood solubility. So, it has made it a popular anesthetic for outpatient surgery. Desflurane not used for inhalation inductions because it is irritating to the airway and can cause laryngospasm, coughing, and excessive secretions. Its degradation is minimal, and, therefore, tissue toxicity is rare.

4. Sevoflurane

Sevoflurane [see-voe-FLOOR-ane] has low pungency, allowing rapid induction without irritating the airway, thus making it suitable for inhalation induction in pediatric patients. It is replacing halothane for this purpose. This agent has rapid onset and recovery due to low blood solubility. Sevoflurane is metabolized by the liver, and compounds formed in the anesthesia circuit may be nephrotoxic if fresh gas flow is too low

5. Nitrous oxide :

Nitrous oxide [NYE-truss-ox-ide) is non-irritating and potent analgesic but a weak general anesthetic. For example, nitrous oxide is frequently employed at concentrations of 30-50 percent in. combination with oxygen for analgesia, particularly in dental surgery. This anesthetic does not depress respiration, and it does not produce muscle relaxation, moderate to no effect on the cardiovascular system or on increasing cerebral blood flow, and it is the least hepatotoxic of the inhalation anesthetics. Therefore, it is probably the safest of these anesthetics

General Anesthesia

Edition by
Dr.Firas Alaasam
M.Sc. Pharmacology & Toxicology

L .N (10)

INTRAVENOUS ANESTHTICS

IV anesthetics cause the rapid induction of anesthesia .Anesthesia may then be maintained with an appropriate inhalation agent .IV anesthetics may be used alone for short procedures or administered as infusion to maintain anesthesia during longer procedures . The exact mode of action of the IV anesthesia drugs is unknown .

1-Propofol:

Propofol is an IV sedative /hypnotic used in the induction or maintenance of anesthesia . It is widely used and has replaced thiopental as the first choice for anesthesia induction and sedation because it produce a euphoric feeling in the patient and dose not cause post anesthesia nausea and vomiting .

- The induction of anesthesia is accurse with 30-40 seconds .the pharmacokinetics of propofol are not altered by moderate hepatic or renal failure . It is occasionally accompanied by excitatory phenomena ,

Such as muscle twitching and spontaneous movement . It decrease B.P without depressing the myocardium and it reduce intracranial pressure , mainly due to systemic vasodilation . Propofol is infused in lower doses to provide for outpatient procedures

2- Fospropofol :

Fospropofol is a new, water – soluble drug approved only for sedation . Following the administration of fopropofol , loss of consciousness takes about 4 minutes.

3- Barbiturates :

thiopental is a potent anesthesia but a weak analgesic . It is an ultra-short-acting barbiturate with high lipid solubility :

Adverse effects :

Apnea , coughing ,chest wall spasm , laryngospasm , and bronchospasm . Thiopental has minor effect on the cardiovascular system causes sever hypotension in patients with hypervolemia or shock .

4- Benzodiazepines :

The benzodiazepines are used in conjunction with anesthesia to sedate the patient . The most commonly used is :

1- Midazolam 2- Diazepam 3- Lorazepam

-they have little depressant effects on cardiovascular and respiratory system

4- Opioids

They are analgesic commonly used with anesthetics ,such as nitrous oxide or volatile halogenated anesthesia . The most commonly used opioids are :

1-fentanyl 2- sufentanil 3- remifentanil

They induce analgesia more rapidly than morphine dose . Opioids are not good amnesic ,cause hypotension , respiratory depression , muscle rigidity , post anesthetic nausea and vomiting . Opioid effect can be antagonize by naloxone

5- Etomidate :

Etomidate is used to induce anesthesia . It is a hypnotic agent but lacks analgesic activity . The induction is rapid ,and the drug is short acting .it is usually only used for patient with coronary artery disease or cardiovascular dysfunction such as chock . Etomidate

Has little effect on the heart and circulation .

Its adverse effect :

include a decrease in plasma cortisol and aldosterone level , which can persist for up to 8 h

6- Ketamine :

Ketamine s short-acting nonbarbiturate anesthetic , induce unconscious but , patient may be appear to be awake and dose not feel pain . It stimulates sympathetic NS , which cause stimulation of the heart with increased B.P and CO .this property is beneficial in patients with asthma , hypovolemic or cardiogenic shock . Therefor , ketamine is not use in hypertensive or stroke patient .it is use mainly in children and elderly adult for short procedure . However ,it is not widely used because it increase cerebral blood flow and induce postoperative hallucination (nightmares), particularly in adult .

7- Dexmedtomidine :

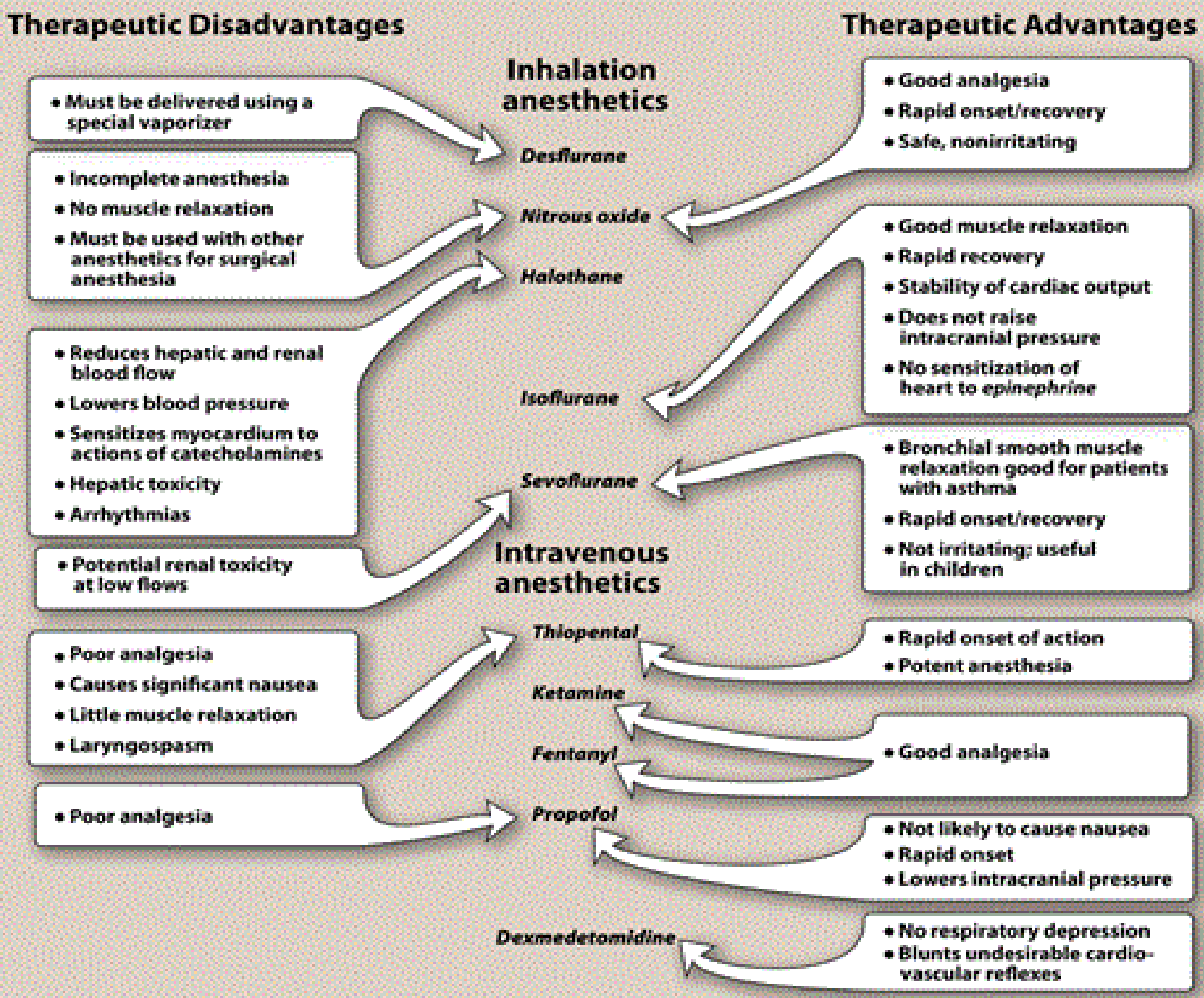
Is a sedative with out causing respiratory depression , analgesic , sympatholytic and anxiolytic. Like clonidine , its mechanism of action is stimulation alfa2 receptors in the brain . It reduce the requirement of the patient for volatile anesthetic ,sedative and analgesic

PARALYTICS/NEUROMUSCULAR BLOCKERS

Neuromuscular blocker are used to inhibit the reflex to facilitate tracheal intubation ,and to provide muscle relation as needed for certain types of surgery . These agent include cistracrium , pancuronium , rocuronium ,succinylcholine and vecuronium

MECHANISM OF ACTION :

They block the nicotinic acetylcholine receptors in the neuromuscular junction


Therapeutic Disadvantages
Therapeutic Advantages
Inhalation anesthetics
• Must be delivered using a special vaporizer
• Good analgesia
• Rapid onset/recovery
• Safe, nonirritating
Desflurane
• Incomplete anesthesia
• No muscle relaxation
• Must be used with other anesthetics for surgical anesthesia
Nitrous oxide
Halothane
• Good muscle relaxation
• Rapid recovery
• Stability of cardiac output
• Does not raise intracranial pressure
• No sensitization of heart to epinephrine
• Reduces hepatic and renal blood flow
• Lowers blood pressure
• Sensitizes myocardium to actions of catecholamines
• Hepatic toxicity
• Arrhythmias
Isoflurane
Sevoflurane
• Bronchial smooth muscle relaxation good for patients with asthma
• Rapid onset/recovery
• Not irritating; useful in children
• Potential renal toxicity at low flows
Intravenous anesthetics
Thiopental
• Rapid onset of action
• Potent anesthesia
• Poor analgesia
• Causes significant nausea
• Little muscle relaxation
• Laryngospasm
Ketamine
Fentanyl
• Good analgesia
• Poor analgesia
Propofol
• Not likely to cause nausea
• Rapid onset
• Lowers intracranial pressure
Dexmedetomidine
• No respiratory depression
• Blunts undesirable cardiovascular reflexes

Local Anesthesia

Edition by
Dr.Firas Alaasam
M.Sc. Pharmacology & Toxicology

L .N (11)

Local anesthetic

-Local anesthetics abolish sensation and in higher concentrations , motor activity in a limited area of the body . They are applied or injected to block nerve conduction of sensory impulses from the periphery to the NS . So , the sensation cannot be transmitted from the source of stimulation to the brain

Mechanism of action

Local anesthetics work by blocking sodium ion channels to prevent the transient increase in permeability of the nerve membrane to sodium that is required for an action potential to occur .

Delivery techniques :

1- Topical administration ; can be used to numb any area of the skin , front of eyeball , inside of the nose , ear , throat , anus and genitals

. 2 . Infiltration : produced by injection of local anesthetic solution directly into an ar a that is painful or about to be operated on .

3 - Spinal ; injection of a local anesthetic into the subarachnoid space , generally through a fine needle ,

4- Epidural anesthetic injected into the epidural space of the spine

5-caudal blocks : injection of an anesthetic into the sacral canal .

Structure of local anesthetics :

They have a lipophili group , joined by an amide or ester linkage to a carbon chain , which , in turn , is joined to a hydrophilic group

1 - Esters : Cocaine , Procaine , Tetracaine and Benzocaine .

2 . Amides : Lidocaine (Xylocaine) Mepivacaine , Bupivacaine , Ropivacaine and Articaine

The most widely used of the local anesthetic compounds are

1 . Bupivacaine : It is often the agent of choice for epidural infusions used for postoperative pain control and for labor o analgesia , It is noted for its cardiotoxicity .

2 , Lidocaine; the most commonly used , lidocaine has had an excellent record as an intermediate duration anesthetic , and remains the reference Standard against which most anesthetics are compared .

3- Mepivacaine : should not be used in obstetric anesthesia due to its increased toxicity to the neonate ,

4 . Procaine:

5 . Ropivacaine

. 6 . Articaine : a shorter plasma half - life approximately 20 minutes , These characteristics have led to widespread popularity in denital anesthesia , where it is generally considered to be more effective , and possibly safer than lidocaine .

-The choice of drug depends on the speed of onset and duration required

Absorption

Systemic absorption of injected local anesthetic from the site of administration is determined by several factors :

1 . Dosage .

2 . Site of injection .

3 . Drug - tissue binding ,

4 . Local tissue blood flow

. 5 . Use of a vasoconstrictor (eg , epinephrine) .

6 . Physicochemical properties of the drug itself .

- Anesthetics that are more lipid soluble are generally more potent , longer duration of action , and take longer to achieve their clinical effect Application of a local anesthetic to a highly vascular area such as the tracheal mucosa or the tissue surrounding intercostal nerves results in more rapid absorption and thus higher blood levels than if the local anesthetic is injected into a poorly perfused tissue such as subcutaneous fat .

Metabolism :

1 . Biotransformation of amides : Occurs primarily in the liver . Prilocaine is also metabolized in the plasma and kidney , and one of its metabolites may lead to methemoglobinemia

2- Esters : are biotransformed by plasma (pseudocholinesterase) , Patients with pseudocholinesterase deficiency may be expected to metabolize ester local anesthetics more slowly . However , at normal doses , this has little clinical effect . Reduced hepatic function predisposes the patient to toxic effects but should not significantly increase the duration of action of local anesthetics

Onset and duration of action

Onset and duration of action of local anesthetics are influenced by

1 . pH , pKa of the drug ,

2 . Nerve morphology .

3 . Concentration and lipid solubility of the drug .

Actions

Local anesthetics cause vasodilation which leads to rapid diffusion away from the site of action and results in a short duration of action when these drugs are administered alone . By adding the epinephrine (vasoconstrictor) the local anesthetic , the rate of local anesthetic diffusion and absorption is decreased . So , it minimizes both the systemic toxicity and increases the duration of action of the local anesthetic . Hepatic function does not affect the duration of action of local anesthesia , which is determined by redistribution and not biotransformation . Some of these local anesthetics agents give additional benefits such as antiarrhythmic effect of lidocaine when administered intravenously ,

Allergic reactions

Allergic reactions to local anesthetics are common , but most of these are of psychogenic origin , with signs such as urticaria , edera , and bronchospasm . True allergy to an amide is rare , whereas the ester procaine is somewhat more allergenic . An allergy to one ester rules out use of another ester , because the allergenic component is para - amino benzoic acid , and metabolism of all esters yields this Compound , In contrast , an allergy to one amide does not rule out use of another amide . A patient may be allergic to other compounds in the local anesthetic as preservatives in multidose vials

Administration to children and the elderly

Before administration of local anesthetic to a child , the maximum dose based on the child ' s weight should be calculated to ovoid overdose . There are no significant differences in the response to local anesthetics between younger and older adults (regardless of patient age) . However , it is best to below the maximum doses in elderly patients who often have some problem in liver function of heart and reducing the dose of epinephrine Imay be reasonable

Systemic local anesthetic toxicity

Toxic blood levels of the drug may be due to :

1 . Repeated injections .

2 . or from a single IV injection ,

CNS toxicity : An early symptom of local anesthetic toxicity is circumoral and tongue numbness and a metallic _ taste . At higher concentrations , nystagmus and muscular twitching occur , followed by tonic - clonic convulsions .

- **Cardiotoxicity :** The most complications associated with local anesthetic administration result from the effects these agents on conduction and function . Use of bupivacaine and etidocaine had greater potential cardiotoxicity (Cinduce arrhythmias) and cardiac arrest could occur concurrently or immediately following seizures and , most importantly , in the absence of hypoxia or acidosis .

Treatment for systemic local anesthetic toxicity includes :

1 . Airway management and support of breathing and circulation ,

2 . Seizure suppression ,

.3- If needed , cardiopulmonary resuscitation ,

4 . Administering a 20 - percent lipid emulsion infusion (lipid rescue therapy) is a promising in treating local anesthetic toxicity

Antimicrobial drugs

Edition by
Dr.Firas Alaasam
M.Sc. Pharmacology & Toxicology

L .N (12)

Antimicrobial drugs

Antimicrobial drugs are effective in the treatment of infections because of their ability injure or kill an invading microorganism without harming the cells of the host , Selection of antimicrobial agent requires Knowing :

1)Organism ' s identity ,

2) Organism ' s susceptibility to agent .

3) Site of the infection ,

4) Safety of the agent

5) Patient factors ,

6) Cost of therapy

Antibiotics: Substances produced by some microorganisms and their synthetic analogues that selectively kill or inhibit the growth of another microorganisms

Antimicrobial drugs are classified as either :

1 . Bactericidal (kill bacteria) .(Destroying of bacterial cells)

2 . Bacteriostatic (arrest the growth and replication of bacteria) .

Chemotherapeutic spectra

1 . Narrow - spectrum antibiotics : act only on a single or a limited group of microorganisms like isoniazid which is active only against mycobatria.

2- Extended - spectrum antibiotics : are effective against gram - positive and some gram - negative bacteria like ampicillin ,

3 . Broad - spectrum antibiotics : such as tetracycline and chloramphenicol affect a wide variety of microbial species , Administration of broad spectrum antibiotics can alter the nature of the normal bacterial flora and precipitate a super infection of an organism .

Drug resistance

Bacteria are said to be resistant to an antibiotic if the maximal level of that antibiotic that can be tolerated by the host does not stop their growth

. Sites antibacterial actions

Antimicrobial drugs can be classified according to their :

1 . Chemical structure , for example β-lactams or aminoglycosides

2 . Mechanism of action for example cell wall synthesis inhibitors

. 3- Activity against particular types of organisms for example, bacteria ,fungi, or viruses.

Cell wall inhibitors

The B-lactam, pencillins and vancomycin antibiotics interfere with synthesis of the bacterial cell wall (bacteriçidal)

A)Penicillins:

Penicillins are susceptible to inactivation by B-lactamases (penicillinases)

1. Amoxicillin and ampicillin: are more effective against gram-negative bacilli. Therefore, they are referred to as extended-spectrum penicillins. Resistance to these antibiotics is now a major problem because of inactivation by penicillinases .formulation with a B lactamase inhibitor clavulanic acid or sulbactam, protects amoxicillin or ampicillin from hydrolysis and extends their antimicrobial spectrum

2. Dicloxacillin, cloxacillin, Nafcillin, Oxacillin:

Are penicillinase- resistant penicillins and their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci

3. Penicillin G: only as injection because of its poor absorption.

4. Penicillin V: is more acid stable than pencillin G and is used orally.

5. Piperacillin, carbenicillin: are called antipseudomonal penicillins

6. Depot forms: They are administered IM and slowly absorbed into circulation and persist at low levels over a long time, like procaine penicillin G (12 hrs) and benzathine penicillin G(I month)

Adverse effects: Hypersensitivity, Diarrhea, Neurotoxicity, Nephritis.

B) Cephalosporins

Cephalosporins have been classified into four generations, based largely on their bacterial susceptibility patterns and resistance to B-lactamases.

1. **First generation:** Cefazolin, Cefadroxil and Cephalexin are resistant the staphylococcal penicillinase

2. **Second generation:** cefotetan and cefoxitin and_ Cefuróxime display. greater activity against gram-negative organisms.

3. **Third generation:** Ceftriaxone and cefotaxime are available. injection and become agents of choice in the treatment of meningitis Cefdinir and Cefixime are administered orally once daily

4. **Fourth generation**: Cefepime is áctive against Pseudomonas aeruginosa and must be administered parenterally

Other B-Lactam antibiotics

Carbapenems: meropenem, imipenem, doripenem and ertapenem are the drugs of this group. Imipenem resists hydrolysis by most against B- lactamase-producing gram-positive and gram-negative organisms, anaerobes, and P. aeruginosa.

Vancomycin: It is a trcycire glycopeptide, effectiveness against multiple drug resistant organism

Protein Synthesis Inhibitors

They inhibit bacterial protein synthesis by binding interfering with ribosomes. Most are bacteriostatic, but a few are bactericidal against certain organisms

A)Tetracyclines:

include tetracycline, doxycycline, and demeclocycline, Politetracycline

1. Tetracycline HCl: available as suspension or capsules given every 6 hours.

2. Doxycycline: requires less frequent administration because of its słow elimination from the body (once daily)

3. Politetracycline: is suitable for parenteral administration.

Adverse eftects: Gastric upset, hepatotoxicity, phototoxicity, discoloration,hypoplasia of the teeth and a temporary stopping of the o growth

Contraindications: contraindicated pregnant or breast-feeding women, children below 8 years patient with renal impairment.

B) Aminoglycosides:

Include streptomýcin, gentamycin, tobramycin, amikacin, spectinomycin and neomycin which are: bactericidal antibiotics used to treat serious infections caused by gram - ve bacilli and some gram + ve organisms. They are available injection except neomycin which is given orally

Adverse effects: ototoxicity nephrotoxicity neuromuscular paralysis

C)Macrolides

They include erythromycin, azithromycin and clarithromycin Erythromycin may be use in patients who are allergic to the penicillins. Clarithromycin and azithromycin are seemed to be better tolerated by the patient and given as a single dose.

Adverse effects: Epigasrtic distress, cholestatic jaundice, ototoxicity ,nephrotoxicity and contraindications in patients with hepatic dysfunction

D)Chloramphenicol

Because of its adverse effects, the use of chloramphenicol is limited life-threatening infections such as typhoid.

Adverse effects: reversible anemia which is dose-related and aplastic anemia which usually fatal and dose-independent but is rare.

E)Lincoomycin

It effective against certain gram positive organisms and has been replaced by clindamycin which produces excellent results in treatment of anaerobic infections. Severe pseudomembraneous colitis has occurred in some patients which limit the usefulness of lincomycin

Fluoroquinolones (DNA gyrase inhibitors)

Quinolones block bacterial DNA synthesis by inhibiting bacterial DNA gyrase and prevents the normal transcription and replication. They include four generatins:

1t generation: Naladixic acid which is restricted for uncomplicated UTIs.

2nd generation: Norfloxacin and ciprofloxacin which has had wide clinical applications especially for UTIs and typhoid.

3rd generation: Levofioxacin because of its broad spectrum of activity, it is utilized for skin infections, acute sinusitis, UTIs, chronic bronchitis, and pneumonia.

4th generation: Moxifloxacin has an enhanced activity against gram- positive organisms (S. pneumoniae) and excellent activity against many anaerobes but it does not concentrate in urine and is not indicated for the treatment of UTIs

Adverse, effects:

nausea, vomiting, and diarrhea, CNS problems, phototoxicity, Fluoroquinolones should be avoided in pregnancy, in nursing mothers, and in children under 18 years of age, because articular cartilage erosion (arthropathy) .

Inhibitors of folate synthesis

Sulfonamides

In many microorganisms, dihydrofolic acid is synthesized from p- aminobenzoic acid (PABA), pteridine, and glutamate. All the sulfonamides are synthetic analogs of PABA. Because of their structural similarity to PABA, the sulfonamides compete with this substrate for the bacterial enzyme, dihydropteroate synthetase. They thus inhibit the synthesis of bacterial dihydrofolic acid and, thereby, the formation of its essential cofactor forms. The sulfa drugs are bacteriostatic and include sulfamethoxazole, Sulfisoxazole and cotrimoxazole.

Adverse effects:

crystalluria, hemolytic anemia is encountered in patients with glucose 6-phosphate dehydrogenase deficiency and kernicterus in newborns

Trimethoprim

is a potent inhibitor of bacterial dihydrofolate reductase and exhibits an antibacterial spectrum similar to that of the sulfonamides. The active form of folate is the tetrahydro-derivative that through reduction of dihydrofolic acid by dihydrofolate reductase. This enzyme is inhibited by trimethoprim, leading to a decreased availability of the tetrahydrofolate coenzymes required for purine, pyrimidine, and amino acid synthesis.

Trimethoprim is most often compounded with sulfamethoxazole producing the combination called cotrimoxazole

Trimethoprim+ sulfamethoxazolee → otrimoxazole


Thank you

Antifungal drugs

Edition by

Dr.Firas Alaasam

M.Sc. Pharmacology & Toxicology

L .N (13)

Antifungal drugs

Infectious diseases caused by fungi are called mycoses, and they are often chronic in nature. Some mycotic infections are superficial and some involve the skin (cutaneous, subcutaneous mycoses)

-Drugs for subcutaneous and systemic mycotic infections

1. Amphotericin B

It is a polyene macrolide antibiotic which is the drug of choice for the treatment of life-threatening systemic mycoses.

Mechanism of action:

bind to ergosterol in the plasma membranes of fungal cells and disrupt membrane function, allowing electrolytes and small molecules to leak from the cell, resulting in cell death.

Adverse effects: Fever and chills after I.V injection and renal impairment.

2. Flucytosine

It is used in combination with amphotericin B for the treatment of systemic mycoses and for meningitis caused by Candida albicans.
Adverse effects: bone marrow depression and hepatic dysfunction

3. Ketoconazole :

It is the first orally active azole available for the treatment of systemic mycoses. It has endocrine side effects and due to its teratogenic effect it should not be given during pregnancy

4. Fluconazole

It is a member of the triazole class of antifungal products. It is clinically important because of its lack of the endocrine side effects of ketoconazole and its excellent penetrability into the CSF. For the treatment of vaginal candidiasis, the dose is 150 mg as a single oral dose

Adverse effects: they are less than those with ketoconazole; nausea vomiting, and rashes. It is teratogenic and should not be used during pregnancy

5. Itraconazole :

is a synthetic triazole, and like fluconazole, it lacks the endocrine side effects of ketoconazole.

Adverse effects: rash, hypertension, edema, it should be avoided in pregnancy and patients with CHF

6. Voriconazole: is triazole, available for both IV and oral administration

7. Posaconazole:

is a new oral antifungal agent to prevent Candida albicans

Drugs for cutaneous and mycotic infections

Mold-like fungi that cause cutaneous skin infections are called dermatophytes or tinea that appears as rings or round red Patches.

A. Squalene epoxidase inhibitors

These agents act by inhibiting squalene epoxidase, resulting in the blocking of the biosynthesis of ergosterol of fungal cell membrane

1. Terbinafine: Oral terbinafine is the drug of choice for treating dermatophytoses and onychomycoses (fungal infections of nails). It is better tolerated, requires short duration of therapy and is more effective than either itraconazole or griseofulvin.

Adverse effects: GIT upset, rash, taste and visual disturbances.

2. Naftifine:

Naftifine 1 % cream and gel is used for topical treatment of tinea .

3. Butenafine: for topical treatment of tinea.

B. Griseofulvin :

Griseofulvin has been largely replaced by oral terbinafine for the treatment of dermatophytic infections of the nails. Griseofulvin requircs treatment of 6-12 months in duration.

C. Nystatin :

Nystatin use is restricted to topical treatment of Candida infections. The drug is not absorbed well from the GIT and it is administered as an oral agent (swish and swallow) for the topical treatment of oral candidiasis.

D. Imidazoles :

Imidazoles include butoconazole, clotrimazole, econazole, ketoconazole, miconazole, sertaconazole and sulconazole. miconazole is a potent inhibitor of warfarin metabolism and has produced bleeding in warfarin- treated patients even when applied locally.

E. Ciclopirox olerated:

Ciclopirox disrupts the synthesis of DNA, RNA, and protein. It is used for treatment of seborrheic dermatitis, onychomycosis and dermatomycosis, candidiasis, and tinea.

F. Tolnaftate :

Tolnaftate is not effective against Candida but it is used to treat tinea. It is available as a 1 % solution , cream , and powder


Thank you