Drugs work on sympathetic Nervous System

Sympathomimetics

- Drugs Produce action similar to sympathetic nervous system
- Are devicded into
  - Catecholamine
  - Non Chatacholamine

and that's according to
- The Chemistry
- The mechanism of action

- Works on α_1 α_2 β_1 β_2 β_3 receptors
- Are called Adrenergic Drugs

Sympatholytic

Drugs produce action to block the sympathetic nervous system

- Blockers of
  - α receptors
  - β receptors
  - Ganglia
  - neuron
- work as Anti adrenergic Drugs centrally

- Are called Anti Adrenergic Drugs

Sympatholytic Drugs

Review

Drugs produce action to block the sympathetic nervous system

- Blockers of: α receptors, β receptors, Ganglia, neuron
- work as Anti adrenergic Drugs centrally
- Are called Anti Adrenergic Drugs

First: Centrally Acting α_2 Agonist:

if stimulate central α_2 adreno receptors

↓

if reduce the sympathetic outflow from the CNS

- Decrease the heart rate → reduction of cardiac output
- reduce the vasoconstriction → reduction of Peripheral vasoconstriction

→ Reduce The Blood Pressure

Drugs work on that mechanism:

Clonidine — used in cases of Hypertension

Second: Ganglion Blocker

Drugs work on that method: Trimethaphan IV infusion

Third: Adrenergic neuron blocker

Drugs work on that method: Reserpine, Guanethidine

Fourth: Adrenergic Receptors Blockers

- Alpha adrenergic Blockers
- Beta adrenergic Blocker

Totally the opposite of adrenergic receptors

Receptor	Location	G Protein	Second Messenger	Major Functions
α_1	Effector tissues: smooth muscle, glands	G_q	↑ IP_3, DAG	↑ Ca^{2+}, causes contraction, secretion
α_2	Nerve endings, some smooth muscle	G_i	↓ cAMP	↓ Transmitter release, causes contraction
β_1	Cardiac muscle, juxtaglomerular apparatus	G_s	↑ cAMP	↑ Heart rate, ↑ force; ↑ renin release
β_2	Smooth muscle, cardiac muscle	G_s	↑ cAMP	Relax smooth muscle; ↑ glycogenolysis; ↑ heart rate, force
β_3	Adipose cells	G_s	↑ cAMP	↑ Lipolysis

Alpha Adrenergic Blockers

- Selective α_1 blocker
  - Prazocin
  - Tamsulosin
- Non Selective α blocker
  - Phenoxybenzamine
  - Phentolamine
  - Tolazoline
- Selective α_2 blocker
  - Yohambine

Work on Gq Protein receptors : Inhibit Phospholipase C
- ↓ IP_3 , DAG
- ↓ Intracellular Ca+

Prazocin

Action	Therapeutic uses	Side effect
→ VD of veins (↓ venous return	→ Hypertension	→ orthostatic Hypotension [1st dose]
→ VD of arteries [↓ TPR & Congestion]	→ Benign Prostatic Hyperthrophy (BPH)	→ Dry mouth, GIT upset ✓ [gastrointestinal disease]
→ relax the sphincter of UB	→ Peripheral Vascular Diseases (PVD)	→ Headache & drowsiness
→ no reflex Tachycardia	→ Heart failure	→ Oedema
		→ rash & Pruritis

Tamsulosin

Selective α_1 Blocker in certain tissue

used in treatment of : Benign prostatic Hypotrophy (BPH)

Beta Adrenergic Blockers

- Selectivity
  - non selectiv :
  - Cardio selective :
  - Block α & β receptor
- Generation :
  - 1st generation
  - 2nd generation
  - 3rd generation
- ISA
  - no ISA
  - have ISA

Intrinsic Sympathetic Activity

① Selectivity : The more selective, the less side effects

- non selectiv : Block β_1, β_2
- Cardio selective : Block β_1
- Block α & β receptor labetalol

② Generation :

1st generation : non selective β blocker

2nd generation : Cardio selective β_1 blocker

3rd generation : VD β blocker, have either.

- β_2 agonistic activity : Celiprolol - Dilevalol
- direct VD and α blocking effect : Carvedilol

③ ISA : Intrinsic Sympathetic Activity

✓ ISA [Partial agonist] : oXprelol - Acebutolol - Pindolol - Practolol

x ISA [Antagonist] : Propranolol - Timolol - Atenolol - Metoprolol

They act as antagonist, but when the dose increases they act as agonist.

Non selective Beta blockers: Propranolol - Pindolol - Nadolol - Timolol

Propranolol: The Godfather

- non selective Beta blocks [B_1 & B_2]
- no ISA

Kinetics:

- well absorped orally [highly lipophilic].
- extensivly metabolized in the liver.
- (90-95)% bound to PP
- metabolites excreted in the urine

Action on:

CNS → ↓ sympathetic flow ↓ adrenaline release → anti anxiety
as ↑ adrenaline lead case anxiety

RS → Bronchoconstriction

Metabolism → Prevent glycogenolysis → hypoglycemia

Eye → Timolol ↓ IOP due to ↓ aqueos humour synthesis
has no effect on Pupil size

Increas K release [hyperKalemia]

CVS

Heart → -ve inotropic, -ve dromotropic,
-ve Chronotropic [↓ C.O.P + ↓ Cardiac work + ↓ O_2 consumption]

BL.V → ↓ blood flow to tissue

Blood Pressure ↓ BP, through:
- ↓ C.O.P
- Inhibition of renin release
- resetting of baroreceptor
- Presynaptic B_2 Blockade decreases NE release
- central inhibition of sympathetic flow
- modulation of Prostaglandin synthesis in favore of the vasodilator ones eg Prostacyclin

Cardio Selective Beta blockers (B_1)

- Atenolol
- Acebutolol
- Esmolol
- Bisoprolol
- Metoprolol

Therapeutic Uses

1. Hypertension
2. IHD: Angina - MI : → Decreas oxygen demand by decreasing Cardiac work
3. Portal hypertension
4. Glucoma
5. Hyperthyroidism
6. Anxiety and essential tremors
7. Prophylaxis in migrain headache
8. Pheochromocytoma with alpha blockers
9. ventricular and supra ventricular arrhythmias

→ Increas oxygen supply by:
- increasing diastolic coronary Perfusion time
- Shifting Subepicardial blood flow to subendocardial flow
- Inhibition of Platelet aggregation

The Side effect:

- bronchoconstriction.
- arrhythmia.
- Sexual impairment.
- Fatigue - dizzyness - vivid dreams - nightmers.
- Cold hand and allergic reactions.
- Prolonged hypoglycemia, and mask the hypoglycemic symptoms.
- increas VLDL, Triglyceride, and low HDL
- Oculo - muco - Cutaneous syndrome with Practolol

Precautions & Contraindications

- bronchial asthma
- Partial heart block and A.V block
- Varient angina
- Peripheral vascular disease
- Used with cautions in DM
- Cannot be stoped suddenly as abrupt discontinution increas the risk of IHD upregulation of B receptor

Drugs work on parasympathetic nervous system

Parasympathomimetics [Cholinomimetics]

- Drugs that facilitate or mimic some or all the action of parasympathetic nervous system
- They are drugs work on cholinergic receptors
  - Muscarinic receptors
  - Nicotinic receptors

Parasympatholytic [Anticholinergic]

- Drugs that inhibit or reduce some or all the action of parasympathetic nervous system
- Drugs that works on cholinergic receptors
  - Muscarinic receptors antagonist
  - Nicotinic receptors antagonist
    - ganglionic blocking drugs (Nn)
    - neuromuscular blocking drugs (Nm)

Parasympathomimetic Drugs

Ach : Acetyl choline

Review

Drugs that facilitate or mimic some or all
→ the action of Parasympathetic nervous system [PNS]

also cholinergic drugs
→ They are drugs work on Cholinergic
receptors → Muscarinic receptors
→ Nicotinic receptors

Cholinergic receptors are receptors that respond to Acetyl Choline and it analogues [nicotine]

Cholinergic Receptors

Muscarinic Receptors

→ They respond to Ach
→ Found in the Surface of the effector cells
[heart - Endothelium of the bloodvessles - Smooth muscles - presynaptic nerve terminals - Exocrine gland]

→ The muscarine receptors have several subtypes
M1 M2 M3 M4 M5

blocked by Atropine

Nicotinic Receptors

→ The respond to nicotine
→ They are found in [CNS adrenal medulla - autonomic ganglia - Skeletal muscles

→ The nicotinic receptor has 2 subtyps
- Nm : found in motor end plate skeletal muscle
  blocked by Curare
- Nn : found in autonomic ganglia and adrenal medulla
  blocked by ganglion blockers

Receptor type	Molecular transduction mechanism
M1 & M3 & M5	Increas ↑ [inositol triphosphat IP3 and Diacylglycerol DAG]
M2 & M4	Decreases ↓ [cAMP]
Nn nicotinic muscular	Increas intracellular Sodium [depolarization]
Nm Nicotinic nueral	Increas intracellular Sodium [depolarization]

block the action

Mechanism of action of Muscarine Receptors

① GProtein coupling of [M1-M3] to PhosPholipase C
→ Release of second messenger [IP3 and DAG]
- IP3 → evokes the release of (Ca^{+}) from Intercellular site . resulting the contraction of muscles
- DAG → modulate the action of protein kinase [important is Secretion]

② Coupling of M_2 to adenyle Cyclase, through the inhabition of G Protein

③ Coupling of muscarine receptor directly to Potassium Channels in the heart and elsewher
muscarine agonist facilitate opening of these channels

What is the action of Parasympathomimetic Drugs?

Reminder found in lec 15

	Sympathetic action	Parasympathetic action
CVS Heart	Increase all cardiac properities	Decrease all cardiac properities except atrial conduction
Blood vessels	VC of skin and mm VD of skeletal and coronary blood vessels	Non innervated
Blood pressure	Hypertension	Hypotension
SMF Eye	Active mydriasis	Miosis
Bronchi	Bronchodilatation	Bronchocnstriction
GIT	Inhibit motility of wall Contract sphincter	Contract wall Relax sphincter
Urinary tract	Inhibit motility of wall Contract sphincter	Contract wall Relax sphincter
Sex organ	Ejaculation in males Relax uterine wall in female	Erection in male
Exocrine glands Salivary glands	Thick viscid secretion	Profuse watery secretion
Sweet glands	Increase	No effect

CVS
1. decrees ↓ the heart rate and cardiac output
2. decrees ↓ blood Pressure : as it cacs vasodilation. by indirect mechanism of action
   * as acetyl choline Activate M3 receptors found in endothelium smooth muscle in blood vessle. This result in the production of Nitric Oxide, which diffuses to vascular smooth muscle cells to Stimulate Protein Kinase G Production, leading to hyperpolarization and smooth muscle relaxation.

Eyes → Stimulating Ciliary muscle contraction for near vision.
- → Constriction of Papillac Sphicter muscle Causing miosis [marked muscle contraction of Pupil
- → Stimulate tears
- → Reduction of IntraOcular Pressure IOP ↓

Bronchi → Bronchoconstriction

GIT → Increas Saliveg Secretion and Stimulate intestinal secretion motality

Genitourinary tract → increase the tone causig expulsion of the urine

Cholinergic agent adverse effect:

- → Bradycardia & Hypotension
- → miosis - lacrimation - Salivation - Sweating
- → urgency and spontaneous micturition
- → Bronchospasm and ↑ bronchial secretion.
- → Colic - vomiting - diarrhea - hyperacidity & Peptic ulcer

General Contraindication of Parasympathomimetics:

- → Brady cardia - heart failure - Heart block
- → Bronchial asthma
- → Parkinson
- → Peptic ulcer
- → mechanical obstruction of GIT and urinary bladder

Action related to Stimulation nicotinic receptors:

Nm: Skeletal muscle twitches

Nn : in Autonomic ganglia and adrenal gland so increase E and NE [adrenaline and noradrenaline]. so hypertension in atropinized dogs.

"Parasympathomimetic"
"Cholinomimetic"

according to the mechanism

Direct Acting

- Muscarinic receptor agonist
- Nicotinic receptor agonist

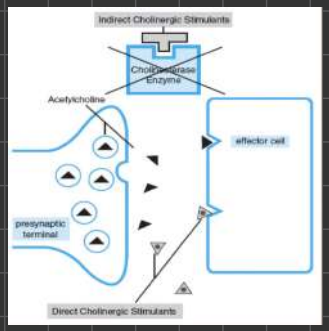
→ cholines esters - Alkaloid
→ Stimulate muscarinic receptor directly

Indirect Acting

Anti Cholinesterase

- Reversible
- Irreversible

→ They inhibit cholinesterase enzyme, leading to accumulation of endogenous Ach at both muscarinic and nicotinic receptors.



	Physiostigmine	Neostigmine
	Natural	Synthetic
	Tertiary amin (not charged, can pass the BBB)	Quaternary amine (charged, cannot pass BBB)
Dynamics	N: miosis on eye M: muscle twitch, no direct action CNS: Stimulation	N: GIT - urinary M: muscle twitch, direct Stimulation CNS: no
USES	→ Ht of alzheimer disease → Glaucoma → Counteract action of mydriatic → Alternative with mydriatic to → Cut recent adhesion iris & lens	→ Myasthenia gravies → Antidot to Curare toxicity → Paralytic ileus → Post-operative urine retention

	Acetylcholin	methacholine	Bethanicol	Carbachol
nicotinic	+	−	−	+
muscarinic	+	+	+	+

N.B: never given IV or IM
Ach never given oral

	Reversible	Irreversible
binding to enzyme	loose	firm
enzyme activity	can be regained	can not
Action duration	Short	long
	Physiostigmine neostigmine Edrophonium	organo phosphorus compound Echothiopate (anti glaucoma) Malathion - Parathion (antiscabs) Metriphonate (anti helminthic)

Irreversible Anticholine Esterase:

Organo Phosphorus compound:

→ synthetic compound.
→ Have the capacity to bind covalently to Acetylcholin esterase.
→ The result is long lasting increas acetylcholine at all site where it is released.
→ Many of these drugs are toxic: ?

- Bradycardia & hypotension
- Constricted Pupill (Miosis)
- Tightness in the chest with dyspnea
- nausea - vomiting - abdominal colic - diarrhea
- Increas in Salivation and sweating.
- muscle twitch
- convulsion

→ Management of organophosphorus poisoning:
- endotracheal intubation with artificial respiration
- Atropine [2mg IV] until the Signes of atrophinization appear [dry mouth - dilated Pupill - Tachycardia].
- Barbiturate to check convulsion.
- fresh blood transfusion.

- Oximes [PAM & Praxolmes]

The treatment with oximes should be within hours [2gm with 5% Dextrose IV drip]

Oximes Produce their effect through:
→ Direct reaction with inhibited enzymes.
→ Reactivation with inhibited enzyme.

NICOTIN AND SMOKING:

* Mechanism of action :
  - Stimulate sympathetic ganglia and adrenal medulla.
  - Releas catacholamines from nerve end and Chromaffin cells.

CVS → The cardiovescular effect of nicotine is due to increase releas of adrenaline from Suprarenal gland as a result of stimulation of nicotinic receptor in Suprarenal gland.

Tachycardia → Due to increas cardiac output
Increas excitability → extrasystole
Angina → Due to increas the cardiac work without coronary dilation
vasoconstriction of all blood vessles, leading to :
Hypertension, due to constriction of systemic arterioles

Retinal ischemia and scotomata [localized loss of vision due to constriction of retinal arterioles].
Peripheral ischemia due to peripheral vasscular disease.
Teratogenicity due to constriction of uterine blood vessles in pregnent women

free fatty acid : Platelet stickiness – atherosclerosis – Thromposis.

Uses : nicotine lozenges are used in treatment for addiction of cigarette smoking.

They maintain long standing minimal concentration of nicotine in plasma and prevent symptos of nicotine withdrawal

now replaced by Varenicline

Review :<

Parasympatholytic Drugs

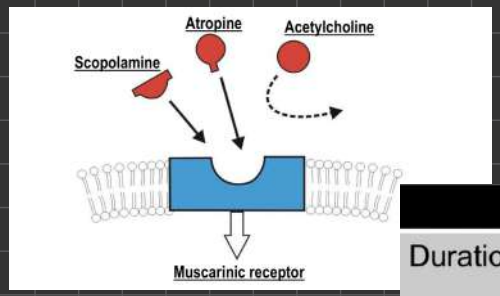
[Anticholinergic]

- Drugs that inhibit or reduce some or all the action of Parasympathetic nervous system
- Drugs that works on Cholinergic receptors
  - Muscarinic receptors antagonist
  - Nicotinic receptors antagonist
    - ganglionic Blocking Drugs (N_n)
    - neuromuscular Blocking Drugs (N_m)

As we know already that Atropine Scopolamine are muscarinic receptor blockers and Acetylcholine is Parasympathomimetic.

A competition of atropine and Scopolamine with acetylcholine for the muscarine receptor.

Atropine is competitive reversible antagonist at all types of muscarinic receptors.



Antimuscarinic Agents:

The block M receptors

Inhibition of all Parasympathetic functions

* in addition, The Antimuscarinic agent block few exceptional sympathetic neurons that are Cholinergic [Sweat glands]
* The Antimuscarinic agents, don't block N receptors so they have little or no action on neuromuscular junctions and autonomic ganglia

Anti Muscarinic Agent

- Natural
  - Atropine
  - Hyoscine AKA "Scopolamine"
- Synthetic Atropine Substitutes
  - bronchodilator
  - Antisecretory
  - Antispasmodic
  - Antiparkinsonism
  - Mydriatic

	Atropine	hyoscine
Duration of action	Long duration 7-10 days	Short duration 4-7 hours
Action :1-dominant PS action	CVS , GIT, Urinary	Eye and secretions
2- CNS	Both stimulant and depressant but mainly stimulant	Both stimulant and depressant but mainly depressant -sedation, hypnosis and --amnesia to recent events - Antimotion sickness -Antiparkinsonial
		Stimulant effect ++RC Excitation and hallucination with over dose
Local anesthetic action	Present	absent

first ATROPINE

→ Mechanism of action. is competitive antagonist to Ach at M1 M2 M3 receptors

Has Parasympathetic effect on:

CVS:

Heart: low dose → initial bradycardia
larger dose → the cardiac M2 receptor is blocked
then increas in the heart rate

Circulation: Therapeutic use - no effect due to lack of parasympathetic innervation to vasscular beds blood vessles.

Atropine: revers hypotensive effect of Ach - carbacol - neostymine (M-N) action

It abolish hypotensive effect of Methacholine Bethanecol - Pilocarbine (M) action only.

SMF

Eye →
- Passive mydriasis
- cycloplegia [inability to Focus for near vision].
- ↑ IOP & loss of light reflex & ↓ lacrimation

Bronchioles → Bronchodilation & ↓ bronchial secretion

GIT → used as antispasmodic to reduce the activity of GIT. ↓ gastric motality
HCl is not produced → not very effective in healing of Peptic ulcer

Pirenzepine is M1 muscarinic antagonist, is effective in reducing gastric acid secretion

Urinary System:

reduce hypermotality stole in the urinary bladder occasionally in enuress in children

Emepronium is better than Atropine

Secretion inhibit all body secretion
[bronchial - saliva - lacrimal - sweat]
↳ drying effect on membrane [xerotsomia]
* Except in [Milk - Bile - Urine] secretion.

CNS Stimulant 2/3 and Depressant

Stimulant:
→ Therapeutic dose stimulat C.I.C leading to initial bradycardia if it is given IV

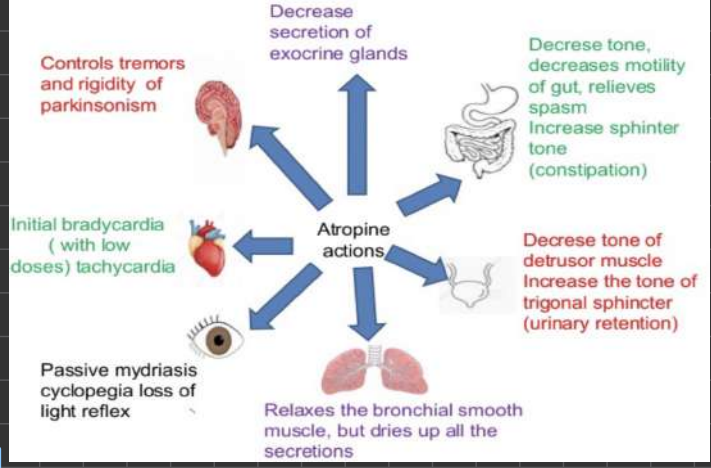
→ large dose Stimulate R.S leading to tachypnea

→ Toxic doses causes: restlessness - hallucination delirium followed by depression and coma.

Depression:
→ Muscle tone [Parkinsonian effect = treatment of rigidity and tremor in Parkinsonism]

→ vomitting center [antiemetic effect]

→ it has local Anesthetic effect.



Therapeutic uses:

→ Preanesthetic medication:
* Counteract excess in vagal tone during operations.
* ↓ salivary secretion [Prevent bronchopneumonia.
* ↓ bronchial secretion [Prevent lung collaps].

→ Treatment of physiostigmine and organophosphory toxicity.

→ Parasympatholytic (Systems):

CVS: heart block due to [infraction and digitalis toxicity] sever bradycardia.

Eye: Fundus examination [derivatives is better] due to long duration of action.

Respiration: bronchial asthma [Ipratropium is better]

GIT: Intestinal colic - antidiarrhea - antiemetic - Peptic ulcer

Urinary: renal colic - nocturnal enuresis [Emepronium is better]

Secretion: hyperhydrosis [excess sweating]

CNS: anti Parkinsonal

Side effect of Atropine:

- Dryness of the mouth, blurred vision, Sinus tachycardia
- retention of urine especially in old Patient with enlarged Prostate.
- Acute glaucoma: old Patient are more susceptible
- Increase temperature in Children.

Contraindication of Atropine

- Tachycardia or arrhythmia.
- Glaucoma.
- Constipation or Paralytic ileus.
- Senile enlargment of prostate.

Acute Atropine Poisoning:

- ParaSympathetic depressant symptoms:

  Dry mouth - Tachycardia - Mydriasis loss of accommodation - decrease sweating [fever]

- Skin: hot - Dry - flushed [compensatory superficial Cutaneous vasodilation to Increas heat loss]

- CNS: restless - excitment - hallucination - mania - delirium - depression - death.

Treatment of Atropine Poisoning

- Gastric lavage orally - Artificial respiration - Ice bages - Alcohol ⇒ Decrease fever

- ParaSympathomimetics [neostigmine, is specific anti dot]. & Sedative.

Hyoscine [scopolamine]

- Premedication medication preferred to atropine bcu2 it produce more CNS depression.
  it is Potent amnesic, Stronger antisecretory and antiemetic

- Anti spasmodic
- Prophylaxis for motion sickness
- Sedative in mania
- Antiparkinsonian agent.

	Atropine	hyoscine
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		Stimulant effect ++RC Excitation and hallucination with over dose
Local anesthetic action	Present	absent

Main clinical use of muscarinic antagonist

CVS: treatment of Sinus bradycardia [after MI: Atropine

ophthalmic: to dilate the Pupil: tropicamid eye drop or cyclopentolate eye drop (longer acting)

neurological: prevention of motion sickness. hyoscine orally or Transdermally.
Parkinsonism especially to Conteract movement disorder caused by antipsychotic drugs benztropine

Respiratory: asthma Ipratopium by inhalation.

Anasthetic premedication: To dry secretion: e.g Atropine - Hyoscine
[However, current anasthetics relativly non-irritant less important]

GIT: to facilitate endoscopy and gastrointestinal radiology by relaxation of GI smooth muscle
Antispasmodic action Hyoscine

as antispasmodic irritable bowel syndrome or Colonic diverticular disease

To treat peptic ulcer disease by suppressing gastric acid secretion Pirenzepine
[M1 selective antagonist] now less used

Introduction of Histamine H_2 antagonist and Proton Pump Inhibitors.

Eicosanoids

Eicosa [GreeK] = 20

→ They are compound that are derived form Polyunsaturated fatty acid with 18 & 20 & 22 carbon skeleton.
That needs receptors either plasma membrane or binding protein.

Eicosanoids
- Prostaglandins PGs
- Prostacyclins PGI_2
- Thromboxanes TX
- Leukotrienes LT
- Lipoxins LX

Fatty acids
- Unsaturated
  - Monounsaturated
  - Poly unsaturated
    - Arachidonic acid 4 double bond
    - linolenic acid 3 double bonds
    - linoleic acid 2 double bonds
- Saturated

Stimuli [ligand: Physiological or Pathological]

Arachidonic acid esterified in membrane Phospholipid

Corticosteroid (Annexin A1) [cortisol] — Phospholipase A_2

Arachidonic Acid

LOX — Zileuton
- leukotriens (LT)
  - montelukast
  - zafirlukast

COX1 inducible, COX2 — Aspirin irreversible block; NSAID reversible block (Indomethacin, Phenylbutazon)
- Prostanoids:
  - Prostaglandin PG
  - Prostacyclin PGI_2
  - Thromboxane TXA_2

Prostaglandis are more produce in time of: Fever - Pain - nausea and vomiting - Inflammation

[PGE_1 - PGE_2 - PGI_2]:

Biological effect:

VD [Physiologically].

Lung → Bronchodilation
GIT → ++ mucus production

Uterine → Contraction of Pregnant uterus (in labor); relaxation of non Pregnt uterus

Kidney → ++ Renal Blood flow [RBF]. Promot urine formation, and urine out Put help removing waste out of the body.

PGI_2: Platelet aggregation [no thrombosis]

$PF_{2\alpha}$ - TXA_2 - LTB_4:
- → VC - [LTs Produce inflamm VD]
- → lung: broncho spasm [severe]
- → GIT: -- mucus production
- → Uterine: contraction of pregnant uterus (in labor)
- → Kidney: -- RBF. Promot urine formation and urine out Put [may cause renal failure]

TXA_2: Platelet aggregation

LT_s: Chemotaxis

USES: PGE_1:
- to Produce controlled hypotension
- intracavernous in cases of impotence [erectile dysfunction]
- Used as vasodilator in Peripheral vascular diseases [α blockers]
- TGV: Transposition of Great vessels [switch between Pulmonary and Aorta]
- MisoProstol [Cytotec] PGE_1 analogue used orally in Peptic ulcer

Epoprostenol [PGI_2] anti platelet aggregation

PGE_2. 1. used in bronchial antispasm but its irritant
2. used in organ transplantation to revers rejection

PGE_2 & $PGF_{2\alpha}$: for induction of abortion and labor

$PGF_{2\alpha}$: [latanoprost] used topically in treatment of Glaucoma

PG_3: ++ Renal Blood flow [RBF]. Promot urine formation, and urine out Put. help removing waste out of the body.

Prostacyclins [PGI_2]

- Are type of eicosanoids / Prostaglandins
- Principlly found in vascular endothelium
- They prevent platelet aggregation [inhibitor factors]
- Biosynthesized by enzyme: Prostacyclin synthase

The role of [PGI_2]

- They are vasodilator
- They inhibit platelet aggregation
- They prevent thrombus / clot formation

Thrompoxane

- They are produced by Thrompocytes (Platelet)
- They act on formation of blood clot (platelet aggregation)
- Reduction of blood flow to the site of blood clot by vasoconstriction ↑
- They increase lymphocyte Proliferation
- They increase bronchoconstriction

LiPoXins

Doctor said if you want to know it only.

- are Eicosanoid, Produced in leukocytes in human body.
- are essential in maintaining tissue homeostasis and resolve inflammation

LiPoxins are:

- Vasoactive / vasodilator
- Anti inflammatory
- Anti proliferative
- Pro-resolving
- Immunoregulatory
- Chemotactic substance

Leukotriens (LT)

[LTB_4 - LTC_4 - LTD_4 - LTE_4]

mechanism of action

Kinin act by Stimulation 2 types of G_q coupled receptors, that increases intracellular [Ca^{++}], through increasing IP3 and DAG

Effect of Leukotrienes:

- LT are biologicly active compont of Slow reacting substances [SRS-R], Causes fluid leakage form blood vessels to inflammed area.
- LT are 100 - 1000 more potent than histamine in allergic reactions. [SRS-A] are released during Allergic / Anaphylactic Shock.
- LTB_4 is Potent chemotactic agent: chemical substance which mediate movement of cells.
- Leukotriens action:
  - Bronchoconstriction
  - Vasoconstriction
- The levels of LT is increased in:
  - Allergies
  - Allergic rhinitis
  - Asthma
  - over production of LT is in Anaphylactic shock
- Drug affecting: an anti asthmatic drug. Prednisone inhibits LT biosynthesis.

Montilucast - Zafirlucast: block receptors

Zileuton: inhibits lipooxygenase enzymes

Role of Drug:

Glucocorticoids administration → induce production of lipocrotin & Macrocrotin → Inhibit the activity of Phospholipase A_2 → Decrees the synthesis of leukotriens & Prostaglanding → Decreases inflammatory respons

Pharmcolijic pplications on Eicosanoids

Cardiovascular: Pulmonary arterial hypertension - Peripheral vascular disease, for keeping the ductus arteriosus open until surgery in neonate correcting certain cardiac malformation and Platelet anti aggregation agent

Digestive: indicates in the treatment of gastric duodenal ulcer and for the prevention of NSAID - induced ulcer.

Gynecology & Abstrical: They induce cervical dilatation and uterine contraction, Particularly in late Pregnancy used for medical termination of Pregnancy and Induction of labor

Aphthalmologic: ↓ IOP (lowering)

Anti Inflammatory: Inhibitors of cyclooxygenase that have anti inflammatory properties including non steroidal anti inflammatory drug "NSAID"

- The useful effect of therapeutic use are:
  - Anti inflammatory effect
  - Anti Pyretic effect
  - Analgesic effect

Inhibition of Platelet aggregation and decrees thromboembolic risk [well known with aspirin with low dose]