β-ADRENERGIC BLOCKING AGENT

- All are competitive Antagonist
- NOT induce postural Hypoten.
- There is NO clinically useful β_2-ag antagonist

PROPRANOLOL: A NON-SELECTIVE β-Anta

- Prototype
- Block both β_1 & β_2 equally
- High First-pass metabo.
- Sust. release prep — once daily avail.

ACTIONS

CV-Sys
- -ve ionotropic
- -ve chronotropic
- ↓se SA, AV activity
- CO↓, workload↓, O₂ consumption↓ ↓HR (These effects are useful in angina)
- ↓ SV-arrhythmias (supraventricular) But generally NOT effective for ventricular arrhyth. (except for those induced by exercise)

Peripheral vaso-cons.
- vasoconstr. ↑PVR [Due to β_2-block vasodilatory effect]
- ↓CO = ↓B.P (β_1) ⇩ Reflex vasoconstric ⇩ leads to ↓B.F (Blood Flow) to periphery
- In HT pt. The PVR ↓ or normal ē longterm use and resulting systolic & diaB.P↓

Broncho-Cons.
- (β_2) Cause exacerbation of COPD or Asthma
- Non-selective β-blockers are contraind. (CI)

Gluco. metabo.
- ↓ Hypoglyamia causes
- Insulin + β-blocker = Caution & monitoring or dose red. is required to avoid pronounced Hypoglycemia.

Blockade of action of Isoproterenol.
- Block effect of isoproter. & epineph (β-action but NOT α-action).

THERAPEUTIC ACTIONS/USES

Hypertension
- lower BP by diff. mechanisms
- ↓CO = Primary effect
- ↓ renin, ↓PVR ē prolong use, ↓symp. outflow from CNS = ↓B.P.
- use in HT pt ē: Tachyarrhythmias, MI, Angina, Chronic HF

Angina pectoris
- ↓O₂ requirement
- ↓ chest pain on exertion
- Chronic mang. of Stable angina.

MI
- After HA — Prophylactic use ↓ 2nd Heart Attack
- ↓ infarct size
- Hasten recovery
- ↓ incidence of sudden arrhythmic death after MI (↓mortality)

Migraine
- effective prophylactically — Lipophilic Nature → Penetrate CNS
- For acute mang — Serotonin agonists (SUMATRIPTA) are also used

Hyperthyroidis.
- ↓ sympathetic stimulation that occur in Hyperthyroi
- In thyroid storm (acute form) ↓ propra. is life-saving!
- HT due to Hypertropic cardiomyopathy
- again arrhythmias

KINETICS:- 25% bioavail, Vd = 4L/kg, cross-BBB, excreted via urine.

Interaction: inhibitors of metab. (Cimetidine, Paroxetine, Fluoxetine, Ritonavir (Protease inhib. PI)) (CPR); inducer of metab. (Barbiturate, Phenytoin, & rifampin (BPR))

ADRs:-
- Bronchoconstriction
- Arrhythmias
- Sexual impairment
- Hypoglycemia
- β_2 & β_3 { ↑LDL (Bad cholesterol), ↓HDL, ↑TG
- Selective β_1 → metoprolol → NO effect on lipids
- must be tapered off over few weeks
- causes up-regulation of receptors → on suspension → worsen angina or HT
- CNS effects: depression, dizziness, lethargy, visual distu., short-Term memory loss, Nightmares.
- Atenolol → Can't cross BBB → No effect CNS

AA BB ME-Nebi Acebut - [olol]

ATENO-BISO-ESMO-meto-Nebiv, Betaxo

- Selective β_1-antagonist
- 50-100 fold less dose req. to block β_1 than β_2
- Cardioselectivity more pronounced at low doses, and lost at high doses.

ACTIONS:- Lower BP & ↑se exercise tolerance in angina

ESMOLOL:- Short $t_{1/2}$, → ester linkage metabolism

- ONLY IV, to control BP or heart rhythms during surgery or diagnostic procedure

NEBIVOLOL:- In addition to cardioselective β-blockade, it release NO from endothelial cells & cause vasodilation.

⇒ These agents have fewer effect on pulmonary function, PVR, & carbo-metabolism (hydrate)

THERAPEUTIC USES:-

1) Hypertension ē pulmonary disease
2) 1st Line — chronic stable angina or exertional
3) Bisoprolol & extended-release formu. of metoprolol → chronic HF

⇒ Raynaud pheno. is common, due to less effect on β_2 [in which fingers/toes color change to blue/red/pale and + pins/needles]

★-ACEBUTOLOL & PINDOLOL:

(Antagonist ē partial agonist activity)

- weakly stimulate β_1 & β_2 & inhibit stimulation by more potent endogenous catecho. (epi & Nor-epi)

↓ less ↓HR, and CO — compared to β-blockers

- Minimize lipid & carbo. metabolism

Use in Hypertensive pt. ē moderate bradycardia.

NT Release/Re-uptake INHIBITOR

- **Reserpine:** Plant alkaloid
- Block Mg^{2+}/ATP dependent transport of (epi, NE, Dopa, serotonin) from cytoplasm into storage vesicles ⇒ Depletion

LABETALOL & Carvedilol

- Antagonist of both α_1 & β adrenoceptors (non-selective)

ACTIONS:- (effective in pt, who don't require ↑PVR)

- Vasodilation (initially → vasoconstr. then dilation) — differ from other β-blockers

Carvedilol — ↓lipid peroxidation & vascular wall thickening, effect that 're benefit in HF [lipid perox → free radical damage cell damage ← lipids]

APPLICATION:-

Labetalol use as alternative to methyldopa in pregnancy induce Hypertension

- IV - labetalol → in emergencies

⇒ NOT give in acute exacerbation of HF
β-blockers

HOWEVER ∴ carvedilol is prob. subs. of P-glyco

carvedilol, Bisoprolol & metoprolol are beneficial in stable chronic HF — These agents work by ↓effect of symp. stimulation on heart → worsen HF over the time

ADRs:- orthostatic hypotension and dizziness due to α_1-blockade

NADOLOL & TIMOLOL:-

- β_1 & β_2 antag. • more potent than propranolol.
- used for chronic open-angle glaucoma & sometimes for systemic treatment of Hypertension

Treatment of Glaucoma:- work by ↓sing the secretion of aq. humor by ciliary body

Intraocular adm = 30min ONSET, 12-24hr duration

⇒ β-blocker = CHRONIC MANAG. OF GLAUCOMA.

⇒ PILOCARPINE = EMERGENCY ↓ IOP.

⇒
- Slow onset
- long duration (many days after discontinuation)
- For HT
- Now replaced ē other drugs.

ALPHA- ADRENERGIC BLOCKING AGENTS

(profoundly affect Blood pressure) → ↓se symp. tone

Induce Reflex Tachycardia ← ↓B.P ← ↓PVR (vasodilation) ←

All α- adr. blocker = cause epinep. reversal

[Prazosin, Terazosin, Doxazosin, Tamsulosin & ALFUZOSIN]

- Selective competitive α_1 blocker
- Doxazosin, the longest acting drug, excreted in feces.
- Tamsulosin & alfuzosin indicated for treatment of benign Hyperplasia of Prostate (BPH). — metabolite excreted in urine.

MECHANISM

- Relax arterial & venous smooth muscle → ↓PVR → ↓B.P.
- unlike phentolamine & phenoxybenzamine (α_1 & α_2), cause minimal changes in CO, RBF, & GFR

Tamsulosin or Prazosin → more selective for → α1A recep. → present on prostate & bladder. ↓ ↓se tone in smooth muscle of bladder neck (Sphincter) & prostate → Improve urine flow.

α1B — found on blood vessels.

THERAPEUTIC USES

★ Hypertension (NOT used as monotherapy) ↳ First dose cause orthostatic Hypotension → Syncope (fainting) (↓se BP on standing or from lying → sitting) ⇓ Should be reduce to 1/3 or 1/4 of normal dose & give at bedtime

★ BPH, as alternative to surgery in Symptomatic BPH esp. Tamsulosine.

★. These drugs cause modest improv. in lipid profi & glucose meta.

ADVERSE EFFECTS

- Dizziness
- lack of energy
- Nasal congestion or stiffness
- Headache
- orthostatic Hypotension
- ↓ dose when use ē vasodilators (nitrates or PDE-5 inhibitor sildenafil)
- ↓ ejaculation — sexual dysfunction (as in symp. sys: ejaculation occur).
- Floppy IRIS SYNDROM [observed during cataract surgery? and effect surg. Flaccid iris due to α-antagonist (tamsulosin)]

★- YOHIMBINE:-

- competitive α_2 - blocker
- component of bark Yohimbe tree
- Sexual stimulant & in treatment of erectile dysfunction. (But NOT reccom.)
- ↑se Symp. outflow to periphery.

CI = CV disorder, psychiatric cond. renal dys. function.

★- PHENTOLAMINE.

- α_1 & α_2 blocker. ← DOC in cheese rex (CI K in orthostasis)
- DOA = 4hr (injec.)
- Postural Hypotens. cause
- cause Reflex tachycardia
- CI = CV disorders.

Uses:

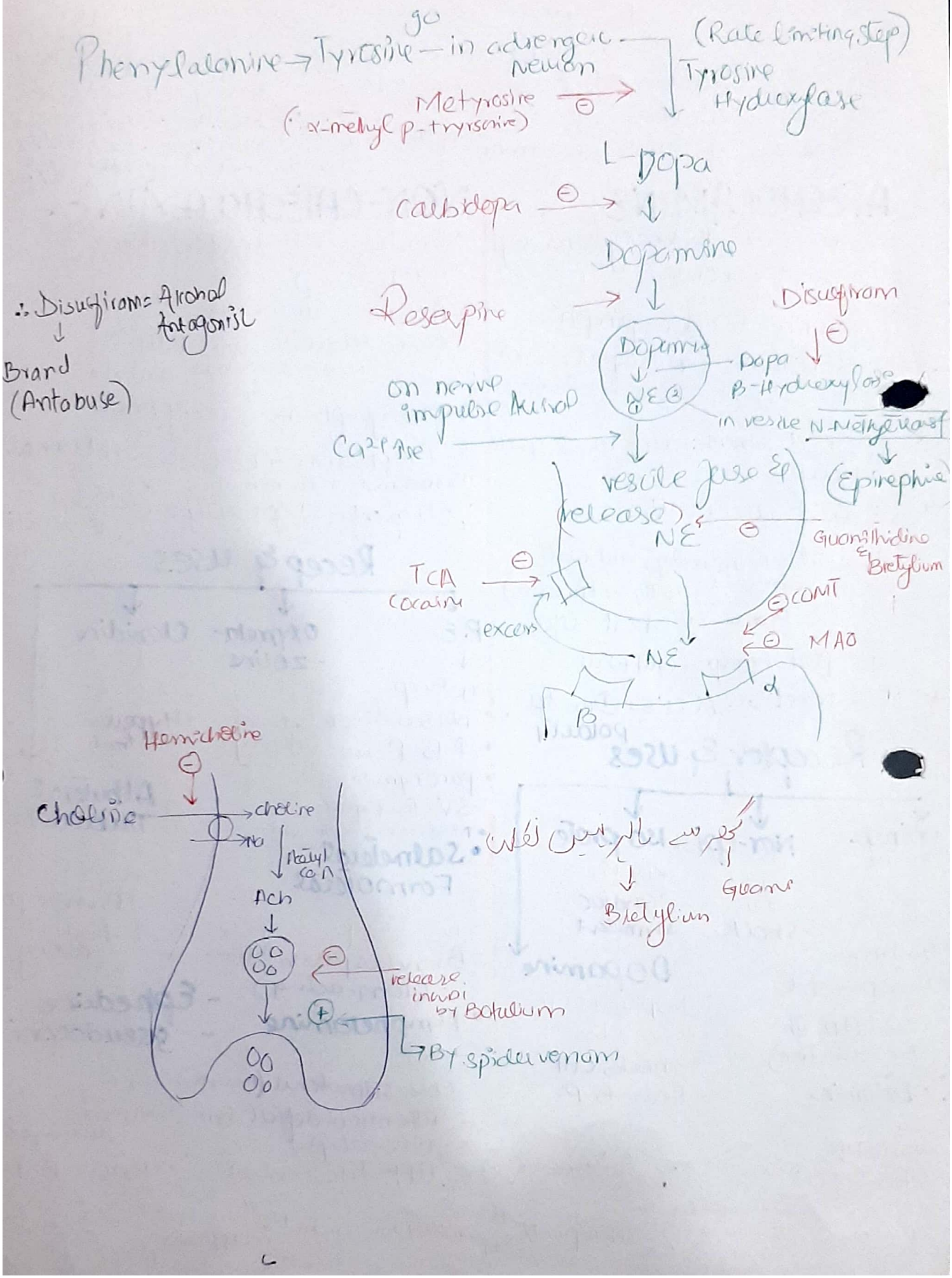
1- use in dermal necrosis
2- In HT crisis, due to clonidine withdrawal or after (Tyramine food + MOA Inhibitors)
Short Term mercy / Pheochromocytoma

★- PHENOXYBENZAMINE

- α_1 & α_2
- irrevs. + Non-compet
- ↓PVR ↑CO
- use in Pheochromocytoma (Dark color cell) [catechol. secreting Tumor of cell of adrenal medulla]
- In inoperable tumors
- Raynaud disease & frostbite

Dictionary:-

- Raynaud disease: cause smaller arteries that supply BF to skin to narrow in response to cold or stress — finger/toes migh Turn white/blue & feel cold & numb.
- Frostbite: Injury caused by freezing of skin & underlying tissues — Cold → red → Numb → Hard → pale
  mostly occur on finger, toes, Nose, ear, Cheeks & Chin.
- Floppy iris syndrome.


Phenylalanine → Tyrosine — in adrenergic neuron
(Rate limiting step)
Tyrosine Hydroxylase
Metyrosine
(α-methyl p-tyrosine)
L-Dopa
carbidopa
Dopamine
∴ Disulfiram: Alcohol Antagonist
Brand (Antabuse)
Reserpine
Disulfiram
Dopamine
NE
Dopa β-Hydroxylase
in vesicle
N-Methyltransferase
(Epinephrine)
on nerve impulse
Ca2+ influx
vesicle fuse & release
NE
Guanethidine & Bretylium
TCA
cocaine
excess
COMT
MAO
NE
α
β
Hemicholine
Choline
choline
Na
Acetyl CoA
Ach
release inhibited by Botulinum
By spider venom
گوانیدین سے ملتا جلتا نام
Guanethidine
Bretylium