King Saud University
College of Medicine
1st Year, 4th Block

Alpha & Beta Adrenergic Blockers 1&2

Cardiovascular Block

Adrenergic drugs

- Adrenergic stimulants (Sympathomimetics)
- Adrenergic Depressants
  - **Adrenoceptor Blockers Adrenolytics**
    - Alpha-adrenergic receptor blockers
    - Beta-adrenergic receptor blockers
  - **Adrenergic Neuron Blockers sympatholytics**

What are a_2-adrenoceptors?
Why are they called autoreceptors? Or presynaptics?

1- Methyldopa: acts as agonist at a2-adrenoceptors. Thus inhibits the release of NE leading to decrease blood pressure.
2-Clonidine: similar to Methyldopa.

1- False transmitters (alpha-2 agonist):
-Methylodopa (a-methyl tyrosine): used as antihypertensive in pregnancy.

2- Deplete storage:
-Reserpine (not used anymore)

3-Inhibit release & enhance uptake:
-Gaunthidine (not used anymore)

a-Adrenoceptor Blockers

Non-selective (act on both: $\mathbf{a}_1$, $\mathbf{a}_2$)	
Irreversible (long acting):	**Phenoxybenzamine:** Used in irreversible shock, and before removal of **Pheochromocytoma** to prevent Hypertensive crisis.
Reversible (short acting):	**Phentolamine:** Before removal of **Pheochromocytoma** to prevent Hypertensive crisis.
Selective ($\mathbf{a}_1$ blockers)	
Prazosin: (short acting) **Doxazosin**: (long acting)	-Used in *Raynaud's disease: induce peripheral vasodilatation. -Benign prostatic hypertrophy (BPH). -Can be used in hypertension & heart failure. Adverse effects: Postural hypotension, syncope, fluid retention, headache, nasal stuffiness, decreased ejaculation & impotence.
Tamsulosin **(uroselective):**	used in Benign prostatic hypertrophy **to cause** contraction of the bladder wall, relaxes bladder neck & sphincters.

***Raynaud's phenomenon** is excessively reduced blood flow in response to cold or emotional stress, causing discoloration of the fingers, toes, and occasionally other areas.

β-Adrenoceptor Blockers

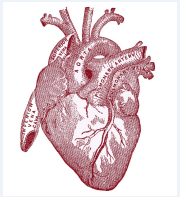
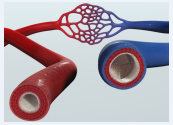
Pharmacodynamic Classification

1-According to extent of blocked of each type:			2-According to presence of agonistic/antagonistic action (ISA)* = Partial agonists or only antagonistic action * intrinsic sympathomimetic activity	
Non-Selective		Selective	Without ISA	With ISA
Block B & a_1: Labetalol Carvedilol	Block B_1 and B_2: Propranolol Timolol	Block b_1 more than b_2: Atenolol Bisoprolol	Propranolol Timolol Atenolol Bisoprolol Carvedilol	Labetalol

Pharmacokinetic Classification
(According to their lipid solubility)

	Lipophilic	Hydrophilic
Oral absorption	Complete	Irregular
Liver metabolism	Yes	No
$t_{1/2}$	Short	Long
CNS side effects	High	Low
Examples	Propranolol Timolol Labetalol >Carvedilol	Atenolol Bisoprolol

Propranolol

Characterized	Non-Selective Blocker of b_1 & b_2, has membrane stabilizing action, has sedative action, completely absorbed 70% destroyed during 1st pass hepatic metabolism, 90-95% protein bound, cross BBB.
Actions	 -In Heart by blocking B1: 1- Inhibit heart properties: ↓ cardiac output. 2- Has anti-anginal effects: ↓ cardiac work + ↓ O2 consumption. 3- Has anti-arrhythmic effects: ↓excitability, automaticity & conductivity + by membrane stabilizing activity.  -In Blood Vessels by blocking B2: Vasoconstriction: ↓blood flow to all organs except brain → cold extremities + intermittent claudications.  -In BP by blocking B_1 and B_2: 1- Antihypertensive action by inhibiting heart properties: ↓cardiac output. 2- Vasoconstriction to kidney BV: ↓ renin & aldosterone secretion.  -In Bronchi by blocking b_2: Bronchospasm specially in susceptible patients.  -In Intestine by blocking b_2:↑ Intestinal motility. **- Metabolism** by blocking mainly b_2: In liver: ↓ Glycogenolysis → Hypoglycaemia In pancreas: ↓ Glucagon secretion In adipocytes: ↓ Lipolysis In skeletal muscles: ↓Glycolysis  -On peripheral & CNS: Decrease tremors and anxiety.
Indications of B-blockes	Propranolol used in hypertension, arrhythmias, myocardial infarction, migraine, tremors, anxiety, hyperthyroidism Atenolol used in hypertension, angina, pheochromocytoma (used with α-blockers), myocardial infarction Bisoprolol used in hypertension, angina Metoprolol used in hypertension Timolol used in Chronic glaucoma, migraine.

Propranolol's Adverse Side Effects

Due to block of cardiac β_1-receptors: **heart failure,** bradycardia, hypotension,

Due to blockade of β_2- receptor (only with non-selective b-blockers) :
Asthma, emphysema, chronic bronchitis, Erectile dysfunction & impotence, Hypoglycemia & ↑ triglycerides & Cold extremities & intermittent claudication

All β -blockers:
mask hypo-glycaemic manifestations (headache, tremor & tachycardia)→ devlop COMA (If the patient is diabetic and the doctor gave him B-blocker drugs, it may lead to COMA. Because B-blocker drugs cause suppression of the sympathetic action, so the patient wont know that he is having hypoglycemia (no tremors or tachycardia)).

Selective (β1) <u>safer in :</u> asthma, Diabetes, Dyslipidemias, Rauynaud's phenomenon & vascular diseases.

*Propranolol with ISA

Better in patients that exhibit excessive bradycardia Also in non compliant for fear of sudden stoppage.
*Sudden stoppage will give rise to a withdrawal manifestations So the drug must be withdrawn gradually ➔ to prevent Rebound angina, arrhythmia, myocardial infarction & hypertension.

Contraindications:

*Depressed myocardial function as in; Uncompensated Heart Failure, Massive Myocardial Infarction, Heart Block.
*Bronchial Asthma (safer with cardio-selective β-blockers).
*Peripheral vascular disease (safer with cardio-selective β-blockers).
*Hypotension.
*Diabetic patients > (Type I) (specially on Insulin) for fear of hypoglycemia.

Propranolol interaction:

1-with verapamil (block Ca Channel) ➔ severe bradycadia \ heart block.
2- with anti-diabetic drugs (insulin > sulfonylureas) > Non selective β-blockers ➔ may lead to hypo-glycaemia.
3-with NSAIDs ➔hypertensive effect , because they ↓formation of vasodilating prostaglandins.
4-with quinidine ➔ HF
5-with cocaine, amphetamine or a-blocker overdose ➔ Rebound hypertension & impaired tissue perfusion.
6- with Tubocurarine ➔ Enhanced neuromuscular blockade.
7- with ergot alkaloids in migraine ➔ Claudications, parasthesia.

	LABETALOL	CARVEDILOL
Receptors	Blocks β & α_1	Blocks β > α_1
Pharmacokinetic	- Rapid acting, - non-selective with little ISA & local anesthetic effect - Do not alter serum lipids or blood glucose	-Non-selective with no ISA & no local anesthetic effect. -Has antioxidant (Favorable metabolic profile). -more vasodialating.
Uses	Severe hypertension in pheochromocytoma & hypertensive crisis (e.g. during abrupt withdraw of clonidine) - Can be used pregnancy-induced hypertension but better alpha-methyldopa	congestive heart failure → reverses its patho-physiological changes
Adverse Side Effects	Orthostatic hypotension (postural hypotension), sedation & dizziness	Edema

SUMMARY

Drug	Type	Uses	Note
Methyledopa	Sympatholytic	Anti-hypertension in pregnancy	-False Transmitters of a-methyl tyrosine
Phenoxybenzamine	N.S , Irreversible , a_1 & a_2	In Irreversible shock *Before removal of Pheochromocytoma	_
Prazosin	S, Short acting , a_1	Raynaud's disease	nasal stuffiness, ↓ ejaculation & impotence
Tamsulosin	S, uroselective	Benign prostatic hypertrophy	-
Propranolol	N.S.B_1& B_2	Arrhythmias Migraine Hyperthyroidism Anxiety Tremors	Has membrane stabilizing action Has sedative action
Timolol	N.S.	Chronic glaucoma migraine prophylaxis	_
Labetalol	N.S. b & a_1	Severe hypertension in pheochromocytoma hypertensive crisis	local anesthetic effect
Carvedilol	N.S. b & a_1	congestive heart failure	Has antioxidant
Atenolol	S. B_1	Hypertension Angina Pheochromocytoma myocardial infarction	Block B_1>> B_2 Hydrophilic Long T 1/2

S= Selective N.S = Non-Selective *: to prevent Hypertensive crisis

MCQs

1-Which one of the following is uroselective ?
A-Tamsulosin.
B-Doxazosin.
c-Prazosin.
D-Phenoxybenzamine.

2-Which one of the following is used to treat Raynaud's disease ?
A-Prazosin .
B-Doxazosin.
C-Timolol.
D-A & B.

3- Patient with cardiac problems came to the clinic and he has asthma, which drug should the doctor give him ?
A-Selective B_1 Blockers.
B-Non-Selective b Blockers.
C-selective B_2 Blockers.
D-Non of above.

1-A 2-D 3-A 4-D 5-C 6-A

4-The interaction between Verapamil and Propranolol will lead to ?
A-Bradycardia.
B-heart block.
C- tachycardia.
D- A & B.

5- If a patient is diabetic and he was given B-blockers. He would be susceptible to?
A-Tachycardia.
B-Tremors.
C- Coma.
D-A & B.

6-Patient has irreversible shock, what drug should we give him?
A-Phenoxybenzamine
B-Atenolol
C-Labetalol
D-Timolol

PHARMACOLOGY 433

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We hope that we made this lecture easier for you

Good Luck !