BETA ADRENOCEPTOR ANTAGONISTS

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BETA ADRENOCEPTOR ANTAGONISTS

- *Drugs block β-adrenergic receptors*

Classification

1. β_1 + β_2 Antagonist

Propranolol, pindolol, penbutolol, nadolol, carteolol, timolol, sotalol

2. Mainly β_1 Antagonist

Acebutalol, atenolol, alprenolol, betaxolol, celiprolol, esmolol, metoprolol

3. Mainly β_2 antagonists

Butoxamine

BETA ADRENOCEPTOR ANTAGONISTS

- Chemically resemble Isoproterenol
- None of clinically available β-blocker is absolutely specific for β_1 receptor
- Selectivity for receptors is dose-related, diminish at higher drug conc.
- All members differ in their pharmacokinetic properties

Pharmacokinetic properties

Absorption

- Route is oral & parenteral inj.; sustained released preparation (prop. & metoprolol)
- Well absorbed after oral intake
- Peak conc. at 1-3h

Bioavailability

- D/f agents have d/f bioavailability
- Bioavailability of prop. =30%

cont.

Distribution & Clearance

- Rapid distribution; ↑Vd; e.g. prop. & penbut. ↑ lipophilic → ☞ readily cross BBB
- Most have half life ~3-10 h (esmolol →10 min)
- Nadolol → ☞ longest half life (24 h; ↑ in renal failure)

Metabolism & Excretion

- ✓ ***Prop. & metoprolol*** ➔☞ extensive 1st pass metabol.+ excreted in urine (🡅 in liver disease)
- ✓ ***Atenolol, celiprolol & pindolol*** ➔☞less metabol.
- ✓ ***Nadolol*** excreted as unchanged in urine

Pharmacodynamics

MOA

A. ***Blockade of β-receptors (main)***
B. Partial agonist activity at β -receptors
C. Local anesthetic action

cont.

Effects

1. Cardiovascular system

Chronic admin. ➔☞ ⬇ BP of HTN patients (not in healthy persons) by:

Effect on heart +BV

Suppression of renin-angiotensin system

Effects on CNS or elsewhere

a) Heart

- ⬇chronotropic (HR)+inotropic (contr.)➔☞⬇CO➔ ⬇BP
- Use in **angina**, **CHF**; following **MI**

b) Vascular system

- Acute effect➔ constriction of arterioles (blockade of β_2-receptors)
- Chronic effect ➔dilatation of arterioles➔ ⬇PVR ➔ ⬇BP (unknown mech.)

c) Kidney

- Inhibition of release of renin from kidney ➔🡻Angio.II➔ 🡻BP

2. Respiratory Tract

- Blockade (non specific agents) of β_2-recept.(bronchial sm mus)➔ ↑ airway resistance especially in asthmatic patients

- Avoided in asthmatic patients with exception of selective β_1 antagonists (metoprolol, atenolol)

3. Eye

↓secretion of aqueous humor by ciliary body→ ↓intraocular press. in glaucoma

4. Metabolic & Endocrine

i) *Lipid metabolism → inhibition of lipolysis*

ii) *CHO metabolism* → *partial inhibition of glycogenolysis*

- Use of β-blocker in insulin-dependent diabetics with caution b/c of hypoglycemia
- Comparatively safer in type2 D

Cont.

iii) Plasma lipid

- Chronic use ➔↑plasma VLDL; ↓HDL ➔↑risk of CAD

- Pindolol, acebutalol (with partial agonist activity) have less effect on plasma lipid profile

5) Effects unrelated to β-blockade

1) Partial agonist (intrinsic sympathomimetic) activity

- Some β-blockers partially stimulate β -adrenoceptors; desirable to avoid adverse effects (precipitation of asthma or excessive bradycardia)
- e.g., Pindolol, penbutolol, celiprolol, carteolol, acebutalol, labetalol, bopindolol

2) Local anesthetic (memb. stablizing) activity

- Local anesthetic blockade of Na^+ channels
- Demonstrated only experimentally (not clinically) in isolated neurons, heart, muscle & skeletal muscle membrane

Properties of specific agents

Propranolol (Inderal; non specific)

- Prototype drug; ↓ & dose-dependent bioavailability
- Long-acting preparation with prolonged absorption
- Negligible effect on ***α*** & ***muscarinic*** receptors
- Block some **5-HT**-receptors in brain

Clinical Uses

HTN, Angina pectoris, cardiac arrhythmias, MI

Metoprolol (Lopressor); Atenolol (Tenormin); Acebutalol (Sectral) (β_1-selective)

- Safer in patients with **Asthma** (compared to prop.)
- β_1-selectivity is modest ; use with caution in **Asthma**
- Risk in **COPD** & **MI**
- Preferable in **Diabetes** (recovery from hypoglycemia) or **PVD** (vasodilatation) patients

Nadolol (Corgard; β_1+ β_2)

- Long duration of action

Clinical Uses

HTN , Angina pectoris

Timolol (Blocadren; β_1+ β_2)

- Non selective ; -ve local anesthetic activity
- Good ocular hypotensive effect on eye

Preparations: tablets; eye drops (0.25%; 0.5%)

Use: glaucoma

Levobunonol (Betagan; non-selective) ➔glaucoma

Betaxolol (Kerione; β_1-selective) ➔ **HTN; glaucoma**

Carteolol (Teoptic; non-selective) ➔ glaucoma

Pindolol, Acebutolol, Carteolol, Bopindolol, Oxyprenolol, Celiprolol, Penbutalol

- Partial β-agonist activity
- Effective in HTN & angina
- Less ability to produce bradycardia & abnormalities in plasma lipids

cont.

Esmolol (Brevibloc; β_1-selective)

- Ultra short-acting adrenoceptor antagonist (half life~10 min)
- Contains **ester** linkage, rapidly metabolized by **Estrases**→ Metabolite (less affinity for β-receptors)
- Therapeutic action terminates rapidly

Clinical uses of Esmolol (Safer in critically ill patients)

- Supraventricular arrhythmias, arrhythmias with thyrotoxicosis, pre-operative HTN, myocardial ischemia

Butoxamine (selective for β_2-receptors)

- Research drug; no clinical use

Alpha & Beta Adrenoceptor Antagonists

- ***Drugs block both α & β-adrenoceptors***

e.g. Labetalol (α_1 selective +β-antagonistic), Carvedilol, Medroxalol, Bucindolol

Labetalol

- **Blocks α_1+β-adrenoceptors**
- **Partial agonist activity at β_2-adrenoceptors**

Pharmacokinetics

- **Well absorbed after oral intake; undergoes 1st pass effect**
- **Bioavailability is 30%**
- **Plasma half lie is 5 h**

Labetalol

Clinical Uses

HTN, Pheochromocytoma

Carvedilol, Medroxalol & Bucindolol

- Non-selective β-receptor antagonist with some capacity to block α_1-adrenergic receptors

Carvedilol antagonizes the actions of catechol. more potently at β-receptors than at α-receptors

Clinical Uses: HTN, Angina, Cardiac failure

Clinical Pharmacology of β-blocking Drugs

1) Hypertension

Given alone or + Diuretics or vasodilators

2) Ischemic Heart Disease (IHD)

a) Angina (temporary deficiency of supply of O_2 to a part of heart)

cont.

Beta-blockers ⇓ Frequency of episodes + improves Exercise Tolerance

MOA → Block β_1-receptors

a) ⇓force of contraction → ⇓ Cardiac work → ⇓ O_2 demand

b) ⇓HR → ⇑diastolic period → ⇑blood supply to heart→⇑ O_2 supply to heart

b) Myocardial infarction (MI)

- ***Permanent deficiency of O_2 supply to a part of heart***
- Long term use of **timolol**, **propranolol** or **metoprolol** ⇒ prolongation of life in patients (already attack of MI)

3) Cardiac Arrhythmias

Supraventricular arrhythmias, Ventricular arrhythmias, Ventricular ectopic beats; e.g.sotalol (inhibit ion channel+block β-receptors)

4) Heart Failure

Not effective (worsen symptoms) ⇒ Acute congestive heart failure

Metoprolol, Bisoprolol & Carvedilol ⇒ effective in Chronic HF (selected patients) ⇒ prolong life

MOA: unclear ⇒ ⇓ remodeling of heart+ ⇓ risk of death

5) Other cardiovascular disorders

Obstructive cardiomyopathy

Beta blockers ⇒ ⇓vent.ejection + ⇓ outflow resistance ⇒ ⇑ stroke volume

6) Glaucoma

β-blockers ⇓ secretion of aqueous humor ⇒ ⇓ intraocular pressure; e.g., ***timolol, betaxolol, levobunolol, carteolol, metipronalol***

7) Hyperthyroidism

Clinical syndrome associated with ⇑ T_3 & T_4; excessive catechol. actions not level(⇑ HR, palpitations, tremors, sweating etc)

β -blockers ⇒ block adrenoceptors + inhibit conversion of T_4 to T_3

Propranolol use in **thyroid storm** ⇒ Supraventricular tachycardia ⇒ HF

8) Neurologic Diseases

a) Prophylaxis of Migraine

Propr. (others, met.,aten.) ⇒ ⇓ freq.+intensity of migraine

MOA ⇒ unknown

b) Tremors

β-blockers ⇓ Tremors by blocking β_2-receptors of skeletal muscles

cont.

c) Somatic symptoms of anxiety

Propr. ⇒ treatment + prevention of palpitations, tachycardia, tremors, sweating e.g., musicians

d) Alcohol withdrawal syndrome

β-blockers ⇒ sympathomimetic treatment in alcoholics (tremors, sweating, palpitations, convulsions)

9) Bleeding from esophageal varices

- Veins of lower part of esophagus are enlarged in liver cirrhosis & can bleed
- Prop. & nadolol (+isosorbide mononitrate) $\Rightarrow$ prevent bleeding from esophageal veins in liver cirrhosis

Adverse effects of β-blockers

1. Precipitation of Asthma

- Non-specific agents precipitate attacks of asthma , whereas β1-selective agents are less liable

2. Cardiac failure

- CF ⇒ severe + sign & symptoms ⇑ (depressant effect)

3. Hypoglycemia

- Non-specific agents prolog hypoglycemia
- β1-selective are preferred

cont.

4) Abrupt withdrawal

Abrupt withdrawal (angina) ⇒ severe attack of angina or MI

5) CNS

Prop., & other lipid soluble agents pass BBB ⇒sedation, depression & sleep disturbances

Contra-indications & Cautions

- Asthma, COPD, Cardiac failure, Heart block, insulin-dependent diabetes, PVD (severe)