Clinical Pharmacology & Toxicology Pearl of the Week

The following are a series of Pearls of the Week pertaining to anti-hypertensives and their clinical pharmacology with key points to drive effective prescribing.

Part 2- Hypertension Series: Cardio-selective Beta-blockers

β-1 receptors:

- ✓ Predominantly located on cardiac myocytes, kidney cells, and adipocytes
- ✓ Stimulated by adrenergic signaling molecules: (epinephrine/norepinephrine or dopamine)
- ✓ Adrenergic stimulation of G-PCR →↑cAMP→↑ phosphorylated calcium channels →↑ calcium release → sarcoplasmic reticulum release of calcium → muscle contraction/effector action
    - Cardiac myocytes: ↑ sinoatrial and AV node firing + ventricular muscle firing → increased contractility and heart rate
    - Kidney: ↑ smooth muscle release of **renin**
    - Adipocytes: ↑ lipolysis

β-2 receptors:

- ✓ Found on smooth muscles (GI tract, bronchi, detrusor muscles, uterus, seminal tract), pancreas (For insulin and glucagon secretion), eye
- ✓ Stimulation leads to:
    - Smooth muscle relaxation
    - Increased ocular pressures (increased aqueous humour production)
- ✓ Less relevance in hypertension management

β-1 receptor antagonists:

- Indications: Hypertension, coronary-artery disease, heart failure, arrhythmias, angina-pectoris
- Examples:
    - **Cardio-selective (β-1 selective):** Atenolol, bisoprolol, esmolol, metoprolol
    - **Non-selective:** Nadolol, propranolol, timolol
    - **Non-selective with alpha-1 antagonism:** Carvedilol, labetalol
- **Anti-hypertensive mechanism of action**: Decreased renin (Decreased RAAS activity) and decreased inotropy and chronotropy.
- Anti-anginal mechanism of action: As above; mostly through negative chronotropy and inotropy (Lower O2 demand within myocardium)

Pharmacokinetics: ADME – Cardio-selective β-blockers

	Absorption	**Distribution**	**Metabolism**	**Elimination**
Atenolol	50% T_{peak}: 2-4hr	V_d: 0.9-1.6L/Kg 6-16% protein bound	85-90% unaltered Small amounts of conjugation	85% renal ½ life: 6-7hrs
Bisoprolol	>80% T_{peak}: 2-4hr	V_d: 2.9L/Kg 30% protein bound	CYP 3A4 – inactive metabolites	98% renal 50% unaltered, 50% metabolites ½ life: 9-12hrs

Esmolol	IV only	V_d: Unknown	RBC esterases	~80% renal (<2% unaltered) ½ life: 9 min
Metoprolol	~75% T_{peak}: 1-2hr	V_d: 4.2L/kg 11% protein bound	CYP 2D6 – inactive metabolites	>95% renal <5% unaltered ½ life: 3-7hrs

- ✓ **Anti-hypertensive effect:** Flat response curve (increasing the dose will change chronotropic response, but does not cause further reduction of blood pressure)
- ✓ Prescribing situations: Hypertension and…
  - Less than 60 years old (signal towards stroke in people on b-blockers over the age of 60)
  - Coronary artery disease (Within the last 18 months)
  - Heart failure
  - Angina
  - Arrhythmia, including atrial fibrillation
- ✓ Combinations:
  - RAAS additive effect: β-blocker + ACEi/ARB, β-blocker + thiazide/thiazide-like diuretic
  - RAAS + vasodilation: β-blocker + CCB

Adverse effects/Toxicity:

- ✓ Side effects: bradycardia, hypotension, diarrhea, fatigue +/- depression
- ✓ Caution initiating/Escalating: Decompensated heart failure, pre-syncope, bradycardia
- ✓ Toxicity: bradycardia + hypotension, less β-1 selectivity in toxic ingestions leading to bronchospasm, hypoglycemia, altered mental status

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Click HERE for clinical issues the CP service can assist with.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.

References:

1. Wong, G.W., Boyda, H.N., Wright, J.M., 2016. Blood pressure lowering efficacy of beta-1 selective beta blockers for primary hypertension. Cochrane Database of Systematic Reviews. doi:10.1002/14651858.cd007451.pub2
2. Westfall TC, Westfall DP. Adrenergic Agonists and Antagonists. In: Brunton LL, Chabner BA, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e. McGraw-Hill
3. Benowitz NL. Antihypertensive Agents. In: Katzung BG. eds. Basic & Clinical Pharmacology, 14e. McGraw-Hill;
4. Micromedex: https://www-micromedexsolutions-com.ahs.idm.oclc.org/
5. Drugbank: https://go.drugbank.com/