Clinical Pharmacology & Toxicology Pearl of the Week

~Antihypertensives, Part 1: Dihydropyridine Calcium Channel Blockers (CCBs)~

- ✓ Dihydropyridine members: **Amlodipine**, nifedipine, felodipine, nicardipine
  - Non-dihydropyridine members: Diltiazem and Verapamil
- ✓ Indications: Hypertension and angina-pectoris
- ✓ Excellent adjunct anti-hypertensive that is safe with renal dysfunction
  - Arterial vasodilators cause an increase in RAAS activity. Therefore, CCBs can be used as monotherapy, but work best when combined with medications that block RAAS activity (ACEi/ARB, diuretics, or beta-blockers)
  - **Typical combinations:** Diuretic + CCB, ACEi/ARB + CCB, Beta-blocker + CCB

Pharmacokinetics: (Amlodipine) – Note other CCBs have slightly different PK/PD profiles

- ✓ Oral Bioavailability >65%
- ✓ Peak plasma concentration: 6-12hrs
- ✓ Half-life: 30-50hrs; time to steady state: **7-8 days**
- ✓ Metabolism: Hepatic **– CYP 3A4** (90% metabolized). **Metabolites: Inactive**
  - Dose will increase in the presence of a CYP 3A4 inhibitor
  - Beware of grapefruit juice – inhibits gut CYP 3A4 activity. Result: Increased peak plasma levels
    - Higher peak = More effect; watch out for transient hypotension
- ✓ Typical dosing (Amlodipine) 2.5mg-10mg/day (Single-daily dose)
  - "Start low and go slow"- Adjustments should be made no more than **weekly**
  - Decreased metabolism in individuals with Child-Pugh C cirrhosis
    - Monitor for hypotension

Pharmacodynamics:

- ✓ Linear dose response curve: The more amlodipine given the greater the effect on blood pressure
- ✓ Inhibits peripheral (Smooth muscle) L-type calcium channels
- ✓ Mechanism of action: Depolarization of a membrane (cardiac myocyte or peripheral muscle) via influx of sodium → activates voltage sensitive calcium channels → influx of calcium → activation of ryanodine receptor and release of calcium from sarcoplasmic reticulum → muscle contraction
  - CCBs – inhibition of L-type channels → impaired smooth muscle contraction i.e. smooth muscle relaxation → resulting in arterial vasodilation → drop in arterial blood pressure
- ✓ Minimal sinoatrial node or atrioventricular node activity and minimal to no cardiac involvement (Does NOT lower cardiac inotropy)
  - SAFE IN REDUCED EJECTION FRACTION (Unlike non-dihydropyridine CCBs, e.g. diltiazem and verapamil)
- ✓ Anti-anginal agent: Mechanism – Decreased afterload and coronary vasodilation

Adverse Effects/Toxicity:

- ✓ Peripheral edema (Common) – 2-10% – improves with concomitant ACEi/ARB prescription
- ✓ Other adverse effects: abdominal pain, nausea, fatigue
- ✓ Hypersensitivity reactions (Very rare) – typically type I hypersensitivity/angioedema
- ✓ Toxicity: >20mg (or >0.3mg/kg in children)
    - Profound hypotension – may require inotropic/vasoconstrictor support
    - Loss of peripheral L-channel selectivity – resulting in hypotension + bradycardia (high-degree block)

Take home points:

- ✓ CCBs inhibit smooth muscle L-type calcium channels, causing smooth muscle (arterial) relaxation
- ✓ Dihydropyridine CCBs, i.e. amlodipine, have minimal cardiac L-type calcium channel activity (Therefore minimal bradycardia or effects on cardiac inotropy, unless in toxic doses)
- ✓ CYP3A4 Metabolism
- ✓ Prolonged half-life: 7-8 days to steady-state; be patient – Increase the dose ONCE per week!
    - Typical dose: Amlodipine 2.5-10mg daily
- ✓ Main side effect: peripheral edema. Rare angioedema or cutaneous hypersensitivity reactions
- ✓ Work best when combined with agents that block RAAS activity – ACEi/ARB, Diuretics, or beta-blockers

References:

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4. Michel T, Hoffman BB. Treatment of Myocardial Ischemia and Hypertension. In: Brunton LL, Chabner BA, Knollmann BC. eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e*. McGraw-Hill.
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7. Micromedex: https://www-micromedexsolutions-com.ahs.idm.oclc.org
8. Indiana University Department of Medicine Clinical Pharmacology - Flockhart Tables: https://drug-interactions.medicine.iu.edu/MainTable.aspx

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

More CPT Pearls of the Week can be found HERE.

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