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 1- Hypertension Series: Dihydropyridine Calcium Channel Blockers (CCBs) – Amlodipine

- ✓ Peripheral arterial vasodilators (Dihydropyridine CCBs: Mostly peripheral smooth muscle activity vs. non-dihydropyridine members with mixed cardiac and smooth muscle activity)
- ✓ Dihydropyridine members: **Amlodipine**, nifedipine, felodipine, nicardipine
    - Non-dihydropyridine members: Diltiazem and Verapamil
- ✓ Mechanism of action (Dihydropyridine CCBs): Smooth muscle L-type calcium channel inhibitors (See below for more details)
- ✓ 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 medication 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
    - Check for other drug-drug interactions (Flockhart table): https://drug-interactions.medicine.iu.edu/MainTable.aspx
    - 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

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:

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