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 5- Hypertension Series: Alpha-2 adrenergic receptor agonists

Main members: Clonidine, Guanfacine, Dexmedetomidine

Clonidine	Guanfacine	Dexmedetomidine
✓ **Primary indication:** Hypertension ✓ **Other indications:** Anxiety, ADHD, addictions and craving, chronic pain	✓ **Primary indications:** Hypertension and ADHD	✓ **Primary indications:** ICU sedation, ICU delirium management, and procedural sedation

Mechanism of action:

- ✓ Alpha-2 adrenergic receptor: Inhibit neural firing resulting in **inhibition of epinephrine/norepinephrine release**, sedation and analgesia
- ✓ Receptor locations: On post-synaptic neurons, adrenergic terminals, and some vascular smooth muscle (3 subtypes: Alpha 2a, Alpha 2b, Alpha 2c)
    - Alpha 2a – Brain, spinal cord, locus ceruleus → Supressed release of norepinephrine/epinephrine **(Main receptor)**
    - Alpha 2b – Peripheral smooth muscle (Skin, mucosa, abdominal viscera, coronary vasculature → vasoconstriction
    - Alpha 2c - Basal ganglia, hippocampus, and cerebral cortex → Sedation and analgesia
- ✓ Binding to alpha-2 adrenergic receptors→activates inhibitory G-protein coupled receptor → decreased cAMP levels → calcium-activated channel supressing neural firing
- ✓ Blood pressure response:
    - Alpha 2a → reduced epinephrine/norepinephrine release →decreased peripheral resistance, heart rate, and renin-release → **net effect: lower blood pressure**
    - Alpha 2b → vasoconstriction: May lead to transient hypertension before dominant alpha-2a effect predominates and blood pressure drops
- ✓ Other tissue response: Pancreas (insulin release inhibition), mucosa (dry mouth and nasal congestion), adipose tissue (lipolysis inhibition), salivary glands, ciliary body (decreased aqueous humour)

Pharmacokinetics and Pharmacodynamics:

	Clonidine	Guanfacine	Dexmedetomidine
A:	Oral/transdermal Bioavailability: 75-85%	Oral Bioavailability: ~80%	IV only Bioavailability: 100%
D:	Vd: 1.7-2.5L/Kg	Vd:6.3L/Kg	Vd: 1.6-1.7L/kg
M:	Liver: (CYP 2D6)	Hepatic: CYP 3A4/5 + oxidation	Hepatic: glucuronidation +/- CYP 2A6 (minor)
E:	Renal: 50% unaltered, 30% metabolites Fecal: 20% ½ life: 12-16hr	Renal: 50% unaltered, 50% metabolite ½ life: ~17hrs	Renal: 60% unaltered, ~35% metabolite Fecal: ~4% ½ life: 2-2.67 hrs
Receptor affinity:	Alpha 2a > alpha 2b > alpha 2c	Alpha 2a >>>alpha 2b >alpha 2c	Alpha 2a > alpha 2b > alpha 2c

Hypertension prescribing: (For clonidine and guanfacine)

- ✓ Clonidine has 10x higher potency than guanfacine
- ✓ Lower side-effect profile (See below) with guanfacine because of higher Alpha 2a affinity
- ✓ Linear dose response: increasing dose results in more blood pressure lowering
- ✓ Adrenergic rebound when abruptly stopped (Clonidine > Guanfacine) – therefore need to be tapered off and NOT a good choice for PRN blood pressure management (Rebound hypertension)
- ✓ Typical dosing:
  - Clonidine (oral): 0.1-0.3mg po BID
  - Guanfacine: 0.5-3mg Po daily
- ✓ 4th-5th line choice: Typically use Thiazide/Thiazide-like → ACEi/ARB → CCBs → MRA → Clonidine/guanfacine
- ✓ Very effective for sympathetic driven hypertension – e.g HTN in the young, baroreceptor driven HTN, etc)

Adverse effects/Toxicity:

- ✓ Orthostasis (pre-syncope and syncope) and bradycardia (including atrioventricular block) → lower cardiac output → heart failure
- ✓ Fatigue and dry mouth
- ✓ Nasal congestion (Vasoconstriction)
- ✓ Rebound hypertension
- ✓ Drug interactions: Caution with sinus-blocking agents, beta-blockers, Non-dihydropyridine CCBs as may cause bradycardia
- ✓ Toxicity:
  - Hypotension and bradyarrhythmia

- Respiratory depression
- Sedation and altered level of consciousness → Coma
- Sedation: primarily through alpha 2a/2c activity → downstream effect may result in endogenous opioid release → Exacerbating sedation?
    - Naloxone in clonidine overdose? Questionable utility: opioid effect on presentation is thought to be fairly minimal and naloxone will not inhibit clonidine binding to alpha 2a/2c adrenergic receptors (The primary driver of sedation in this context).

Take home points:

- ✓ Hypertensive agents: clonidine and guanfacine
- ✓ Anti-hypertensive effect mediated through alpha-2A adrenergic receptor agonism → inhibit norepinephrine/epinephrine release → smooth muscle vasodilation → decreased blood pressure
- ✓ Catecholamine excess and rebound hypertension if abruptly stopped
- ✓ Linear dose response: The higher the dose the greater the anti-hypertensive effect

The Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. 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. 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;
2. Benowitz NL. Antihypertensive Agents. In: Katzung BG. eds. *Basic & Clinical Pharmacology, 14e*. McGraw-Hill
3. Seedat YK. Clonidine and guanfacine--comparison of their effects on haemodynamics in hypertension. S Afr Med J. 1985 Apr 6;67(14):557-9.
4. Giovannitti JA Jr, Thoms SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: a review of current clinical applications. *Anesth Prog*. 2015;62(1):31-39.
5. Drugbank: https://go.drugbank.com/drugs
6. Micromedex: https://www-micromedexsolutions-com.ahs.idm.oclc.org
7. Indiana University Department of Medicine Clinical Pharmacology - Flockhart Tables: https://drug-interactions.medicine.iu.edu/MainTable.aspx