Clinical Pharmacology & Toxicology Pearl of the Week

~Antihypertensives, Part 5: 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 coeruleus → suppressed 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 suppressing 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 desirable choice for PRN blood pressure management (Rebound hypertension)
- ✓ Typical dosing:
  - Clonidine (oral): 0.1-0.3mg po BID
  - Guanfacine: 0.5-3mg Po daily
- ✓ 4^{th}-5^{th} line choice: Typically use Thiazide/Thiazide-like → ACEi/ARB → CCBs → MRA → Clonidine/guanfacine
- ✓ Highly 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

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

References:

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3. Seedat YK. Clonidine and guanfacine--comparison of their effects on hemodynamics 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

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.

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