Drug Effects

System	Effect	Assessment by Hx	PE	Test
CV	Increases BP, CO, HR, SVR, arrhythmias	Recent/chronic use	Vital signs	ECG
RESP	Respiratory stimulation	Recent/chronic use	Pulm exam	ABG
CNS	Increased alertness, electrical activity Overdose: Anxiety, psychoses, seizures	Recent/chronic use	CNS exam	EEG
METAB	Renal failure, lactic acidosis Dehydration	Recent/chronic use	Vital signs, PE	ABG, lytes
OTHER	Mydriasis, diaphoresis, hyperthermia, decreased GI motility	Recent/chronic use	Vital signs, PE	

Key References: Johnston RR, Way WL, Miller RD: Alteration of anesthetic requirement by amphetamine, *Anesthesiology* 36(4):357–363, 1972; Carvalho M, Carmo H, Costa VM, et al.: Toxicity of amphetamines: an update, *Arch Toxicol* 86(8):1167–1231, 2012.

Perioperative Implications

Preoperative Concerns

- Cancel case (when appropriate) if acute intoxication is suspected; urine drug screen may be appropriate when suspected.
- Catecholamine drip (i.e., norepinephrine) may be needed in chronic users.
- Ensure that any other psychotropic or analgesic medications are taken on the morning of surgery.

Induction/Maintenance

- Volatile anesthetic requirements may be affected in acute versus chronic users; increased in the acute setting and decreased with chronic users.
- Hypotension
  - Rule out cardiotoxic manifestations if acute use is suspected.
  - Ephedrine likely less effective in chronic amphetamine users.
  - Catecholamine infusion should be readily available.
- Hypertension
  - Rule out cardiotoxic manifestations if acute use suspected.
  - Deepen anesthesia and treat pain when appropriate.
  - Calcium channel blockers and/or beta blockers when appropriate.

Postoperative Period

- Regional anesthetics if consent obtained preop.
- Nonopioid medications (i.e., acetaminophen) where appropriate.
- If hypotension persists, rule out myocardial complications.

Adjuvants/Regional Anesthesia

- Multimodal analgesia
- RA and/or monitored anesthetic care

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Angiotensin II Receptor Blocking Drugs

Davide Cattano

Uses

- AT1–receptor antagonists, or sartans, are a group of pharmaceuticals that modulate the renin-angiotensin-aldosterone system. Their main use is in hypertension, diabetic nephropathy, and CHF.

Perioperative Risks

- ARBs do not inhibit ACE; they do not cause an increase in bradykinin, which contributes to the vasodilation produced by ACE inhibitors and also some of the side effects of ACE inhibitors (cough and angioedema).
- Dementia: It has been found that pts with Alzheimer's disease or dementia are up to 50% less likely to have to be admitted to a nursing home or to die if they were taking an ARB.

Worry About

- Rebound Htn if drug is withdrawn acutely, especially with longer-acting agents.
- Refractory hypotension in pts undergoing general anesthesia. BP responds to vasopressin agonists.
- Questionable increased risk of MI with ARBs.

Overview/Pharmacology

- Renin-angiotensin cascade begins with the cleavage of angiotensin by renin, angiotensin I converted by ACE to angiotensin II, angiotensin II receptors activated by binding of angiotensin.
- Clinical effects of angiotensin II (e.g., vasoconstriction, sodium/water retention, renin suppression) are mediated by AT1.
- Blockade of AT1 receptors directly causes vasodilation, reduces secretion of vasopressin, and reduces production and secretion of aldosterone, among other actions—the combined effect of which is reduction of BP.
- Three important PD/PK factors: Pressor inhibition, AT1 affinity, biologic half-life (e.g., losartan 100 mg, 25–40%, 1000-fold, 6 h, or valsartan 80 mg, 30%, 20,000-fold, 6 h).
- Contraindicated in pregnancy

Mechanism of Action/Usual Dose

- The activated receptor, in turn, couples to Gq/11 and thus activates phospholipase C and increases the cytosolic Ca^{2+} concentrations, which in turn trigger cellular responses such as stimulation of protein kinase C. The activated receptor also inhibits adenylate cyclase and activates various tyrosine kinases.
- Available in once-daily dosing:
  - Candesartan (Atacand) 4–32 mg
  - Irbesartan (Avapro) 150–300 mg
  - Losartan (Cozaar) 50–100 mg
  - Telmisartan (Micardis) 40–80 mg
  - Valsartan (Diovan) 80–320 mg

Drug Effects

System	Effect	Assessment by Hx	PE	Test
CV	Lowers BP	Assess response to Rx	BP	Monitor BP, can also have tachycardia and bradycardia with lowering BP, careful when discontinuing
GI	Increase in LFTs Rare reversible hepatotoxicity reported			Watch for rebound Htn, change in LFTs
METAB	Hyperkalemia			K^+
DERM	Angioedema reported	Ask pts for clinical Hx		
HEME	Microcytic anemia			CBC
RENAL	Can cause ARF in pts with renal artery stenosis or diffuse infrarenal stenosis			BUN/Cr
CNS		Rare headache, dizziness, fatigue insomnia		

Key References: Li EC, Heran BS, Wright JM: Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension, *Cochr Database Syst Rev* 8:CD009096, 2014; Hajjar I, Brown L, Mack WJ, et al.: Impact of angiotensin receptor blockers on Alzheimer disease neuropathology in a large brain autopsy series, *Arch Neurol* 69(12):1632–1638, 2012.

Perioperative Risks

- Reduced responsiveness to vasopressor, potential risk of rebound Htn in withdrawal (potential risks in general/neurologic/vascular surgery).
- Potential risk of ARF in major bleeding and kidney ischemia.

Induction/Maintenance

- Watch for refractory hypotension, which requires treatment with a vasopressin agonist.

Adjuvants/Regional Anesthesia/Reversal

- No known interactions

Postoperative Period

- Resume preop drugs for BP control if no ARF
- Only available in "per os" forms

Anticipated Problems/Concerns

- Recommended preop withdrawal for 24–48 h

Antianxiety Medications

Ijeoma Nwachukwu | Lee A. Fleisher

Uses

- Preop anxiolysis, anterograde amnesia, IV sedation, IV induction of anesthesia, suppression of seizure activity, muscle relaxation

Perioperative Risks

- Sedation
- Respiratory depression
- Apnea
- Airway obstruction
- Delayed emergence
- Delirium

Worry About

- Potentiation of respiratory depression with opioids

Overview/Pharmacology

- Benzodiazepines (midazolam and diazepam) are the most commonly used antianxiety medications in the periop period.
- Benzodiazepines:
  - Highly lipid-soluble, allowing a rapid onset of action and quick termination of effects.
  - Antianxiety effect via activation of the GABA receptor by binding to the gamma subunit.
  - Metabolized in the liver by microsomal oxidation or glucuronide conjugation.
  - Effects can be reversed by flumazenil, a selective benzodiazepine antagonist.

Drug Class/Mechanism of Action/Usual Dose

- Benzodiazepines
- GABA activator
- Chronically taken for generalized anxiety, panic attacks, muscle spasms, phobias
- Acutely taken for periop anxiolysis, IV sedation, induction of general anesthesia, seizures
- Anxiolysis dose for midazolam is 1–2.5 mg IV q5 min or 0.07–0.08 mg/kg IM q30–60 min
- Alternatives: Other benzodiazepines (clonazepam, alprazolam), beta blockers (propranolol), tricyclic antidepressants (amitriptyline), SSRIs (duloxetine), anticonvulsants, propofol

Drug Effects

System	Effect	Assessment by Hx	PE	Test
CNS	CNS depression, decreased cerebral metabolic rate, decreased cerebral blood flow, decreased seizure activity	Headache, anterograde amnesia		
CV	Decreased SVR, decreased systolic BP		Hypotension	ECG
RESP	Dose-dependent respiratory depression, decreased ventilatory response to CO_2	Drowsiness, sedation	Hypoventilation, apnea, hiccoughs, cough	ABG
GI	Decreased to increased N/V		Increased secretions	
DERM	Eruptions	Pain at IV injection site, pruritus, burning	Erythema Hives	
Toxicity				
CV	Cardiac arrhythmias including premature ventricular contraction, bradycardia, and tachycardia		Hypotension	ECG
RESP	Respiratory arrest, airway obstruction, laryngospasm, bronchospasm		Apnea, shallow respirations	ABG
DERM	Thrombophlebitis	Pruritus	Hives	
CNS	Unconsciousness, physical dependence, anterograde amnesia		Unresponsiveness, delirium, dysphoria	

Key References: Olkkola KT, Ahonen J: Midazolam and other benzodiazepines, *Handb Exp Pharmacol* 182:335–360, 2008; Eilers H: Intravenous anesthetics. In Miller RD, Pardo M editors: *Basics of anesthesia*, 6th ed. Philadelphia, 2011, Elsevier, pp 99–114.

Perioperative Implications

Preoperative Concerns

- Antianxiety medications have a synergistic effect with opioids and propofol and may potentiate respiratory depression, leading to airway obstruction or respiratory arrest.
- Effects of benzodiazepines can be prolonged in the elderly and in pts with severe liver disease.

Induction/Maintenance

- Benzodiazepines can be used for the induction of general anesthesia. A dose of 0.1–0.3 mg/kg of midazolam is sufficient to produce unconsciousness.
- When administered with other induction agents, benzodiazepines decrease the speed of induction and decrease minimal anesthetic concentration MAC requirements.

Reversal

- Effects of benzodiazepines can be reversed by flumazenil, a benzodiazepine antagonist.

Anticipated Problems/Concerns

- Flumazenil has a shorter half-life than benzodiazepines; hence medication should be redosed to avoid resedation.