Drug Effects

System	Effect	Assessment by Hx	PE	Test
CV	Increased SVR (with initiation) Decreased SVR Decreased inotropy Decreased chronotropy	Headache, palpitations, dizziness, diaphoresis, abdominal pain	Pulse, BP, skin temperature and turgor	ECG PA cath TEE
RESP	Usually minimally reduced Minute ventilation and preserved CO_2 Responsivity		Hypopnea, apnea, cyanosis	Spirometry Pulse oximetry Capnogram
CNS	Sedation Amnesia Analgesia Reduced CBF	Ramsay sedation scale Recall Pain	Somnolence	BIS Blood glucose
OTHER	Xerostomia/antisialagogue Plt aggregation Lipolysis inhibition Insulin secretion inhibition	Dry mouth/nasal decongestion		

Key References: Carollo DS, Nossaman BD, Ramadhyani U: Dexmedetomidine: a review of clinical applications, *Curr Opin Anaesthesiol* 21(4)457–461, 2008; Giovannitti JA Jr, Thoms SM, Crawford JJ: Alpha-2 adrenergic receptor agonists: a review of current clinical applications, *Anesth Prog* 62(1):31–39, 2015.

Perioperative Implications

Preoperative Preparation

- Pts who do not take their dose of clonidine on the morning of surgery commonly develop rebound hypertension. Pts on clonidine often take it for refractory Htn; labile BP should be anticipated. Baroreceptor sensitivity is generally preserved.
- Clonidine has shown some effectiveness for myocardial protection in CV surgery and can be considered in pts who would benefit from but have a contraindication to periop beta blockade.
- When $alpha_2$ agonists are used for sedation during awake FOI, consider adding low-dose (30–70 μg/kg) midazolam if definitive amnesia is desired.
- Concomitant use of inhibitors of cytochrome P450 enzymes (i.e., cimetidine, some fluoroquinolones, verapamil) may lead to increased serum levels of clonidine and tizanidine.

Induction/Maintenance

- Slow, controlled induction is preferred when not contraindicated. Decreases in SVR and inotropy may be exaggerated in pts receiving $alpha_2$ agonists.
- Pts on clonidine and dexmedetomidine can have significant reductions in MAC requirements (30–50% in some studies but wide ranges seen). Titration to hemodynamic variables or BIS may be useful.

Postoperative Period

- Pts already taking clonidine should continue it to avoid rebound Htn.
- Rebound Htn is unlikely with dexmedetomidine infusions of <24 h duration.
- Dexmedetomidine infusion has been used in the immediate postop setting to reduce narcotic requirements in certain populations where narcotic use is undesirable (e.g., morbidly obese).

Anticipated Problems/Concerns

- Treatment of hypotension and dysrhythmias such as symptomatic bradycardia and AV block may become necessary. Treatment of hypotensive bradycardia with anticholinergics alone (esp. in those in whom coronary perfusion is SVR-dependent) may precipitate myocardial ischemia in pts with low SVR (altered supply/demand ratio).

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Amphetamines

Luis R. Sauceda-Cerda | Jeffrey R. Kirsch

Uses

- Attention deficit hyperactivity disorder
- Weight loss
- Narcolepsy
- Recreational

Perioperative Risks

- Possible increased requirement for volatile anesthetic with acute use
- Possible decreased requirement for volatile anesthetic with chronic use (CNS depression)
- Catecholamine depletion with chronic use
- Increases in temperature with acute intoxication
- Increases in blood pressure and heart rate with acute intoxication
- Altered mentation, dysphoria, and euphoria with acute intoxication
- Acute intoxication can mimic preeclampsia or eclampsia in parturient pt

Worry About

- Severe Htn, palpitations, confusion, dizziness, and vasomotor disturbances especially in pts with ischemic heart disease, Htn, rhabdomyolysis, and hyperthyroidism

Overview/Pharmacology

- Consumed enterally, inhaled (i.e., smoked), snorted, or administered IV
- Psychoactive substance with CNS stimulation and mood-altering properties; several amphetamine derivatives used for illicit purposes (i.e., meth, Ecstasy).
- Consumption of amphetamine-producing plants occurs in some geographical areas (i.e., East Africa).
- Endogenous (i.e., beta-phenethylamine) amines may have amphetamine-like effects
  - Found in trace quantities in the peripheral nervous system and CNS.
  - Metabolized rapidly by monoamine oxidase.
- Elimination half-life ranges between 6–12 h (renal and hepatic clearance); urine alkalization prolongs half-life, so abusers may ingest HCO_3 to prolong half-life.
- Cardiotoxic manifestations include stress cardiomyopathy, MI, and arrhythmias.

Drug Class/Mechanism of Action/Usual Dose

- Amphetamine
- Complicated mechanism of action likely involves
  - Downregulation of monoamine transporters at synaptic cleft
  - Competitive inhibition of monoamine reuptake at synaptic cleft
  - Stimulation of monoamines at nerve terminals
- Dose variable depending on indication

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.