ACE Inhibitors

Thai T. Nguyen | Lee A. Fleisher

Uses

- Treatment of essential Htn, CHF, and mitral regurgitation.
- Numerous studies show that ACE-I use improves symptoms and quality of life, as well as reduces mortality rate in elderly with heart failure and decreased LVEF.
- Decreases mortality after myocardial infarction.
- Safe and effective treatment of Htn in diabetics; strong evidence that ACE-I delays the progression of diabetic renal disease.

Perioperative Risks

- Severe and prolonged hypotension in pts undergoing general anesthesia
- May increase insulin sensitivity and hypoglycemia in diabetics
- Conflicting evidence regarding risk of AKI

Worry About

- Decreased GFR and not recommended in pts with renal artery stenosis.
- Life-threatening angioedema involves the swelling of head, neck, and tongue.
- Hyperkalemia because of decreased production of aldosterone.
- Fetal anomalies and fetal and neonatal death.

Overview/Pharmacology/Dose

- A recent systematic review did not find evidence to support that periop ACEIs or ARBs can prevent mortality, morbidity, and complications (hypotension, periop cerebrovascular complications, and cardiac surgery–related renal failure).
- Captopril is available in oral dose and very effective in treating Htn.
- Enalapril has to be converted by esterase in liver to the active metabolite enalaprilat.
- Both captopril and enalapril are renally excreted and should be reduced in pt with renal dysfunction.
- Lisinopril is absorbed as the active form and offered as once-daily dosing.

Characteristic	Captopril	Enalapril	Lisinopril	Benazepril	Fosinopril	Quinapril	Ramipril
Elimination	Renal	Renal	Renal	Renal	50% renal 50% hepatic	61% renal 37% hepatic	Renal
Onset of hypotensive action (h)	0.25	1	1	1	1	1	1–2
Peak hypotensive effects (h)	1–1.5	4–6	6	2–4	2–6	2	3–6
Duration of hypotensive effects (h)	Dose related	24 (18–30)	24 (18–30)	24	24	24	>24 (24–60)
Dose (mg)	25–150, max 450	5–40, max 40	10–40, max 80	20–80, max 80	10–40, max 80	10–80, max 80	2.5–20, max 20

Drug Class

- Affects the renin-angiotensin system by blocking the conversion of angiotensin I to the active angiotensin II and delaying bradykinin breakdown and associated prostaglandins.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
HEENT	Angioedema Bronchospasm	Swelling of face, neck, tongue Dyspnea	Difficulty speaking, swallowing Wheezing	Airway exam
CV	Hypotension	Assess CV response to Rx		
GU	Renal failure Hyperkalemia	Orthopnea, dyspnea	Edema	BUN, Cr, lytes
HEME	Leukopenia, agranulocytosis	Fever	CBC with diff	

Key References: Zou Z, Yuan HB, Yang B, et al.: Perioperative angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers for preventing mortality and morbidity in adults, *Cochrane Database Syst Rev* (1):CD009210, 2016; Mets B: To stop or not? *Anesth Analg* 120(6):1413–1419, 2015.

Drug Interactions

Preoperative Period

- Assess for evidence of renal insufficiency.
- Monitor for hyperkalemia.
- ACE-I can be continued until the day of surgery because of the potential benefits in reducing mortality and morbidity, but many hold the day of surgery. This issue is controversial.

Induction/Maintenance

- Consider reducing the ACE-I dose so that hypotension can be avoided.
- Severe and refractory hypotension can be resistant to vasopressors such as phenylephrine, ephedrine, and norepinephrine.
- Vasopressin and analogs can be useful to restore BP.
- Use of succinylcholine with elevated K^+ may be associated with cardiac arrhythmia.

Adjuvant/Regional Anesthesia/Reversal

- Hypotensive episodes may be associated with spinal and epidural anesthesia.

Postoperative Period

- Monitor for hypotension.

Acetaminophen

William J. Fawcett

Uses

- Minor analgesic for acute and chronic pain.
- First-line agent in WHO analgesia treatment ladder.
- First-line agent in treatment of pain in pregnancy and compatible with breastfeeding.
- Commonly administered in combination with codeine phosphate (e.g., paracetamol 500-mg and codeine 8-mg or paracetamol 500-mg and codeine 30-mg tablets).
- Commonly used as multimodal analgesic with an opioid-sparing effect.

Risk

- Well tolerated in normal therapeutic doses.
- Overdose associated with hepatotoxicity and nephrotoxicity.
- Unlike NSAIDs, negligible clinical antiinflammatory and antiplatelet effects.

Overview/Pharmacology

- Rapidly absorbed in GI tract, mostly in the small intestine.
- Rectal bioavailability is variable (30–70%).
- IV preparation has been associated with flushing, tachycardia, and hypotension.
- Half-life 1.25–3 h, peak plasma concentration 30–60 min
- 20% is protein-bound.
- Serum therapeutic levels 10–30 μg/mL.
- Analgesic effect lasts for approximately 6 h.
- 25% of dose undergoes first-pass effect in the liver; this is reduced with larger doses as liver's enzymatic capacity is overwhelmed.
- 90% is metabolized by conjugation in the liver via mainly by glucuronidation conjugation (and to a lesser extent sulfate conjugation), forming nontoxic metabolites (saturated at doses >150 mg/kg) and renally excreted (90–100% is recovered in urine within 24 h). Less than 5% is excreted unchanged in the urine.
- 10% undergoes oxidative metabolism via cytochrome P450 isoenzymes CYP2E1, CYP1A2, CYP3A4, and CYP2D6 to form the potentially hepatotoxic and nephrotoxic metabolite N-acetyl-p-benzoquinoneimine NAPQI. This metabolite is readily detoxified by glutathione.

- High levels of NAPQI (e.g., in overdose, cytochrome P450 system induction, low glutathione levels) results in NAPQI forming covalent bonds to hepatocyte cysteinyl-sulfhydryl groups. The loss of glutathione leads to increased formation of reactive oxygen and nitrogen species, causing mitochondrial permeability transition with loss of membrane potential and ultimately failure to synthesize ATP, leading to hepatic necrosis.

Drug Class/Mechanism of Action/ Usual Dose

- Mechanism of action remains unclear.
- COX isoenzymes (which produce prostaglandins and other eicosanoids) are pivotal in treating pain and inflammation. Peripheral COX-1 (constitutive) and COX-2 (inducible) isoenzymes are inhibited by a variety of peripherally acting NSAIDs, but paracetamol has little or no effect here.
- A central mechanism of action likely due to
  - COX-2 inhibition.
  - Cannabinoid receptor agonism.
  - Indirect augmentation of descending serotoninergic pathways.
  - Transient potential receptor (TPR) channel activity. The metabolite NAPQI causes spinal-level analgesia by activating the transient receptor potential ankyrin-1 (TRPA1) receptor.
  - Other suggested mechanisms include inhibition of L-arginine-NO-pathway (preventing NO synthesis) and activation of another TPR, the transient receptor potential vanilloid-1 (TRPV1) receptor. Inhibition of a COX-3 receptor is no longer accepted as a significant mechanism.

Available in oral, rectal, and parenteral preparations.

- Maximum dose 4 g q24h; dosage, 1 g q4–6h.
- Adjust dose for renal impairment. If estimated GFR is <30 mL/min per 1.73 m^2, increase dose interval to 6 h.
- If body weight is <50 kg, adjust dose to a maximum of 60 mg/kg/d.

Assessment Points

System	Effect	Assessment by Hx	Test
CNS	Encephalopathy, antipyretic effects, analgesia (following overdose)	Coma	GCS, CT/MRI (cerebral edema)
GI	Hepatic dysfunction (following overdose)	N/V, anorexia, sequelae of liver failure	Transaminases, INR, bilirubin, hypoglycemia
RENAL	Renal dysfunction, acute tubular necrosis (following overdose)	Oliguria	BMP, Cr, UA
METAB	Metabolic acidosis (following overdose)		Lactate, ABG
DERM	Stevens-Johnson syndrome Toxic epidermal necrolysis		Full blood count, C-reactive protein
HEME	Thrombocytopenia Leukopenia Neutropenia		FBC
RESP	Bronchoconstriction	Labored breathing, wheeze	Increased peak/plateau airway pressure, auscultation

Key References: Sharma CV, Mehta V: Paracetamol: mechanisms and updates, *CEACCP* 14(4):153-158, 2015; http://www.evidence.nhs.uk/formulary/bnf/current/4-central-nervous-system/47-analgesics/471-non-opioid-analgesics-and-compound-analgesic-preparations/paracetamol (Accessed February 15, 2017).

Suspected Toxicity and Treatment

- Overdose accounts for nearly 50% of acute liver failure in USA and UK.
- Can occur with 150 mg/kg taken in <1 h.
- Rare with doses <75 mg/kg.
- Half of acetaminophen overdoses leading to hospitalization were unintentional.
- Nephrotoxicity occurred in only 1–2% of pts with acetaminophen overdose.
- If toxicity is suspected, do not delay giving N-acetylcysteine (NAC). Proposed mechanisms of action for antidote include increasing glutathione stores and conjugation to NAPQI, antioxidant effects, antiinflammatory effects, and increases in NO resulting in microvascular perfusion.
- Serum acetaminophen concentration and treatment plotted according to normograms (e.g., Rumack-Matthew).
- Serum concentrations unreliable at <4 h; uncertain prognostic accuracy at >15 h.

Symptoms

- Phase I (0–24 h): Asymptomatic, anorexia, N/V, malaise, subclinical rise in serum transaminases
- Phase II (18–72 h): Right-upper-quadrant abdominal pain, anorexia, N/V, increased transaminases levels
- Phase III (72–96 h): Centrolobular hepatic necrosis, jaundice, coagulopathy, hepatic encephalopathy, renal failure, fulminant hepatitis, death
- Phase IV (96 h–3 wk): Complete resolution of symptoms and organ failure

Treatment

- Gastric decontamination: Within 4 h of ingestion (charcoal 1g/kg PO)
- NAC administration IV (150 mg/kg over 60 min, then 50 mg/kg over 4 h, then 100 mg/kg over 16 h). Sometimes the oral route is used (140 mg/kg, then 70 mg/kg for 72 h).
- Side effects of IV NAC: Anaphylactoid reactions; oral NAC, N/V.
- Supportive measures.

Perioperative Implications

- Ensure pts have not been self-medicating with acetaminophen prior to admission.
- Loading dose often administered in pediatric pts is 20–30 mg/kg, but do not exceed 75 mg/kg or 4 g in 24 h.
- Need to know dose 24 h prior to any acetaminophen administration.
- Care required in pts with reduced liver capacity (e.g., preexisting liver impairment, following liver resection).
- Increased periop morbidity in pts with abnormal liver function tests.

Drug Interactions

- CYP inducers: Barbiturates, buproprion, caffeine, carbamazepine, charcoal-broiled food, cruciferous vegetables, dihydralazine, isoniazid, phenytoin, primidone, rifampin, ritonavir, sulfinpyrazone, ethanol, isoniazid.
- Warfarin, NSAIDs: Coagulopathic effects may be potentiated by acetaminophen.
- Potential antinociceptive effect by 5-HT_3 receptor antagonists.

Alkylating Agents

Raymond D. Sroka | Mark J. Lema

Uses

- Bone marrow transplants
- Breast and bladder cancers
- Lymphomas and leukemias
- Cancers of the lung, pancreas, and brain
- Ovarian and testicular cancers
- Multiple myeloma
- Sarcomas and melanomas

Perioperative Risks

- Increased risk of infection
- Aspiration (subsequent to N/V)
- Prolonged succinylcholine action (CTX, thiotepa)
- Fluid retention (HN_2)
- Prolonged bleeding (thrombocytopenia)

Worry About

- Extravasation if given by IV infusion

Overview/Pharmacology

- First chemotherapy agents (1940s)
- First used in chemical weapons during World War I
- Structurally diverse compounds
- Generate reactive, electron-deficient intermediates
- Covalently bind to DNA bases, especially guanine, often during mitosis
- Disrupt DNA replication and transcription
- Side effects (acute) 1–3 wk after therapy
- High incidence of cytotoxicity to normal, rapidly dividing cells:
  - Bone marrow suppression
  - GI distress
  - Sterility
  - Increased risk of secondary malignancies (leukemia)
  - Alopecia
- End-organ toxicities:
  - CNS
  - Hepatic
  - Pulm
  - Renal