- 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

Drug Effects

Class	Name	Abbrev	Special Indication	Adverse Effects
Nitrogen Mustards				
Mechlorethamine	Mustargen	HN_2	LM	N/V, phlebitis, hyperuricemia, potent vesicant
Cyclophosphamide	Cytoxan	CTX	LM, Brt, Bl, Lu, Ov	Decreases pseudo-ChE; myocardial toxicity, hemorrhagic cystitis
Ifosfamide	Ifex		LM, Ov, Te, Sa	Hemorrhagic cystitis, N/V, CNS toxicity, metabolic acidosis
L-Phenylalanine	Alkeran (melphalan)	L-PAM	MM	Mild N/V
Chlorambucil	Leukeran	CLR	CLL, LM	N/V, seizures
Ethyleneamines				
Triethylene-thiophosphoramide	Thiotepa	T-TEPA	BMT	Can lower pseudo-ChE, prolongs succinylcholine action
Alkyl Sulfonates				
Busulfan	Myleran	MYL	CML	Pulm toxicity, N/V, seizures, mucositis, hyperbilirubinemia
Nitrosoureas				
Chloroethyl-cyclohexyl-nitrosourea	Lomustine	CCNU	LM, Brn	N/V, hepatic toxicity, pulm toxicity, renal toxicity
Bis-chloroethyl-nitrosourea	Carmustine	BCNU	LM, Brn	N/V, phlebitis, pulm toxicity
Streptozocin	Zanosar	STZ	Pa	N/V, dose-related renal toxicity
Triazenes				
Dimethyltriazenoimidazole carboxamide	Dacarbazine	DTIC	HD, Sa, Me	N/V, anaphylaxis, phlebitis, hepatotoxicity

Bl, bladder; *BMT*, bone marrow transplant; *Brn*, brain; *Brt*, breast; *CLL*, *CML*, leukemias; *HD*, Hodgkin disease; *LM*, lymphoma; *Lu*, lung; *Me*, melanoma; *MM*, multiple myeloma; *Ov*, ovarian; *Pa*, pancreatic; *Sa*, sarcoma; *Te*, testicular.

Key References: Cytotoxic agents. In Brunton LL, Chabner BA, Knollmann BC *Goodman & Gilman's the pharmacological basis of therapeutics*, ed 12, New York, 2011, McGraw-Hill; Huettemann E, Sakka SG: Anaesthesia and anti-cancer chemotherapeutic drugs. *Curr Opin Anaesthesiol* 18:307–314, 2005.

Perioperative Implications

Preoperative Preparation
- Full-stomach precautions.
- Risk of infection secondary to leukopenia.
- Adequate hydration to prevent additional nephrotoxicity.
- Check CBC due to myelosuppression.
- Consider PFTs (busulfan, cyclophosphamide).
- Consider ECHO or MUGA (if concern for cyclophosphamide-induced pericarditis/myocarditis).

Intraoperative Considerations
- Risk of aspiration during induction.
- Prolonged bleeding.
- Consider RBC transfusion.
- Maintain UO.
- Reduced dose of succinylcholine (CTX, thiotepa).

Postoperative Period
- Risk of N/V (most agents).
- Continued fluid hydration.
- Monitor for cardiac or pulm dysfunction.
- Monitor renal and hepatic function.

Alpha$_1$ Antagonists

Patrick F. Wouters

Uses
- First-line drug treatment for male lower urinary tract symptoms
- Treatment of primary hypertension (not as first-line therapy)
- Preop treatment of pheochromocytoma
- Emerging role in treatment of autonomic dysreflexia
- Occasionally used in treatment of Raynaud phenomenon
- Less commonly used in congenital heart surgery to reduce SVR and correct systemic-to-pulmonary blood flow ratio
- Less commonly used to achieve controlled hypotension intraop
- Being explored as a potential treatment of posttraumatic stress disorder

Perioperative Risks
- Intraop hypotension with attenuated response to the effect of alpha$_1$-agonist therapy
- Intraop floppy iris syndrome: Inhibition of iris dilator muscle contraction and tendency of iris to protrude through surgical incision

Worry About
- Orthostatic hypotension, syncope (less with α_{1A}-selective blockers; more when combined with antihypertensive medication
- Reflex tachycardia (less with selective alpha$_1$ blockers)
- Volume expansion of interstitium and plasma (secondary hyperaldosteronism)
- Priapism, urinary incontinence
- Other adverse events: Asthenia, nasal congestion, headache, dizziness

Overview/Pharmacology
- Also known as α_1-adrenoceptor antagonists (α_1-blockers)
- Mechanism of action: reversible competitive antagonism of postsynaptic alpha$_1$-adrenergic receptors
- Primarily active in tissues that sustain high levels of alpha-adrenergic sympathetic tone (resistance arteries, capacitance veins, urinary bladder outflow tract)
- Effect proportional to baseline sympathetic tone
- Nonselective (alpha$_1$ and alpha$_2$) adrenergic blockers: Phenoxybenzamine (irreversible) and phentolamine
- Selective alpha$_1$-adrenergic blockers: Prazosin (highest affinity), doxazosin, terazosin, silodosin, tamsulosin, bunazosin, alfuzosin
- Mixed alpha$_1$ and beta-adrenergic blocker: Labetalol
- Mixed alpha$_1$-adrenergic and 5-HT1A blocker: Urapidil

Usual Dose
- Treatment of hypertension: Prazosin 1–20 mg 2–3x/d; terazosin 1–20 mg 1–2x/d; doxazosin 1–16 mg 1x/d
- Treatment of benign prostatic hypertrophy: Alfuzosin 5 mg 1–2x/d; silodosin 4–8 mg 1x/d; tamsulosin 0.4 mg 1x/d; terazosin 1–10 mg 1x/d

Toxicity
- Safety unknown during pregnancy; many pass through breast milk
- No safety studies in children