Overview/Pharmacology

- Inhibitor of plt aggregation through action at plt ADP receptor
- Two types:
  - Thienopyridine derivatives (clopidogrel, ticlopidine, prasugrel): Prodrugs—metabolized by the liver to active metabolites. Irreversibly bind to the receptor, thus inhibiting plt aggregation for the life span of the plt.
  - Direct acting $P2Y_{12}$ RBs (cangrelor, ticagrelor, elinogrel): Competitively bind to receptors causing conformational changes. Reversible concentration-dependent effect.

Drug Class/Mechanism of Action/Usual Dose

- Clopidogrel: 300-600 mg loading (PO), 75 mg daily for maintenance. Used pre-PCI, ischemic stroke/TIA (if pt is ASA-intolerant), NSTEMI (with ASA), AF if intolerant of warfarin (with ASA). Genetic polymorphisms—CYP2C19 poor metabolizers; need 150 mg maintenance. Half-life 7–9 h.
- Prasugrel: 60 mg loading (PO), 5-10 mg daily for maintenance. Used with ASA for ACS undergoing PCI (alternative to clopidogrel). Half-life 7 h, plt function recovers in 2–3 d. More effective and faster than clopidogrel, but higher risk of bleeding.
- Cangrelor: IV preparation. Used for ACS/PCI if pt has not yet received oral $P2Y_{12}$ RB. 30 mg/kg bolus then 4 mg/kg per min infusion for 2 h or duration of intervention. Half-life 3–6 min, rapid recovery of plt function (5 min).
- Ticagrelor: With ASA for pts with ACS. 180 mg (PO), then 90 mg twice daily. Alternative to clopidogrel for PCI. More rapid onset of action and more potent than clopidogrel/prasugrel.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV		ACS/MI, stroke, PVD	Pulse	ECG, BP
CNS	Dizziness, headache, vertigo, intracranial hemorrhage	Intracranial hemorrhage	Decreased LOC	CT (if required)
GI	Abdominal pain, diarrhea, constipation, nausea, GI bleeding	GI hemorrhage	Stool guaiac	
GU	Acute renal failure (uncommon with cangrelor)			Renal function
DERM	Pruritus, ecchymosis, rash	Rash, pruritus		
HEME	Anemia, purpura, epistaxis, bleeding, thrombocytopenia (rare)	TTP (rare)		FBC, coagulation screen

Key References: Oprea AD, Pepescu WM: Perioperative management of antiplatelet therapy, *Br J Anaesth* 111(Suppl 1):i3–i17, 2013; Levine GN, Bates ER, Bittl JA, et al.: 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery, *Circulation* 134(10):e123–e155, 2016.

Perioperative Implications

Preoperative Concerns

- Significantly increased risk of surgical bleeding if $P2Y_{12}$ RB is discontinued <7 d before surgery

Bleeding Risk

- If procedure involves a low bleeding risk (e.g., dental extraction, plastic surgery), continue DAPT.
- If intermediate bleeding risk, stop $P2Y_{12}$ RB, continue ASA.
- If high risk bleeding, postpone surgery if possible. If urgent, stop DAPT and consider bridging therapy.

Urgent Procedures

- Plt transfusion to counteract effects; however, be aware of the risk of ST.
- If plts given within half-life of $P2Y_{12}$ RB, new plts can also be affected by drug.

Anticipated Problems/Concerns

- If on $P2Y_{12}$ RB for AF or primary prevention of cardiac/CNS events, drug may be stopped preop without major consequences.
- If $P2Y_{12}$ RBs are part of DAPT for pre- or post-PCI stenting, need to consider (1) appropriate and safe time frame between stent placement and embarking on surgery, (2) potential consequences of stopping DAPT, (3) urgency of intervention, and (4) bleeding risk associated with the intervention. Need to make a thorough risk-benefit analysis of stopping or continuing.
- Bridging therapy: Poor evidence for best practice. Options include unfractionated heparin or LMWH, short-acting glycoprotein IIb/IIIa inhibitors (tirofiban/eptifibatide), or cangrelor as an IV preparation.
- RA: A vertebral canal hematoma is a rare but potentially catastrophic complication of neuroaxial blockade. Actual risk of vertebral canal hematoma with $P2Y_{12}$ RBs is unknown; however, published international guidelines, including those from the American Society of Regional Anesthesia and Pain Medicine, support the recommendation of discontinuing for at least 7 d and extending up to 10 d for prasugrel because of its higher incidence of bleeding when compared with clopidogrel.

Management of Intraoperative Bleeding on Dual Antiplatelet Therapy

- Surgical management of bleeding.
- Plt transfusion to reverse effects of $P2Y_{12}$ RBs.
- Make sure other causes of coagulopathy are identified and treated (point-of-care testing if available).
- Other blood products as clinically indicated.
- No specific reversal agents to $P2Y_{12}$ RBs.

Penicillins

Lucy Waskell

Uses

- Prescribed for pts with infections due to sensitive organisms, primarily *Pneumococcus* and those in genera *Streptococcus*, *Staphylococcus*, *Neisseria*, *Pseudomonas*, *Proteus*, *Haemophilus*, *Helicobacter*, *Moraxella*, and so on; used as prophylaxis for subacute bacterial endocarditis (penicillin G benzathine).
- Can be administered PO, IM as regular or slow-release repository form, or IV.

Worry About

- Hypersensitivity reactions (0.7–4%): rash, fever, bronchospasm, vasculitis, serum sickness, exfoliative dermatitis, Stevens-Johnson syndrome, angioedema, anaphylaxis
- Hyperkalemia when penicillin G potassium is administered IV (1.7 mEq K^+/1 × 10^6 units penicillin G), especially if administered rapidly
- Plt dysfunction, defective hemostasis after ticarcillin, and penicillin G
- Rare bone marrow depression, granulocytopenia, hepatitis
- Headaches, seizures after 1 dose of 5 MU of penicillin G procaine
- Clearance lower in neonates and infants
- After ingestion, nausea and diarrhea, rarely *Clostridium difficile* pseudomembranous colitis

Overview/Pharmacology

- Used to treat wide spectrum of infectious diseases.
- Many penicillins are acid-labile (pH 2 destroys antibiotic); often not administered orally.
- Actively and rapidly excreted by renal tubule.
- Half-life markedly increased in anuria.
- Dosage should be decreased in renal failure.
- Other organic acids (e.g., probenecid) can compete at the renal tubule for excretion, prolonging half-life of the antibiotic.
- High concentration in urine.
- Ampicillin and amoxicillin often administered with β-lactamase inhibitors such as clavulanate and sulbactam.
- Ticarcillin and piperacillin marketed in combination with β-lactamase inhibitors clavulanate, and tazobactam respectively.

Drug Class/Mechanism of Action/Usual Dose

- Organic acids consisting of a β-lactam ring to which is attached a side chain and a thiazolidine ring; they inhibit bacterial cell wall synthesis primarily by inhibiting the transpeptidase reaction, which is essential for bacterial cell-wall synthesis.
- Dose and route of administration depend on type of penicillin used and severity of disease treated.

Drug Effects

Drug	Absorption After Oral Dose	Resistance to Penicillinase	Dose IV	Antimicrobial Spectrum	Side Effects
Penicillin G	Poor; about one third of dose; taken on empty stomach	No	1–10 MU q4–6h	*Streptococcus, Neisseria*	Increased K^+ (1.7 mEq K^+/1 × 10^6 units penicillin G); greater than 20 1 × 10^6 U/d can cause seizures; inhibits platelet aggregation
Penicillin V	Moderate; 2–5 times greater than penicillin G	No	0.5 g q6h PO	Like penicillin G	K^+ salt
Dicloxacillin	Good (30–80% of dose taken on empty stomach)	Yes	0.5–1 g PO q6h	*Staphylococcus aureus*	90–95% bound to albumin; not removed by dialysis
Ampicillin	Good; taken on empty stomach	No	1–2 g q6h (250–500 mg q6h PO)	Gram + cocci, gram negative, *H. influenza, Escherichia coli, P. mirabilis*	
Amoxicillin	Good (better absorption than ampicillin)	No	0.75–1.5 g PO q8h	Like ampicillin	Colitis when taken with clavulanate
Ticarcillin	Poor	No	50–75 mg/kg q6h	*Pseudomonas, Enterobacter, Proteus* (indole +) + ampicillin spectrum	CHF secondary to Na^+ overload; 5 mEq Na^+/g; low K^+ secondary to obligatory cation excretion with anion; decline in platelet aggregation
Piperacillin	Poor	No	2–6 g q8h	*P. aeruginosa, Enterobacter, some Klebsiella,* other gram negatives, gram + *cocci, Listeria monocytogenes,* ampicillin spectrum	Same as ticarcillin: 2 mEq Na^+/g

Key Reference: Petri WA: Penicillins, cephalosporins, and other β-lactam antibiotics. In Brunton LL, Chabner B, Knollman B, editors: *Goodman & Gilman's the pharmacological basis of therapeutics,* ed 12, New York, 2011, McGraw-Hill, pp 1477–1504; Bhattacharyya RP, Grad YH, Hung DT: Genomics and infectious disease. In Kasper D, Fauci A, Hauser S, et al, editors: *Harrison's principles of internal medicine,* ed 19, New York, 2015, McGraw-Hill, Chapter 146.

Perioperative Implications

Preoperative Concerns

- Is pt allergic to any penicillins? What exactly happens when the drug is taken (rash vs. anaphylaxis)?
- If pt is on large doses of penicillin G, ticarcillin, or piperacillin, are serum electrolytes normal?
- Hemostasis, especially platelet aggregation, may be inhibited by the antibiotics.
- If pt has renal insufficiency or failure, dose of antibiotic should be q12h or less frequently.

Induction/Maintenance/Postoperative Period

- Penicillins should have no effect on induction or maintenance unless allergic reaction occurs; no known interactions with any anesthetic agents.

Anticipated Problems/Concerns

- Relate to administration of large amounts of Na^+, K^+, and organic anions (acids). Possible bleeding problems due to platelet dysfunction.

Phencyclidine

Davide Cattano

Uses

- DEA Schedule I drug of abuse with no present medical indications; street terms for PCP include angel dust, supergrass, killer weed, embalming fluid, rocket fuel, wack, and ozone.
- Common routes of administration: Smoking (often laced in marijuana cigarettes), oral ingestion; less common is IV injection.
- Experimentally used for animal models of schizophrenia, neurodegenerative diseases and seizure disorders, ischemic neuroprotection, and anesthesia-induced neurotoxicity.

Risk

- Psychosis, seizures, anticholinergic-type syndrome.
- Experimentally, PCP causes irreversible brain damage through excitotoxicity, with the typical bull's eye neuronal cell and vacuolization.

Perioperative Risks

- Aggressive and/or psychotic behavior, hypertension, stroke, hyperthermia, rhabdomyolysis, aspiration

Worry About

- Kidney failure, aspiration, malignant Htn, prolonged action

Overview/Pharmacology

- Effects due to parent compound, highly lipid-soluble, pK_a of 8.6, peak effects in 15 min when smoked and 2 h by ingestion, distribution in 4 h, elimination takes up to 48 h. Metabolites are active and present for weeks in chronic users.
- Metabolized in the liver; urinary excretion of metabolites at low doses, excretion of free drug at high doses, only a small fraction of the drug is excreted unchanged.
- Produces an acute state of intoxication lasting 4–6 h but may produce a chronic state of psychosis that can last up to several days. With low to moderate doses, acute intoxication includes staggering gait, slurred speech, nystagmus, numbness of extremities, sweating, catatonic muscular rigidity, blank stare, changes in body image, disorganized thought, drowsiness, apathy, anterograde amnesia, and possibly aggressive behavior.
- With moderate to high doses, intoxication includes elevated HR and BP, hypersalivation, sweating, fever, repetitive movements, and muscle rigidity on stimulation.
- With high doses, anesthesia, stupor, coma, and convulsions can occur.

Drug Class/Mechanism of Action/Usual Dose

- Arylcyclohexylamine
- Acts at the *N*-methyl-D-aspartate receptor as a noncompetitive antagonist but a weak dopamine, serotonin, and noradrenergic agonist; there is also PCP-induced dephosphorylation of ERK ½ and Akt and dephosphorylation of GSK3-beta (activation) that is prevented by lithium.