Drug Effects

Drug Class	Examples	Mechanism of Action	Adverse Effects	Contraindications	Perioperative Concerns	Perioperative Implications
Sulfonylureas	Glibenclamide Gliclazide Glipizide Tolbutamide Glimepiride	Binds to an ATP-sensitive channel on the cell membrane of pancreatic beta cells Resultant depolarization leads increased secretion of (pro)insulin	Hypoglycemia GI disturbances Blood disorders	Type 1 diabetes Hepatic impairment Severe renal impairment Ketoacidosis	Hypoglycemia Blood disorders	Omit during period of starvation
Meglitinides	Repaglinide Nateglinide	Binds to the ATP-dependent K+ channel on the cell membrane of pancreatic beta cells in a similar manner to sulfonylureas but have a weaker binding affinity Resultant depolarization leads to increased secretion of (pro)insulin	Hypoglycemia GI disturbances	Type 1 diabetes Hepatic impairment Severe renal impairment Pregnancy	Hypoglycemia	Omit during period of starvation
Alpha-glucosidase inhibitors	Acarbose Voglibose	Inhibits digestive enzymes needed to digest complex carbohydrates in the gut Less glucose is absorbed because carbohydrates are not broken down into absorbable glucose molecules	GI disturbances	IBS Predisposition to intestinal obstruction	GI disturbances	Omit during period of starvation
SGLT-2 inhibitors	Dapagliflozin Canagliflozin Empagliflozin	Prevents the kidneys from reabsorbing filtered glucose and thus promotes glucose loss	Increased risk of UTI Dysuria Dehydration and renal impairment Ketoacidosis	Ketoacidosis Renal impairment Pregnancy and breast feeding	Ketoacidosis Dehydration	Omit during period of starvation
Biguanides	Metformin	Decreases hyperglycemia primarily by suppressing hepatic gluconeogenesis Enhances peripheral glucose uptake Decreases absorption of glucose from the GI tract	GI disturbances Taste disturbance Lactic acidosis	Ketoacidosis Surgery	Metformin associated lactic acidosis	Generally omit However, may be continued if starvation is short and there is no risk of AKI
Thiazolidinediones	Pioglitazone	Increases the expression of insulin cell-surface receptors in the tissues Increases insulin sensitivity Is glucose-dependent; therefore the risk of hypoglycemia is low	Heart failure Bladder cancer (small risk) Bone fractures GI disturbance Anemia Macular edema	Heart failure Bladder cancer Hematuria	Heart failure Fluid retention	May be continued if periop period of starvation is short
Incretin mimetics/ GLP-1 analogues	Exenatide Liraglutide Lixisenatide Dulaglutide	Stimulates insulin release in response to food Reduces gluconeogenesis Reduces gastric emptying Promotes satiety (therefore reduces calorific intake)	Delayed gastric emptying	Ketoacidosis Severe GI disease	Delayed gastric emptying	May be continued Supraglottic airways may be contraindicated
The gliptins/DPP IV inhibitors	Sitagliptin Vildagliptin Saxagliptin Alogliptin Linagliptin	Inhibit breakdown of the naturally occurring incretins Prolongs action of naturally occurring incretins	GI disturbances Delayed gastric emptying Pancreatitis	Ketoacidosis	Delayed gastric emptying	May be continued Supraglottic airway may be contraindicated

Key References: Dhatariya K, Levy N, Flanagan D, et al.: Management of adults with diabetes undergoing surgery and elective procedures: improving standards. Joint British Diabetes Societies. Revised March 2016. http://www.diabetologists-abcd.org.uk/JBDS/Surgical_guidelines_2015_full_FINAL_amended_Mar_2016.pdf (Accessed February, 21 2017); Inzucchi SE, Bergenstal RM, Buse JB, et al.: Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 38(1):140–149, 2015.

Perioperative Implications

- Pts on glucose-lowering drugs must be assessed preop to determine suitability for continuation of drugs.
- Continued use is associated with severe metabolic disturbance and is class-specific.
- Continued use is associated with risk of PONV.
- Most of these drugs must be discontinued during the periop period.
- If these drugs are omitted during the periop period, alternative strategies must be implemented to maintain and ensure periop glycemic control.
- Renal function must be monitored and ensured.
- If omitted, these agents should be reintroduced only once normal diet has been resumed and adequate renal function is ensured.

$P2Y_{12}$ Receptor Blockers

Johanna Paterson | Michelle R. Cole

Uses

- $P2Y_{12}$ RBs used alone or in combination with ASA (DAPT).
- ACS, those undergoing PCI with stent placement, and pts with NSTEMI or STEMI.
- Continue for 6–12 mo after insertion of drug-eluting stent (DES), and 4–6 wk after insertion of bare metal stent (BMS).
- Peripheral arterial disease
- AF when warfarin/coumadin is contraindicated
- Ischemic cerebrovascular disease, carotid or vertebral artery dissection (3–6 mo), postcarotid endarterectomy (long term), and carotid artery stenting (DAPT for 30 d).

Perioperative Risks

- Plt dysfunction
- Bleeding if $P2Y_{12}$ RB not stopped 5 d before surgery; ASA to be continued if possible
- Coronary event due to stent thrombosis after DES implantation if $P2Y_{12}$ RB stoppedl risk of ST to be balanced against risk of delay to surgery

Worry About

- Increased bleeding intra- and postop
- Surgery undertaken <30 d after BMS insertion or <6 mo after DES insertion due to increased stent thrombosis risk

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.