dysfunction, especially after platin, vincristine, or vinblastine use. Posterior reversible leukoencephalopathy and stroke have been reported in pts treated with antiangiogenic agents. Cognitive impairment is commonly reported in women treated with tamoxifen.
- Endocrine adverse events, such as hyperglycemia in pts taking dexamethasone and abnormal thyroid function in those treated with targeted therapies, have been reported.
- Musculoskeletal symptoms include cramps, myalgia, bone pain, and arthralgias.
- Ophthalmologic complications such as blepharitis, keratitis, xerophthalmia, and corneal ulcerations have been reported in pts treated with targeted therapies. Nasolacrimal tear duct obstruction has been reported after paclitaxel, radioactive iodine administration, and external beam radiation to the head/neck area causing profound xerophthalmia.
- Dermatologic adverse events can range from mild skin rashes to panniculitis and Stevens-Johnsons syndrome. They can also result from graft-versus-host disease in pts who have undergone stem cell or bone marrow transplants. Mucositis and stomatitis are frequent with most chemotherapeutic agents as well as radiation to the head and neck. Wound healing can be affected after the use of bevacizumab.

Vascular Access
- Vascular fragility, venous sclerosing, and poor venous access are commonly seen in pts who have received multiple regimens of chemotherapy. The need for a peripheral inserted central venous catheter should be considered in the preop visit. Occasionally, preanesthesia placement of a central venous cath is required.

Airway
- Difficult ventilation or endotracheal intubation should be considered in pts receiving corticosteroids or who have undergone radiation to the head and neck. Pts with oral mucositis and thrombocytopenia are at risk for airway trauma and bleeding. Pts with ocular toxicities might be at risk for eye injuries during airway instrumentation.

Induction (General Anesthesia)
- Rapid sequence induction might be needed in pts with moderate to severe GER. Hyperkalemia should be considered in pts with renal failure or tumor lysis syndrome in whom rapid sequence induction is indicated. Careful titration of hypnotics such as propofol is recommended in pts who have received cardiotoxic agents. Pts with autonomic dysfunction (due to taxanes) can develop significant arterial hypotension during induction of general anesthesia. Prolonged muscle relaxation after succinylcholine can be seen in pts treated with cyclophosphamide (inhibition of pseudocholinesterase). Dehydration should be considered in pts with protracted vomiting and diarrhea; therefore intravascular volume replacement and careful induction of general anesthesia is warranted in these pts.

Maintenance (General Anesthesia)
- Careful titration of anesthetic agents, analgesics, and muscle relaxants is recommended in pts treated with procarbazine, thalidomide, and muscle-wasting chemotherapies such as vincristine. Pulm edema can occur after aggressive fluid resuscitation in pts treated with agents such as IL-2, cardiotoxic drugs, or bleomycin and can complicate assessment and replacement of the intravascular volume where indicated in pts treated with nephrotoxic agents.

Positioning
- Careful positioning should be considered in pts with mononeuropathies or polyneuropathies, alopecias, skin bruises, blisters, and osteopenias. Pts with ocular toxicities need proper care of the eye to diminish the risk of corneal abrasions.

Regional Anesthesia
- Thrombocytopenia (due to myelosuppressive drugs), coagulopathy (associated with Mythramycin), and the presence of mononeuropathy or polyneuropathy might contraindicate the use of regional anesthesia.

Postoperative Period
- NSAIDs and acetaminophen should be used carefully in pts treated with nephrotoxic (cisplatin) and hepatotoxic (mithramycin, L-asparaginase) agents and targeted therapies. Cognitive impairment should be taken into consideration in pts treated with tamoxifen.
- Monitoring of hemodynamics and fluid status can be complicated in pts who have received anthracyclines and targeted chemotherapeutic agents that can possibly induce myocardial dysfunction, especially under high workload stress, which cannot be predicted by coronary artery evaluation (such as an adenosine-nuclear perfusion test) where coronary workload reserve has been compromised but coronary anatomy remains intact. Drugs that affect alveolar vascular permeability (such as bleomycin) can also complicate postop hemodynamic management, especially in the face of profound periop blood loss with resuscitation.

Hyperthermic Intraoperative Chemotherapy
- Complex surgical procedure involving extensive peritoneal stripping, tumor debulking, multiple visceral resections, and the delivery of high-dose hyperthermic chemotherapy to the abdominal cavity. Adequate fluid resuscitation is needed, particularly when cisplatin (risk of nephrotoxicity) is used. The need for fluid status monitoring can persist well into the postoperative period.

Cilostazol

C. David Mazer | Niamh McAuliffe

Uses
- Phosphodiesterase inhibitor with antiplatelet aggregation and arteriolar vasodilator properties.
- Prescribed for intermittent claudication in pts with peripheral arterial disease.
- Lowers restenosis rates after peripheral endovascular procedures in Asian populations.
- Secondary prevention of cerebral infarction with less hemorrhagic conversion than aspirin in Asian populations.
- Use has been limited by tolerability due to high incidence of side effects.

Perioperative Risks
- Plt dysfunction
- Unknown effect on periop blood loss
- Drug interactions
- Tachycardia

Overview/Pharmacology
- 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl) butoxy]-3,4-dihydro-2(1*H*)-quinolinone
- Pharmacodynamics:
  - Antiplatelet effect: Strong and specific reversible inhibitor of PDEIII, which increases cAMP in plts, smooth muscle, myocytes, and adipose tissue. This decreases thromboxane A2 production and inhibits plt, aggregation.
  - Reversible plt, inhibition, with duration of up to 12 h. Recovery of plt function 48–96 h after drug cessation with no rebound increase in plt aggregation.
  - Vasodilatation: It targets PDE3 in smooth muscle cells resulting in vessel relaxation.
  - Antiproliferative effect: Increased cAMP upregulates antioncogenes P53 and P21 and hepatocyte growth factor, which induces apoptosis in vascular smooth muscle and inhibits smooth muscle proliferation in vascular beds.
  - Anti atherosclerotic: Alters monocyte chemoattractant protein-1, which recruits monocytes to atherosclerotic lesions.
- Pharmacokinetics:
  - Absorption: Dose—100 mg twice daily to reduce stent restenosis in cardiac patients. Oral administration with peak plasma concentration at 2 h. Steady state is achieved within 4 d. Dietary fat increases absorption and max concentration with potential toxic effects, therefore administer 30 min before or 2 h after meals.
  - Distribution: Cilostazol is 95–98% protein-bound, predominantly to albumin.
  - Metabolism: Hepatic metabolism by cytochrome p450 pathway giving rise to potential drug interactions. Hepatic metabolism involves CYP3A4 (major), CYP1A2 (minor), CYP2C19 (major), and CYP2D6 (minor). There are two major metabolites, the dehydrometabolite is 4–7 times as active as a plt inhibitor and the 4′-trans-hydroxy metabolite is one fifth as active.
  - Excretion: Excretion is predominantly renal, with 74% of metabolites in urine. The elimination half-life is 11–13 h.
- Clinical:
  - Peripheral arterial disease: Approved by the USA FDA for treatment of intermittent claudication because of the drug's ability to decrease plt function and increase vasodilation. Modest improvement in initial claudication distance as compared with placebo (31.41 meters, 95% CI 22.38–40.45 meters). Indicated when lifestyle changes and other therapies have not provided adequate benefit. No evidence of mortality benefit. Has been shown to reduce restenosis and reocclusion rates after peripheral endovascular procedures. May result in lower in-stent stenosis rates after carotid artery stenting.
  - Cerebrovascular disease: Shown to be noninferior to aspirin in secondary stroke prevention in a large RCT in an Asian population, with fewer bleeding events compared with aspirin. May have a role in prevention of intracranial arterial stenosis.
  - Cardiac disease: No reduction in MACE or mortality. Has been associated with a reduction in in-stent restenosis after coronary stent placement in some pt populations. No significant increase in bleeding noted; however, caution advised when used with aspirin or clopidogrel. Genetic polymorphisms in CYP2C19 reduce effectiveness of clopidogrel; this does not seem to be the case with cilostazol, making it a potential option in cases of "clopidogrel resistance." Cilostazol is contraindicated in pts with CHF because of its mechanism of action as a phosphodiesterase enzyme III inhibitor; also contraindicated in pts with moderate to severe renal or hepatic dysfunction. Contraindicated in pts with

hemostatic disorders or active pathologic bleeding. Caution advised in pts with a recent ACS/PCI or history of severe tachyarrhythmia.
  - Plasma lipids: Has been shown to decrease triglycerides by 15% and increase HDL cholesterol by 10%
- Drug interactions:
  - Dose reduction: Required with medications metabolized by cytochrome p450 pathway. CYP3A4 and CYP2C19 inhibitors may increase cilostazol levels and require dose reduction to 50 mg (e.g., erythromycin, clarithromycin, ketoconazole, diltiazem, statins, cisapride, ergot, omeprazole).
  - Dose increase: Caution with CYP3A4 and CYP2C19 inducers such as statins, which may decrease cilostazol plasma concentration. Smoking (which induces CYP1A2) has been shown to decrease cilostazol plasma concentrations by 18%.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Increased HR and palpitations Decreased BP Increased HDL cholesterol Decreased TG Worsens class 3-4 CHF	Avoid if Hx of severe tachyarrhythmia, ACS, or PCI in last 6 mo, class III-IV heart failure	Two-flight walk, Signs of CHF.	ECG ECHO
PVS	Arteriolar vasodilatation	Walking distance	Peripheral pulses	Ankle-brachial pressure index
GI	GI upset	Diarrhea, bloating		
HEPAT	Metabolized by cytochrome P450 with active metabolites	Hepatic failure, nausea, anorexia	Jaundice	ALT, AST, albumin, bilirubin
RENAL	Renal excretion; mot removed by dialysis	Severe renal insufficiency		CrCl <25 mL/min
HEME	Plt dysfunction Agranulocytosis	Temp, sore throat Hx of hemostatic disorders	Evidence of thrombocytopenia	CBC No effect on PT, APTT, INR
CNS	Headaches, dizziness, vertigo			

Key References: Rogers KC, Oliphant CS, Finks SW: Clinical efficacy and safety of cilostazol: a critical review of the literature, *Drugs* 75(4):377–395, 2015; Gogarten W, Vandermeulen E, Van Aken H, et al.: Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology, *Eur J Anaesthesiol* 27(12):999–1015, 2010.

Perioperative Implications

Preoperative Concerns

- Discontinue 2–5 d before surgery depending on type and anticipated blood loss. Limited data available on risk of preop surgical bleeding and no standard guidelines available.
- Discontinue 2 d (>42 h according to European Society of Regional Anaesthesia guidelines) before neuraxial or regional anesthesia. Avoid indwelling cath while pt is taking cilostazol.
- Preop: CBC, ECG. No effect on INR/APTT.
- Emergency surgery: No reversal agent. Consider plt transfusion.
- Plt function assessment can be done using cytometry, aggregatory, or point-of-care P2Y12 assays. Thrombin generation does not appear to be affected by cilostazol; therefore no evidence that TEG/rotational thromboelastometry are suitable for monitoring.

Induction/Maintenance

- Positive inotrope and chronotope in pts prone to tachyarrhythmias.
- May cause hypotension due to arteriolar vasodilation.

Postoperative Period

- Restart regular dose 24 h postop.
- Wait at least 5 h after regional/neuraxial cath removal to restart dose.

Anticipated Problems/Concerns

- Inhibitor of plt aggregation with increased risk surrounding regional anesthesia and invasive monitoring
- Caution in pts with heart failure, tachyarrhythmias, hemostatic disorders, renal or hepatic dysfunction, or concomitant administration of CYP3A4 or CYP2C19 inhibitors
- Predominantly studied in Asian populations; more studies required to extrapolate findings to broader population

Cocaine

Zeev N. Kain | Navid Alem

Uses

- Cocaine (benzoylmethylecgonine) is a commonly abused stimulant drug isolated from leaves of the coca plant (*Erythroxylon coca*).
- Administered IV, to mucosa, "snorted," or smoked ("crack"); lipophilic and crosses BBB.
- Extremely addictive; 5 million Americans are regular users and 30 million have tried it at least once (2012 National Survey on Drug Use and Health).
- Drug that is most commonly associated with mortality.

Perioperative Risks

- Hemodynamic instability, increased sympathetic discharge
- Myocardial ischemia: supply/demand imbalance
  - Increased myocardial O_2 demand (increased HR, BP, and LV contractility)
  - Decreased myocardial O_2 supply (increased endothelin and decreased NO, resulting in coronary vasoconstriction)

Worry About

- CV: Htn, tachycardia, dysrhythmias, MI, cardiomyopathy, premature coronary atherosclerosis, LV hypertrophy, sudden cardiac death, aortic dissection
- Neurologic: Intracerebral bleed, seizures, euphoria, delusions, hallucinations, coma
- Pulmonary: Pneumomediastinum, cocaine-induced asthma, hypersensitivity pneumonitis, chronic cough, pulm edema, abnormal diffusing capacity, perforation of nasal septum
- OB: Placenta previa, abruptio placentae, premature labor, fetal distress or demise

Overview/Pharmacology

- Cocaine is an ester local anesthetic and sodium channel–blocking drug; it is a class I antiarrhythmic agent.
- Blocks presynaptic reuptake of norepinephrine, dopamine, and serotonin, resulting in activation of the SNS. Note: Does not release catecholamines.
- Accumulation of dopamine in the synaptic cleft may lead to acute euphoria, increased alertness, and out-of-body experiences.
- The USA FDA approves cocaine 4% topical solution as a local anesthetic to be used on mucous membranes. Cocaine is useful for ENT surgery and awake fiberoptic intubation (dosage not to exceed 1-3 mg/kg).

Etiology

- Cocaine abuse
- Iatrogenic: OD during ENT surgery; ER use (part of tetracaine, epinephrine, cocaine mix)

Usual Treatment

- Supportive
- Myocardial ischemia induced by cocaine should be treated initially with O_2, sublingual aspirin, and benzodiazepines. If there is ongoing myocardial ischemia, use of nitroglycerine, verapamil, or phentolamine to reverse cocaine-induced coronary vasoconstriction may be necessary.