Aspirin (Acetylsalicylic Acid)

Lee A. Fleisher

Uses

- People in USA consume 10,000–20,000 tons annually.
- Rx for mild and/or moderate pain, fever, arthritis, and prevention of MI.

Perioperative Risks

- Peptic ulcer disease
- Plt dysfunction
- Increased bleeding risk
- Stroke
- Interstitial nephritis
- Reye syndrome

Worry About

- Displacement of protein-bound drugs (e.g., warfarin, sulfonylureas, thiopental, methotrexate)
- Potentiation of anticoagulants.
- Thrombosis secondary to aspirin withdrawal.

Overview/Pharmacology

- Cyclooxygenase inhibition prevents platelet aggregation and vasoconstriction.
- Platelet inhibition irreversible for the life of the platelet.
- Aspirin
  - Is metabolized by the liver and excreted by the kidney
  - Mildly antagonizes antihypertensive medications (beta-blockers, vasodilators, diuretics)
  - Displaces protein-bound drugs, increasing their effects
- Not shown to decrease risk of periop cardiac events; some increased risk of bleeding in large-scale trials.

Drug Class/Mechanism of Action/ Usual Dose

- NSAID
- Cyclooxygenase inhibitor
- Chronically taken for:
  - MS pain (e.g., arthritis, neuralgia)
  - Prevention of CV events
  - Claudication
- Acutely taken for:
  - Acute, mild to moderate pain (e.g., headache, myalgia)
  - Fever
  - Dysmenorrhea
- Usual dose is 325–1000 mg q3–4h for acute illnesses and pain.
- 62.5–325 mg for platelet inhibitor effects.
- Alternatives include acetaminophen, other NSAIDs (ibuprofen, naproxen), steroids, opioids, gold, ticlopidine, dipyridamole, and pentoxifylline.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
RESP	Hyperventilation, respiratory alkalosis		Tachypnea	ABG
GI	Gastritis PUD	Dyspepsia N/V, hematemesis, melena		Endoscopy Upper GI, x-rays, stool heme, Hgb
ENDO	Hyperglycemia, corticosteroid release			Glucose
HEME	Plt dysfunction	Bleeding, bruising	Hematomata, petechiae	Bleeding time
HEPAT	Hepatocellular damage	Nausea, anorexia	Hepatomegaly, jaundice	SGOT, SGPT, alk phos
Toxicity				
CV	Vasomotor paralysis		Hypotension	
RESP	Hypoventilation, respiratory acidosis		Hypopnea	ABG
DERM	Eruptions	Pruritus	Acneiform, erythematous, pruritic, eczematoid, or desquamative lesions	
RENAL	Renal failure due to analgesic nephropathy	Oliguria, anuria	Edema, rales	BUN/Cr, UA, CXR
CNS	Headache, tinnitus, drowsiness, dizziness, diminished vision and hearing		Sweating, confusion, convulsions, coma	
ACID-BASE	Metabolic acidosis			ABG

Key References: Wong SS, Irwin MG: Peri-operative cardiac protection for non-cardiac surgery, *Anaesthesia* 71(Suppl 1):29–39, 2016; Vela Vásquez RS, Peláez Romero R: Aspirin and spinal haematoma after neuraxial anaesthesia: myth or reality? *Br J Anaesth* 115(5):688–698, 2015.

Perioperative Implications

Preoperative Concerns

- D/C 1 wk prior to surgery for full reversal of plt inhibition (need only 1/7 of normally functioning platelets, so if no dilution effect expected, need only 48 h off low-dose ASA); may see hyperthrombotic state around 7–10 d, particularly in pts with coronary stents.
- Continue aspirin in pts with coronary stents unless contraindicated.
- May potentiate the effects of protein-bound drugs.

Induction/Maintenance

- Possible mildly exaggerated effects of thiopental

Adjuvants/Regional Anesthesia/Reversal

- May increase the risk of hemorrhagic complications of regional anesthesia. Aspirin does not contraindicate regional anesthesia, but those techniques with low potential for bleeding are preferable (e.g., spinal may be preferred over epidural).
- May increase the risk of hemorrhagic complications of invasive monitoring.

Special Considerations

- A potent inhibitor of plt aggregation that can seriously impair surgical hemostasis. Most surgeons request D/C of aspirin 1 wk prior to surgery. However, if CAD or other vascular occlusive disease will be left untreated, consult with surgeon, pt's primary physician, and pt about advisability of D/C aspirin.
- Risks of regional anesthesia and invasive monitoring may be increased.
- May displace protein-bound drugs (e.g., warfarin, sulfonylureas, thiopental, methotrexate), thus augmenting their effects.
- Associated with gastritis, PUD, GI bleeding, and increased risk for aspiration of gastric contents.
- Associated with Reye syndrome and contraindicated in febrile viral illness in children.

Benzodiazepines

Robert I. Cohen

Uses

- Prescribed for the treatment of anxiety
- Used for premedication and procedural (moderate and deep) sedation

Perioperative Risks

- High levels associated with hypnosis, unconsciousness, apnea/respiratory depression

Worry About

- Combination (synergy) with opioids and other CNS depressants may result in severe respiratory depression, apnea, hypotension.

Overview/Pharmacology

- Anxiolysis, sedation, hypnosis, muscle relaxation, anterograde amnesia, anticonvulsant
- Midazolam: Short-elimination half-life (2.5 h)
- Lorazepam: Intermediate-elimination half-life (15 h)
- Diazepam: Long-elimination half-life (30 h)
- Metabolized by hepatic microsomal oxidation and glucuronide conjugation.
- Active metabolites: Diazepam (P450-2C19 and 3A4) → nordazepam; (P450-3A4) → temazepam → oxazepam

- Midazolam:
  - IV: Peak effect in 2–4 min
  - IM: Peak effect in 30–60 min
- Lorazepam:
  - IV: Peak effect in 5–15 min, painful injection, thrombophlebitis
  - IM: Peak effect in 60–90 min
  - Oral: Peak effect in 2 h
- Diazepam:
  - IV: Peak effect in 1–2 min, painful injection, thrombophlebitis
  - IM: Painful, unpredictable absorption, do not use
  - Oral: Peak effect in 30–60 min, well absorbed; food, aluminum-containing antacids delay absorption
- No clear difference in speed of recovery from diazepam and midazolam drug effect after low dose for sedation in short procedures; differentially shorter clinical recovery times for midazolam after larger dose/prolonged administration.
- Lorazepam provides long duration (>4 h) of sedation and amnesia by any route of administration; do not use in benzodiazepine-naïve pts when rapid recovery from drug effect is desired.
- Prolonged use can lead to tolerance.

Drug Class/Mechanism of Action/Usual Dose

- Anxiolytic, sedative, hypnotic, antispasmodic, antiseizure (DEA Schedule IV).
- Potentiation of GABA–mediated neural inhibition (Ca^{2+} outflow leading to cell hyperpolarization).
- Safe use involves careful titration to the desired effect.
- Usual dosage for premedication and moderate (conscious) sedation
  - Midazolam
    - IV: 0.5–1 mg, repeated; maintenance infusion: 0.04–0.10 mg/kg per h
    - IM: 0.07 mg/kg
    - Oral: 15 mg (0.5 mg/kg in children up to 20 kg)
  - Lorazepam
    - IV: 0.25 mg, repeated
    - IM: 0.05 mg/kg, max 4 mg
    - Oral: 0.5–4 mg
  - Diazepam
    - IV: 1–2 mg, repeated
    - Oral: 5–10 mg

Drug Effects

System	Effect	PE	Test
CV	Decreased systemic vascular resistance and cardiac output	Arterial BP	
RESP	Central respiratory depression Apnea	Respiratory rate	Tidal volume Minute volume, capnography, oximetry
CNS	Anxiolysis Sedation Hypnosis Amnesia Anticonvulsant Decreased cerebral metabolic rate and cerebral blood flow	Slurred speech, drowsiness, ataxia Unresponsiveness	

Key References: Griffin CE, Kaye AM, Bueno FR, et al.: Benzodiazepine pharmacology and central nervous system–mediated effects, *Ochsner J* 13(2):214–223, 2013; Vuyk J, Sitsen E, Reekers M: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleisher LA, et al., editors: *Miller's anesthesia*, ed 8. Philadelphia, 2015, Elsevier, pp 821–863.

Perioperative Implications/Possible Drug Interactions

Preoperative Concerns

- Elderly: Reduce dose up to fivefold (5–10% reduction per decade)
- Cimetidine, ranitidine (microsomal cytochrome P450 inhibitors), and liver cirrhosis decrease clearance; enhanced effect may be seen.
- Smoking and enzyme-inducing drugs increase diazepam clearance.
- Renal failure increases half-life of diazepam.
- Monitor ventilation.

Induction/Maintenance

- Synergistic interaction with anesthesia induction agents and opioids.
- In pts reporting intense pain, consider analgesic titration first before titrating anxiolytic.
- Provide education and instruction for postop care prior to administration of benzodiazepine.

Monitoring

- End-tidal CO_2

Airway

- May require support

Extubation

- Consider benzodiazepine reversal with flumazenil (prior to naloxone) after major surgery for intubated pts who are slow to emerge from general anesthesia, have return of spontaneous ventilation at a normal rate, and received benzodiazepine. Caveat: Increase intensity and duration of postop monitoring.

Regional Anesthesia

- May exacerbate respiratory depression during spinal anesthesia (mechanism unknown).

Postoperative Period

- Additional monitoring time and care required if benzodiazepine reversal agent (flumazenil) administered owing to unequal duration of active and reversal agent.
- Provide written postop education/instructions and/or offer prior to first administration of benzodiazepine, as amnestic effect may last several times the elimination half-life.

Anticipated Problems/Concerns

- Combination with opioids or other CNS depressants may result in severe respiratory depression, apnea, and hypotension.
- Large doses result in prolonged drowsiness and respiratory depression, especially in the elderly; reverse with flumazenil.
- Undesirable intensity/duration of amnesia for some pts.
- Amnesia is anterograde (retrograde amnesia can occur after head injury and ECT but not from administration of benzodiazepine).
- May not be safe to reverse with flumazenil in pts receiving chronic benzodiazepine, particularly as part of an antiseizure regimen.

Beta-Adrenergic Receptor Antagonists (Blockers)

Duminda N. Wijeysundera

Uses

- Available PO and IV.
- Prescribed long term for stable angina, systolic CHF, MI (secondary prevention), Htn, and AFIB (for control of heart rate). No longer considered first-line Rx for essential Htn, especially in elderly pts.
- Long-term Rx must be continued periop (Class I ACC/AHA recommendation).
- Risk-benefit balance of periop (prophylactic) beta-blocker Rx is unclear.
- Periop Rx prevents MI after surgery, but increases risks of CVA and hypotension.
- Periop Rx may be reasonable for selected pts with ischemia on cardiac stress testing or three or more risk factors on the Revised Cardiac Risk Index (Class IIb ACC/AHA recommendation).

Perioperative Risks

- Increases risks of hypotension, bradycardia, and CVA. Risks may be further elevated in the presence of anemia, nonselective beta-blockers, or short duration of preop medication (<5 d).
- Periop beta-blockade should be avoided in pts with CVD.
- Contraindicated in pts with asthma. Nonselective beta-blockers may precipitate bronchospasm in COPD with significant reversible airway obstruction.
- May worsen or precipitate CHF in pts with decreased LV function.

Worry About

- May cause hypotension and CVA, especially in the presence of anemia or nonselective beta-blockers.
- May worsen underlying systolic cardiac dysfunction.
- Can precipitate bronchospasm, especially with nonspecific beta-blockers and COPD with known reversible airway obstruction.