- Volume of distribution and total body clearance of colchicine are significantly reduced in the elderly, which can lead to higher plasma concentrations and increased risk of toxicity.
- Onset of toxic effects occurs several hours after acute overdose, initially with nausea, vomiting, abdominal pain, and diarrhea leading to extensive vascular damage and shock, kidney injury, muscle weakness, ascending paralysis, delirium, and ultimately death due to respiratory arrest.

Overview/Pharmacology

- Lipid-soluble alkaloid prepared from *Colchicum autumnale*.
- Has a long terminal half-life of 20–40 h. Bioavailability from 24–88%. About 40% of colchicine binds to albumin in the bloodstream. Peak plasma levels occur 1 h after administration, with maximal anti-inflammatory effects occurring over 24-48 h, reaching their highest concentration within leukocytes.
- Primarily eliminated by hepatobiliary excretion. Renal excretion accounts for 10–20% of colchicine elimination in pts with normal renal function.
- Preferentially binds tubulin, cytochrome P3A4, and P-glycoprotein. It persists on tubulin for 20–40 h, preventing fusion of autophagic vacuoles within lysosomes in neuronal, marrow, and muscle cells, risking damage of these organs. CYP3A4 metabolizes colchicine to 2- and 3-demethylcolchicine in hepatocytes and enterocytes. P-glycoprotein, an ATPase efflux pump, extrudes colchicine from the GI tract to limit GI absorption.
- Because of CYP3A4 interactions, there is decreased metabolism of colchicine in pts taking clarithromycin, fluoxetine, paroxetine, nefazodone, protease inhibitors, tolbutamide, azole antifungals, cimetidine, and several nondihydropyridine calcium channel blockers. P-glycoprotein may interact with macrolides, protease inhibitors, chemotherapeutic agents, glucocorticoids, statins, and calcium channel blockers.

Drug Class/Mechanism of Action/Usual Dose

- Tricyclic alkaloid antiinflammatory agent used to treat acute attacks of gouty arthritis.
- Binds tubulins, blocking microtubule assembly and polymerization, arresting microtubule growth at low doses, and promoting depolymerization at higher doses.
- Antiinflammatory effects due to disruption of microtubules and downstream cellular functions of leukocytes. Inhibition of neutrophil chemotaxis, adhesion and mobilization, superoxide production, NALP3, and interleukin 1B processing and release.
- Lactic acid production is reduced; there is decreased uric acid deposition and a reduction in phagocytosis, leading to a decreased anti-inflammatory response.
- Its CV effects are via inhibition of intimal hyperplasia and VEGF expression
- For acute gout, ACR guidelines recommend a loading dose of 1.2 mg followed by 0.6 mg. In the treatment of osteoarthritis, 0.5 mg twice daily. In treatment of recurrent pericarditis 1-2 mg day 1 and maintenance 0.5–1.0 mg/day. For postpericardiotomy syndrome on POD3, 1 mg twice daily and for maintenance, 0.5 mg twice daily.
- Recommend reducing dose by up to 50% in pts >70 y.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Circulatory collapse	Within 7 d of ingestion	Vital signs	
RESP	Respiratory failure		Vital signs	ABG
GI	N/V diarrhea	Symptoms within 24 h of ingestion		LFTs
RENAL	Renal failure	Within 7 d of ingestion		BUN/Cr
MS	Rhabdomyolysis, muscle weakness	Within 7 d of ingestion; concomitant use with statins		Creatinine kinase, LDH
HEME	Blood dyscrasias, marrow failure	Within 7 d of ingestion		CBC
CNS	Delirium, ascending paralysis, convulsions	Within 7 d of ingestion	Mental status exam, neurologic assessment	EEG

Key References: Leung YY, Yao Hui LL, Kraus VB: Colchicine—update on mechanisms of action and therapeutic uses. *Semin Arthritis Rheum* 45(3):341–350, 2015; Ismaeil MS, Tkachenko I, Hickey RF, et al.: Colchicine inhibits isoflurane-induced preconditioning. *Anesthesiology* 91(6):1816–1822, 1999.

Perioperative Implications

Preoperative Concerns

- Surgery and even minor procedures can precipitate acute gouty arthropathy. Prophylaxis against attacks of gout in pt undergoing surgery can be initiated 3 d before and 3 d after surgery.
- Narrow therapeutic index can cause toxicities in the setting of renal impairment or drug interactions.
- Recommended that colchicine be held on the morning of surgery and resumed when pt is again able to tolerate oral medications.

Monitoring

- Standard ASA monitoring

Induction/Maintenance

- Colchicine has been shown to abolish the myocardial protective effect of pretreatment with isoflurane.
- Owing to alterations in neuromuscular function, colchicine may increase sensitivity to CNS depressants, heighten response to sympathomimetic compounds, and depress the respiratory center.
- To decrease risk of toxicity, adequate urine output must be maintained and renal impairment avoided.

Possible Drug Interactions

- Interactions with calcium channel blockers, glucocorticoids, macrolides, statins, cimetidine, clarithromycin, fluoxetine, paroxetine, nefazodone, azole antifungals, protease inhibitors, tolbutamide, and chemotherapeutic agents owing to metabolism with CYP3A4 and P-glycoprotein.

Anticipated Problems/Concerns

- Colchicine IV is not available in USA; therefore if pt should develop an acute flare of gout postop and be unable to tolerate oral medications, intra-articular or systemic steroids can be used.

Cromolyn Sodium

Gregory A. Wolff | Christopher Ciarallo | Lee A. Fleisher

Uses

- Approved by the FDA in 1973 as the first prophylactic nonsteroidal drug available for treatment of chronic asthma.
- Alternative initial maintenance therapy for mild persistent and moderate persistent asthma.
- Preventative only; not effective during acute episodes of bronchospasm.
- Beneficial for allergic-component and exercise-induced asthma.
- May be beneficial in allergic rhinitis and atopic ocular diseases.
- Oral formulations for the management of mastocytosis, ulcerative colitis, and food allergies.
- Leukotriene receptor antagonists have largely replaced cromolyn sodium as the non-corticosteroid treatment of choice in the treatment of asthma.

Overview/Pharmacology

- Inhibits antigen-induced degranulation of pulm mast cells, eosinophils, neutrophils, monocytes, and lymphocytes.
- Prevents release of histamine, leukotrienes, and other autacoids.
- Reverses and suppresses leukocyte activation.
- Inhibits cough reflex.
- Does not directly relax bronchial smooth muscle.
- No apparent steroid-sparing effects and considered inferior to inhaled corticosteroids on measures of lung function and morbidity in 2006 Cochrane Review.
- Administered by inhalation to treat asthma.
- 8–10% of inhaled dose reaches lung parenchyma and is readily absorbed.
- $T_{½}$: 80–90 min; peak plasma concentration within 15 min.
- Active drug excreted unchanged in urine (50%) and bile (50%).
- Can be taken prophylactically 15–20 min before exercise or exposure to known allergen to prevent bronchospasm.

Drug Class/Mechanism of Action

- Cromolyn sodium (disodium cromoglycate) is a derivative of 2-chromone–carboxylic acid.
- Direct mechanism of action in asthma is poorly defined.
  - One proposed explanation is decrease in accumulation of intracellular Ca^{2+} in sensitized mast cells.
  - Another possible mechanism is Cl^- channel blockade in antigen-sensitized pulm C-fibers.
- Effective in preventing degranulation of mast cells only if given prior to antigenic challenge.

Usual Dose

- Cromolyn sodium inhalation (Intal) via a special nebulizer (20 mg/2 mL) or metered spray (2 puffs [1 mg/puff] 3–4 times daily for asthma).
- 4% liquid nasal spray (Nasalcrom) given as 1 spray to each nostril 3–6 times daily for allergic rhinitis.
- 4% ophthalmic solution (Opticrom) given as 1–2 drops to each eye 4–6 times daily for atopic eye conditions.

Assessment Points

System	Effect	Assessment by Hx	Test
RESP	Inhibition of pulm mast cell degranulation; decreased release of histamine and leukotrienes; reverse or suppress leukocyte activation	Decreased episodes of exercise- or antigen-induced bronchospasm after chronic use	Decreased bronchial hyperactivity as measured by histamine or methacholine challenge

Key References: Undem BJ: Pharmacotherapy of asthma. In Brunton LL, Lazo JS, Parker KL, editors: *Goodman & Gilman's the pharmacological basis of therapeutics*, ed 11, New York, 2006, McGraw-Hill Medical, pp 717–736; Netzer NC, Küpper T, Voss HW, et al.: The actual role of sodium cromoglycate in the treatment of asthma—a critical review, *Sleep Breath* 16(4):1027–1023, 2012.

Perioperative Implications/Possible Drug Interactions

- Continue administration periop. Do not discontinue abruptly.
- Cromolyn sodium is of no benefit in treating an acute exacerbation of asthma.
- Adverse effects are infrequent:
  - Unpleasant taste (most common)
  - Direct irritation (e.g., wheezing, coughing)
  - Dizziness, nausea, rash
  - Urticaria, anaphylaxis (extremely rare)
- No significant drug-drug interactions with cromolyn sodium are known.
- Compatible in a nebulized solution with albuterol, levalbuterol, ipratropium, and budesonide.
- Pregnancy category B, with no known evidence of teratogenicity.

Dabigatran

Kelly Byrne | Antony Aho

Uses

- Stroke prevention in nonvalvular AFIB
- Thromboembolism prophylaxis after total hip and knee replacement
- Treatment and prevention of DVT and PE not related to surgery

Worry About

- Contraindicated in pts with creatinine clearance less than 30 mL/min.
- Use with other anticoagulants will increase the risk of bleeding and is not recommended.
- Use with strong inhibitors of p-glycoprotein (e.g., ketoconazole, itraconazole, cyclosporine) is contraindicated as they increase plasma concentrations of dabigatran.
- Use with mild inhibitors of p-glycoprotein (e.g., amiodarone, quinidine, verapamil) should proceed with caution.
- P-glycoprotein inducers (e.g., rifampicin) will reduce dabigatran plasma concentrations.
- Major hemorrhage occurs in roughly 3.5% and fatal hemorrhage in 0.07% of pts.
- Gastrointestinal upset has been reported in postmarketing surveillance.

Overview/Pharmacology

- Competitive direct thrombin inhibitor that is active after a single dose.
- Inhibits both free and clot-bound thrombin and thrombin-induced platelet aggregation.
- For oral administration, available in 75-, 110-, and 150-mg capsules.
- Doses vary by country, but an indicative dose regime would be as follows: Dosing for prevention of stroke is usually 150 mg 2 times daily; this may be reduced to 110 mg 2 times daily in pts with renal impairment. Dosing for DVT treatment is usually also 150 mg 2 times daily. For prophylaxis following hip or knee joint replacement the usual dose is 110 mg on day 1 followed by 220 mg once daily.
- Oral bioavailability is 3–7%. Not much altered when administered with food but will increase significantly if capsule is broken before oral administration.
- Peak plasma concentration is reached within 2 h
- Approximately 35% plasma protein binding with volume of distribution 50–70 L.
- 80% of dabigatran is renally excreted.
- Half-life is 12–17 h, which is prolonged by renal impairment.
- Not metabolized by and does not induce cytochrome P450.

Test	Effect of Dabigatran	Clinical Usefulness
INR	May be normal or elevated in the presence of therapeutic levels of dabigatran	Not useful
APTT	Usually elevated in presence of therapeutic levels of dabigatran (around 1.3 times normal at steady state)	High APTT in a pt on dabigatran indicates therapeutic levels of dabigatran. However, this lacks sensitivity and a normal result does not exclude therapeutic levels of dabigatran.
TCT	Elevated in presence of even small amounts of dabigatran	Very sensitive predictor of the presence of dabigatran. Can also be elevated by other drugs that effect thrombin (e.g., heparin).
TEG	Unpredictable effect of dabigatran	Not currently useful, but may improve with the use of novel activating agents (e.g., ecarin)
Ecarin clotting time	Sensitive to the presence of small amounts of dabigatran Plasma is diluted in a standard fashion and thrombin time is carried out to estimate dabigatran levels when calibrated against known levels of dabigatran	Not widely available; tends to be used mainly as research tool Shown to be accurate in measuring dabigatran levels but unclear as to how the level correlates with degree of anticoagulation (i.e., at what dabigatran level it is safe to proceed to surgery).

Key References: van RJ, Stangier J, Haertter S, et al.: Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity, *Thromb Haemost* 103(6):1116–1127, 2010; von Heymann C, Rosenthal C, Kaufner L, et al.: Management of direct oral anticoagulants-associated bleeding in the trauma patient, *Curr Opin Anaesthesiol* 29(2):220–228, 2016.