- Initial distribution in extracellular fluid, subsequent accumulation in tissues.
- Eliminated exclusively by renal excretion with a half-life of 20–27 h after a single dose. One-third to two-thirds of acute dose excreted in 6–12 h; 80% reabsorbed in the proximal convoluted tubules.
- Reabsorption is related to sodium balance. Na^+ depletion causes retention of lithium; increase lithium levels from thiazide diuretics, extracellular carbonic anhydrase, furosemide; Na^+ loading causes increased excretion of lithium.
- Lithium clearance is 20% of creatinine clearance; toxic at levels >1.5 mEq/L.

Drug Class/Usual Dose

- Lithium salt, alkali metal, monovalent cation; is minimally protein bound.
- Daily dose is individualized; regular monitoring of lithium levels required. Usual adult dose varies: 900-2400 mg/d in 3–4 divided doses or 900–1800 mg/d in 2 divided doses of sustained release formulation.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Therapeutic levels cause benign ST interval/T-wave changes Toxicity: Malignant arrhythmias, heart block, hypotension	Dose, intercurrent illness, drugs precipitating toxicity	CVS examination	ECG
ENDO	Enlarged tender thyroid; hypothyroidism rare	Neck pain, hypothyroid symptoms	Thyroid	FT_4E/TSH
GU	Nephrogenic DI	Polyuria, polydipsia		Urine/serum lytes/osmolality
CNS	Toxicity: Tremor, drowsiness, coma, convulsions Therapeutic: May cause drowsiness, slowing of EEG	Dose, concomitant therapy, illnesses	CNS exam	Lithium level
DERM	Dermatitis			

Key References: Huyse FJ, Touw DJ, Schijndel RS, et al.: Psychotropic drugs and the perioperative period: a proposal for a guideline in elective surgery, *Psychosomatics* 47(1):8–22, 2006; Fox C, Kaye AD, Liu H: Psychopharmacologic agents and psychiatric drug considerations. In Kaye AD, Kaye AM, Urman RD, editors: *Essentials of pharmacology for anesthesia, pain medicine, and critical care.* New York, 2015, Springer, pp 581–594.

Perioperative Implications

Preoperative Concerns

- Drugs that affect GFR or promote renal sodium wasting lead to increased lithium levels and risk of toxicity: Thiazide diuretics, eplerenone, furosemide, ACE inhibitors, carbamazepine, NSAIDs.
- Increased risk of neurotoxicity: Verapamil, diltiazem, metronidazole.
- Increased risk of serotonin syndrome with SSRIs, tramadol, meperidine, and other serotoninergic agents.

Induction/Maintenance

- Must be aware of signs of lithium toxicity, which include skeletal muscle weakness, ataxia, sedation, widening of the QRS complex.
- Generally believed to reduce requirement for inhaled and injected anesthesia (e.g., reduced MAC), most likely related to decreased release of neurotransmitters.
- Possibility of prolonged NM blocking effects.
- Delayed recovery from barbiturates reported in literature.

Anticipated Problems/Concerns

- Toxic levels can be decreased with osmotic diuretics (do not use HCTZ), administration of saline, or dialysis.
- Renal toxicity is common with chronic lithium therapy. Nephrogenic DI is the most common manifestation and occurs in up to 20% of pts taking lithium. Electrolyte and fluid balance is very important.
- Hypothyroidism is the most common endocrine disorder cause by chronic lithium therapy.
- Acute exposure can cause leukocytosis; chronic exposure may cause aplastic anemia.
- Severe CV collapse; arrhythmias, heart block possible with toxicity.
- No abrupt withdrawal effects are associated with discontinuation of lithium; therefore lithium should be held in the periop period unless there is a risk/benefit reason related to the pt's mental status.
- Contraindicated in pregnancy, with increased risk of cardiac anomalies (Ebstein anomaly). May be excreted in breast milk. Lithium should be avoided in the first trimester of pregnancy.
- Pts using lithium have serious drug-drug interactions and because of this qualify for at least an American Society of Anesthesiologist classification 3.

Magnesium Sulfate

Sara A. Skrlin

Uses

- Treatment of hypomagnesemia and magnesium deficiency in critically ill pts
- Treatment of torsade de pointes, atrial or ventricular arrhythmias, digoxin toxicity
- Prevention of seizures due to preeclampsia/eclampsia
- Decrease risk of cerebral palsy in the early preterm fetus
- Management of conditions with catecholamine excess (tetanus, pheochromocytoma, attenuation of stress response during laryngoscopy)
- Orally as cathartic or laxative
- Treatment of acute severe asthma exacerbation not responding to conventional approaches
- Adjuvant to other agents during general anesthesia to reduce the requirements of analgesics, muscle relaxants, and hypnotics
- Treatment of refractory hypokalemia

Perioperative Risks

- Hypotension via decrease in SVR, worse with rapid administration.
- Muscle weakness in pts with high levels of serum magnesium (>8 mEq/L^{-1}).
- Inadvertent use in pts with impaired renal function can lead to a state of hypermagnesemia.

Worry About

- Potentiation of nondepolarizing NMBs. NMB dose adjustment and monitoring train of four is necessary. Adverse effects on neuromuscular function may occur at lower concentrations in pts with neuromuscular disease (e.g., myasthenia gravis).
- Magnesium deficiency is highly undesirable in the periop period and in critical care owing to the increased risk of arrhythmias.
- Decreased responsiveness to vasopressors due to effect of magnesium on catecholamine reuptake and hypotension due to decreased SVR.

Overview/Pharmacology

- Magnesium is the fourth most common cation in the body and second most common intracellular cation after potassium.
- Physiologic antagonist of calcium and has a fundamental role as a cofactor in over 300 enzymatic reactions.
- Conversion: 1 g of magnesium sulfate is 4 mmoL, 8 mEq, or 98 mg of elemental magnesium.
- CVS: Reduces SVR in high doses. Prolongs SA-node conduction time and reduces the rate of SA-node impulse formation. Excess catecholamine–induced vasoconstriction, arrhythmogenic effects, and diastolic dysfunction are attenuated by magnesium.
- Antiepileptic properties and the action on the CNS are not well defined. Various postulations for neuroprotection include cerebral vasodilation, blood-brain barrier protection, and anticonvulsant actions.
- Potentiation of nondepolarizing blockade is due to its presynaptic action.
- Studies have shown it to be a physiologic and pharmacologic antagonist of NMDA receptors in the CNS.
- Kinetics: 30% protein-bound, 50% renal excretion, half-life 4 h, only 1–2% is extracellular.

Drug Class/Mechanism of Action/Usual Dose

- Key actions are calcium antagonism via calcium channels, regulation of energy transfer, membrane sealing, or stabilization. Presynaptically inhibits release of acetylcholine at the NM junction.
- Emergency treatment: IV 2 to 4 g (8–16 mmoL) initially over 20 min, followed by 10 g (40 mmoL) over next 5 h.
- It can be given by IM route, but this is very painful.
- Torsade de pointes: 1–2 g IV push over 5–20 min.
- Acute severe asthma: 2 g IV (single dose) over 20 min.
- Preeclampsia/eclampsia: 4–6 g IV over 15–20 min followed by 1–2 g/h. Therapeutic levels: 4–8 mEq/L. Clinical signs of toxicity include loss of reflexes and respiratory insufficiency.
- Decrease dose by 50% in pts with impaired renal function and monitor levels closely.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Vasodilatation, sympathetic blockade, inhibition of catecholamine release, decreased myocardial contractility, antiarrhythmic	Light-headedness, flushing or sensation of warmth if given in an awake pt	Bradycardia, low BP, poor peripheral and systemic perfusion due to vasodilation and low cardiac output	Check Mg^{2+} levels, ECG, CO_2 monitoring (noninvasive and invasive)
RESP	Respiratory depressant effect due to NMB Bronchodilator	Respiratory insufficiency Improvement in asthmatic pts	Hypoxia, hypoventilation, sedation, hypercapnia	Monitor levels, pulse oximetry, ABG, end-tidal CO_2
CNS	Antiepileptic, NMDA receptor blockade, potentiation of NMB	Cessation of convulsions Analgesic adjuvant Muscle weakness	Postictal phase Decreased deep tendon reflexes Improvement in analgesia	Monitor levels
MS	Weakness, increased sensitivity to non-depolarizing relaxants	Respiratory depression Heightened response to muscle relaxants	Weakness, lethargy, absent or reduced DTRs	Monitor DTRs, twitch monitoring
OB	Tocolytic	Arrests labor	Decreased uterine tone	Uterine activity

Key References: Herroeder S, Schönherr ME, De Hert SG, et al.: Magnesium—essentials for anesthesiologists, *Anesthesiology* 114(4):971–993, 2011; Dubé L, Granry J: The therapeutic use of magnesium in anesthesiology, intensive care and emergency medicine: a review, *Can J Anesth* 50(7):723–746, 2003.

Perioperative Implications

Preoperative Concerns

- Assess baseline respiratory and CV, muscle strength, electrolytes including Mg^{2+}, renal function, and ECG prior to any anesthetic.

Induction/Maintenance

- Dose of induction agent to be titrated as an exaggerated hemodynamic response and drop in BP can occur.
- Use of muscle relaxants to be avoided unless indicated. Consider decreasing the maintenance dose and monitoring TOF. Succinylcholine can be used safely.
- Volatile agents can compound the drop in SVR. MAC may be reduced by 20%.
- When central neuraxial blockade is used, careful titration of local anesthetics dose is needed.
- Vasopressors may be required to maintain adequate MAP and SVR if serum levels are high.

Adjuvants/Regional Anesthesia/Reversal

- Depresses the stress response to laryngoscopy, intraop BP control during surgery for pheochromocytoma, hypotensive anesthesia for surgeries requiring bloodless fields.
- Magnesium is a useful analgesic adjuvant (IV, RA) as a part of multimodal therapy.
- Calcium is used as an antidote to magnesium toxicity. However, it does not reverse the effects on the NM junction.

Postoperative Period

- Assess the reversal of NMB before extubation. Muscle weakness and respiratory insufficiency may warrant extended ventilatory support.
- Risk of pulm edema.

Anticipated Problems/Concerns

- Intensive monitoring required if magnesium infusion is continued postop.
- Postpartum hemorrhage due to tocolytic effect of magnesium (decreased uterine tone) if used in labor.
- Residual NMB and watch for respiratory failure.

Acknowledgment

The author would like to acknowledge the contributions of Drs. Subramanian Sathishkumar and Sanjib Adhikary to this chapter in the previous edition.

Marijuana

Luis R. Sauceda-Cerda | Jeffrey R. Kirsch

Uses

- Antiemetic
- Appetite stimulation
- Analgesia
- Recreational
- Epilepsy
- Glaucoma
- Mood disorders
- Spastic disorders

Perioperative Risks

- Cross-tolerance with barbiturates, opioids, benzodiazepines, and phenothiazines
- Tachycardia, vasodilation with hypotension, anxiety, dysphoria, hallucinations (acute use)
- Airway hyperreactivity from chronic smoking (carbon monoxide inhalation)
- Decreased efficacy of oral birth control medication
- Possible procoagulant effect in immunocompromised and certain other populations

Worry About

- Multiple drug consumption

Overview/Pharmacology

- Marijuana flower is commonly smoked, vaporized, or turned into edible products.
  - Absorption via inhalation is rapid and effects are felt within minutes.
  - Enteral administration is slower and effects are felt within 30–120 min.
- Sublingual and topical preparations of cannabinoids are also available.
- Over 60 different cannabinoids have been identified.
  - Primary psychoactive agent is δ-9 THC.
  - Cannabidiol has no hallucinogenic properties and is under investigation in the treatment of epilepsy, psychotic disorders, and other neuropsychiatric conditions.
- Endogenous cannabinoid system involved in analgesia, cognition, memory, locomotor activity, appetite, vomiting, and immune control.
  - Endogenous ligands include anandamide, 2-arachidonoylglycerol, palmitoylethanolamide.

Drug Class/Mechanism of Action/Usual Dose

- Cannabinoid.
- Two G protein–coupled cannabinoid receptors (CB_1 and CB_2) have been identified.
  - CB_1 receptors found widely in central and peripheral nervous systems: Hippocampus, cortex, olfactory areas, basal ganglia, cerebellum, spinal cord.
  - CB_2 receptors found peripherally and linked to immunity (i.e., spleen, macrophages)
  - Leads to inhibition of adenyl cyclase and decreased cAMP.
  - Neurons become hyperpolarized by activating Ca^{2+} and K^+ channels
- Cannabidiol antagonizes and activates a variety of noncannabinoid receptors; reduces psychoactivity of THC.
- Dosage varies depending on indication.