Leukotriene Antagonists

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Uses

- Include the leukotriene receptor antagonists montelukast, zafirlukast, and pranlukast (not available in USA) as well as the 5-lipoxygenase (5-LO) inhibitor zileuton. Montelukast is the most commonly used drug of this class in USA.
- Montelukast is a once-daily oral drug approved for the prevention of exercise-induced bronchospasm.
- Most commonly used as adjuvant anti-inflammatory agents in the treatment of chronic asthma in addition to inhaled corticosteroids.
- Mixed evidence exists for the use of leukotriene antagonists for other lung diseases, such as COPD, interstitial lung diseases, and obstructive sleep apnea.
- These drugs may have a possible benefit in various malignancies as well as pulmonary and systemic vascular diseases; studies are ongoing.

Perioperative Risks

- Small risk (1.9%) of hepatic dysfunction in pts on zileuton. LFTs are usually monitored in these pts.
- Small risk of increased INR in pts taking zileuton and warfarin.

Worry About

- Potentiation of effects of warfarin, theophylline, and propranolol with zileuton.
- Pts on any of these second-line asthma therapies may have more severe asthma at baseline and may be more prone to bronchoconstriction/bronchospasm in the periop period.

Overview/Pharmacology

- Antagonism of the effects of leukotrienes decreases bronchoconstriction and inflammation associated with asthma.
- Montelukast: 99% protein-bound; metabolized in liver by CYP3A4 and CYP2C9; predominantly excreted in bile.
- Zafirlukast: 99% protein-bound; metabolized in liver, mainly by CYP2C9; 90% excreted in bile, remainder in urine.
- Zileuton: Metabolized by P450 system in liver, can inhibit CYP1A2 activity; CYP1A2 inhibition can increase serum concentrations of theophylline, propranolol, and warfarin (only the R enantiomer, metabolism of which has less of an impact on the therapeutic effect of warfarin when compared with metabolism of the S enantiomer).

Drug Class/Mechanism of Action/Usual Dose

- Activated leukocytes express 5-LO, which catalyzes the conversion of arachidonic acid to leukotriene precursors and eventually activated leukotrienes.
- The cysteinyl leukotrienes (C_4, D_4, and E_4) bind to endothelial receptors such as cysteinyl leukotriene receptor 1 ($cysLT_1$) and activate a signaling cascade that results in bronchoconstriction, inflammation, endothelial permeability, and mucus secretion.
- Leukotriene antagonists either inhibit $cysLT_1$ (montelukast, zafirlukast, and pranlukast) or inhibit 5-LO (zileuton). Both result in decreased cysLT signaling, decreasing bronchoconstriction and other leukotriene effects.
- Usual doses:
  - Montelukast: 10 mg daily (5 mg daily for children)
  - Zafirlukast: 20 mg twice daily
  - Zileuton: 2400 mg daily in divided doses (600 mg 4 times daily of the immediate release or 1200 mg twice daily of the continuous-release formulation)

Assessment Points

System	Effect	Assessment by Hx	PE	Test
RESP	Decreased bronchoconstriction Decreased mucous production	Improved symptoms of asthma Fewer asthma attacks	Decreased wheezing	PFTs
GI	Dyspepsia	GI discomfort		
CNS	Headache	Headache		
HEPAT (zileuton only)	Hepatocyte damage Inhibition of CYP1A2	Toxicity of coadministered theophylline, propranolol, or warfarin	Jaundice Other signs specific to which drug levels have been increased	LFTs Serum drug levels

Key References: Scott JP, Peters-Golden M: Antileukotriene agents for the treatment of lung disease, *Am J Respir Crit Care Med* 188(5):538–544, 2013; Watts K, Chavasse RJ: Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children, *Cochrane Database Syst Rev* (5):CD006100, 2012.

Perioperative Implications

Preoperative Concerns

- Pts on second-line therapy for asthma may have more severe asthma at baseline. A detailed asthma history should be taken; pretreatment with inhaled beta agonists may be beneficial.
- There is no evidence of a withdrawal syndrome or of a rebound of symptoms after short-term discontinuation of use.

Induction/Maintenance

- Low index of suspicion for the development of bronchospasm.
- Intermittent administration of inhaled beta agonists may be beneficial.
- No reported interactions between any of the leukotriene antagonists and commonly used anesthetic medications.

Regional Anesthesia

- No reported impact on the effectiveness or safety of regional anesthetic techniques

Anticipated Problems/Concerns

- Although there have been reports of mood change and suicidal ideation in pts treated with montelukast, a review of clinical trial data has not supported a link between this drug and these adverse effects.
- The vasculitis Churg-Strauss syndrome has been associated with the use of leukotriene antagonists in pts with asthma. However, whether this is a causative relationship or merely an unmasking of the vasculitis by the allowed reduction in corticosteroid dosing after initiation of antileukotriene therapy has yet to be definitively shown.

Lithium Carbonate (Lithobid)

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Uses

- For treatment of manic episodes of bipolar disorder and some schizoaffective disorders.
- Approved for maintenance therapy to help prevent episodes of mania or depression.
- As an augmenting agent for antidepressants. Has also been used to treat aggression, PTSD, and conduct disorder in children.
- For hyperthyroidism (e.g., Graves disease) (may eventually lead to hypothyroidism).

Perioperative Risks

- Extremely narrow therapeutic level with desired serum levels of 0.4-1 mmol/L.
- Interaction with depolarizing and nondepolarizing muscle relaxants causes a prolonged response, specifically with pancuronium and succinylcholine.
- Decreased dose requirement for IV and inhalational anesthetics (reduced MAC).
- Elderly pts are especially at risk for toxicity. Problems include GI (e.g., nausea, vomiting, and diarrhea), neurologic (e.g., sluggish, ataxia, confusion, agitation, tremors), cardiac (e.g., prolonged QTc, bradycardia, arrhythmias), and somatic (e.g., fatigue, chills, rhinorrhea, myalgias) symptoms.

Pharmacokinetics/Pharmacodynamics

- At the cellular level, acts as imperfect substitute for Na^+; intracellular accumulation of lithium decreases phosphatidylinositides by interfering with hydrolysis of myoinositol-1-phosphate in the brain. Specific mechanism of action is unknown.
- Decreases availability of norepinephrine at the central adrenergic synaptic cleft because it increases reabsorption into storage granules. Also interferes with calcium depolarization–mediated release of norepinephrine and dopamine centrally.
- May also inhibit the ability of some hormones to activate adenylyl cyclase.
- Apparent volume of distribution of 0.6–1 L/kg with no plasma protein binding.
- Almost complete absorption from GI tract; peak levels reached 2–4 h after oral dose.

- 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

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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.