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.