LITHIUM

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Learning Objectives

- List common and severe adverse effects associated with lithium therapy.
- Predict onset and duration of adverse effects associated with lithium (i.e. What is time to onset for each adverse effect? If an adverse effect occurs, is it expected to be transient or chronic?)
- Provide recommendations for managing or minimizing lithium ADEs.
- Describe when lithium levels should be checked following initiation of lithium or dosage change to ensure steady state trough levels are obtained.
- Interpret and evaluate lithium levels (based on time of lab draw as well as lithium level) to make therapeutic decisions regarding lithium dosing.
- Recognize signs and symptoms of lithium toxicity.
- Describe management options for lithium toxicity.
- Identify common drug interactions that occur with lithium, and the impact of these interactions on lithium levels (i.e. elevated or reduced).
- Describe how drug interactions with lithium should be managed in practice (i.e. monitoring or proactive dose adjustment).
- Describe the risks and complications of using lithium during pregnancy
- Recommend baseline and follow-up laboratory values to evaluate the safety and efficacy of lithium in the management of bipolar disorder. (including timing intervals for monitoring each parameter)
- List important education points for a patient newly starting on lithium therapy for bipolar disorder

Lithium

- Considered gold standard for bipolar disorder
  - Effective in acute mania, and as maintenance for both manic and depressive episodes
  - Less support for use in acute bipolar depression
  - Associated with reduced suicide rates

- Mechanism of action
  - Exact MOA in mood disorders unknown
  - Affects transmission of NE, 5-HT, and DA

- Onset of action (monotherapy)
  - 5-10 days for acute mania
  - Up to 6-8 weeks for acute depression

Lithium Pharmacokinetics

- 100% renally eliminated
- Steady stated achieved after 3-5 half lives
- T ½ of 24 hours

- 1st order linear pharmacokinetics
  - Dose and blood level directly proportional
  - Double the dose double the blood level
  - Halve the dose, halve the blood level

Lithium Dosing

- Lithium carbonate
  - Extended release: 2-3 times per day
  - Immediate release: 3-4 times per day
- Lithium citrate (oral syrup 300mg / 5mL)

- Acute Mania:
  - Start at 300 mg 2-3 times daily
  - Usual therapeutic range: 900-1800 mg/d
  - Generally titrate in 300 mg dose increments every 5-7 days

- Maintenance:
  - 900-1200 mg/d

Lithium Dosing

- Ideal dose determined by combination of drug level and clinical signs and symptoms

- Drug Levels
  - 0.6 – 0.8 mEq/L in patients prescribed lithium for first time
  - 0.8 – 1.0 mEq/L in patients who have relapsed while taking lithium in the past or are taking lithium and still have impairing symptoms
  - Can go up to 1.2 mEq/L if needed to control symptoms (acute phase)

  - Peak level reached 1-2 hours after immediate release product; and 4-5 hours after extended release
  - Draw levels 12 hours post dose (trough level)
  - First level should be drawn within 5-7 days (steady state)
  - Repeat level weekly until stabilized and then every 3 – 6 months

Lithium Side Effects

Transient

- N/V, GI upset
- Diarrhea
- Fine hand tremor
- Polyuria and polydipsia
- Somnolence
- Ataxia
- Cognitive impairment

Long-Term

- Weight gain
- Tremor
- Polyuria and polydipsia
- Increased WBC
- Hypothyroidism
- Hypercalcemia & hyperparathyroidism
- Renal failure (rare)
- Cardiac abnormalities

Lithium Side Effect Management

- **Tremor**: Lower dose, extended release, split daily or QHS dosing, propranolol, avoid caffeine
- **GI**: take w/ food, lower Dose, extended release, split daily or QHS dosing, Li citrate
- **Ataxia or cognitive impairment**: Check lithium level, lower dose and titrate at slower rate, split daily dosing
- **Polydipsia, polyuria**: Lower dose, extended release, amiloride
- **Weight Gain**: Diet, exercise
- **Hypothyroidism**: Thyroid supplement

Lithium Drug Interactions

Table 1. Clin Pharmacokinet (2016) 55:925–941

Medication class	Effect on lithium concentration[a]	Risk rating[b]	Comment
Diuretics			
Thiazides	↑↑	D	
Loops	↑–↑↑	C	↑ Risk if elderly, medical co-morbidities
K+ sparing	No effect	A	
Osmotic	↓↓↓	C	
Methyl xanthine	↓↓↓	C	
ACE inhibitors	↑↑	D	Delayed toxicity; ↑ risk if elderly
ARBs	↑	C	
NSAIDs	↑–↑↑	C	Variable effects; caution with all
Antidepressants	No effect	B	Rare 5-HT syndrome
Antipsychotics	No effect	B	Rare neurotoxicity
AEDs	No effect	B	Rare neurotoxicity with carbamazepine
Neuromuscular blockers	No effect	C	Prolonged neuromuscular blockade
Calcium channel antagonists (blockers)	No effect	C	↑ Intracellular lithium (?)

Lithium Toxicity

- Mild/Early Toxicity: 1.5- 2 mEq/L
  - Develops gradually over several days
    - drowsiness
    - confusion
    - course hand tremor
    - ataxia
    - dysarthria / slurred speech
    - reappearance or worsening of GI symptoms
- Management
  - Hold dose, check blood level, monitor vitals/symptoms
  - Determine cause of elevated level and educate patient
  - Adjust lithium dose if interacting medication cannot be stopped

Lithium Toxicity

- Moderate-Severe Toxicity: > 2.5 mEq/L
  - Gradual or sudden onset

    -Muscle tremor -Hyperreflexia

    -Seizures -Cardiovascular collapse

    -Coma -Death

- Management

    -Hold doses -Supportive Therapy

    -Li Level -ECG

    -Hydration -Labs

    -Gastric Lavage -Hemodialysis

Lithium in Pregnancy

- Freely crosses the placenta

- Avoid use in pregnancy if possible
  - Pregnancy category D
  - 1st Trimester: risk of cardiac malformations
  - Associated with Ebstein's anomaly
    - abnormalities of the tricuspid valve and right ventricle
    - 1 in 1,000 vs 1 in 20,000

Lithium in Pregnancy

- Physiological alterations
  - Increased GFR and volume of distribution (especially in 3rd trimester)
  - More frequent monitoring of lithium levels and dose adjustment
  - Dose reduction following delivery and monitoring for s/sx lithium toxicity

Lithium Monitoring

Baseline

- SCr / BUN / eGFR
- Thyroid function
- CBC
- Electrolytes
- Pregnancy test
- Weight or BMI
- ECG if CVD or risk factors

Continued

- SCr / BUN / eGFR
  - Q 3 mo x 6 mo, then Q 6-12mo
- Thyroid function
  - At 3-6mo, then Q 6-12 mo
- Lithium level Q 3-6 months once stabilized
- Additional parameters yearly

Important Lithium Education Points

- Do not alter dose or stop lithium without contacting HCP—poor adherence or rapid discontinuation increases risk for relapse
- Birth control recommended while taking lithium—contact HCP if pregnant or considering
- Review s/sx of lithium toxicity and to seek medical attention immediately if experienced
- Common ADEs of lithium and how to manage
- Maintain adequate fluid intake to avoid dehydration, contact HCP if diarrhea or vomiting or acutely ill
- Avoid OTC NSAIDS—acetaminophen is an OTC pain/fever med that won't interact with lithium
- Importance of consistent f/u with prescriber and lab monitoring

Questions??

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