**Lithium Pharmacokinetics**

**Advanced Clinical Pharmacokinetics (P-313)**

# Spring 2014

Course Instructor: Susan Kent, PharmD, CGP

Clinical Assistant Professor

Office: Room 524

Telephone: 215-707-2143

Email: [susan.kent@temple.edu](mailto:susan.kent@temple.edu)

Office hours: By appointment

**Readings:**

Chapter 17 Applied Clinical Pharmacokinetics. Larry A. Bauer, 2nd edition, 2008.

**Learning Objectives:**

1. Explain the effect of specific disease states on the pharmacokinetics of lithium.
2. Identify clinically significant drug-drug interactions with lithium therapy.
3. Given pertinent medical history and laboratory values, recommend a maintenance dose for a patient being started on lithium.
4. Given a patient’s lithium serum concentration, medical history, and relevant laboratory values, recommend a new dosing regimen to achieve desired lithium serum concentration.
5. Discuss relevant monitoring parameters for efficacy and toxicity for a patient receiving lithium.

**Lithium: What is it?**

Alkali metal administered as a monovalent cation (Li+)

Indication: Bipolar Disorder (BPAD, bipolar affective disorder)

## MOA and related theories

1. Competition with other cations at receptor and tissue sites
2. DA-receptor supersensitivity blockage
3. Decreased stimulation of β-receptor induced adenylate cyclase
4. Enhanced sensitivity to serotonin (5-HT), acetylcholine, and γ-aminobutyric acid (GABA)

Acts at multiple sites to modulate neurotransmission through complex mechanisms 🡪 alter the balance among neurotransmitter and neuropeptide signaling in key brain regions

## Therapeutic concentrations

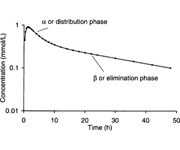
1. General: 0.6-1.5 mmol/L or mEq/L
2. Dependent on the clinical situation of the patient:

0.6 --- 0.8 --- 1 -- 1.5

|  |  |
| --- | --- |
| Therapeutic | 0.6 - 1.5 mmol/L |
| Acute manic attack | 0.8 - 1 mmol/L |
| Long term goal | 0.6 - 0.8 mmol/L |

1. Therapeutic ranges are based on steady-state (SS) lithium serum concentrations obtained **12 hours after a dose**
2. Using a uniform time to draw SS concentrations to assess dose and response is very important in establishing ranges

* Significant interpatient variability in time needed for distribution between serum and tissue



|  |  |  |
| --- | --- | --- |
| **PK Parameter** | **Lithium** | **Notes** |
| Bioavailability (F) | F = 1 |  |
| Half-life elimination (t½) | t½ = 24 hours  Elderly or renally impaired: >36 hrs  Renal failure: 40 - 50 hours | SS achieved: 3 - 5 t1/2 |
| Absorption | Rapid and complete |  |
| Distribution | Two compartment model:  Initial Vd = 0.3-0.4 L/kg  SS Vdss = 0.7-1 L/kg  Complete in 6-10 hours | CSF/Liver: ⅓ - ½ serum  ♥, lung, kidney, muscle = serum concentration  Saliva: 2-3 x serum  Thyroid, bone, brain tissue: ↑ 50% over serum |
| Protein binding | No protein binding |  |
| Metabolism |  |  |
| Excretion | <5% saliva, sweat, feces |  |
| Lithium clearance | 100% eliminated renally  80% reabsorbed in proximal convoluted tubules  20% is excreted |  |

## Product availability - Oral carbonate or citrate salts

|  |  |
| --- | --- |
| Lithium carbonate capsules | 150 mg, 300 mg, 600 mg |
| Lithium carbonate tablets   * Immediate release * Extended release | 300 mg  300 mg, 450 mg (Lithobid® 300 mg) |
| Lithium citrate syrup | 8 mmol/5 ml (~300 mg/5 ml)  8.12 mmol Li = 300 mg Li carbonate |

**Typical adult dose**

* 900-2400 mg/day in 3-4 divided doses
* 900-1800 mg/day in two divided doses of controlled release formulation
* For TID regimens: 12 hour lithium free period
  + 9am, 3pm, 9pm -----(12 hours)----- 9am, 3pm, 9pm

## Side effect panel

Short term: GI and CNS

|  |  |
| --- | --- |
| Muscle weakness | Headache |
| Lethargy | Memory or concentration impairment |
| Polydipsia | Confusion |
| Polyuria | Impaired fine motor function |
| Hand tremor | Nocturia |

Long term

|  |  |
| --- | --- |
| Drug-induced diabetes insipidus | Hypothyroidism |
| EKG abnormalities | Leukocytosis |
| Weight gain | Dermatologic changes |
| Renal toxicity - glomerular sclerosis, renal tubular atrophy, interstitial nephritis, urinary casts |  |

## Toxicity

Acute

* Ingestion of a large single dose of lithium
* Most present with altered mental status; less threatening type of toxicity
* Follow serial serum concentrations

Acute on chronic

* Patient being treated with lithium and overdose occurs
* More severe than acute toxicity
* Lithium elimination half-life ↑ with chronic administration

Chronic

* Occurs with a dose increase or when renal function decreases 🡪 increased lithium concentration
* Symptoms may be present even if lithium serum concentrations in range
* Primarily presents as neurotoxicity

**Normal 0.6 - 1.5 mmol/L**

## Serum concentration: 1.2-1.5 mmol/L

|  |  |
| --- | --- |
| ↓ memory & concentration | Lack of coordination |
| Drowsiness | Nausea |
| Fine hand tremor | Diarrhea |
| Weakness | Fatigue |

**Serum concentration: 1.5-3 mmol/L**

|  |  |  |  |
| --- | --- | --- | --- |
| Confusion | Lethargy | Nystagmus | Hypertonia |
| Giddiness | Blackouts | Blurred vision | Coarse hand tremor |
| Agitation | Ataxia | Tinnitus | Muscle twitching |
| Slurred speech | Dysarthria | Vertigo | Hyperreflexia |

## Severe toxicity: > 3 mmol/L

|  |  |
| --- | --- |
| Choreoathetosis | Respiratory & CV complications |
| Seizures | Stupor |
| Irreversible brain damage | Coma |
| Arrhythmias | Death |
| Hypotension |  |

## Toxic levels

Toxic lithium concentration

⇓

Decreased glomerular filtration

⇓

Decreased lithium clearance

⇓

Further increase in lithium concentration

⇓

and this cycle repeats….

## Hemodialysis

* Only effective method to remove lithium
* Charcoal ineffective

## Effect of disease states on lithium PK parameters

Manic phase of BPAD

* Li clearance increases by 50%
* Effect on half-life: shorter
* Therefore, increase dose

Elderly *Start low…go slow!!!*

Renal dysfunction

* Li clearance: decrease in proportion with CrCl
* ARF: If acute renal failure, Li is contraindicated
* CRF: use with caution

Pregnancy (Category D)

* First trimester: not recommended
* ↑ clearance during pregnancy: in 3rd trimester
* Breast feeding: 50% Li reaches milk. D/C if possible

Renal replacement therapy (HD, PD)

Li given after dialysis

Sodium balance

* **Lithium follows Na**
* Li is reabsorbed in the proximal tubule by the same mechanisms used to maintain sodium balance

## Causes of Na depletion and/or dehydration

|  |  |
| --- | --- |
| Na-restricted diet | Heavy or intense exercise |
| Excessive sweating | Sauna or hot-tub use |
| Hot weather | Viral or other illness  Vomiting  Diarrhea  Fever |

## Drug Interactions

* Thiazide diuretics
  + Na and water depletion 🡪 compensatory increase in Na reabsorption in the proximal tubule of the kidney
  + Lithium is reabsorbed via same mechanisms as Na 🡪 increased Li reabsorption and resultant decreased Li clearance (↓ 40-50%)
  + When adding thiazide to lithium therapy: ↓ lithium dose by ½ to reduce risk of toxicity
* NSAIDs (chronic use)
  + Decrease Li clearance and increase Li concentrations
  + MOA: probable NSAID-induced ↓ in renal blood flow via prostaglandin inhibition
  + Sulindac (Clinoril®) and aspirin: ? less risk of drug-drug interaction
* Methylxanthines (theophylline, aminophylline, caffeine)
  + Increase lithium elimination by altering Na disposition in the kidney
  + Theophylline: increases Li renal clearance; decreases Li trough concentrations by 20-30%
* ACEIs/ARBs
  + Inhibit lithium elimination by undefined mechanism
  + Uncommon drug interaction with gradual onset
  + More documentation with ACEIs over ARBs
* SSRIs
  + Serotonergic hyperarousal syndrome
  + Case reports with fluoxetine, sertraline, fluvoxamine
  + Patients also develop: arm/leg stiffness, course tremor, dizziness, ataxia, seizures
  + Use caution when concurrent treatment is indicated
* Anti-psychotics
  + Rare but severe drug interaction
  + ↑ susceptibility to development of EPS symptoms or irreversible brain damage
  + Close monitoring for adverse drug reactions with this combination

**Clinical monitoring parameters**

Signs and symptoms of BPAD

* Depression: decreased affect, sad mood, lack of interest, decreased appetite, weight loss
* Mania: abnormally elevated mood, grandiosity, decreased need for sleep, pressured speech, flight of ideas, decreased attention, distractibility, involvement in high-risk activities

Onset of action

* General: 1-2 weeks
* Complete response: 4-6 weeks

Prior to lithium initiation

* Complete physical exam
* Chemistry panel (electrolytes, serum creatinine)
* CBC with differential
* Thyroid function tests
* Urine analysis
* Urine toxicology screen
* Consider pregnancy test for women of childbearing age
* Follow-up every 6-12 months (electrolytes, thyroid function tests, CBC)

## When to measure lithium serum concentrations?

|  |  |
| --- | --- |
| Upon initiation | Toxicity suspected |
| Once SS achieved | Change in renal function |
| Manic period | Adherence concern |
| Maintenance | Addition or deletion of DD interaction |
| Dosing change (1-2 weeks after) | Unexpected change in disease symptoms |

**Timing of sampling**

*\*\* Serum samples at least 12 hours after dose\*\**

* Standard practice:
* SS achieved in 3-5 days

## Patient counseling

Important points for a patient to understand:

* Take lithium as instructed for 3-5 days before lab sampling
* Can check level in 2-3 days in patients predisposed to lithium toxicity
* Have blood drawn at least 12 hours after last dose
* Report any discrepancies in compliance or lab sampling to MD
* Avoid alcohol and overuse of coffee, tea, soft drinks or other caffeine-containing beverages
* Maintain adequate fluid intake (2.5-3L/day), especially during and after strenuous exercise

## Cases

1. MJ is a 50-year old, 70 kg (5’10”) male with bipolar disease. He is not currently experiencing an episode of acute mania. His Scr = 0.9 mg/dL. Your medicine team has asked you for an oral lithium dose for this patient for maintenance therapy. Round dose to available product strength.

***Estimate Crcl:***

97 ml/min

***Estimate lithium drug clearance* (L/day)*:***

Use drug clearance vs crcl relationship to estimate Li clearance for this patient

Maintenance: Cl = 0.288 x (Crcl) (on equation sheet)

Cl = 27.9 L/day

***Use average SS concentration equation to calculate Li maintenance dose*.**

(desired conc for maintenance therapy = 0.6 mmol/L)

D/τ = (Css x Cl)/F

F = 1

Cl = 27.9 L/day

Css = 0.6

Plug in

D/τ = 16.7

8.12 mmol Li = 300 mg Li

convert

617 mg/day 🡪 600 mg/day 🡪 300 mg carbonate CR q12h

**Monitoring:**

.

1. Same patient as in #1, but his Scr = 3.5 mg/dL

***Estimate Crcl:***

25 ml/min?

***Estimate lithium drug clearance* (L/day)*:***

Acute mania: Cl = 0.432 x (Crcl)

7.2 L/day?

***Use average SS concentration equation to calculate Li maintenance dose***

D/τ = (Css x Cl)/F

160 mg/day?

***Convert mmol/day to mg/day* *(8.12 mmol Li = 300 mg Li carbonate)***

**Recommended dosing regimen**\_\_\_\_150 daily?\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Monitoring:**

1. KR is a 21-year old, 70 kg (5’9”) female with bipolar disease. She needs lithium therapy and is currently experiencing an acute manic phase. Her Scr = 0.8 mg/dL. Suggest an initial lithium carbonate dosage regimen to achieve a SS lithium concentration of 0.8 mmol/L.

***Estimate Crcl:***

123?

***Estimate lithium drug clearance* (L/day)*:***

Use drug clearance vs. crcl relationship to estimate Li clearance for this patient

53 L/day?

***Use average SS concentration equation to calculate Li maintenance dose*.**

(acute mania desired conc = 0.8-1)

D/τ = (Css x Cl)/F

***Convert mmol/day to mg/day* *(8.12 mmol Li = 300 mg Li carbonate)***

**Recommended dosing regime:** 1566 mg/day or 800 mg BID

**Monitoring:**

1. YC is a 37-year old, 55 kg (5’1”) female with bipolar disease. She is currently not experiencing an acute manic episode and requires treatment with lithium. Her Scr = 0.6 mg/dL. She is receiving 900 mg of lithium carbonate at 0800, 1400, and 2000 (8am, 2pm, 8pm), and her 12-hr postdose steady-state lithium serum concentration equals 1.1 mmol/L. Calculate her new lithium dose to achieve a SS concentration of 0.6 mmol/L.

### **Calculate new dose to achieve desired serum concentration**

Use linear, dose-proportional PK (Css changes in proportion to dose)

Dnew/Css, new = Dold/Css,old

Dnew = 1472?

**Recommended dosing regimen** 450 mg at 0800, 1400, and 2000 ?

**Monitoring:**

1. MC is a 55-year old woman receiving lithium carbonate 300 mg po bid. At 11:30 am her blood was drawn and the plasma lithium concentration was reported to be 2.7 mEq/L. List 4 reasons why lithium levels may be elevated and discuss how MC should be managed.

Blood not drawn 12 hours after last dose?

Old = renal?