Pharmacokinetics of Lithium

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Learning Objectives

After completing this presentation, the participant should be able to:

1) Appreciate the relevance of renal elimination for lithium metabolism.
2) Summarize how therapeutic drug monitoring (TDM) is used for lithium dosing.
3) Be familiar with major drug-drug interactions (DDIs) and personal variables that need to be considered in lithium dosing.
4) Remember that lithium overdosing is a frequent problem and that contributing factors include a) changes in the patient's sodium and water status, b) DDIs, c) intercurrent infection, and d) surgery.

Abbreviations

- ACE : angiotensin converting enzyme inhibitor
- ADR: adverse drug reaction
- AGNP: Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (German TDM expert group)
- COX-2: cyclooxygenase-2 (prostaglandin-endoperoxide synthase 2)
- CNS: central nervous system
- DDI: drug-drug interaction
- ER: extended release
- EPS: extrapyramidal symptoms
- GFR: glomerular filtration rate
- GI: gastro-intestinal
- ID: intellectual disability
- IV: intravenous
- NSAID: nonsteroidal anti-inflammatory drug
- TCA: tricyclic antidepressant
- TDM: therapeutic drug monitoring

Lecture Content

0. Historical Relevance of Lithium Pharmacokinetics

1. Renal Elimination
2. TDM

3. Formulations and Dosing

4. Dosing Modifications

5. Pharmacogenetics
6. Overdoses

Lecture Content

0. Historical Relevance of Lithium Pharmacokinetics

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0.1. Introduction of Lithium by Cade
0.2. Relevance of Lithium Pharmacokinetics
0.3. TDM in Psychiatry in the 1980s
0.4. TDM in Psychiatry in the 21st Century

0.1. Introduction of Lithium by Cade

0.1. Introduction of Lithium by Cade

- The introduction of lithium in modern psychiatry by Cade was essentially serendipitous:

  http://www.ncbi.nlm.nih.gov/pubmed/5643667

- In a 1949 article, Cade: http://www.ncbi.nlm.nih.gov/pubmed/18142718
  - described his study of lithium in guinea pigs:
    - to protect from urea toxicity;
    - also observed that lithium caused sedation.
  - reported his trial of lithium in manic patients.
    - 10 manic patients improved.
    - 6 patients with schizophrenia: no change
    - 3 patients with chronic depression: no change
  - described the symptoms of overdose.

0.2. Relevance of Lithium Pharmacokinetics

0.2. Relevance of Lithium Pharmacokinetics

- Trautner et al., 1955 (from Cade's hospital):

  http://www.ncbi.nlm.nih.gov/pubmed/13264856

  - reported that lithium was "controversial":
    - others had confirmed anti-manic effects,
    - but "occasional occurrence grave toxic complications".
  - studied:
    - dosing in controls and patients
    - lithium elimination and the influence of water and sodium
  - described:
    - in acute mania: therapeutic and toxic doses were close
    - what we now call "the concentration therapeutic range":
      plasma levels <1.5 mEq/L: no concern if toxic symptoms
      2.5-3.0 mEq/L potentially dangerous even in the absence of toxic symptoms

0.3. TDM in Psychiatry in the 1980s

0.3. TDM in Psychiatry in the 1980s

- Lithium was the first psychiatric drug used in the practice of TDM.
  TDM for TCAs became standard, too:
  http://www.ncbi.nlm.nih.gov/pubmed/3881999
- Therefore, in the 1980s:
  psychiatrists were experienced in lithium and TCA TDM.
- In the 2010s, many US psychiatry residents have limited:
  - exposure to prescription of
    - lithium and
    - TCAs.
  - exposure to TDM in psychiatry, and
  - understanding of pharmacokinetics.
- Dr. de Leon thinks that, in psychiatry,
  - for personalizing doses, it is crucial to master pharmacokinetics, and
  - for teaching pharmacokinetics, it is best to use cases with TDM

0.4. TDM in Psychiatry in the 21st Century

0.4. TDM in Psychiatry in the 21st Century

Psychiatrists need to become experts in TDM again, as they were in the 1980s.

0.4. TDM in Psychiatry in the 21st Century

- This psychopharmacology course using PowerPoint emphasizes TDM and the teaching of pharmacokinetics by including:
  - a lecture on pharmacokinetics for each drug class
  - the use of TDM in the interpretation of many cases
  - discussions on how:
    - genetics,
    - environmental and
    - personal factors

    influence dosing
  - explaining that pharmacogenetic testing is best incorporated into the clinical practice of psychiatry by combining it with TDM.

1. Lithium Renal Elimination

1. Renal Elimination

- Lithium is not metabolized and is eliminated by:
  - urine: almost all (90–98%)
  - other : minimal elimination in sweat and feces
- Renal elimination is:
  - controlled by osmotic factors and
  - a function of renal sufficiency

1. Renal Elimination

- Renal mechanisms: http://www.ncbi.nlm.nih.gov/pubmed/19384328
  - GFR: all lithium is filtered
    - 80% is absorbed in proximal convoluted tubules similar to sodium.
    - 20% is cleared (20–40 mL/min or 1/5 GFR).
  - Reabsorption in the distal parts of the nephron by the epithelium sodium channel
    - is blocked by amiloride.
    - is ↑ by NSAIDS.

1. Renal Elimination

- Dr. de Leon recommends reading Thomsen & Schou, 1999: http://www.ncbi.nlm.nih.gov/pubmed/10463373 if you need more information.
- Remember renal mechanisms when thinking how lithium dosing is influenced by:
  - DDIs, and
  - personal characteristics.

  They act through one/several of 3 mechanisms:
    - GFR
    - sodium-retaining mechanisms
    - sodium-excreting mechanisms

1. Renal Elimination

- In everyday life, the most important determinant of lithium clearance is the balance between:
  - sodium-retaining mechanisms and
  - sodium-excreting mechanisms.
- Sodium-retaining mechanisms are activated by
  - ↓ blood pressure
  - ↓ renal perfusion or
    contraction of afferent glomerular arteriole
- Sodium-excretion mechanisms are activated by
  - ↑ blood pressure
  - ↑ renal perfusion or
    dilation of afferent glomerular arteriole

1. Renal Elimination

- Activation of sodium-retaining mechanisms and ↓ lithium elimination occur by:
  - dehydration, and/or low sodium intake
  - edema formation
  - treatment with some
    - diuretics
    - anti-hypertensive drugs
- Polyuric patients: particular risk for dehydration when they cannot drink to compensate
- Consider ↓ or temporarily stopping lithium:
  - physical illness with fever:
    - ↓ water and sodium intake
    - ↑ water and sodium elimination in sweat
  - protracted vomiting and/or diarrhea
  - unconsciousness for several hours

2. Lithium TDM

2. Lithium TDM

2.0. Interpreting Lithium Concentrations
2.1. Therapeutic Concentration Ranges
2.2. Therapeutic Window/Index
2.3. TDM in the Clinical Environment
2.4. Reflections on Safety and Efficacy

2.0. Interpreting Lithium Concentrations

2.0. Interpreting Lithium Concentrations

- Grandjean & Aubry, 2009: http://www.ncbi.nlm.nih.gov/pubmed/19374461
  - Use ER formulation results
    - in 30-50% lower peak plasma concentrations
    - with no major changes in bioavailability.
  - Brain lithium distribution, as measured by ^{7}Li magnetic resonance spectroscopy, showed brain concentrations:
    - approximately 1/2 serum,
    - occasionally ↑ 75-80%
    - weakly correlated with serum concentrations
  - Measure serum concentration:
    - optimally 12 hours after the last dose
    - for a single dose: better 24 hours after the last dose.

2.1. Lithium
Therapeutic Concentration Ranges

2.1. Lithium Therapeutic Concentration Ranges

2.1.0. Definition
2.1.1. Bipolar Disorder
2.1.2. Other Disorders
2.1.3. References

2.1.0. Lithium Therapeutic Concentration Ranges: Definition

2.1.0. Lithium Therapeutic Reference Ranges: Definition

- The AGNP, a German TDM expert group, updated a consensus guideline in 2011.
  http://www.ncbi.nlm.nih.gov/pubmed/22053351
- They define therapeutic reference ranges = ranges of medication concentrations with:
  - a lower limit: below which therapeutic response is relatively unlikely to occur
  - an upper limit:
    - tolerability is ↓
    - above which it is relatively unlikely that therapeutic improvement may still be enhanced.

2.1.0. Lithium Therapeutic Reference Ranges: Definition

- The AGNP definition refers to the risk-benefit decision that Dr. de Leon describes by using the terms:
  - efficacy, and
  - safety.

  This is represented in the next slide.
- Always remember that therapeutic ranges are used in reference to average patients:
  - but not all patients are average patients.
  - however, you should assume your patient is average until it is demonstrated he/she is not.

2.1.0. Lithium Therapeutic Reference Ranges: Definition

CONCENTRATION IS TOO HIGH:

↓ safety or

↑ efficacy is relatively unlikely

Upper limit_____

THERAPEUTIC CONCENTRATION

REFERENCE RANGE

Lower limit_____

CONCENTRATION IS TOO LOW:

efficacy relatively unlikely to occur

2.1.1. Lithium Therapeutic Concentration Ranges: Bipolar Disorder

2.1.1. Lithium Therapeutic Ranges in mEq/l or mM/l: Bipolar Disorder

- Mania: □ up to 1.2 (Hiemke et al. 2012)
  - □ 0.6–1.2 (Lexicomp, 2015)
  - □ 0.8–2.0 (Sproule 2002)
- Maintenance treatment in adults with bipolar disorder:

	Non-elderly	Elderly[1]
Grandjean & Aubry, 2009	0.6-0.8 0.8-1.0 for ER[3]	Controversial[2]
Hiemke et al., 2012	0.5-0.8	
Lexicomp, 2015	0.8-1.0	0.4-0.6
Severus et al., 2008	0.6-0.75	
Sproule, 2002	0.8-1.0 0.4-0.7 in some[4]	0.5-0.8

[1]Some think the elderly may need lower doses.

[2]These authors think the controversial elderly may need lower doses.

[3]With ER preparations and because of the later peak of serum lithium concentration, this author recommends maintaining serum concentrations within the upper range, 0.8–1.0.

[4]According to this author, some patients can be maintained at this lower range, but these patients cannot be identified a priori.

2.1.2. Lithium Therapeutic Concentration Ranges: Other Disorders

2.1.2. Lithium Therapeutic Ranges in mEq/l or mM/l

- Depression augmentation:
  - 0.6–0.9 (Boschr et al., 2014)
    - Once in this range, observe for 2 weeks.
    - If there is no response, discontinue.

- Self- or hetero-aggressive behavior in adults with ID:
  - 0.7-1.0 (Wickman & Reed,1987)

2.1.3. Lithium Therapeutic Concentration Ranges: References

2.1.3. Lithium References for Therapeutic Concentration Ranges

- Boschr et al., 2014: http://www.ncbi.nlm.nih.gov/pubmed/25467053
- Grandjean & Aubry, 2009: http://www.ncbi.nlm.nih.gov/pubmed/19374461
- Hiemke et al., 2012: http://www.ncbi.nlm.nih.gov/pubmed/22053351
- Lexicomp: http://www.ncbi.nlm.nih.gov/pubmed/25467053
  http://www.amazon.com/Drug-Information-Handbook-Lexicomp/dp/1591953421/ref=sr_1_1?s=books&ie=UTF8&qid=1457718666&sr=1-1&keywords=drug+information+handbook
- Severus et al., 2008: http://www.ncbi.nlm.nih.gov/pubmed/18271901
- Sproule, 2002: http://www.ncbi.nlm.nih.gov/pubmed/12126457
- Wickman & Reed, 1987: http://www.ncbi.nlm.nih.gov/pubmed/3320183

2.2. Lithium Therapeutic Window/ Index

2.2. Therapeutic Window or Index

- To determine the therapeutic window:
  divide the upper limit by the lower limit.
  For example, here are ranges from Lexicomp, 2015:
  - mania: 0.6–1.2
    therapeutic window = 2 (1.2/0.6=2)
  - maintenance in the non-elderly: 0.8-1.0
    therapeutic window = 1.25 (1.0/0.8=1.25)
  - maintenance in the elderly: 0.4-0.6
    therapeutic window = 1.5 (0.6/0.4=1.5)
- Lithium is a narrow therapeutic window drug.
  All results using Lexicomp, 2005: value <3.
  Ranges from other authors: also provide a value <3.

2.3. Lithium TDM in the Clinical Environment

2.3. Lithium TDM in the Clinical Environment

- Remember:
  - Metabolized drugs tend to have stable TDM after reaching steady state; metabolism is stable unless inhibitors/inducers change it.
  - Lithium is eliminated by the kidneys; its elimination varies a lot depending on
    - water intake/elimination and/or
    - sodium intake/elimination
  - Educate your patients to have stable water and sodium metabolisms:
    - ↓ ADR risk
    - ↑ TDM stability

2.3. Lithium TDM in the Clinical Environment

- International guidelines http://www.ncbi.nlm.nih.gov/pubmed/19689501 recommend serum levels:
  - get 2 levels to establish therapeutic dose,
  - then every 3–6 months,
  - after dose increases, and
  - as clinically indicated.
- Malhi & Berk, 2012: http://www.ncbi.nlm.nih.gov/pubmed/22265701
  - Concentrations indicating incipient intoxication should prompt immediate dose ↓

2.4. Lithium TDM
Reflections on Efficacy vs. Safety

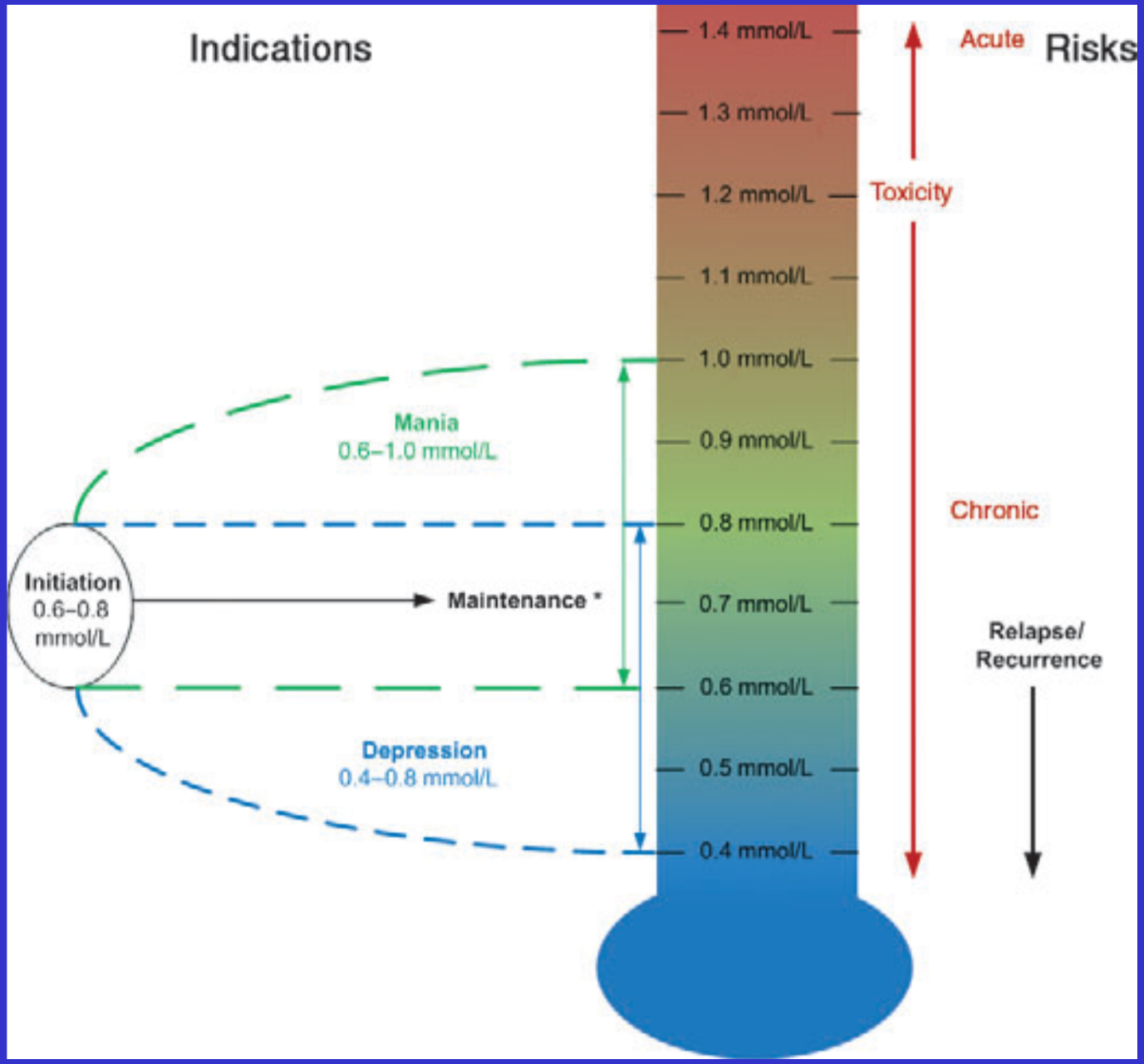
2.4. Lithium TDM Reflections on Efficacy vs. Safety

- Malhi & Berk, 2012: http://www.ncbi.nlm.nih.gov/pubmed/22265701
  - the therapeutic range is "reasonably well defined" (0.4–0.8 mmol/L).
  - Greater efficacy of concentrations (>0.6 mmol/L)
    - is of greater necessity for acute mania
    - and, to a lesser extent, for maintenance

    comes at a cost in terms of tolerability,
  - whereas lower plasma concentrations
    - that might be adequate for depression prophylaxis
    - and ↓ risks of long-term toxicity

    might not be optimal to ↓ mania recurrence.
- They use a visual representation: the "lithiumeter". See the next slide. http://www.ncbi.nlm.nih.gov/pubmed/21676125

2.4. Lithium TDM Reflections: The Lithiumeter



3. Lithium Formulations And Dosing

3. Lithium Formulations and Dosing

3.1. Formulations
3.2. Dosing
3.3. Number of Doses
3.4. General Instructions
3.5. Predicting Dosing

3.1. Lithium Formulations

3.1. Lithium Formulations

- In the US, lithium preparations are generic and keep changing:
  - ask your pharmacist
  - check dailymed https://dailymed.nlm.nih.gov/dailymed/index.cfm

    There are:
    - few oral solutions (liquid):
    - many lithium carbonate tablets that provide immediate release
    - some lithium carbonate ER tablets

3.1. Lithium Formulations

- Grandjean & Aubry, 2009 http://www.ncbi.nlm.nih.gov/pubmed/19374461

  Lithium carbonate:

  - after a single dose, peak serum concentration is
    - 1.0-2.0 hours for standard (immediate) forms
    - 4-5 hours for ER forms
  - peak/trough concentration ratio:
    - 1.9/1
    - 1.6/1 ER forms
  - bioavailability = 80-100%,
  - total clearance = 10-40 mL/min
  - elimination half-life is 18-36 hours

  They recommend waiting 1 week after any lithium dose change to collect TDM to be sure steady state has been reached.

3.2. Lithium Dosing

3.2. Lithium Dosing

- Grandjean & Aubry, 2009: http://www.ncbi.nlm.nih.gov/pubmed/19374461

  For lithium carbonate:

  - Initial recommended dose: 450–900 mg/day, but it depends on age and body weight.
  - Typical maintenance doses: 550-1,300 mg/day but it depends on TDM.

  Approximated doses by age:

  - <40 years: 925-1300 mg/day
  - 40-60 years: 740-925 mg/day
  - >60 years: 550-740 mg/day

3.3. Lithium: Number of Doses

3.3. Lithium: Number of Doses

- Number of doses:
  - Many authors recommend a single daily dosing with ER tablets to ↓ ADRs, as well as the possibility of less risk of renal damage. Malhi & Tanious, 2011:

    http://www.ncbi.nlm.nih.gov/pubmed/21425882

  - Carter et al. 2013: http://www.ncbi.nlm.nih.gov/pubmed/24165107 recommend starting a twice-a-day dosing pattern to establish the target dose and then switching to a single daily dosing pattern.

3.4. Lithium: General Instructions

3.4. Lithium: General Instructions

- ER tablets must be swallowed whole.
- Lithium can be taken with meals to avoid GI upset.
- Recommend that the patient have:
  - proper hydration (at least 2–3 liters/day) and
  - normal quantities of salt,
  - particularly during infections.

3.5. Lithium: Predicting Dosing

3.5. Lithium: Predicting Dosing

- Many methods have been developed for:
  - lithium dose estimation or
  - level prediction at the initiation of therapy.

  None of them appears optimal, according to
    - Lobeck, 1988: http://www.ncbi.nlm.nih.gov/pubmed/3057477
    - Sienaert et al. 2013: http://www.ncbi.nlm.nih.gov/pubmed/22944190
- Dr. de Leon has used 1 method when he needed to use lithium to control mania and accelerate lithium titration in patients with normal lithium elimination (having none of the factors described in Section 4).
  - Dr. de Leon likes its simplicity (see the next slide),
  - but he may be biased because it was developed by his mentor: Dr. Simpson.

3.5. Lithium: Predicting Dosing

- Cooper et al., 1973: http://www.ncbi.nlm.nih.gov/pubmed/4699934
- Description: □ give 600 mg loading dose
  □ after 24 hours collect lithium level

Table with Approximate Target Daily Doses

Level mEq/L	Recommended Dose
0.10-0.14	1800 mg/day
0.15-0.19	1200 mg/day
0.20-0.23	900 mg/day
0.24-0.30	600 mg/day
>0.30	600 mg/day, use extreme caution

- After reaching steady state level, Dr. de Leon verifies that the dose provides adequate levels, and consider the need to ↑ dose for mania control.

4. Lithium Dosing Modifications

4. Lithium Dosing Modifications

4.1. Associated with Pharmacokinetic DDIs
4.2. Associated with Personal Variables

4.1. Lithium Dosing and Pharmacokinetic DDIs

http://www.ncbi.nlm.nih.gov/pubmed/26936045
http://www.ncbi.nlm.nih.gov/pubmed/10463373

4.1. Lithium Dosing and Pharmacokinetic DDIs

4.1.1. Higher Lithium Doses Due to ↑ Elimination

4.1.2. Drugs to Avoid Due to ↓ Elimination

4.1.3. Drugs with Which to Use Caution

4.1.1. DDIs Requiring Higher Lithium Doses Due to ↑ Lithium Elimination

4.1.1. DDIs Requiring Higher Lithium Doses Due to ↑ Elimination

- DDIs requiring higher lithium dosages due to ↑ elimination include:
  - sodium bicarbonate and sodium chloride
  - osmotic diuretics: urea and mannitol
  - acetazolamide,
  - methyl xanthines: theophylline
    aminophylline
    caffeine

You should recommend that your patient maintain stable caffeine intake.

Sudden ↓ in high caffeine intake can lead to intoxication.

4.1.2. Drugs to Avoid Due to ↑ Lithium Elimination

4.1.2. Drugs Better to Avoid Due to ↑ Lithium Elimination

- Some drugs ↓ lithium elimination;
  it is better to avoid co-prescription with lithium and:
  - mineral corticoids
  - thiazides: ↑ serum lithium concentration by 25%
  - diuretic herbs may ↓ lithium levels,
    but there is no information on their composition.
  - anti-hypertensives associated with intoxications:
    - ACE inhibitors
    - angiotensin II receptor antagonists
  - NSAIDs and COX-2 inhibitors

4.1.3. Drugs to Use with Caution in Patients on Lithium

4.1.3. Drugs to Use with Caution

4.1.3.1. Diuretics
4.1.3.2. Other Anti-Hypertensive Drugs
4.1.3.3. Anti-Inflammatory Drugs
4.1.1.4. Other Drugs

4.1.3.1. Lithium and Diuretics

4.1.3.1. Lithium and Diuretics

- Avoid thiazides.
- Loop diuretics: furosemide (best study):
  - prospective studies: suggest they are safe
  - case reports: intoxications in
    - the elderly or
    - patients with medical complication
  - pharmacoepidemiological studies on intoxication: taking furosemide ↑ risk of lithium intoxication
- Potassium-sparing diuretics:
  - amiloride:
    - safe and
    - used for lithium-induced polyuria
  - spironolactone: not studied
  - triamterene: not studied but probably safe

4.1.3.2. Lithium and Other Anti-Hypertensive Drugs

4.1.3.2. Lithium and Other Anti-Hypertensive Drugs

- Avoid those associated with intoxications:
  - ACE inhibitors
  - angiotensin II receptor antagonists
- Calcium channel blockers:
  - case reports: both ↑ and ↓ lithium levels.
  - according to lithium prescribing information, these agents may ↑ neurotoxicity risk
  - cases of severe bradycardia have been reported when lithium and verapamil were combined
- Other anti-hypertensives: b-blockers and methyldopa

by ↓ renal perfusion, may ↓ lithium elimination.

4.1.3.3. Lithium and Anti-Inflammatory Drugs

4.1.3.3. Lithium and Anti-Inflammatory Drugs

- Avoid:
  - COX-2 inhibitors
  - NSAIDs

  Tell your patient to avoid over-the-counter NSAIDs. Insist that intermittent NSAID use can easily lead to a lithium intoxication.
- If you need to use an anti-inflammatory with lithium, it is safer to use:
  - aspirin
  - sulindac

  Anyway, be careful and follow lithium TDM:
  - old reviews suggest these drugs are safe
  - case reports: occasionally can ↑ lithium levels

http://www.ncbi.nlm.nih.gov/pubmed/14658947

4.1.3.4. Lithium and Other Drugs

4.1.3.4. Lithium and Other Drugs

- Topiramate:
  - A small controlled study of topiramate 200 mg/day showed little effect on lithium levels.

    http://www.ncbi.nlm.nih.gov/pubmed/15355124
  - Case reports using high topiramate doses revealed ↑ lithium levels (possible inhibition of carbonic anhidrase)

    http://www.ncbi.nlm.nih.gov/pubmed/12006910 http://www.ncbi.nlm.nih.gov/pubmed/15349023
- Cyclosporin may ↑ lithium levels (↓ renal perfusion)
- Antibiotics:
  - In the 1980s, metronidazole and tetracycline were associated with intoxications. http://www.ncbi.nlm.nih.gov/pubmed/10463373
  - In recent pharmacoepidmilogical studies, any antibiotic use may be a marker of serious infections, which are risks for intoxication.

    http://www.ncbi.nlm.nih.gov/pubmed/15898965

4.2. Lithium Dosing and Personal Variables

4.2. Lithium Dosing and Personal Variables

4.2.1. ↓ in Renal Function
Including ↓ Due to Aging

4.2.2. Pregnancy

4.2.3. Unexpected Medical Complications

4.2.1. Lithium Dosing and ↓ in Renal Function Including ↓ Due to Aging

4.2.1. Lithium Dosing:↓ in Renal Function Including ↓ Due to Aging

- Renal impairment:
  - If creatinine clearance is 10–50 mL/min:
    ↓ lithium dose to 50–75% of the normal dose.

http://www.ncbi.nlm.nih.gov/pubmed/25467053 http://www.amazon.com/Drug-Information-Handbook-Lexicomp/dp/1591953421/ref=sr_1_1?s=books&ie=UTF8&qid=1457718666&sr=1-1&keywords=drug+information+handbook

- Elderly age and lithium:
  - Pharmacokinetics on elderly:
    - ↓ GFRs
    - a total body water of 10–15% leading to a ↓ distribution volume by 10–15%
  - Lower the dose:
    - initial: 300 mg once/twice a day
    - maintenance: weekly increases of 300 mg
    - maximum: >1,200 mg/day rarely needed
  - Lower serum concentrations are recommended by some.

4.2.2. Lithium Dosing and Pregnancy

4.2.2. Lithium Dosing: Pregnancy

- During the last months of pregnancy:
  - ↑ GFR: ↑ lithium clearance increases by 30–50%

    http://www.ncbi.nlm.nih.gov/pubmed/10463373
- At the time of delivery:
  - lithium clearance ↓ abruptly to prepregnancy values; lithium may need to be adjusted after delivery.

    http://www.ncbi.nlm.nih.gov/pubmed/19384328

4.2.3. Lithium Dosing and Unexpected Medical Complications

4.2.3. Lithium Dosing: Unexpected Medical Complications

- Hyperglycemic states:
  - ↑ elimination: osmotic diuresis due to glycosuria need ↑ lithium doses

    http://www.ncbi.nlm.nih.gov/pubmed/11898805

- Unrecognized hyperthyroidism:
  - may be a risk factor for lithium intoxication

    http://www.ncbi.nlm.nih.gov/pubmed/10866336

5. Lithium Pharmacogenetics

5. Lithium Pharmacogenetics

- Lithium pharmacogenetics:
  not ready for clinical practice.

  http://www.ncbi.nlm.nih.gov/pubmed/26806517

6. Lithium Overdoses

6. Lithium Overdoses

- To prevent lithium intoxications that are potentially lethal, psychiatrists need to:
  - be experts in lithium pharmacokinetics, and
  - educate their patients about risk factors.
- Be careful: tubes with lithium heparin as an anticoagulant can give you false lithium intoxications.
- This section focuses on:
  - a practical classification of lithium overdoses by Bailey & McGuigan, 2000

    http://www.ncbi.nlm.nih.gov/pubmed/11128231
  - a brief review of management: a medical issue

6. Lithium Overdose

6.1. Practical Classification
6.2. Management

6.1. Lithium Overdoses: Practical Classification

http://www.ncbi.nlm.nih.gov/pubmed/11128231

6.1. Lithium Overdoses: Practical Classification

- From a poisoning center, Bailey & McGuigan, 2000, describe 3 overdose situations:
  - acute overdose: when the patient was not taking long-term lithium treatment
  - acute-on-chronic overdose: acute ingestion in a patient who is receiving treatment

  and
  - chronic poisoning: intoxication in the absence of a history of acute ingestion.

http://www.ncbi.nlm.nih.gov/pubmed/11128231

6.1. Lithium Overdose Classification

6.1.1. Acute Overdose
6.1.2. Acute-on-Chronic Overdose
6.1.3. Chronic Overdose

6.1.1. Acute Lithium Overdose

6.1.1. Acute Lithium Overdose

- Acute overdose:
  - definition: when the patient was not taking long-term lithium treatment
  - occurs in only a small percentage of all intoxications
  - symptoms: usually
    - CNS: confused state
      cerebellar signs
      EPS
      neuromuscular symptoms
    - and
    - GI symptoms: nausea/vomiting
      diarrhea
    - others can also be present:
      - renal symptoms
      - arrhythmias

6.1.2. Acute-on-Chronic Lithium Overdose

6.1.2. Acute-on-Chronic Lithium Overdose

- Acute-on-chronic overdose:
  - Definition: acute ingestion in a patient who is receiving lithium treatment
  - Most frequent type of overdose
  - As the brain concentration of lithium has already reached equilibrium with its plasma concentration, even moderately high serum concentrations may be associated with severe symptoms.
  - The half-life of lithium elimination may be prolonged.

6.1.3. Chronic Lithium Overdose

6.1.3. Chronic Lithium Overdose

- Chronic overdose:
  - Definition: intoxication in the absence of a history of acute ingestion
  - Contributing factors include
    - change in daily dose,
    - chronic excessive dosage,
    - any change in the patient's sodium and water status,
    - kidney disease,
    - DDI,
    - intercurrent infection, and
    - surgery.
  - This overdose better follows the classic classification of lithium intoxication proposed by Hansen & Amdisen, 1978 (next slide).

6.1.3. Chronic Lithium Overdose

- In 1978, Hansen & Amdisen: http://www.ncbi.nlm.nih.gov/pubmed/356084 proposed a classification:

Grade 0: asymptomatic	
Grade 1 includes	• nausea, vomiting, • tremor, hyperreflexia, • agitation, • muscle weakness, ataxia, or • drowsiness
Grade 2 includes	• stupor, • rigidity or hypertonia, or • hypotension
Grade 3 includes	• coma, • seizures and myoclonia, and • cardiovascular collapse

6.2. Lithium Overdoses: Management

6.2. Lithium Overdoses: Management

- Management: a medical rather than a psychiatric issue
- Different guidelines provide different recommendations:

  http://www.ncbi.nlm.nih.gov/pubmed/19057466
- According to Grandjean & Aubry, 2009:
  - Conservative measures:
    - induction of vomit,
    - gastric lavage if appropriate,
    - protection of airways, and
    - maintenance of IV line.
  - Dialysis should be considered for severe cases:
    - hemodialysis: treatment of choice

      rebound may occur after 6-12 hours

  http://www.ncbi.nlm.nih.gov/pubmed/19453201

6.2. Lithium Overdoses: Management

- Timmer & Sands, 1999: http://www.ncbi.nlm.nih.gov/pubmed/10073618
  Hemodialysis is indicated according to lithium levels:
  - > 6 mEq/L: any patient
  - > 4 mEq/L: any patient on chronic therapy
  - 2.5-4 mEq/L: any patient with:
    - severe neurological symptoms
    - renal insufficiency
    - unstable hemodynamically or neurologically
  - <2.5 mEq/L: any patient with:
    - end-stage kidney disease
    - lithium levels ↑ after admission
    - fail to reach level < 1 mEq/L in 30 hours
- Alternative to hemodialysis: continuous hemodiafiltration
  http://www.ncbi.nlm.nih.gov/pubmed/17288494

Questions

-Please review the 10 questions on the pdf titled "Questions on the Presentation: Pharmacokinetics of Lithium".

-You will find the answers on the last slide after the "Thank you" slide. No peeking until you have answered all the questions.

-If you do not answer all the questions correctly, please review the Power Point presentation once again to reinforce the pharmacological concepts.

Thank you

Answers

1. B
2. C
3. B
4. B
5. A
6. D
7. D
8. A
9. A
10. D