Lithium

Lect.Dr.
Shaimaa saleh

Uses

- Mania.
- Bipolar manic/depressive disorder.
- Major depression.

THERAPEUTIC AND TOXIC CONCENTRATIONS

- The general therapeutic range for lithium is 0.6–1.5 mmol/L.
- For long-term maintenance use, the usual desired range is 0.6–0.8 mmol/L. If patients do not respond to these levels during maintenance treatment, occasional use of lithium concentrations equal to 0.9–1 mmol/L is required and in some cases concentrations as high as 1–1.2 mmol/L are necessary to gain an adequate outcome.
- When lithium serum concentration monitoring is anticipated for an individual, the patient needs to understand that it is important to take their medication as instructed for 2–3 days before the blood sample is obtained, to have the blood sample withdrawn 12 ± 0.5 hours after the last dose, the distribution phase lasts for 6–10 hours

- In patients with good renal function (creatinine clearance >80 mL/min), the average elimination half-life for lithium is 24 hours
- Short-term side effects observed when starting lithium or after a dosage increase include muscle weakness, lethargy, polydipsia, polyuria, nocturia, headache, impairment of memory or concentration, confusion, impaired fine motor performance, and hand tremors .Many of these adverse effects will diminish with continued dosing of lithium. At lithium serum concentrations within the upper end of the therapeutic range (1.2–1.5 mmol/L), the following adverse effects can be noted in patients: decreased memory and concentration, drowsiness, fine hand tremor, weakness, lack of coordination, nausea, diarrhea, vomiting, or fatigue.
- At concentrations just above the therapeutic range (1.5–3 mmol/L), confusion, agitation, slurred speech, lethargy, blackouts, ataxia, dysarthria, nystagmus, blurred vision, tinnitus, vertigo, hyperreflexia, hypertonia, coarse hand tremors, and muscle fasciculation's may occur in patients.

CLINICAL MONITORING PARAMETERS

- Generally, onset of action for lithium is 1–2 weeks, and a 4- to 6-week treatment period is required to assess complete therapeutic response to the drug
- Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized. Because patients with acute mania can have increased lithium clearance, lithium concentrations should be remeasured in these patients once the manic episode is over and clearance returns to normal.

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

- Lithium is eliminated almost completely (>95%) unchanged in the urine
- Lithium eliminated in the saliva, sweat, and feces accounts for less than 5% of the administered dose
- On average, lithium clearance is approximately 20% of the patient's creatinine clearance
- Oral bioavailability is good for all lithium salts and dosage forms and equals 100%
- The peak lithium concentration occurs 15–30 minutes after a dose of lithium citrate syrup, 1–3 hours after a dose of rapid-release lithium carbonate tablets or capsules, and 4–8 hours after a dose of sustained-release lithium carbonate tablets

- Lithium ion is not plasma protein bound.
- The typical dose of lithium carbonate is 900–2400 mg/d in adult patients with normal renal function.
- Adults with normal renal function (creatinine clearance >80 mL/min) have an average elimination half-life of 24 hours, volume of distribution equal to 0.9 L/kg, and clearance of 20 mL/min for lithium

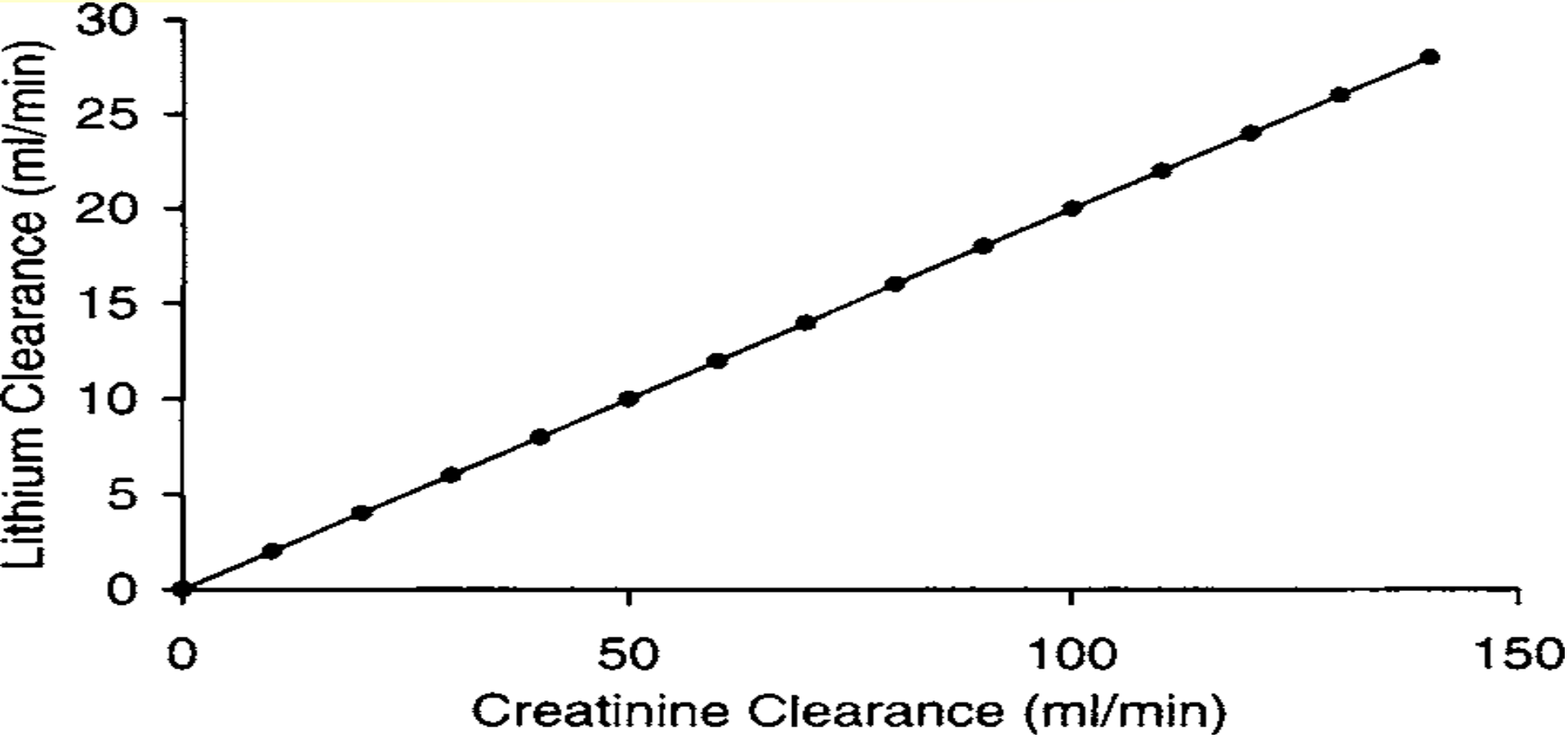
EFFECTS OF DISEASE STATES AND CONDITIONS ON LITHIUM PHARMACOKINETICS

- During an acute manic phase, lithium clearance can increase by as much as 50%, which produces a half-life that is about 1/2 the normal value
- In children 9–12 years of age, average elimination half-life equals 18 hours, volume of distribution is 0.9 L/kg, and clearance equals 40 mL/min for the ion
- Because glomerular filtration and creatinine clearance decrease with age, lithium clearance can be decreased in elderly patients, producing half-lives up to 36 hours
- Because of the circadian rhythm of glomerular filtration, lithium clearance is about 30% higher during daytime hours

INITIAL DOSAGE DETERMINATION METHODS

- pharmacokinetic dosing method
- Literature-based recommended dosing

Pharmacokinetic Dosing Method



- The ratio between lithium clearance and creatinine clearance is 0.2 for patients requiring maintenance therapy with lithium. This relationship is used to estimate lithium clearance for patients requiring initial dosing with the drug.

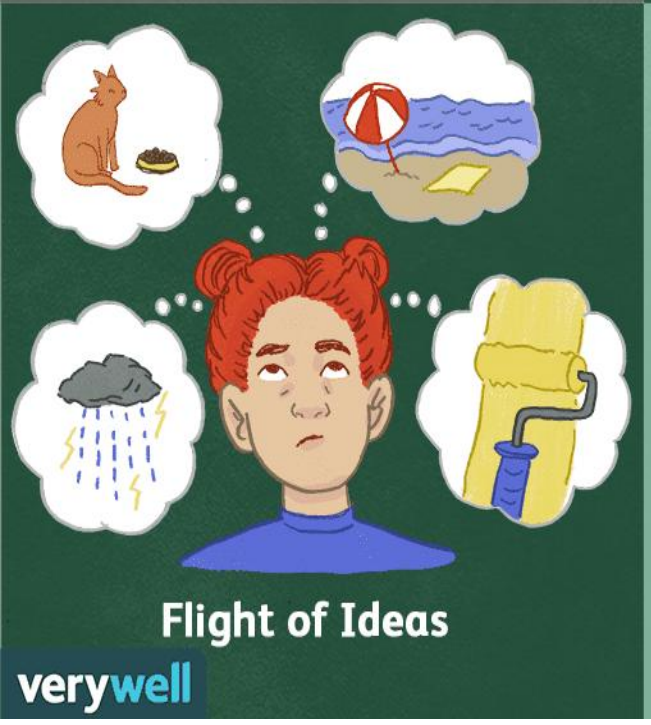
- For long-term maintenance use, lithium clearance is

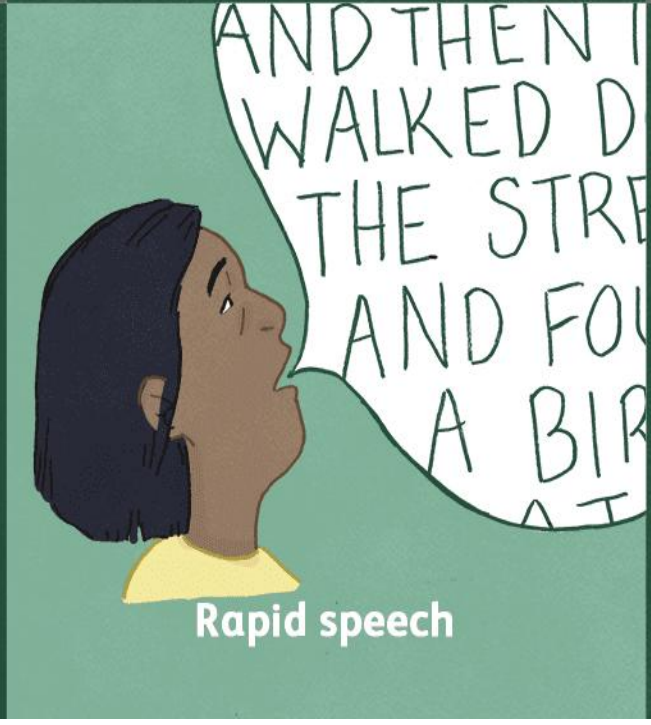
$$Cl = 0.288(CrCl)$$

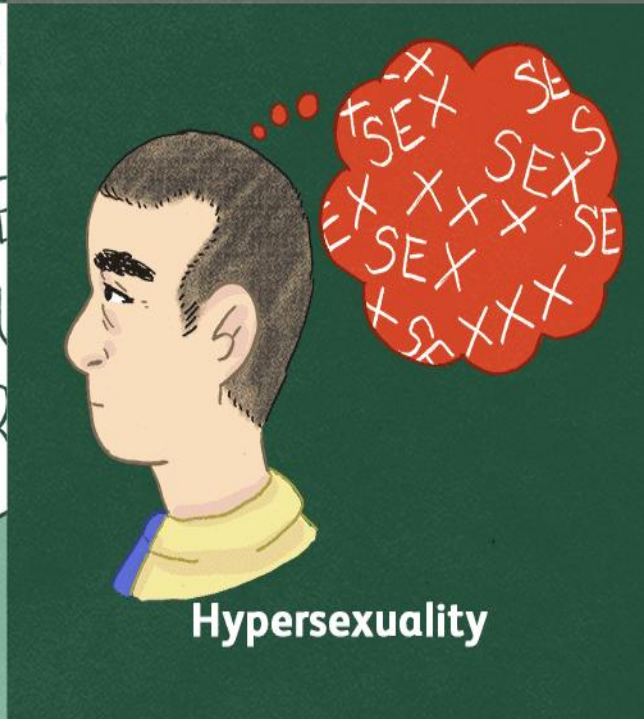
- For patients with acute mania, lithium clearance is increased by about 50%, and the corresponding equation for these individuals is

$$Cl = 0.432(CrCl)$$

Signs of a Manic Episode







SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATION

- When given orally, lithium follows a two-compartment model
- After the peak concentration is achieved, serum concentrations drop rapidly because of distribution of drug from blood to tissues (α or distribution phase).

$$Css = [F(D/\tau)] / Cl \quad or \quad D/\tau = (Css \cdot Cl) / F$$

- Because this equation computes lithium ion requirement and lithium carbonate doses are prescribed in milligrams, the ratio of lithium ion content to lithium carbonate salt (8.12 mmol Li+/300 mg lithium carbonate) is used to convert the result from this equation into a lithium carbonate dose.

STEADY-STATE CONCENTRATION SELECTION

- Lithium serum concentrations are selected based on the presence or absence of acute mania and titrated to response
- For individuals with acute mania, a minimum lithium concentration of 0.8 mmol/L is usually recommended. If patients with acute mania do not respond to these levels, lithium concentrations of 1–1.2 mmol/L and in some instances concentrations as high as 1.2–1.5 mmol/L are needed.
- For long-term maintenance use, the usual desired range is 0.6–0.8 mmol/L. If patients do not respond to these levels during maintenance treatment, occasional use of lithium concentrations equal to 0.9–1 mmol/L is required and in some cases concentrations as high as 1–1.2 mmol/L are necessary to gain an adequate outcome.

- **Example 1** MJ is a 50-year-old, 70-kg (5 ft 10 in) male with bipolar disease. He is not currently experiencing an episode of acute mania. His serum creatinine is 0.9 mg/dL. Compute an oral lithium dose for this patient for maintenance therapy.
- *Estimate creatinine clearance*

CrClest = [(140 − age)BW]/(72 · SCr) = [(140 − 50 y)70 kg]/(72 · 0.9 mg/dL)

CrClest = 97 mL/min

- *Estimate clearance*

Cl = 0.288(CrCl) = 0.288(97 mL/min) = 27.9 L/d

For a patient requiring maintenance therapy for bipolar disease the desired lithium concentration would be 0.6–0.8 mmol/L. A serum concentration equal to 0.6 mmol/L will be chosen for this patient, and oral lithium carbonate will be used (F = 1, 8.12 mmol Li+/ 300 mg of lithium carbonate).

$D/\tau = (Css \cdot Cl) / F = (0.6 \text{ mmol/L} \cdot 27.9 \text{ L/d}) / 1 = 16.7 \text{ mmol/d}$

D/τ = (300-mg lithium carbonate/8.12 mmol Li+) 16.7 mmol/d = 617 mg/d, rounded to 600 mg/d of lithium carbonate. This dose would be given as 300 mg of lithium carbonate every 12 hours.

Example 2 Same patient profile as in example 1, but serum creatinine is 3.5 mg/dL indicating renal impairment.

1. *Estimate creatinine clearance.*

$CrCl_{est} = [(140 - age)BW]/(72 \cdot SCr) = [(140 - 50\ y)70\ kg]/(72 \cdot 3.5\ mg/dL)$

$CrCl_{est} = 25\ mL/min$

$Cl = 0.288(CrCl) = 0.288(25\ mL/min) = 7.2\ L/d$

$D/\tau = (Css \cdot Cl) / F = (0.6\ mmol/L \cdot 7.2\ L/d)/1 = 4.3\ mmol/d$

D/τ = (300 mg lithium carbonate/8.12 mmol Li^+) 4.3 mmol/d = 159 mg/d, rounded to 150 mg/d of lithium carbonate. This dose would be given as 150 mg of lithium carbonate daily.

Literature-Based Recommended Dosing

Choose lithium dose based on disease states and conditions present in the patient.

The patient requires prophylactic lithium therapy for bipolar disease, and has good renal function. A lithium carbonate dose of 600 mg/d, given as 300 mg every 12 hours, is recommended as the initial amount. The dosage rate will be increased 300–600 mg/d every 2–3 days as needed to provide adequate therapeutic effect, avoid adverse effects, and produce therapeutic lithium steady-state concentrations