Therapeutic Drug Monitoring

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Theophylline & Lithium

Theophylline is a methylxanthine compound that is used for the treatment of:

- Asthma
- Chronic obstructive pulmonary disease
- Premature apnea.

The general accepted therapeutic ranges for theophylline are:

- **10-20** µg/mL for the treatment of asthma or chronic obstructive pulmonary disease.
- **6-13** µg/mL for the treatment of premature apnea.
- ✓ Clinical guidelines suggest that for initial treatment of pulmonary disease, clinical response to theophylline concentrations between **5 and 15 µg/mL** should be assessed before higher concentrations are used.

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

- Theophylline is primarily eliminated by **hepatic metabolism (>90%)**.
- About 10% of a theophylline dose is recovered in the urine as unchanged drug.

Dosage forms

Different forms of theophylline are available:

1- Aminophylline is the ethylenediamine salt of theophylline.

2- Anhydrous aminophylline contains about **85%** theophylline.

3- Aminophylline dihydrate contains about **80%** theophylline.

4- Oxtriphylline is the choline salt of theophylline, contains about **65%** theophylline. [available only for oral use]

- The oral bioavailability of all three theophylline-based drugs is very good and generally equals 100% **F = 1**

Disease State/Condition	Half-Life	Volume of Distribution	Comment
Adult, normal liver function	8 h (range: 6-12 h)	0.5 L/kg (range: 0.4-0.6 L/kg)	
Adult, tobacco or marijuana smoker	5 h	0.5 L/kg	Tobacco and marijuana smoke induces CYP1A2 enzyme system and accelerates theophylline clearance.
Adult, hepatic disease (liver cirrhosis or acute hepatitis)	24 h	0.5 L/kg	Theophylline is metabolized >90% by hepatic microsomal enzymes (primary: CYP1A2; secondary: CYP3A, CYP2E1), so loss of functional liver tissue decreases theophylline clearance. Pharmacokinetic parameters highly variable in liver disease patients.
Adult, mild heart failure (NYHA CHF classes I or II)	12 h	0.5 L/kg	Decreased liver blood flow secondary to reduced cardiac output due to heart failure reduces theophylline clearance.
Adult, moderate-severe heart failure (NYHA CHF classes III or IV) or cor pulmonale	24 h	0.5 L/kg	Moderate-severe heart failure reduces cardiac output even more than mild heart failure, resulting in large and variable reductions in theophylline clearance. Cardiac status must be monitored closely in heart failure patients receiving theophylline since theophylline clearance changes with acute changes in cardiac output.
Adult, obese (>30% over ideal body weight (IBW)	According to other disease states/ conditions that affect theophylline pharmacokinetics	0.5 L/kg IBW[a]	Theophylline doses should be based on ideal body weight for patients who weight more that 30% above their IBW.
Children, 1-9 years, normal cardiac and hepatic function	3.5 h	0.5 L/kg	Children have increased theophylline clearance. When puberty is reached, adult doses can be used taking into account disease states and conditions that alter theophylline pharmacokinetics.
Elderly, >65 years	12 h	0.5 L/kg	Elderly individuals with concurrent disease states/conditions known to alter theophylline clearance should be dosed using those specific recommendations.

INITIAL DOSAGE DETERMINATION METHODS

- **The *Pharmacokinetic Dosing method***
- ***Literature-based recommended dosing***

Pharmacokinetic Dosing Method

1- Half-Life and Elimination Rate Constant Estimate

Disease state or condition	T 1/2
Adult, normal liver function	8 hours
Patient with COPD who smokes tobacco-containing Cigarettes	5 hours
Patient with moderate heart failure (NYHA CHF class III)	24 hours
patient with severe liver disease (Child-Pugh score = 12)	
Elderly > 65 y	12 hour
Patient with mild heart failure (NYHA CHF class I or II)	

- Once the correct **half-life** is identified for the patient, it can be converted into the theophylline **elimination rate constant** (ke) using the following equation:

✓ **ke = 0.693/t1/2.**

2- Volume of Distribution Estimate

- Volume of distribution is assumed to equal **0.5 L/kg** for nonobese patients.
- For obese patients (>30% above ideal body weight), ideal body weight is used to compute theophylline volume of distribution.

3- Clearance Estimate

$$Cl = Ke\ V$$

Cl : is theophylline clearance in **L/h**

4- Selection of Appropriate Pharmacokinetic Model and Equations

- When given by continuous intravenous infusion or orally, theophylline follows a one compartment pharmacokinetic model.

Route of administration	Equation
Oral	$Css = [F \cdot S\ (D/\tau)]/Cl$ **or** $D = (Css \cdot Cl \cdot \tau)/(F \cdot S)$
Continuous infusion	$Css = [S \cdot k0]/Cl$ **or** $k0 = (Css \cdot Cl)/S$
Intravenous loading dose	$LD = (Css \cdot V)/S$

- **F** is the bioavailability fraction for the oral dosage form (F = 1 for most oral theophylline sustained-release products)

- **S** is the fraction of the theophylline salt form that is active theophylline
  - S = 1 for theophylline
  - S = 0.85 for anhydrous aminophylline
  - S = 0.80 for aminophylline dihydrate
  - S = 0.65 for oxtriphylline.

- D is the dose of theophylline salt in mg
- τ is the dosage interval in hours ***{8hr for smoker while in normal or liver dysfunction 12 hr}***
- Cl is theophylline clearance in **L/h.**
- Css in μg/mL = mg/L

Literature-Based Recommended Dosing

- In general, the expected theophylline steady-state serum concentration used to compute these doses was **10 μg/mL**

Disease State/Condition	Mean Dose (mg/kg/h)
Children 1-9 y	0.8
Children 9-12 y or adult smokers	0.7
Adolescents 12-16 y	0.5
Adult nonsmokers	0.4
Elderly nonsmokers (>65 years)	0.3
Decompensated CHF, cor pulmonale, cirrhosis	0.2

✓ If theophylline is to be given orally, the dose equal:

D = (theophylline dose • Wt • τ)/S

✓ If theophylline is to be given as a continuous intravenous infusion the following equation is used :

k0 = (theophylline dose • Wt)/S

- If an intravenous loading dose is necessary, theophylline **5 mg/kg** or aminophylline **6 mg/kg** is used.
- Ideal body weight is used to compute loading doses for obese patients (>30% over ideal body weight).

USE OF THEOPHYLLINE SERUM CONCENTRATIONS TO ALTER DOSES

1-Linear pharmacokinetics

2-Pharmacokinetic parameters

Linear Pharmacokinetics Method

- Because theophylline follows linear, dose-proportional pharmacokinetics in most patients with concentrations within and below the therapeutic range, steady-state serum concentrations change in proportion to dose according to the following equation:

$$D_{new} = (C_{ss\,new}/C_{ss\,old})\, D_{old}$$

Pharmacokinetic Parameter Method

1- Actual clearance for patient

Route of administration	Equation
Oral	$Cl = [F \cdot S\,(D/\tau)]/Css$
Continuous intravenous infusion	$Cl = [S \cdot k0]/Css$

2-Actual Vd

$$V = (S \cdot D)/(C_{postdose} - C_{predose})$$

D :is the dose of theophylline salt in mg

C : post dose is the post loading dose concentration in mg/L

C: Predose is the concentration before the loading dose was administered in mg/L.

3- The half-life and elimination rate constant can be computed.

- $ke = Cl/V$
- $t1/2 = (0.693 \cdot V)/Cl$

- *4- Calculate dose*

Route of administration	Equation
Oral	$D = (Css \bullet Cl \bullet \tau)/(F \bullet S)$
Continuous infusion	$k0 = (Css \bullet Cl)/S$
Intravenous loading dose	$LD = (Css \bullet V)/ S$

USE OF THEOPHYLLINE BOOSTER DOSES TO IMMEDIATELY INCREASE SERUM CONCENTRATIONS

- If a patient has a subtherapeutic theophylline serum concentration in an acute situation, it may be desirable to increase the theophylline concentration as quickly as possible. In this setting, it would not be acceptable to simply increase the maintenance dose and wait 3-5 half-lives for therapeutic serum concentrations to be established in the patient.
- A rational way to increase the serum concentrations rapidly is to administer a booster dose of theophylline.

$$BD = [(C_{desired} - C_{actual})V]/S$$

Lithium is an alkali metal that is administered as a monovalent cation (Li^+) for the treatment of:

- Bipolar disorder
- Depression
- Mania.

THERAPEUTIC AND TOXIC CONCENTRATIONS

- The general therapeutic range for lithium is **0.6-1.5 mmol/L**.
- Because lithium is a monovalent cation, the therapeutic range expressed in mEq/L is identical to these values (0.6-1.5 mEq/L).
- For individuals with **acute mania**, a minimum lithium concentration of 0.8 mmol/L is usually recommended. The usual desired range for these individuals is **0.8-1 mmol/L**.

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

Dosage form

- ✓ **Lithium carbonate capsules** (150, 300, 600 mg) and **tablets** (rapid release: 300 mg; sustained release: 300, 450 mg) are available.
- ➢ *There are **8.12 mmol** (or 8.12 mEq) of lithium in **300 mg** of lithium carbonate.*
- ✓ **Lithium citrate syrup** (8 mmol or mEq/5 mL).
- Oral bioavailability is good for all lithium salts and dosage forms and equals **100%**.
- ➢ The typical dose of lithium carbonate is **900-2400 mg/d** in adult patients with normal renal function.

EFFECTS OF DISEASE STATES AND CONDITIONS ON LITHIUM PHARMACOKINETICS

Disease state and conditions	T 1/2	CL	Vd
Adults with normal renal function (CrCl >80 mL/min)	24 hours	20 mL/min	0.9 L/kg
During an acute manic phase	½ the normal value	increase by 50%	
children 9-12 years of age	18 hours	40 mL/min	
elderly patients	36 hours	decrease	

INITIAL DOSAGE DETERMINATION METHODS

1- ***Pharmacokinetic Dosing method***

2-Literature-based recommended dosing

Pharmacokinetic Dosing Method

1- ***Creatinine Clearance Estimate***

2- **Lithium clearance** ***Estimate***

- Cl = 0.288(CrCl) [For normal patients]
- Cl = 0.432(CrCl) [For patients with acute mania]

- where Cl is lithium clearance in **L/d** and CrCl is creatinine clearance in mL/min.

3- Calculate dose

$$D/\tau = (Css \bullet Cl)/F$$

Where:

F=1 for oral lithium

D: dose in millimoles

Cl: lithium clearance in L/d

Css: steady state in mmol/L

τ : dosage interval in days

- ✓ **Note:** The ratio of **(300 mg lithium carbonate/8.12 mmol Li+)** should be used to convert the result from this equation into a lithium carbonate dose & this dose should be given in 2 or 3 times daily.

Literature-Based Recommended Dosing

- For the treatment of **acute mania**, initial doses are usually **900-1200 mg/d** of lithium carbonate.
- If the drug is being used for **bipolar disease** prophylaxis, an initial dose of **600 mg/d** lithium carbonate is recommended. In both cases, the total daily dose is given in 2-3 divided daily doses.
- Recommended doses for children and adolescents with normal renal function are **15-60 mg/kg/d** and **600-1800 mg/d**, respectively, with doses administered 3-4 times daily.

- To avoid adverse side effects, lithium doses are slowly increased by 300-600 mg/d every 2-3 days according to clinical response and lithium serum concentrations.
- **Renal dysfunction** is the major condition that alters lithium pharmacokinetics and dosage.

- If creatinine clearance is 10-50 mL/min, the prescribed initial dose is **50%-75%** of that recommended for patients with normal renal function.
- For creatinine clearance values below 10 mL/min, the prescribed dose should be **25%-50%** of the usual dose in patients with good renal function.

USE OF LITHIUM SERUM CONCENTRATIONS TO ALTER DOSAGES

Linear Pharmacokinetics Method

$$D_{new} = (C_{ss\,new}/C_{ss\,old})D_{old}$$