

THEOPHYLLINE

Theophylline is a bronchial smooth muscle relaxant used in the treatment of bronchial asthma and other respiratory diseases.

- it has a narrow therapeutic index. Fortunately, theophylline serum levels correlate well with both therapeutic and toxic effects.
- Concentrations of 10-20 mg/L are needed to produce bronchodilation with a minimum of side effects.
- Serum levels exceeding 20 mg/L are associated with an unacceptable incidence of adverse reactions.
- Theophylline levels above 35 mg/L increase the incidence of seizures and cardiac arrhythmias.
- Poorly soluble in water
- Usually administered intravenously as the more soluble salt of theophylline, aminophylline.
- Dilute solutions of theophylline (1 mg/L) can be administered intravenously.
- Aminophylline (and other theophylline salts) can be administered rectally (suppositories or solutions).

Loading Dose

- An aminophylline loading dose for a 70-kg patient=250-500 mg (administered by slow i.v. injection). The loading dose is usually followed by intravenous aminophylline infused at a rate $R_o = 30-50$ mg/hr.
- Oral maintenance dose (aminophylline) = 200-300 mg three to four times a day.

PLASMA CONCENTRATION:

A) Therapeutic Conc:

- Therapeutic concentration of theophylline = 10 – 20 mg/L
- Improvement in respiratory function can be observed at $C = 5$ mg/L.

B) Toxic Conc:

- At toxic conc. side effects appear (nausea, vomiting are the most common).
- Side effects occur at $C > 20$ mg/L but sometimes they can occur at lower conc's (13-15 mg/L).
- When $C > 40$ mg/L premature atrial and ventricular contractions occur.
- CNS manifestations (e.g. seizures) usually occur at $C > 50$ mg/L (sometimes less than that).

Pharmacodynamics:

The bronchodilating effects of theophylline are proportional to $(\log C_p)$, therefore, as C_p increases a less than proportional increase in bronchodilation will occur. Thus C_p greater than 20 mg/L will produce almost the same pharmacodynamic effect as C_p less than 20 mg/L, but side-effects are more.

Bioavailability**A) Non-sustained release formulations:**

- Absorption is rapid and complete
- $t_{max} = 1-2$ hrs.

B) Sustained release formulations:

Designed to release the drug slowly so patients who metabolize the drug rapidly (such as smokers and children) can maintain C_p within therapeutic range where = 6-12 hr.

- Absorption of such formulations is complete but different from brand to another.
- Absorption occurs over a time interval 3-4 hrs and sometimes 8-12 hrs. (depending on the formulation)
- Formulations that can be given once daily (e.g., Theo-24) can cause dose-dumping effect especially with high-fat meals; therefore, they are usually avoided.

Volume of Distribution

- $V_d = 0.5$ = 35 L (for a 70-kg patient)
- Distribution follows two-compartment model.
- Toxic effects are associated with high C_p in the initial volume of distribution (in the alpha-phase) so theophylline toxicity may occur after very rapid injection of the drug since it accumulates in the first compartment (blood compartment) while the pharmacologic effect appears after the distribution of the drug in the second compartment (tissue compartment).

- V_d (in premature Neonates) = 0.7 L/kg
- V_d (after one year of age) = 0.5 L/kg
- V_d (in cystic fibrosis patients) = 0.6 L/kg
- V_d (in obese patients) = uncertain

N.B.

In obese patients, the loading dose is calculated according to a body weight less than the actual weight of the patient, but greater than the ideal body weight. This approach does not apply when calculating $t_{1/2}$.

Total Body Clearance:

- The clearance of theophylline is affected by many variables which necessitate carefully individualized dosage. Age, smoking, congestive heart failure, other diseases and drug interactions all contribute to a change in the metabolism of theophylline. These factors all necessitate dosage adjustments in order to achieve and maintain therapeutic serum levels and avoid toxicity.

- CL (average) = 0.04 L/hr/kg (based on LBW).

- **Factors that influence clearance are smoking, diseases, diet and drug interactions:**

1. **Smoking:** increases CL by 1.5 - 2 times (average 1.6 times)
2. **Diseases:**
 - a) CHF: reduces CL by 40%

- b) Pulmonary edema (usually associated with CHF) reduced CL by 40% almost as CHF, but in severe cases, it reduces CL by 85%.
 - c) Severe obstructive pulmonary disease reduces CL to 80%
 - d) Hepatic cirrhosis: reduces CL by 50%
 - e) Acute viral illness reduces CL by 50%
 - f) Premature Newborns: very low CL
3. **Diet:** Affects metabolism of theophylline. High protein/low carbohydrate diet induces hepatic enzymes that metabolize theophylline more rapidly, while caffeine decreases metabolism. But all of these effects are minor.

4. **Drug interactions:**

- a) **Macrolide antibiotics** (e.g. triacetyl **oleandomycin** and **erythromycin**): reduce CL by 25-50%.
- b) **Phenobarbital (PB)**: increases metabolism by 30%
- c) **Phenytoin**: increases CL by a factor of 1.5 (i.e.,150%).
- d) **Cimetidine**: Reduces theophylline metabolism by 40% (therefore, CL should be multiplied by 0.6).

Chiou Method for Clearance Determination

This method involves rapid estimation of the total body clearance of theophylline from two data points; generated from determination of the plasma drug concentration during infusion or after. In this case the two blood samples (C_1 & C_2) will be taken after administration of the loading dose and start of maintenance dose. Although the best results could be obtained if the two samples were taken 1hour (t_1) and 5 hour (t_2) after the commencement of the maintenance dose. Estimation of the clearance (CL) is done by the following equation:

$$CL = \frac{2R_o}{C_1 + C_2} + \frac{2V_d(C_1 - C_2)}{(C_1 + C_2)(t_2 - t_1)}$$

R_o = the infusion rate or the maintenance dose.

V_d = Volume of Distribution of theophylline (population kinetic estimate) (assumed to be 0.5 L/kg).

**Half-Life:**

- Adults = 8 hr.
- Smokers = 3-4 hr
- Severe CHF patients = 18-24 hr
- Obese patients > 8 hr (see the note about V_d in obese patients)

N.B. Use the ideal body weight in calculating V_d to ensure that the longest possible $t_{1/2}$ is used.

Calculation of Loading Dose:

If (S) represents the fraction of the administered dose which is the active drug, then the amount of drug absorbed from a salt form can be calculated as follows:

$$\text{Amount absorbed} = (S)(F)(D)$$

Theophylline is usually given as aminophylline.

Aminophylline is available in two salt forms:

- Anhydrous aminophylline (S = 0.84)
- Hydrous aminophylline (S = 0.80)

Example (1)

What is the loading dose (D_L) that should be given to a 70-kg patient to produce a plasma concentration of 10 mg/L?

Solution:

$$V_d = 0.4 - 0.5 \text{ L/kg (use 0.45 L/kg)}$$

$$V_d (70\text{-kg patient}) = 0.45 \text{ L.kg}^{-1} \times 70 \text{ kg} = 31.5 \text{ L}$$

$$D_L = \frac{V_d \cdot C}{S \cdot F}$$



$$D_L = \frac{31.5 \text{ L} \cdot \text{kg}^{-1} \times 10 \text{ mg} \cdot \text{L}^{-1}}{0.8 \times 1} = 393.75 \text{ mg} \approx 400 \text{ mg (or 5.6 mg/kg)}$$

N.B. In obese patients, the volume of distribution correlates well with total body weight (but not with ideal body weight). In this case, the previous calculations apply also for obese patients. Theophylline exhibits two-compartment pharmacokinetics. The bronchodilating effect correlates with concentrations in the second compartment, but the toxic effects correlate with concentrations in the first compartment (the initial volume of distribution). Therefore, the loading dose of theophylline is usually infused over a 30-minute period to minimize accumulation within the first compartment and to avoid toxicity.

Calculation of Maintenance Dose (D_M):

Example (2)

In example (1) the loading dose was calculated to be 393.75 mg and the plasma concentration was 10 mg/L, What aminophylline infusion rate will maintain an average steady-state level of 10 mg/L for this patient?

Solution:

$$D_M = S \cdot R_o \\ = C_{ss} \cdot CL$$

$$R_o = \frac{C_{ss} \cdot CL}{S}$$

$$D_M = S \times F \times \frac{D}{\tau} \\ = \bar{C}_{ss} \cdot CL$$

$$D = \frac{\bar{C}_{ss} \cdot CL \cdot \tau}{S \cdot F}$$

We know that the average theophylline clearance is 0.04 L/kg.hr.

$$CL = 0.04 \text{ L} \cdot \text{hr}^{-1} \cdot \text{kg}^{-1} \times 70 \text{ kg}^{-1} = 2.8 \text{ L/hr}$$

$$R_o = \frac{10 \text{ mg} \cdot \text{L}^{-1} \times 2.8 \text{ L} \cdot \text{hr}^{-1}}{0.8} = 35 \text{ mg/hr of aminophylline}$$

Let us assume that this patient is obese and his ideal body weight is 60 kg. Unlike volume of distribution, which may correlate better with total body weight, the clearance of theophylline appears to correlate better with ideal body weight. In this case we use the ideal body weight to calculate the clearance:

$$CL = 0.04 \text{ L.hr}^{-1}.\text{kg}^{-1} \times 60 \text{ kg} = 2.4 \text{ L/hr}$$

$$R_o = \frac{10 \text{ mg.L}^{-1} \times 2.4 \text{ L.hr}^{-1}}{0.8} = 30 \text{ mg/hr}$$

Example (3)

Assume that this patient is not obese but he is a heavy smoker suffering from a severe obstructive pulmonary disease and CHF. What is the maintenance dose of aminophylline that will maintain theophylline C_{ss} of 10 mg/L?

Solution:

There are three factors in this patient that alter theophylline clearance, namely; smoking, severe obstructive pulmonary disease and CHF. The product of all the factors which are present should be multiplied by the average clearance value:

Factor by which clearance is altered = the product of all factors

$$= (\text{Smoking}) \times (\text{SOPD}) \times (\text{CHF})$$

$$= 1.6 \times 0.8 \times 0.4 = 0.512$$

$$CL = 0.04 \text{ L/kg.hr} \times 70 \text{ kg} \times 0.512 = 1.4336 \text{ L/hr}$$

$$R_o = \frac{10 \times 1.4336}{0.8} = 17.92 \text{ mg/hr}$$



Example (4)

Assuming that the volume of distribution for this patient is 31.5 Liters as calculated in example (1) and clearance is 1.4336 L/hr as calculated in the last example. What is the $t_{1/2}$ of theophylline in this patient?

Solution:

$$t_{1/2} = \frac{0.693 V_d}{CL} = \frac{0.693 \times 31.5}{1.4336} = 21.16 \text{ hr}$$

This $t_{1/2}$ is longer than the average value of 6-10 hours because this patient has multiple factors that are known to alter theophylline clearance.

Give dose then monitor later (within 2 $t_{1/2}$'s) if C is low then an incremental loading dose should be given.

$$\text{Incremental Loading Dose} = \frac{V_d (C_{\text{desired}} - C_{\text{initial}})}{S.F}$$

Example (5)

Patient' weight = 60 kg (Asthmatic)

Given I.V. $D_L = 375$ mg at 9 p.m. followed by $R_o = 60$ mg/hr - aminophylline.

At 7 a.m. (after 10 hrs) $\Rightarrow C = 18$ mg/L

Calculate $CL = ?$ and $t_{1/2} = ?$

SOLUTION:

This is not a C_{ss}

$C_1 = [\text{Loading dose and its decay}] + [\text{Non-steady state infusion equation}]$

$$C_1 = \left[\frac{S \cdot F \cdot D}{V_d} e^{-k_d t_1} \right] + \left[\frac{S \cdot R_o}{V_d} (1 - e^{-k_d t_1}) \right]$$

$$t_1 = 10 \text{ hr}, \quad k_d = \frac{CL}{V_d}, \quad V_d = 0.5 \text{ L/kg} = 30 \text{ L}$$

$$18 = \left[\frac{18 \times 1 \times 375}{30} e^{-\frac{CL}{30} \times 10} \right] + \left[\frac{0.8 \times 60}{30} (1 - e^{-\frac{CL}{30} \times 10}) \right]$$

You can't solve for CL directly. Use trial and error,
try CL= 0.04 L/hr/kg first = 2.4 L/hr for this patient.

If use this CL $\Rightarrow C_p = 15 \text{ mg/L}$

CL= 2 L/hr $\Rightarrow C = 15 \text{ mg/L}$

CL = 1.65 L/hr $\Rightarrow C = 18 \text{ mg/L}$

$$t_{1/2} = \frac{0.693 V_d}{CL} = \frac{0.693 \times 30}{1.65} = 12.6 \text{ hr}$$

Assume desired C_{ss} is less than 20 mg/L (i.e. 15 mg/L) determine whether D_M needs to be adjusted.

SOLUTION:

Determine first C_{ss} will be produced by the used R_o :

$$C_{ss} = \frac{S \cdot R_o}{CL} = \frac{0.8 \times 60}{1.65} = \frac{48}{1.65} = 29 \text{ mg/L}$$

\therefore We need to reduce R_o

$$R_o = \frac{C_{ss} \cdot CL}{S} = \frac{15 \times 1.65}{0.8} = 30.9 \text{ mg/hr} \approx 30 \text{ mg/hr}$$

Maximum and minimum plasma levels:

$$C_{ss}^{\max} = \frac{S \cdot F \cdot D}{V_d (1 - e^{-k_d t})}$$

$$C_{ss}^{\min} = C_{ss}^{\max} \cdot e^{-k_d t}$$

$$\Delta C_p = \frac{S \cdot F \cdot D}{V_d} = C_{ss}^{\max} - C_{ss}^{\min}$$

Example (6)

A patient (31 kg) receives 200 mg aminophylline q6h (i.e., qid) for several days, a plasma sample was drawn immediately before the scheduled dose and found to be 15 mg/L. Estimate peak plasma conc. after each dose.

SOLUTION:

$$C_{ss}^{\min} = 5 \text{ mg/L (Trough Level)}$$

$$C_{ss}^{\max} = \frac{S \cdot F \cdot D}{V_d} + C_{ss}^{\min} = \left[\frac{0.8 \times 1 \times 200}{0.5 \times 31} \right] + 5 = 10.3 + 5 = 15.3 \text{ mg/L}$$

Practice Problem

A 42-year-old non-smoker man with a total body weight of 78 kg (180 cm) was admitted to Hospital complaining of shortness of breath. The diagnosis was asthma. The physician wanted to start the treatment with theophylline as soon as possible hence sought your advice. The patient has not been taking theophylline before.

You recommended a 450 mg loading dose of aminophylline to be injected slowly over 30 minutes followed by a maintenance dose of 40 mg/h of aminophylline. You also asked for two blood samples 1 and 5 h after the start of the maintenance dose.

The lab results indicated serum theophylline concentrations of 6.5 and 7.2 for samples taken 1 and 5 post-dose h, respectively.

1. Comment on the appropriateness of the recommended dose.
2. Estimate the upcoming theophylline steady-state concentration.
3. Recommend an appropriate dose if a target concentration of 12 ug/mL is desired.

Solution:

- Appropriateness of the recommended dose:

$$D_L, 78 \text{ kg} \times 6 \text{ mg} = \underline{468 \text{ mg}}$$

$$D_M, 0.5 \text{ mg/h} \times \text{kg BW} \times \text{CF}; 0.5 \times 78 \times 1 = \underline{39 \text{ mg/h}}$$

The given dose was appropriate.

- For C_{ss} , first calculate CL from

$$CL = \frac{2R_o}{C_1 + C_2} + \frac{2V_d(C_1 - C_2)}{(C_1 + C_2)(t_2 - t_1)}$$

$$CL = \frac{2 \times 40 \times 0.8}{6.5 + 7.2} + \frac{2 \times 0.5 \times 78(6.5 - 7.2)}{(6.5 + 7.2)(5 - 1)}$$

$$CL = 3.68 \text{ L/h}$$

$$C_{ss} = \text{Dose}/CL = 32 \text{ mg/h} / 3.68 \text{ L/h} = \underline{8.70 \text{ mg/L}} \text{ theophylline}$$

- Dose to give C_{ss} of 12 $\mu\text{g/mL}$:

$$40 \text{ mg/kg} \times 12 / 8.70 = \underline{55 \text{ mg/h}} \text{ aminophylline}$$

For the same patient if he smoked, the appropriate dose would have been 62.4 mg/h of aminophylline; if he was a non-smoker but suffering from congestive heart failure (CHF), the dose would have been 12.5 mg/h.

See if you can come up with the same numbers!

Treatment of Data

1. Assuming a V_d of 0.5 L/kg, calculate the elimination half-life of the drug during the 1st and 2nd steady state.
2. Calculate the total body clearance during both steady states.
3. Adjust the infusion rate in order to achieve the initial C_{ss} . Considering the condition of the patient, do you think an adjustment is needed?



Questions

Answers to the following questions should be substantiated by sufficient literature references.

1. Give the therapeutic and toxic plasma level range of theophylline.
2. Explain the reason(s) for the observed change in C_{ss} .
3. List 3 diseases and 3 drug interactions which can significantly alter C_{ss} of theophylline.
4. Name 2 different theophylline derivatives available in Saudi Arabia and their conversion ratios.
5. Recommend a maintenance dose of aminophylline for an asthmatic but otherwise healthy patient.

Further readings:

1. Michael Winter: Basic Clinical Pharmacokinetics, Second Edition 1988, Applied Therapeutics, Inc, Washington, USA.
2. William Evans et al., Applied Pharmacokinetics: Principles of TDM. Second Edition 1986. Applied Therapeutics, Inc, Washington, USA.

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