Phenytoin

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Introduction

- **Phenytoin** is a hydantoin compound related to the barbiturates used for the treatment of seizures.

- It is an effective anticonvulsant for the chronic treatment of
  - ***tonic clonic (grand mal)***
  - ***partial seizures***
  - ***acute treatment of generalized status epilepticus***

Introduction

- The usual therapeutic range for total (unbound + bound) phenytoin serum concentrations in the treatment of seizures is **10-20 µg/mL.**

- The usual unbound fraction of phenytoin in individuals with normal plasma protein binding is (**10%**).

- Unbound phenytoin serum concentrations **1–2 µg/mL**.

Introduction

- Unbound phenytoin serum concentrations (**free**) should be measured in patients with factors known to **alter** phenytoin plasma protein binding.

- These factors fall into three broad categories:
  1. ***Lack of binding protein where there are insufficient plasma concentrations of albumin.***
  2. ***Displacement of phenytoin from albumin binding sites by endogenous compounds.***
  3. ***Displacement of phenytoin from albumin binding sites by exogenous compounds.***

TABLE 10-2 Disease States and Conditions that Alter Phenytoin Plasma Protein Binding

INSUFFICIENT ALBUMIN CONCENTRATION (HYPOALBUMINEMIA)	DISPLACEMENT BY ENDOGENOUS COMPOUNDS	DISPLACEMENT BY EXOGENOUS COMPOUNDS
Liver disease	Hyperbilirubinemia	Drug interactions
Nephrotic syndrome	Jaundice	Warfarin
Pregnancy	Liver disease	Valproic acid
Cystic fibrosis	Renal dysfunction	Aspirin (>2 g/d)
Burns		NSAIDs with high albumin binding
Trauma		
Malnourishment		
Elderly		

Methods To Estimate Unbound Phenytoin Concentrations (C_f)

1. Normalized total phenytoin concentration

$$C_{Normal\ Binding} = C / (X \cdot Alb + 0.1)$$

- $C_{Normal\ Binding}$ is the normalized total phenytoin concentration in µg/mL,
- C is the actual measured phenytoin concentration in µg/mL,
- X is a constant equal to 0.2 if protein binding measurements were conducted at 37°C or 0.25 if conducted at 25°C, and
- If the patient has end-stage renal disease (Creatinine clearance <10–15 mL/min), the same equation is used with a different constant Value (X = 0.1).
- Alb is the albumin concentration in g/dL

Methods To Estimate Unbound Phenytoin Concentrations (C_f)

2. Compute estimated free concentration (Cf EST) using the following formula:

$$C_{f_{EST}} = 0.1\ C_{Normal\ Binding}$$

3. New free fraction

$$New_{fb} = C_{f_{EST}} / C$$

Example 1 JM is an epileptic patient being treated with phenytoin. He has hypoalbuminemia (albumin = 2.2 g/dL) and normal renal function (creatinine clearance = 90 mL/min). His total phenytoin concentration is 7.5 µg/mL. Assuming that any unbound concentrations performed by the clinical laboratory will be conducted at 25°C, compute an estimated normalized phenytoin concentration for this patient.

1. *Choose appropriate equation to estimate normalized total phenytoin concentration at the appropriate temperature.*

$$C_{\text{Normal Binding}} = C/(0.25 \cdot \text{Alb} + 0.1) = (7.5\ \mu\text{g/mL}) / (0.25 \cdot 2.2\ \text{g/dL} + 0.1) = 11.5\ \mu\text{g/mL}$$

$$C_{f_{EST}} = 0.1\ C_{\text{Normal Binding}} = 0.1 \cdot 11.5\ \mu\text{g/mL} = 1.2\ \mu\text{g/mL}$$

Methods To Estimate Unbound Phenytoin Concentrations (C_f)

- A different approach is taken by the equations used for patients with concurrent valproic acid administration.

- In this case, the unbound phenytoin concentration ($C_{f_{EST}}$) is estimated using simultaneously measured total phenytoin (PHT in µg/mL) and valproic acid (VPA in µg/mL) concentrations:

$$C_{f_{EST}} = (0.095 + 0.001 \cdot VPA)\, PHT$$

Example 3 PM is an epileptic patient being treated with phenytoin and valproic acid. He has a normal albumin concentration (albumin = 4.2 g/dL) and normal renal function (creatinine clearance = 90 mL/min). His steady-state total phenytoin and valproic acid concentrations are 7.5 μg/mL and 100 μg/mL, respectively. Compute an estimated unbound phenytoin concentration for this patient.

1. *Choose appropriate equation to estimate unbound phenytoin concentration.*

$$C_{f_{EST}} = (0.095 + 0.001 \cdot VPA)PHT = (0.095 + 0.001 \cdot 100\ \mu g/mL)7.5\ \mu g/mL = 1.5\ \mu g/mL$$

Dosage Forms

For parenteral use

- Phenytoin is available in two different dosage forms.

1. Phenytoin sodium, the sodium salt of phenytoin, contains 92% phenytoin by weight.

2. A water soluble phosphate ester prodrug of phenytoin, fosphenytoin.

Dosage Forms

For oral use

1. **Capsules** and **injection** contain phenytoin sodium (**92**% phenytoin, by weight) Phenytoin sodium capsules are labeled as extended phenytoin sodium capsules or prompt phenytoin capsules. Extended phenytoin sodium capsules are available in 30 mg, 100 mg, 200 mg, and 300 mg strengths.

2. Tablets and suspension contain phenytoin (100%) Phenytoin tablets (50 mg, chewable) and suspension (125 mg/5 mL)

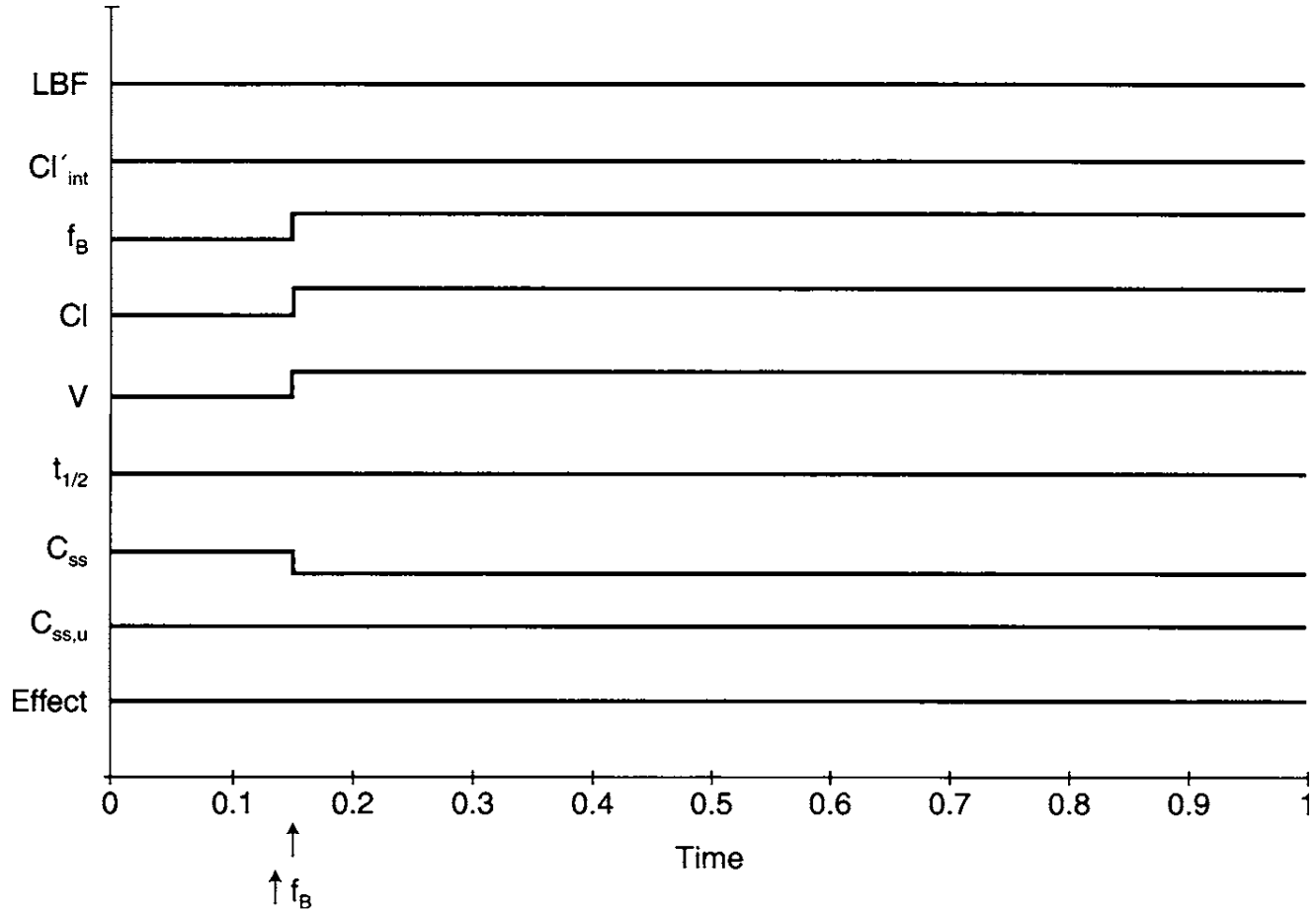

FIGURE 10-2A Schematic representation of physiologic (*LBF* = liver blood flow, Cl'_{int} = intrinsic or unbound clearance, f_B = unbound fraction of drug in blood/plasma), pharmacokinetic (*Cl* = clearance; *V* = volume of distribution; $t_{1/2}$ = half-life; *Css* = total steady-state drug concentration; Css,u = unbound steady-state drug concentration), and pharmacodynamic (Effect = pharmacodynamic effect) changes that occur with decreased protein binding of phenytoin (*arrow* denotes $\uparrow f_B$).

TABLE 10-3 Child-Pugh Scores for Patients with Liver Disease

TEST/SYMPTOM	SCORE 1 POINT	SCORE 2 POINTS	SCORE 3 POINTS
Total bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged over control)	<4	4–6	>6
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

Initial Dosage Determination Methods

1. **Pharmacokinetic Dosing Method**

2. **Literature-Based Recommended Dosing**

Pharmacokinetic Dosing Method

1. **Accurate estimates of Vmax and Km**
   A. Normal adults with normal liver and renal function as well as normal plasma protein binding have an average phenytoin

      Vmax of 7 mg/kg/d and **Km of 4 µg/mL**

   B. Younger children (6 months–6 years)

      Vmax = 12 mg/kg/d and **Km = 6 µg/mL**

   C. Older children (7–16 years)

      Vmax = 9 mg/kg/d and **Km = 6 µg/mL**

Pharmacokinetic Dosing Method

2. <u>Volume of distribution estimate</u>

V= 0.7 L/kg

For obese **V = 0.7 L/kg [IBW + 1.33(TBW – IBW)]**

3. <u>Steady-state concentration selection</u>

For the treatment of seizure,

- required total phenytoin concentration **10- 20 µg/mL**
- required free phenytoin concentration **1-2 µg/mL**

Pharmacokinetic Dosing Method

4. <u>Selection of appropriate pharmacokinetic model and equations</u>

$$MD = \frac{V_{max} \cdot Css}{S(K_m + Css)}$$

$$LD = (Css \cdot V)/S$$

τ = 24 hr. for adult

12 hr for children or I.V dose

S is the fraction of the phenytoin salt form that is active phenytoin (0.92 for phenytoin sodium injection and capsules; 0.92 for fosphenytoin because doses are prescribed as a phenytoin sodium equivalent or PE, 1.0 for phenytoin acid suspensions and tablets)

Literature–Based Recommended Dosing

Phenytoin maintenance doses

for adults

4–6 mg/kg/d

for children (6 months–16 years old)

5–10 mg/kg/d

loading doses

15–20 mg/kg

- For obese individuals (>30% over ideal body weight), adjusted body weight (ABW) should be used to compute loading doses.

ABW (in kg) = IBW + 1.33 (TBW – IBW)

Use of Phenytoin Serum Concentrations to Alter Doses

Adjust phenytoin doses with one steady-state concentrations

- ***Empiric dosing method***
- ***Pseudolinear pharmacokinetic method***
- ***Graves-Cloyd method***
- ***Vozeh-Sheiner method (graphical method)***

Adjust phenytoin doses with one steady-state concentrations

Empiric dosing method

- Increase or decrease the dose according the obtained concentration from the patient and according to the following table

TABLE 10-4 Empiric Phenytoin Dosage Increases Based on a Single Total Steady-State Concentration[65]

MEASURED PHENYTOIN TOTAL SERUM CONCENTRATION (µg/mL)	SUGGESTED DOSAGE INCREASE*
<7	100 mg/d or more
7–12	50–100 mg/d
>12	30–50 mg/d

Adjust phenytoin doses with one steady-state concentrations

Pseudolinear pharmacokinetic method

1. Increase the dose empirically according to previous table
2. Then calculate new Css from the new dose by

$$\mathbf{Css_{new} = (D_{new} / D_{old})\ Css_{old}}$$

3. To account for Michaelis-Menten pharmacokinetics

Add 15–33% for a dosage increase [Multiply the Css by **1.15** and **1.33**]

Or

Subtract 15–33% for a dosage decrease [Multiply Css by **0.85** and **0.67**]

Adjust phenytoin doses with one steady-state concentrations

Graves-Cloyd Method

$$D_{new} = (D_{old} / Css_{old}) \cdot Css_{new}^{0.199} \cdot Css_{old}^{0.804}$$

- Note: The (dose old) should be multiply by **S factor** (**0.92**) in capsule and injection and then after answering the question the resultant (new dose) should be divided by S factor.

Adjust phenytoin doses with two steady-state concentrations

Empiric dosing method

- Increase or decrease the dose empirically according to obtained concentration from the patient.

Adjust phenytoin doses with two steady-state concentrations

Ludden method

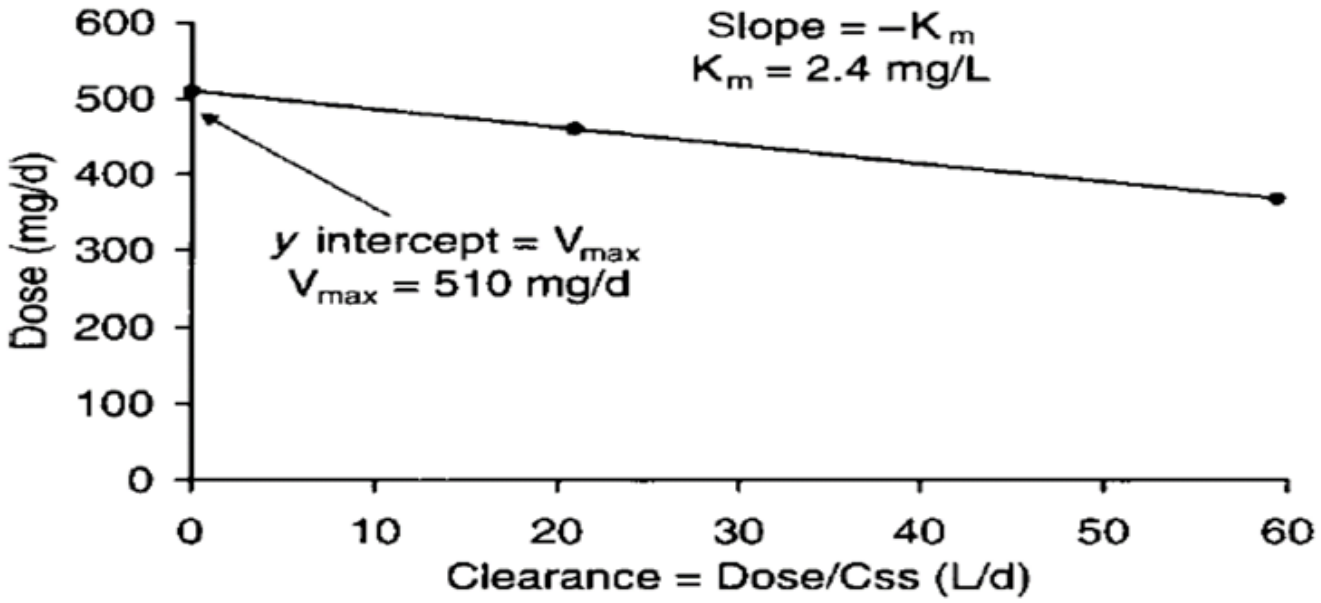

FIGURE 10-7 Ludden graph used to compute Michaelis-Menten parameters and phenytoin dose using two or more steady-state dose/concentration pairs (example 5 data shown). Dose is plotted on the y-axis while clearance (Dose/Css) is plotted on the x-axis for each data pair. The best straight line is drawn through the points. Slope equals − Km, and Vmax is the y-intercept. These values are then used to compute the required maintenance dose (MD) for any desired steady-state serum concentration: MD = (Vmax · Css) / [S(Km + Css)].

Adjust phenytoin doses with two steady-state concentrations

$$MD = Vmax - Km\ (Dose/\ Css)$$

1. Multiply each dose by S before used in equation
2. Calculate actual Km

$$-Km = (MD1 - MD2) / [(MD1/Css1) - (MD2 / Css2)]$$

3. Calculate actual Vmax

$$Vmax = MD + Km\ (MD / Css).$$

4. Use the actual Km & Vmax to calculate new dose

$$MD = (Vmax \cdot Css) / [S\ (Km + Css)]$$

Use of Phenytoin Booster Doses to Immediately Increase Serum Concentrations

- If a patient has a sub-therapeutic phenytoin serum concentration in an acute situation, it may be desirable to increase the phenytoin concentration as quickly as possible.

- In this setting, it would not be acceptable to simply increase the maintenance dose and wait for therapeutic steady-state serum concentrations to be established in the patient.

Use of Phenytoin Booster Doses to Immediately Increase Serum Concentrations

- A modified loading dose equation is used to accomplish computation of the booster dose (BD) which takes into account the current phenytoin concentration present in the patient:

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

$C_{desired}$ is the desired phenytoin concentration

C_{actual} is the actual current phenytoin concentration

Example

- BN is a 22-year-old, 85-kg (6 ft 2 in) male with complex partial seizures who is receiving therapy with intravenous phenytoin sodium. He has normal liver and renal function. After receiving an initial loading dose of phenytoin sodium (1000 mg) and a maintenance dose of 300 mg/d of phenytoin sodium for 5 days, his phenytoin concentration is measured at 5.6 µg/mL immediately after seizure activity was observed. Compute a booster dose of phenytoin to achieve a phenytoin concentration equal to 15 µg/mL.?

$V = 0.7\ L/kg \cdot 85\ kg = 60\ L.$

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

$= [(15\ mg/L - 5.6\ mg/L)\ 60\ L] / 0.92$

$= 613\ mg$, rounded to 600 mg of Phenytoin sodium infused no faster than 50 mg/min.

Thanks

For your attention