TDM of PHENYTOIN

REFERENCE: APPLIED CLINICAL PHARMACOKINETICS

by: Assist Prof Dr. HADEEL D NAJIM

Phenytoin is
high protein bound (~90%)

Phenytoin is
eliminated by hepatic metabolism (>95%).

Phenytoin
follows Mechalis-Menten.

Therapeutic serum concentrations

Phenytoin is high protein bound (~90%)
Unbound fraction (fB) of phenytoin is (~10%)

- The therapeutic range for total (unbound + bound) phenytoin serum concentrations in the treatment of seizures is 10–20 µg/mL
- Unbound phenytoin serum concentrations 1–2 µg/mL.

Adverse effects related to serum conc.

>15 µg/mL ------ minor central nervous system depression such as drowsiness or fatigue.

> 20 µg/mL ------- nystagmus, lateral gaze

> 30 µg/mL ------- ataxia, slurred speech, and/or incoordination

> 40 µg/mL ----- mental status changes, including decreased mentation, severe confusion or lethargy, and coma are possible.

> 50 µg/mL -------Drug-induced seizure activity.

Since phenytoin is highly bound to albumin, you need to know factors cause its displacement from binding site------which lead to increase unbound fraction ($\uparrow f_B$)

(1) Lack of binding protein due to insufficient plasma conc. 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		

Clinical Usefulness of Unbound Phenytoin Concentrations

- Unbound phenytoin concentrations are an extremely useful monitoring tool when used correctly.
- The relationship between total concentration (C), unbound or "free" concentration (C_f), and unbound or "free" fraction (f_B) is:

$$C_f = f_B .C$$

Therapeutic drug monitoring of phenytoin conc.

- Total phenytoin serum concentrations is the mainstream way for routine therapeutic drug monitoring purposes.

- Unbound phenytoin serum concentration monitoring restricted to patients with known reasons to have altered drug plasma protein binding.

For example, if low total phenytoin concentration (C=5 µg/mL), and patient has a satisfactory anticonvulsant response, one possible reason would be abnormal plasma protein binding (f_B = 20%) for some unidentified reason…

$$C_f = f_B . C$$

$C_f = 0.2 . 5$ ←----- not within therapeutic range

$C_f = 1$ µg/mL ←----- within therapeutic range

Conversely,,,,

- If a patient has a possible phenytoin-related adverse drug reaction and the total phenytoin concentration is within the therapeutic range (15 μg/mL),
- A possible reason could be abnormal protein binding (20%) for an unidentified reason,
- $C_f = f_B . C$

  $= 0.2 \cdot 15$ μg/mL ←----- within therapeutic range

  = 3 μg/mL ←----- toxic

Methods to estimate unbound phenytoin concentrations (C_f)

1–Normalized total phenytoin concentration

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

- $C_{\text{Normal Binding}}$ 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 conducted at 37°C)

  0.25 (if conducted at 25°C)

  0.1 (If the patient has end–stage renal disease Crcl<10–15 mL/min),
- Alb is the albumin concentration in g/dL

2- Compute estimated free concentration ($C_{f\ EST}$):

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

3- Then can find the new free fraction

$$\text{new } f_B = C_{f\ EST} / C$$

But for patients with concurrent valproic acid administration

➢ *Do not need Cnormal binding

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

(PHT in μg/mL) total phenytoin concentration

(VPA in μg/mL) valproic acid concentration

➢ $C_{f\,EST}$ is compared to the usual therapeutic range for unbound phenytoin concentrations (1–2 μg/mL) and used for dosage adjustment purposes.

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.

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

  $= C/(0.25 \cdot Alb + 0.1)$

  $= (7.5\ \mu g/mL) / (0.25 \cdot 2.2\ g/dL + 0.1)$

  $= 11.5\ \mu g/mL$

- $C_{f\ EST} = 0.1\ C_{Normal\ Binding}$

  $= 0.1 \cdot 11.5\ \mu g/mL$

  $= 1.2\ \mu g/mL$

Example 2 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.

Choose appropriate equation to estimate unbound phenytoin conc.

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

$$= (0.095 + 0.001 \cdot 100\ \mu g/mL)7.5\ \mu g/mL$$

$$= 1.5\ \mu g/mL$$

Dosage forms

❖ For parenteral use:

1- Phenytoin sodium, the sodium salt of phenytoin, contains (92% phenytoin), Infusion rate <50 mg/min

2- Fosphenytoin, a water soluble phosphate ester prodrug of phenytoin, Infusion rate <150 mg/min

❖ For oral use:

1- Capsules contain phenytoin sodium (92% phenytoin) extended phenytoin sodium capsules or prompt phenytoin capsules

2- Tablets and suspension contain phenytoin (100%)

- Phenytoin tablets (50 mg, chewable) and
- Suspension (125 mg/5 mL)

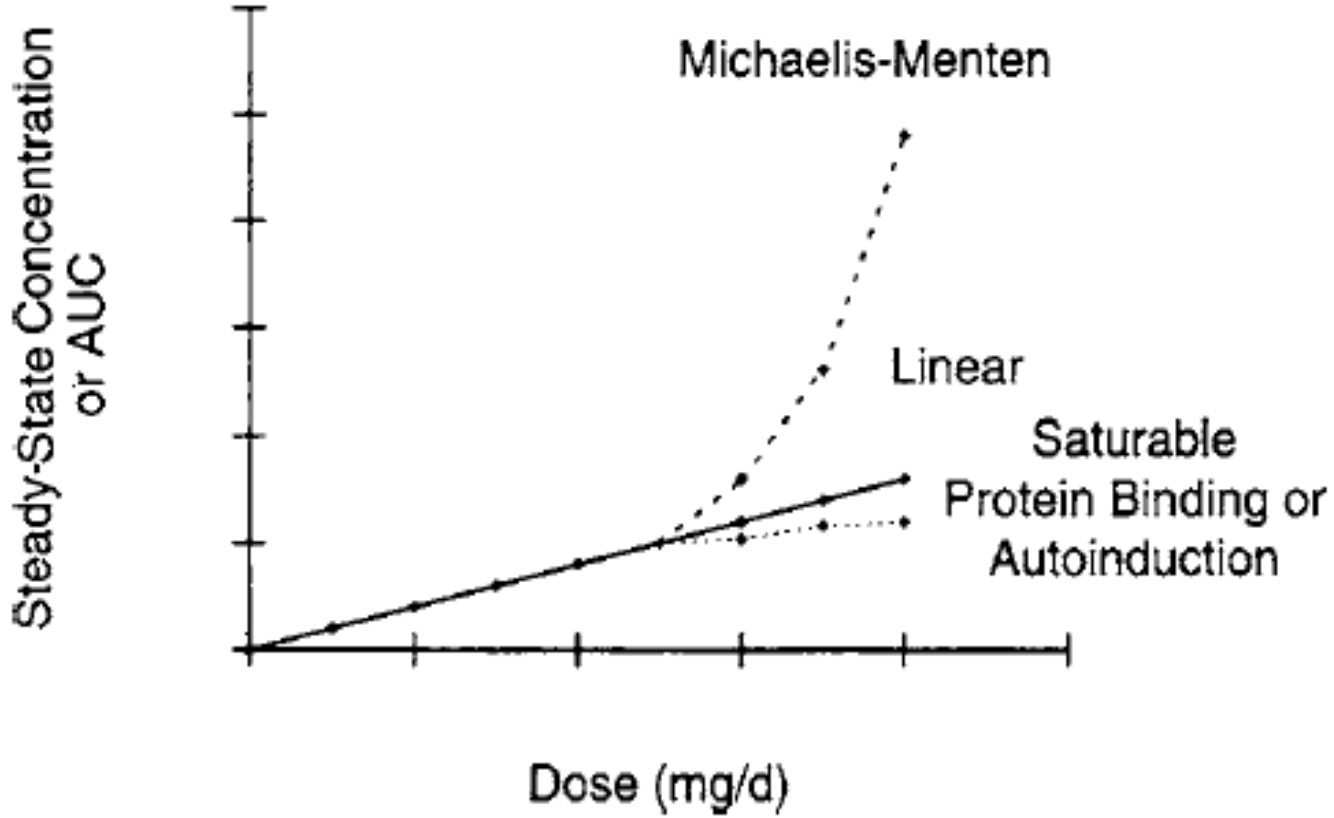


FIGURE 10-1 If a drug follows linear pharmacokinetics, Css or AUC increases proportionally with dose resulting in a straight line on the plot. Nonlinear pharmacokinetics occurs when the Css or AUC versus dose plot results in something other than a straight line. If a drug follows Michaelis-Menten pharmacokinetics (e.g., phenytoin, aspirin), as steady-state drug concentrations approach K_m serum concentrations increase more than expected due to dose increases. If a drug follows nonlinear protein binding (e.g., valproic acid, disopyramide), total steady-state drug concentrations increase less than expected as dose increases.

The clinical implication of Michaelis-Menten pharmacokinetics

1- Clearance of phenytoin

- The clearance of phenytoin is not a constant as it is with linear pharmacokinetics, but is concentration- or dose-dependent.
- As the dose or concentration of phenytoin increases, the clearance rate decreases as the enzyme approaches saturable conditions:

$$Cl\downarrow = Vmax / (Km + C\uparrow)$$

-Vmax is the maximum rate of metabolism in mg/d,

-C is the phenytoin concentration in mg/L,

-Km is the substrate concentration in mg/L,

Half-life

- As clearance decreases ----- half-life becomes longer sccording to the following equation:

$$\uparrow t_{1/2} = (0.693 \bullet V)/\downarrow Cl$$

- On average, the time to steady-state serum concentrations is approximately 5 days at a dosage rate of 300 mg/d and 15 days at a dosage rate of 400 mg/d.

2- Volume of Distribution Estimate

V_d = 0.7 L/kg

For obese ..... Use adjusted body weight

V_d = 0.7 L/kg . ABW

= 0.7 L/kg . [IBW + 1.33(TBW – IBW)]

Example.. phenytoin follows saturable pharmacokinetics with average Michaelis-Menten constants of V_{max} = 500 mg/d and K_m = 4 mg/L. Find the clearance of the therapeutic range of phenytoin (10–20μg/mL).

Cl = Vmax/(Km + C)

= (500 mg/d) / (4 mg/L + 10 mg/L) = 36 L/d

Cl = (500 mg/d) / (4 mg/ + 20 mg/L) = 21 L/d

Then find V_d, $t_{1/2}$ for a 70-kg person…

$V_d = 0.7\ L/kg \cdot 70\ kg \approx 50\ L$

$t_{1/2} = [0.693 \cdot V] / Cl$

$= [0.693 \cdot 50\ L] / 36\ L/d = 1\ d$

$t_{1/2} = [0.693 \cdot 50\ L] / 21\ L/d = 1.7\ d$

Half-life increase as phenytoin serum concentrations increase from (1 day for 10 μg/mL) to (1.7 day for 20 μg/mL).

- The clinical implication of this finding is that the time to steady-state (3-5 $t_{1/2}$) is longer as the dose or concentration is increased for phenytoin.

Return to child pough score and interactions

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF} = f_B \cdot Cl'_{int}$$

Lets for example see what are the changes that occur with decreased protein binding of phenytoin according to the following scheme:

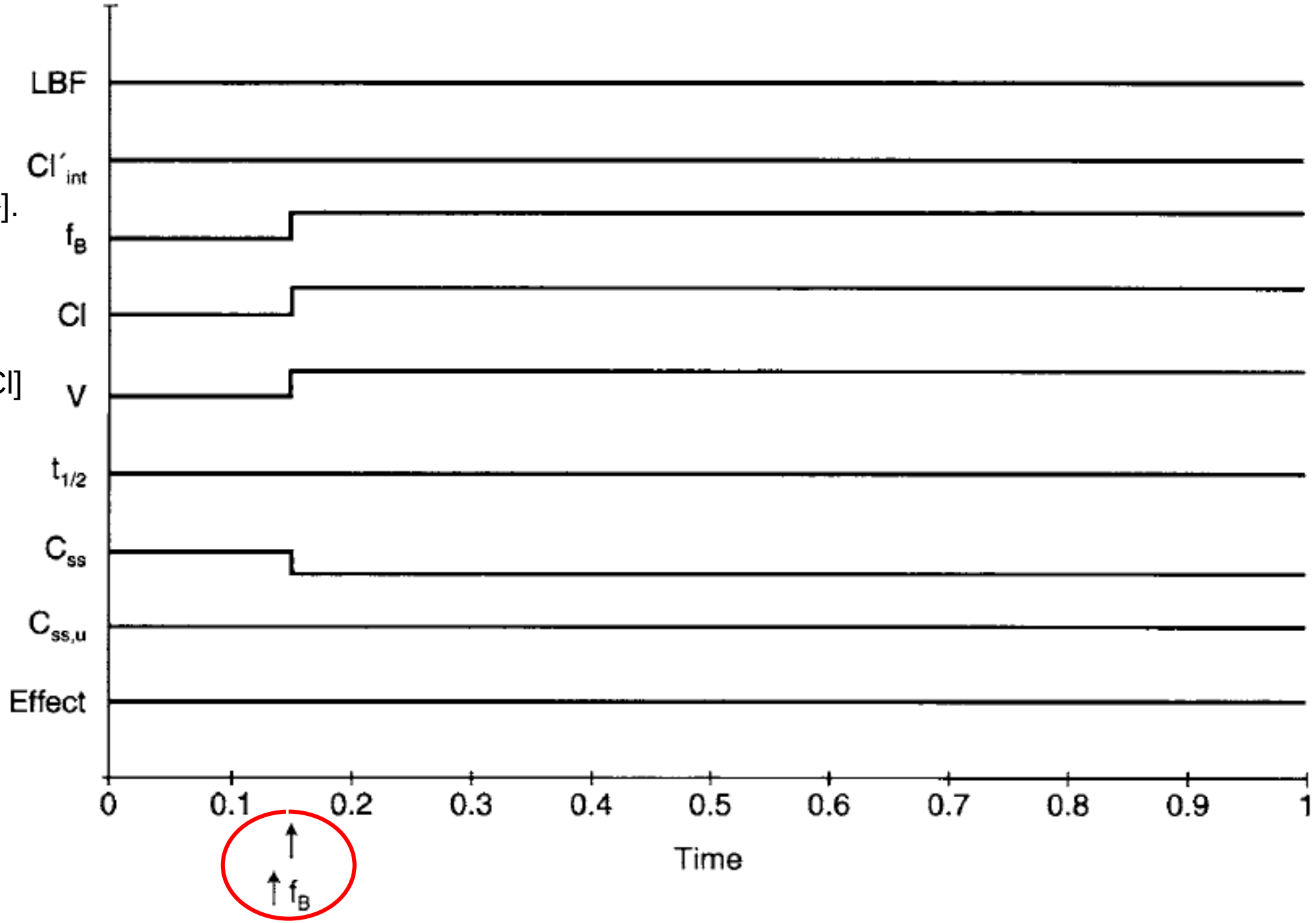
$(\uparrow Cl = \uparrow f_B Cl_{int})$

$[\uparrow V = V_B + (\uparrow f_B / f_T)V_T]$.

$[t_{1/2} = (0.693.\uparrow V) / \uparrow Cl]$

$(\downarrow Css = k_0 / \uparrow Cl)$

$(Css,u = \uparrow f_B \downarrow Css)$

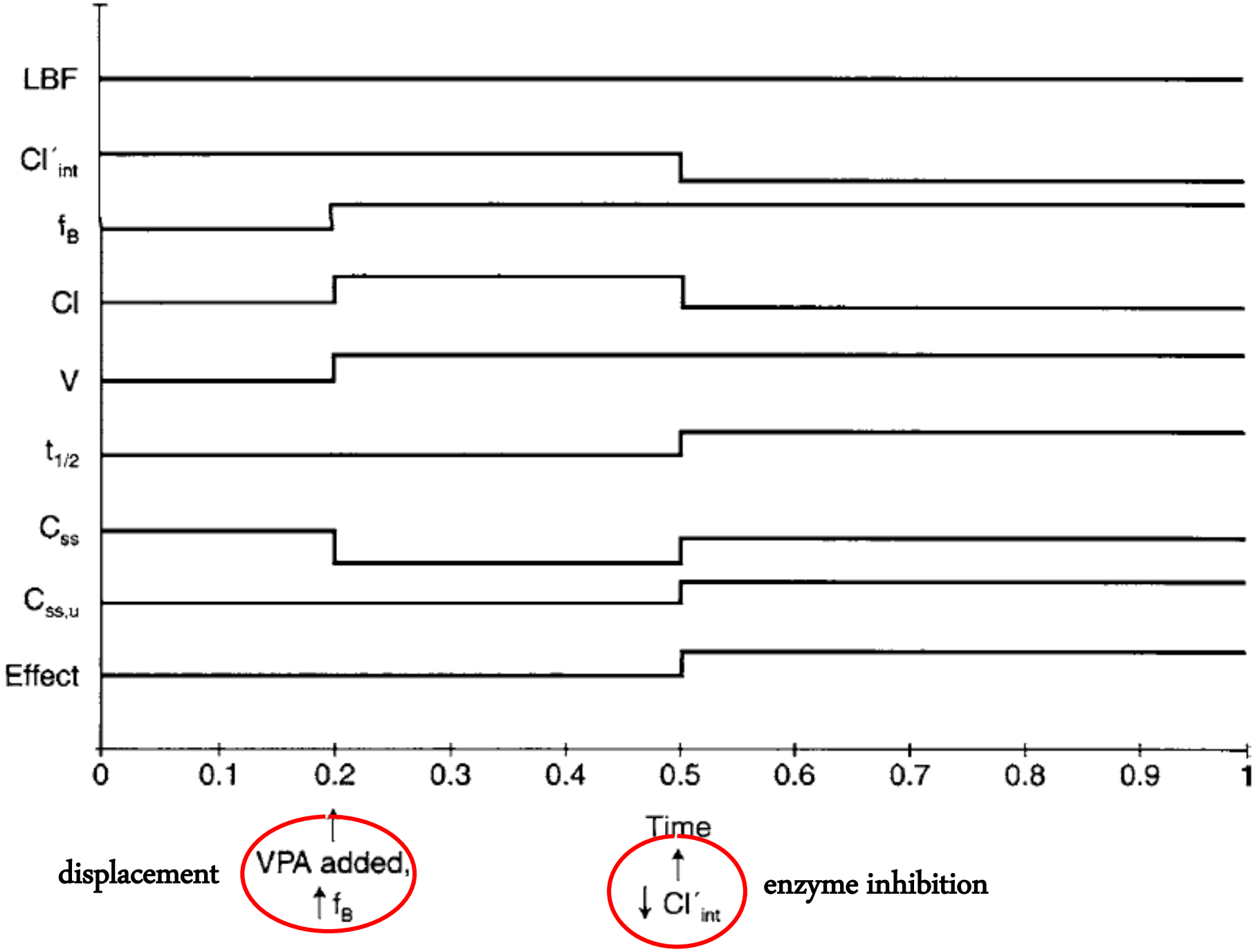


And the Result…

- The pharmacologic effect of the drug does not change because the free concentration of drug in the blood is unchanged.
- This can be an unexpected outcome for the decrease in plasma protein binding,
- Especially because the total steady-state concentration of the drug decreased.

Concomitant use with valproic acid

- Initially, valproic acid decreases phenytoin plasma protein binding via competitive displacement for binding sites on.
- Then, as valproic acid concentrations increase, the hepatic enzyme inhibition component of the drug interaction comes into play ($\downarrow Cl'_{int}$).
- The net result is total phenytoin concentrations are largely unchanged from baseline,
- but unbound phenytoin concentrations and pharmacologic effect increase.


LBF
Cl´int
fB
Cl
V
t1/2
Css
Css,u
Effect
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
Time
displacement
VPA added,
↑ fB
↓ Cl´int
enzyme inhibition

INITIAL DOSAGE DETERMINATION METHODS

- Pharmacokinetic Dosing Method
- Literature-Based Recommended Dosing

Pharmacokinetic Dosing Method

1. *MICHAELIS-MENTEN PARAMETER ESTIMATES (Vmax, Km)*
2. *VOLUME OF DISTRIBUTION ESTIMATE (Vd)*
3. *STEADY-STATE CONCENTRATION SELECTION*
4. *SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS*

1- Estimates Vmax & Km

➢ Adult without any disease states and normal liver, renal plasma protein binding:

- Vmax = 7 mg/kg/d (range: 1.5-14 mg/kg/d)
- Km = 4 µg/mL (range: 1-15 µg/mL).

Always use actual body weight

➢ Children (6 months–6 years):

- Vmax = 12 mg/kg/d
- Km = 6 µg/mL

➢ Older children (7–16 years):

- Vmax = 9 mg/kg/d
- Km = 6 µg/mL.

2-Volume of distribution

V_d for phenytoin = 0.7 L/kg

- For obese individuals 30% or more above their ideal body weight, the volume of distribution can be estimated using the following equation:

$$V_d = 0.7\ L/kg\ [IBW + 1.33(TBW - IBW)]$$

Adjusted body weight

3-Steady-state Concentration Selection

For the treatment of seizure:

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

4-Selection of Appropriate Pharmacokinetic Model and Equations

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

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

$\tau = 24$ hr. for adult / oral

$\tau = 12$ hr for children or I.V dose

- Vmax is the maximum rate of metabolism in mg/d
- S is the fraction of the phenytoin salt form that is active phenytoin

  S=0.92 for injection and capsules and fosphenytoin,

  S=1.0 for suspensions and tablets
- Km is the substrate concentration in mg/L (or µg/mL)
- Css is the phenytoin concentration in mg/L (or µg/mL)

Example 1 TD is a **50-year-old**, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with **oral phenytoin**. He has normal liver and renal function. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration equal to 12 μg/mL.

1. **For this patient.... Vmax = 7 mg/kg/d = 7 mg/kg/d · 75 kg = 525 mg/d.**
2. **Km = 4 mg/L.**
3. **for oral extended phenytoin sodium capsules (S = 0.92).**
4. **(τ) will be set to 24 hour**
5. $$MD = \frac{V_{max} \cdot Css}{S(K_m + Css)} = \frac{525\ mg/d \cdot 12\ mg/L}{0.92(4\ mg/L + 12\ mg/L)} = 428\ mg/d, \text{ rounded to } 400\ mg/d$$

Same patient but need IV phenytoin

1. Vmax = 525, Km = 4, S = 0.92
2. V_d = 0.7 L/kg • 75 kg = 53
3. LD = (V • Css) / S = (53 L • 12 mg/L) / 0.92 = 691 mg, rounded to 700 mg given at a maximal rate of 50 mg/min.
4. MD = 400 mg/d, (τ) will be set to 12 hours….. so MD = 200mg every 12 hours

Example 2 UO is a **10-year**-old, 40-kg male with simple partial seizures who requires therapy with **oral phenytoin**. He has normal liver and renal function. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration equal to **12** μg/mL.

1. **V_{max} = 9 mg/kg/d (child) = 9 mg/kg/d • 40 kg = 360 mg/d.**
2. **Km = 6 mg/L (child)**
3. **Oral phenytoin suspension (S = 1).**
4. **(τ) will be set to 12 hours**
5. $$MD = \frac{V_{max} \cdot Css}{S(K_m + Css)} = \frac{360\ mg/d \cdot 12\ mg/L}{1.0(6\ mg/L + 12\ mg/L)} = 240\ mg/d, \text{ rounded to } 250\ mg/d$$
6. **Phenytoin suspension: 125 mg every 12 hours**

Literature-Based Recommended Dosing

- MD for adult = 4–6 mg/kg/d
- MD for children (6 months–16 years old) = 5–10 mg/kg/d
- LD = 15–20 mg/kg
- For obese individuals, adjusted body weight (ABW) use to compute loading doses. [IBW + 1.33 (TBW – IBW)]
- If the patient has significant hepatic dysfunction (Child-Pugh score $\geq$8), maintenance doses prescribed using this method should be decreased by 25–50%

Example 1 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with **oral phenytoin**. He has normal liver and renal function. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration equal to 12 μg/mL.

- **MD for adult = 4–6 mg/kg/d (نأخذ المتوسط)**
- **Using a rate of 5 mg/kg/d, the initial dose would be:**
- **5 mg/kg/d · 75 kg = 375 mg/d, rounded to 400 mg/d.**
- **Using a dosage interval of 24 hours.**

Repeat it with IV phenytoin dosage

- MD = 5 mg/kg/d,

  = 5 mg/kg/d · 75 kg = 375 mg/d, rounded to 400 mg/d.

(τ) will be set to 12 hours, so give 200 mg of phenytoin sodium injection every 12 hours.

- LD = 15–20 mg/kg.

  = 15 mg/kg · 75 kg = 1125 mg, rounded to 1250 mg given no faster than 50 mg/min.

Use of Phenytoin Serum Concentrations to Alter Doses

Adjust phenytoin doses with one steady-state concentration:

1- Empiric dosing method

2- Pseudolinear pharmacokinetic method

3- Graves-Cloyd method

Adjust phenytoin doses with two steady-state concentrations:

1- Empiric dosing method

2- Ludden method

Adjust phenytoin doses with one steady-state concentrations

1- Empiric Dosing Method

Increase or decrease the dose according to 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

Example 1 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. The patient was prescribed 400 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 6.2 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration within the therapeutic range.

1. Use Table 10-4 to suggest new phenytoin dose.

- **Table 10-4 suggests a dosage increase of ≥100 mg/d for this patient. The dose would be increased to 500 mg/d.**

Note: A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

2- Pseudolinear Pharmacokinetic Method

1- Increase the dose empirically according to previous table.

2- Then calculate new Css from the new dose by linear pharmacokinetics equation:

$$Cssnew = (Dnew / Dold)\ Cssold$$

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**]

Example 3 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. The patient was prescribed **400 mg/d of** extended phenytoin sodium **capsules** for 1 month, and the steady-state phenytoin total concentration equals **6.2 µg/mL**. The patient is assessed to be compliant with his dosage regimen. Suggest phenytoin dosage regimen to achieve a steady-state phenytoin concentration **within the therapeutic range**.

1. A convenient dosage change would be 100 mg/d and the new dose will be 500 mg/d.
2. **Cssnew = (Dnew / Dold)Cssold = (500 mg/d / 400 mg/d) 6.2 µg/mL = 7.8 µg/mL.**
3. To account for Michaelis-Menten pharmacokinetics:

- Serum concentration would be expected to **increase 15%-33% greater** than that predicted Css, then we multiply Css by **1.15 and 1.33**
- **Css = 7.8 µg/mL · 1.15 = 9.0 µg/mL** and **Css = 7.8 µg/mL · 1.33 = 10.4 µg/mL**.
- Thus, a dosage increase of 100 mg/d would be expected to yield a total phenytoin steady-state serum concentration between 9–10 µg/mL.

3- Graves-Cloyd Method

Note: The (dose old) should be multiply by S factor (0.92) in capsule and injection before use it in the equation (below) and then the resultant (new dose) should be divided by S factor.

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

Example 5 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. The patient was prescribed 400 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 6.2 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration within the therapeutic range.

- **Phenytoin sodium 400 mg equals 368 mg of phenytoin (400 mg · 0.92 = 368 mg).**
- **A new total phenytoin steady-state serum concentration equal to 10 μg/mL is chosen for the patient:**
- $$D_{new} = (D_{old} / Css_{old}) \cdot Css_{new}^{0.199} \cdot Css_{old}^{0.804}$$

  = (368 mg/d / 6.2 mg/L) · (10 mg/L)$^{0.199}$ · (6.2 mg/L)$^{0.804}$

  = 407 mg/d.

This is equivalent to 442 mg/d of phenytoin sodium (407 mg/0.92 = 442 mg) rounded to 450 mg/d, or 400 mg/d on even days alternating with 500 mg/d on odd days.

Adjust phenytoin doses with two steady-state concentrations

- Note : If (2) concentrations is given in question use the following methods to calculate the new dose

1- Empiric Dosing Method

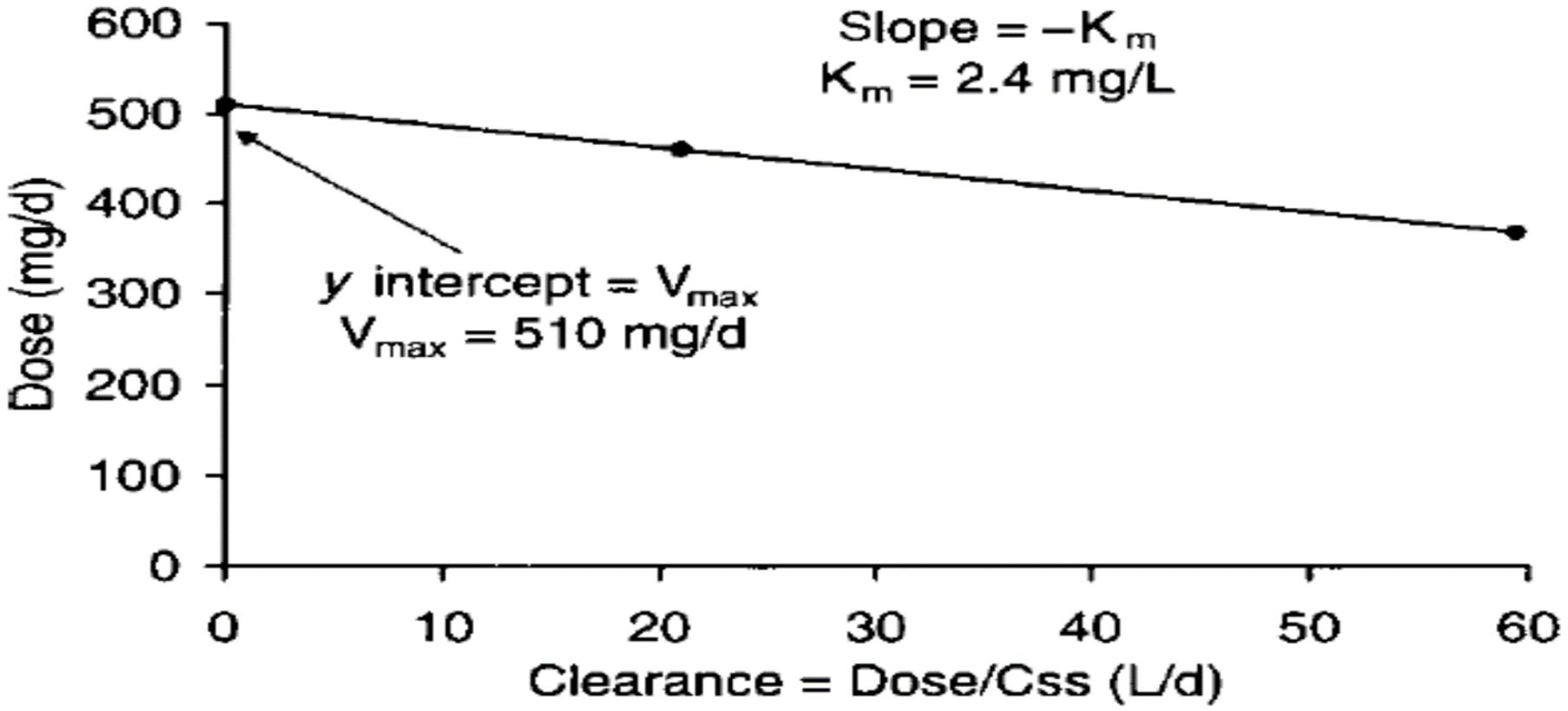
- Increase or decrease the dose empirically according to obtained concentration from the patient.

Example 1 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. The patient was prescribed **400 mg/d** of extended phenytoin sodium **capsules** for 1 month, and the steady-state phenytoin total concentration equals **6.2 mg/mL**. The dosage was increased to **500 mg/d** of extended phenytoin sodium capsules for another month, the steady state phenytoin total concentration equals **22.0 mg/mL**, and the patient has some lateral-gaze nystagmus. The patient is assessed to be compliant with his dosage regimen. Suggest a new phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration within the mid-to-upper end of the therapeutic range.

- **Empirically suggest new phenytoin dose.**

The next logical dose to prescribe is phenytoin sodium 450 mg/d to be taken by the patient as 400 mg/d on even days and 500 mg/d on odd days.

2- Ludden Method



Calculation steps:

- **To answer any question:**

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 · Css) / [S (Km + Css)].**

Example 5 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. The patient was prescribed **400 mg/d** of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals **6.2 μg/mL**. The dosage was increased to **500 mg/d** of extended phenytoin sodium capsules for another month, the steady state phenytoin total concentration equals **22.0 μg/mL**, and the patient has some lateral-gaze nystagmus. The patient is assessed to be compliant with his dosage regimen. Suggest a new phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration within the therapeutic range.

1. **Multiply each dose by S before used in equation:**

- Phenytoin dose 1 = 0.92 · phenytoin sodium
  = 0.92 · 400 mg/d = 368 mg/d,
- phenytoin dose 2 = 0.92 · phenytoin sodium dose
  = 0.92 · 500 mg/d = 460 mg/d,

2. Estimate actual Vmax and Km.

–Km = (MD1 – MD2) / [(MD1/Css1) – (MD2/Css2)] 1: refer to higher dose

= (460 mg/d – 368 mg/d) / [(460 mg/d / 22 mg/L) – (368 mg/d / 6.2 mg/L)]

= –2.4 mg/L, Km = 2.4 mg/L;

Vmax = MD + Km (MD/Css) (ممكن اختيار اي جرعة مع تركيزها)

= 368 mg/d + 2.4 (368 mg/d / 6.2 mg/L), Vmax = 510 mg/d.

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

MD = (Vmax · Css) / [S (Km + Css)].

= (510 . 10) / [0.92 (2.4 + 10)]

MD = 447 rounded to 450mg/d of phenytoin sodium

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.
- 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:

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

- $C_{desired}$ is the desired phenytoin concentration,
- C_{actual} is the actual current phenytoin concentration for the patient

Example 1 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**?

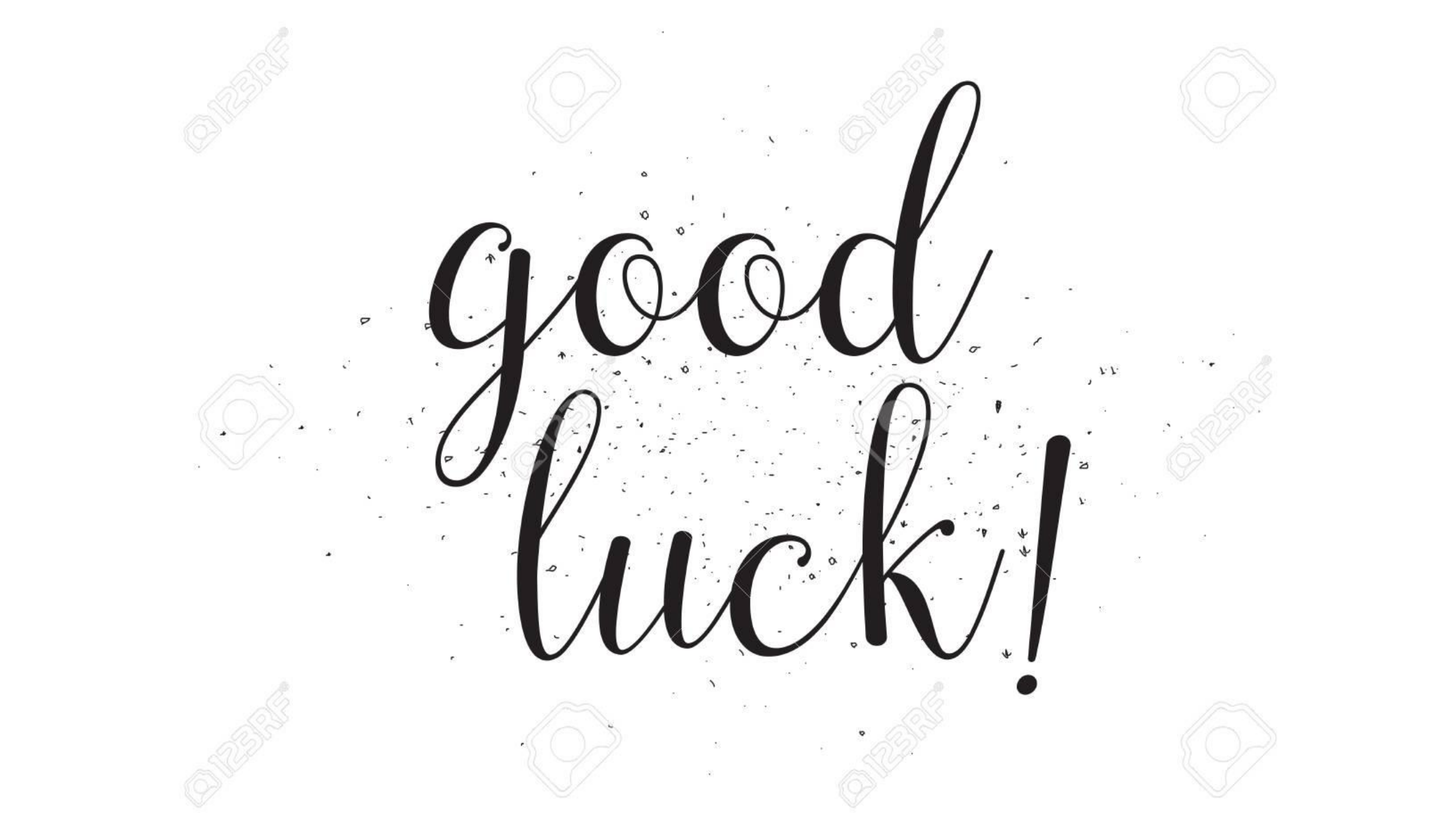
1. Estimate volume of distribution according to disease states and conditions present in the patient.

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

2. Compute booster dose.

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

= [(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.


good
luck!