CLINICAL PHARMACOKINETIC OF PHENYTOIN

Clinical usefulness of unbound phenytoin concentrations

The relationship between total concentration (C), unbound or "free" concentration (C_f), and unbound or "free" fraction (f_B) is:

$$C_f = f_B\, C$$

The equation for **hypoalbuminemia** is:

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

- $C_{\text{Normal Binding}}$: 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 were conducted at 37°C or **0.25** if conducted at 25°C.
- **Alb** is the albumin concentration in g/dL.

Note: 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**)

*Because these methods assume that the normal unbound fraction of phenytoin is 10%, the estimated unbound phenytoin concentration (C_{fEST}) is computed using the following formula:

$$(C_{fEST}) = 0.1\, C_{\text{Normal Binding}}$$

* A different approach is taken by the equations used for patients with concurrent valproic acid administration. In this case, the unbound phenytoin concentration (C_{fEST}) is estimated using simultaneously measured total phenytoin (PHT in μg/mL) and valproic acid (VPA in μg/mL) concentrations:

$$C_{fEST} = (0.095 + 0.001 \cdot VPA)PHT$$

Basic clinical pharmacokinetic parameters

Phenytoin follows Michaelis-Menten or saturable pharmacokinetics.

$$\text{Rate of metabolism} = (V_{max} \cdot C) / (K_m + C),$$

- **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,
- The rate of metabolism = Vmax /2.

*The clinical implication of Michaelis-Menten pharmacokinetics is that 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 (Cl) decreases as the enzyme approaches saturable conditions:

Cl = Vmax / (Km + C).

*Phenytoin volume of distribution (V = 0.7 L/kg) is unaffected by saturable metabolism and is still determined by the physiological volume of blood (VB) and tissues (VT) as well as the unbound concentration of drug in the blood (fB) and tissues (fT):

$$V = V_B + (f_B/f_T)V_T$$

*Half-life (t1/2) is still related to clearance and volume of distribution using the same equation as for linear pharmacokinetics:

$$t_{1/2} = (0.693 \cdot V)/Cl$$

However, since clearance is dose- or concentration-dependent, half-life also changes with phenytoin dosage or concentration changes.

*As doses or concentrations increase for a drug that follows Michaelis- Menten pharmacokinetics, clearance decreases and half-life becomes longer for the drug.

***Under steady-state conditions the rate of drug administration equals the rate of drug removal. Therefore, the Michaelis-Menten equation can be used to compute the maintenance dose (MD in mg/d) required to achieve a target steady-state phenytoin serum concentration

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

When phenytoin steady-state concentrations are far below the Km value for a patient, this equation simplifies to:

MD = (Vmax/Km) Css or, since Vmax/Km is a constant, MD = Cl · Css.

Note *:* For oral use, capsules contain phenytoin sodium (92% phenytoin, by weight) while tablets and suspension contain phenytoin.

However, because phenytoin follows nonlinear pharmacokinetics, an 8% difference in dose can result in major changes in phenytoin serum concentrations.

- **suspension** and **tablets**, 100 mg = 100 mg phenytoin)
- **capsules** and **injection**, 100 mg = 92 mg phenytoin & the remaining is salt)

INITIAL DOSAGE DETERMINATION METHODS

1. The pharmacokinetic dosing method
2. Literature-based recommended dosing is a very commonly used.

1. The pharmacokinetic dosing method

• If the patient has significant hepatic dysfunction (Child-Pugh score ≥8), maintenance doses computed using this method should be decreased by 25–50%

*We will calculate the following:

1. Michaelis-menten parameter estimates
2. Volume of distribution estimate
3. Selection of appropriate pharmacokinetic model and equations
4. Steady-state concentration selection

1.Michaelis-menten parameter estimates (تحفظ للاحتياط)

1. Adults without the disease states and conditions given later in this section, with normal liver and renal function as well as normal plasma protein binding (~90%),

Vmax of 7 mg/kg/d

Km of 4 μg/mL

2. Younger children (6 months–6 years) are

Vmax = 12 mg/kg/d

Km = 6 μg/mL

3. Older children (7–16 years)

Vmax = 9 mg/kg/d

Km = 6 μg/mL.

2.Volume of distribution estimate

• The Vd for patients with normal phenytoin plasma protein binding is estimated at **0.7 L/kg** for adults.

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

V = 0.7 L/kg [IBW + 1.33(TBW − IBW)]

This parameter is used to estimate the loading dose (LD in milligrams) for phenytoin, if one is indicated:

LD = Css · V

LD = Css · V / S (in case of S=0.92)

3.Selection of appropriate pharmacokinetic model and equations

• When given by short-term intravenous infusion or orally, phenytoin follows a one compartment pharmacokinetic model.

• When oral therapy is required, most clinicians utilize an extended phenytoin capsule dosage form that has good bioavailability (F = 1).

Michaelis-Menten pharmacokinetic equation that computes the average phenytoin steady-state serum concentration (Css in μg/mL = mg/L) is widely used and allows maintenance dosage calculation:

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

$$\text{Or, solved for Css: } = \frac{K_m \cdot (S \cdot MD)}{V_{max} - (S \cdot MD)}$$

- **Vmax** is the maximum rate of metabolism in mg/d,
- **S** is the fraction of the phenytoin salt form that is active phenytoin (حفظ)
- **0.92** for phenytoin sodium injection and capsules
- **1** for phenytoin acid suspensions and tablets
- **MD** is the maintenance dose
- **Km i**s the substrate concentration in mg/L
- **Rate of metabolism** = Vmax/2.

4.Steady-state concentration selection

Therapeutic ranges for

• Total phenytoin concentrations 10–20 μg/mL

• Unbound phenytoin concentrations 1–2 μg/mL

2-Literature-Based Recommended Dosing

1. Suggested phenytoin maintenance doses are

4–6 mg/kg/d for adults and

5–10 mg/kg/d for children (6 months–16 years old)

2. Phenytoin loading doses are 15–20 mg/kg

3. 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)

4. If the patient has significant hepatic dysfunction (Child-Pugh score≥8), maintenance doses should be decreased by 25–50% depending on how aggressive therapy is required to be for the individual.

USE OF PHENYTOIN SERUM CONCENTRATIONS TO ALTER DOSES

*A variety of methods are used to estimate new maintenance doses or Michaelis-Menten parameters when **one steady-state** phenytoin serum concentration is available

1. Empiric dosing method

2- Pseudolinear pharmacokinetic method

3. The graves-cloyd method

4. The vozeh-sheiner method غير مطلوبة

*If **two or more steady-state** phenytoin serum concentrations are available from two or more daily dosage rates, it may be possible to calculate and use:

pharmacokinetic parameters to alter the phenytoin dose.

1- Empiric dosing method

2. The Mullen method

3. The Ludden method

Single Total Phenytoin Steady-State Serum Concentration Methods

1. EMPIRIC DOSING METHOD

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

* Higher dosage used if more aggressive therapy desired, lower dosage used if less aggressive therapy desired.

* **Note** : Whenever possible, clinicians should avoid using more than one strength of solid dosage forms (e.g. 30 and 100 mg capsules) to treat patient. An effective way to increase the phenytoin dose to patient who need an increase in the dose of 50 mg /day when using 100mg capsule is to increase the dose 100mg every other day. For example if we need to increase the dose by 50mg/day for patient taking 300mg/day, we can advice the patient to take 300 mg /day alternating with 400mg/day if the patients is comply with this complex dosage regimen**.**

So 300mg/day on odd days, and 400mg/day on even days . وتسهيلا للمريض يستخدم الجرعة الزوجي في اليوم الزوجي والفردي في اليوم الفردي)

2. PSEUDOLINEAR PHARMACOKINETICS METHOD

A simple, easy way to approximate new total serum concentrations after a dosage adjustment with phenytoin is to **temporarily assume** linear pharmacokinetics, then **add 15–33%** for a dosage increase **or subtract 15–33%** for a dosage decrease to **account for Michaelis-Menten pharmacokinetics**:

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

Css_{new} is the expected steady-state concentration from the new phenytoin dose in µg/mL,

Css_{old} is the measured steady-state concentration from the old phenytoin dose in µg/mL,

D_{new} is the new phenytoin dose to be prescribed in mg/d

D_{old} is the currently prescribed phenytoin dose in mg/d

3- GRAVES-CLOYD METHOD

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

- D_{old} is the administered phenytoin dose in mg/d
- Css_{old} is the resulting measured total phenytoin steady-state concentration in µg/mL) at the dosage being given
- Css_{new} the measured concentration and desired concentration in µg/mL)
- D_{new} new dose

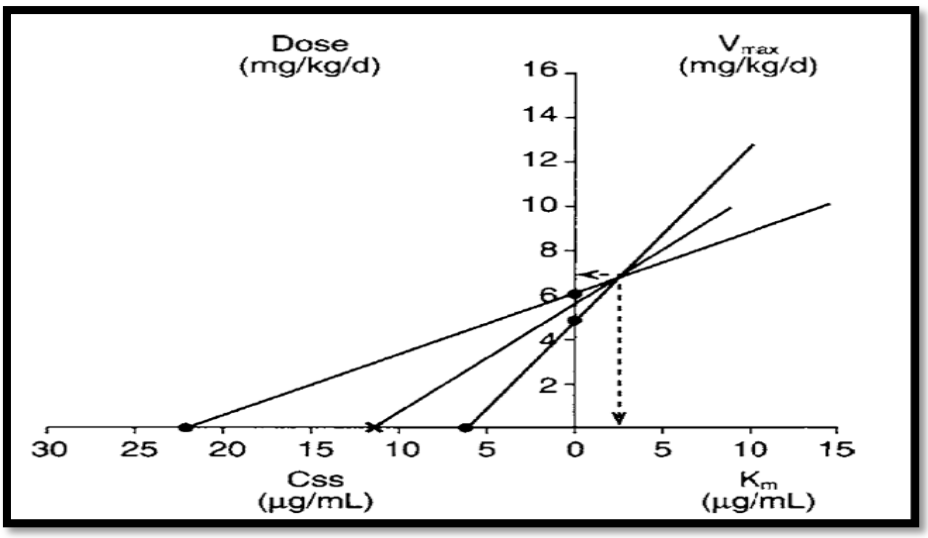
Two or More Phenytoin Steady-State Serum Concentrations at Two or More Dosage Levels Methods

The same of empiric dosing method above but two or more steady state concentration

2. MULLEN METHOD

The graph is divided into **two sectors**.

- X-axis, a steady-state total phenytoin concentration is plotted.
- y-axis, the phenytoin dosage rate **Vmax** (in mg/kg/d of phenytoin)
- S = 0.92 for phenytoin sodium is plotted



3. LUDDEN METHOD

MD = − Km(MD /Css) + Vmax

Vmax = MD + Km(MD / Css)

−Km = (MD1 − MD2) / [(MD1/Css1) − (MD2/Css2)]

MD = (Vmax .Css) / [S(Km + Css)].

USE OF PHENYTOIN BOOSTER DOSES TO IMMEDIATELY INCREASE SERUM CONCENTRATIONS

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

- BD: Booster dose
- $C_{desired}$is the desired phenytoin concentration,
- C_{actual}isthe actual current phenytoin concentration for the patient

(**Note:** This summery is designed only for the lab; it never designed for any exam)

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