# TDM OF
# Valproic acid

Reference: Applied Clinical Pharmacokinetics

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# Valproic acid is:

- An agent that is chemically related to free fatty acids and has the widest spectrum of activity compared to the other currently available antiepileptics.
- Highly protein bound to albumin with typical values of 90%-95%
- 95% metabolized in **liver**
- Follow Non linear pharmacokinetic
- Has **low** hepatic extraction ratio.

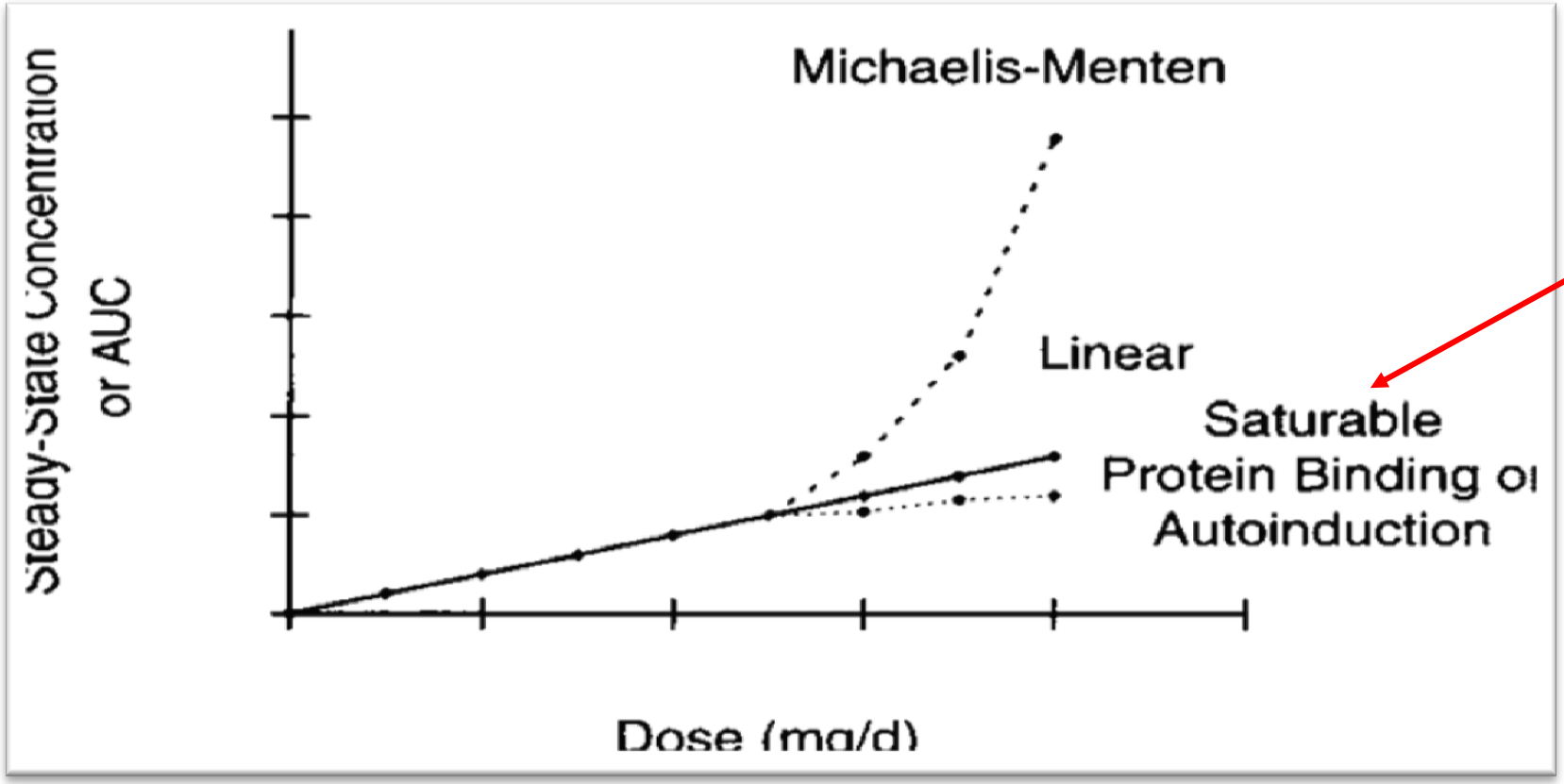
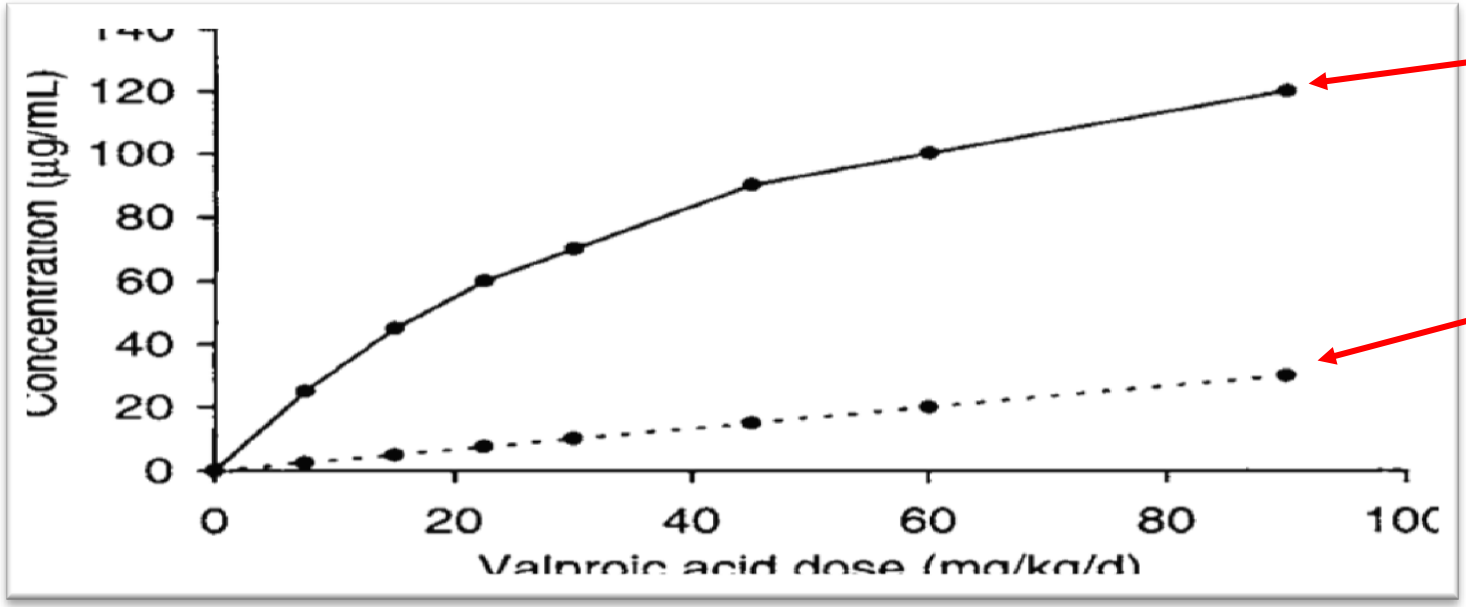



FIGURE 12-1 If a drug follows nonlinear protein binding (eg, valproic acid, disopyramide), total steady-state drug concentrations increase less than expected as dose increases.

# Dose- Total conc.- Free conc. relationship




In the case of valproic acid, when the dose is increased **total drug** steady-state concentration **increases less** than expected, but **unbound** steady-state drug concentration **increases** in a proportional fashion (eg, when the dose is doubled, total serum concentration increases 1.6–1.9 times but unbound steady-state serum concentration doubles;

# Valproic acid : Serum Conc. Related Side effects

**The therapeutic range for total valproic acid steady-state concentrations is 50-100 µg/mL while the unbound concentrations is 2.5-10 µg/mL**

| | |
|---|---|
| > 75 mg/L | Ataxia, sedation, lethargy, and tiredness |
| > 100 mg/ L | Tremor |
| > 175 mg/L | stupor or coma |

Measurement **of unbound valproic acid serum concentration** should be considered in patients with factors that alter valproic acid plasma protein binding, these factors fall into three categories:

1. **INSUFFICIENT ALBUMIN CONCENTRATION (HYPOALBUMINEMIA)**
   - like nephrotic syndrome; sever liver disease; pregnancy ..etc
2. **DISPLACEMENT BY ENDOGENOUS COMPOUNDS**
   - Like in hyperbilirubinemia & uremia
3. **DISPLACEMENT BY EXOGENOUS COMPOUNDS**
   - Like Drugs such as Warfarin , phenytion, asprin >2g , NSAID with highly protein binding

# Disease States and Conditions that Alter Valproic Acid Plasma Protein Binding

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

# Pharmacokinetic Parameters

| | |
|---|---|
| **Clearance (Cl)** | • Adult 7–12 mL/h/kg<br>• Children 10-20 mL/h/kg<br>• With enzyme inducer 15-18 mL/h/kg<br>• With liver disease 3-4 mL/h/kg |
| **Volume of Distribution (Vd)** | • 0.15 Adults – 0.2 L/kg – under 12 years |
| **Half life (t1/2)** | • Adult 12-18 hrs<br>• Children 6–8 hours<br>• With enzyme inducer 4 to 12 hours<br>• With liver disease 25 hours |
| **Bioavailability (F)** | • F = 1 for oral rapid-release products,<br>• F = 0.9 for oral sustained-release tablets |
| **Dosing (PO or IV only)** | • MD (with enzyme inducers)<br>adult 15 mg/kg /day,<br>child 20 mg/kg/day in divided 2- 3 doses<br>• MD (monotherapy) =<br>adult 7.5 mg/kg/day,<br>child 10mg/kg/day |

# راجع

- **Child-Pugh Scores for Patients with Liver Disease**
- **Interactions**

# Initial dosage determination methods

1. Pharmacokinetic dosing method
2. Literature based recommended dosing

# Pharmacokinetic dosing method

1. CLEARANCE ESTIMATE
2. MAINTINANCE and LOADING DOSAGE CALCULATION

# Determine Clearance according to the state

| disease states and conditions | Clearance |
|---|---|
| Adult , normal liver function , not on enzyme inducers | 7-12 ml/hr/kg |
| Adult , on enzyme inducers | 15-18 ml/hr/kg |
| Adult , hepatic disease | 3-4 ml/hr/kg |
| Children | 10-20 ml/hr/kg |
| Children , on enzyme inducers | 20-30 ml/hr/kg |

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

- F = 1 for oral **rapid-release** products,
- F = 0.9 for oral **sustained- release** tablets
- **$\tau$ = 8 to 12 hr.**
- **Css = 50-100 µg/mL**

**For intravenous MD**

$Css = (D/\tau) / Cl$ **or**

$$D = Css \cdot Cl \cdot \tau$$

**For intravenous LD**

$$LD = Css \cdot V$$

KL is a 51-year-old, 75-kg (height = 5 ft 10 in) male with tonic-clonic seizures who requires therapy with oral valproic acid. He has normal liver function and takes no medications that induce hepatic enzymes. Suggest an initial valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration equal to 50 µg/mL.

**Estimate clearance :**

Using a value of 10 mL/h/kg

Cl = 75 kg · 10 mL/h/kg = 750 mL/h or 0.75 L/h.

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**Compute dosage regimen**

$D = (Css \cdot Cl \cdot \tau) / F = (50\ mg/L \cdot 0.75\ L/h \cdot 12\ h) / 1 = 450\ mg$,,,, rounded to 500 every 12 hours

## If you need to get $V_d$ we estimate it by :

- **0.15 L/kg** for **adults**
- **0.2 L/kg** for **children under 12 years** of age.

Patients with cirrhosis or renal failure may have larger volumes of distribution as a result of decreased plasma protein binding.

## If you need to get $t_{1/2}$ & k we estimate it by :

When Cl ,Vd estimates are identified for the patient, they can be converted into the valproic acid half-life ($t_{1/2}$) and elimination rate constant (k) estimates

$$t_{1/2} = (0.693 \cdot V) / Cl, \qquad k = 0.693/t1/2 = Cl/V.$$

**For the same example 1 ➔➔** $V_d = 75\ kg \cdot 0.15\ L/kg =$ **11 L**

$t_{1/2} = (0.693 \cdot V) / Cl = (0.693 \cdot 11\ L) / 0.75\ L/h =$ **10 h**

$k = 0.693/t_{1/2} = 0.693/10\ h =$ **$0.069\ h^{-1}$**.

**A steady-state trough valproic acid serum concentration should be measured after steady-state is attained in 3-5 half-lives.**

The estimated **volume of distribution** would be:
$75\ \text{kg} \cdot 0.15\ \text{L/kg} = \mathbf{11\ L}$.

Valproic acid half–life ($t_{1/2}$):
$t_{1/2} = (0.693 \cdot V)/Cl = (0.693 \cdot 11\ \text{L})/0.75\ \text{L/h} = \mathbf{10\ h}$

**10h * 3–5 = need 30–50 hours will reach to steady state**

# Literature based recommended dosing

| disease states and conditions | Main dose (mg/kg/day) |
|---|---|
| Adult , normal liver function , not on enzyme inducers | 7.5 |
| Adult , on enzyme inducers | 15 |
| Adult , hepatic disease | Dose should be decreased by 25-50% |
| | |
| Children | 10 |
| Children , on enzyme inducers | 20 |

Check child pough score

## For the same example:

**initial MD is 7.5 mg/kg/d: ((Two or three divided daily doses))**

**75 kg · 7.5 mg/kg/d = 563 mg/d or 250 mg every 12 hours.**

**►This dose would be titrated upward in 5–10 mg/kg/d increments every 1–2 weeks**

- **Most adults will require 1500-3000 mg/d of valproic acid and**
- **most children require 30-60 mg/kg/d.**

# To change valproic acid dose

# 1-Pseudolinear pharmacokinetics method

► Temporarily assume linear pharmacokinetics,

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

where ✓Css in μg/mL, ✓D in mg/d

➢ To account for **nonlinear:**

► **Subtract** 10–20% for a dosage **increase** or

► **Add** 10–20% for a dosage **decrease**

**Example 7**

**KL is a 51-year-old, 75-kg (5 ft 10 in) male with tonic-clonic seizures who** requires therapy with oral valproic acid. After dosage titration, the patient was prescribed 500 mg every 12 hours of enteric-coated divalproex sodium tablets **(1000 mg/d)** for 1 month, and the steady-state valproic acid total concentration equals **38 µg/mL**.

The patient is assessed to be compliant with his dosage regimen. Suggest a valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration of **80 µg/ml**.

- **D new = (Css new/Css old) D old** = (80 µg/mL / 38 µg/mL) 1000 mg/d = **2105 mg/d**, rounded to 2000 mg/d or 1000 mg every 12 hr.

**$C_{ss}$** would be expected to be **10% ↓ less, or 0.90 times**, to **20% ↓ less, or 0.80 times** , than that predicted by linear pharmacokinetics:

Css = 80 µg/mL · 0.90 = **72 µg/mL** and Css = 80 µg/mL · 0.80 = **64 µg/mL**. Thus, a dosage rate of 2000 mg/d would be expected to yield a total valproic acid steady-state serum concentration between **64–72 µg/mL**.

# 2-Pharmacokinetics parameter method



It allows the computation of an individual's own, unique pharmacokinetic constants and uses those to calculate a dose that achieves desired valproic acid concentrations

The pharmacokinetic parameter method requires that steady state has been achieved and uses only a steady-state valproic acid concentration (Css)

**For intravenous dosing:** $Cl = (D/\tau) / Css$ ← Old Css

**For oral valproic acid therapy:**

$$Cl = [F(D/\tau)] / Css \qquad F = 1$$

**To compute valproic acid dose:** Valproic acid clearance is used to compute the new dose:

$$D = (Css \cdot Cl \cdot \tau) / F$$ ← new Css

► then subtract 10–20% for a dosage increase or add 10–20% for a dosage decrease

► to account for nonlinear, concentration-dependent plasma protein binding PK

**We can calculate actual Vd also,** using the following equation:

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

**C predose** should be obtained within **30 minutes** of dosage administration;
**C postdose** should be obtained **30–60 minutes** after the end of infusion to avoid the distribution phase.

## Actual Cl can also calculated if concentration at steady state…

The **Cl** , **Vd** , **k** , and $t_{1/2}$ measured using these techniques are **the patient's own**, **unique** valproic acid pharmacokinetic constants and can be used in one-compartment model equations to compute the required dose to achieve any desired serum concentration.

## Example 9

**KL is a 51-year-old, 75-kg (5 ft 10 in) male with tonic-clonic seizures who** requires therapy with **oral valproic acid**. After dosage titration, the patient was prescribed **500 mg every 12 hours** of enteric-coated divalproex sodium tablets **(1000 mg/d)** for 1 month, and the steady-state valproic acid total concentration equals **38 µg/mL**.

The patient is assessed to be compliant with his dosage regimen. Suggest a valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration of **80 µg/mL.**

**1. Compute pharmacokinetic parameters.** steady-state conditions achieved after 2–3 days of therapy. Valproic acid clearance can be computed using a steady-state valproic acid concentration:

**Cl = [F(D/τ)] / Css** = [1(500 mg/12 h)] / (38 mg/L) = **1.1 L/h.**

**2. Compute valproic acid dose.**

Valproic acid clearance is used to compute the new dose:

**D = (Css · Cl · τ) / F** = (80 mg/L · 1.1 L/h · 12 h) / 1 = 1056 mg, rounded to **1000 mg/12h**

expected to be 10% less, or 0.90 times, to 20% less, or 0.80 times , than that predicted by linear pharmacokinetics:

**Css = 80 µg/mL · 0.90 = 72 µg/mL** and **Css = 80 µg/mL · 0.80 = 64 µg/mL**.

Thus, a dosage rate of 2000 mg/d would be expected to yield

**Css = 64–72 µg/mL**


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