ANTICONVULSANTS
Phenytoin & Carbamazepine

- **Phenytoin** is a hydantoin compound related to the barbiturates that are used for the treatment of seizures.
- It is an effective anticonvulsant for the chronic treatment of tonic clonic or partial seizures and the acute treatment of generalized status epilepticus.

THERAPEUTIC AND TOXIC CONCENTRATIONS

- The usual therapeutic range for total (unbound + bound) phenytoin serum concentrations when the drug is used in the treatment of seizures is **10-20 µg/mL**.
- Since phenytoin is highly bound (~90%) to albumin, it is prone to plasma protein–binding displacement due to a large variety of factors. Because of this, unbound or "free" phenytoin concentrations are widely available. The usual unbound fraction (10%) of phenytoin in individuals with normal plasma protein binding.
- Thus, the generally accepted therapeutic range for unbound phenytoin concentrations is **1-2 µg/mL**, which is simply 10% of the lower and upper bounds for the total concentration range, respectively.

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 (Cf), and unbound or "free" fraction (fB) is:
  - **Cf = fB * C**
- In most patients without known or identifiable plasma protein–binding abnormalities, the unbound fraction of phenytoin will be normal (~10%) and unbound drug concentration measurement is unnecessary.

- Generally, unbound phenytoin serum concentration monitoring should be restricted to those patients with known reasons to have altered drug plasma protein binding. Exceptions to this approach are patients with an augmented or excessive pharmacologic response compared to their total phenytoin concentration.

- **For example**, if a patient has a satisfactory anticonvulsant response to a low total phenytoin concentration, one possible reason would be abnormal plasma protein binding (20%) for some unidentified reason, so that even though the total concentration was low (5 µg/mL)
- **Conversely**, if a patient has a possible phenytoin-related adverse drug reaction and the total phenytoin concentration is within the therapeutic range, a possible reason could be abnormal protein binding (20%) for an unidentified reason, so that even though the total concentration appeared to be appropriate (15 µg/mL).

The factors known to alter phenytoin plasma protein binding:

- (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.
- When multiple factors that decrease phenytoin plasma protein binding are present in a patient, the free fraction can be as high as **30%-40%**

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		

- Albumin concentrations below 3 g/dL are associated with high phenytoin-unbound fractions in the plasma.
- Patients with albumin concentrations between 2.5 and 3 g/dL typically have phenytoin-unbound fractions of 15%-20%
- while patients with albumin concentrations between 2.0 and 2.5 g/dL often have unbound phenytoin fractions greater than 20%.

Method to estimate unbound phenytoin concentration (Cf)

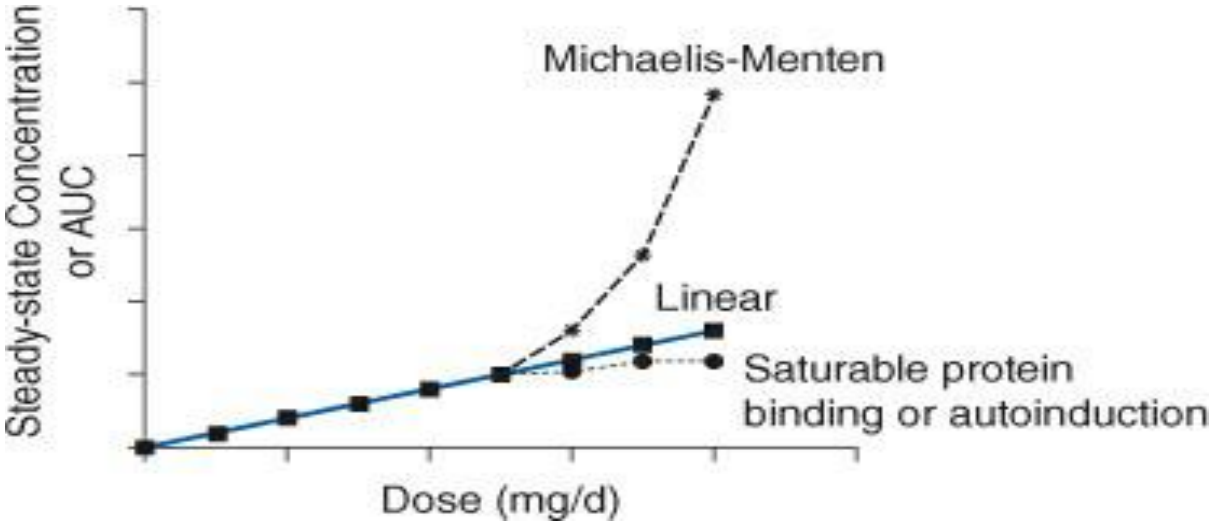
- **Cf =0.1 C total** [for patient with normal albumin 3.5 or slightly more]
- ✓ **Free fraction(f B) = Cf / C total**
- **C normal binding =C/ (x . Alb +0.1)** [for patient with hypoalbuminemia]

[Where X =0.25 if temperature 25ºc , X= 0.2 if temperature 37ºc or X=0.1 if Crcl 10-15 ml\min]

- **C f EST= 0.1 C normal binding**
- **Cf EST = (0.095 + 0.001 • VPA)PHT**

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

- Phenytoin is primarily eliminated by hepatic metabolism (>95%). About 5% of a phenytoin dose is recovered in the urine as unchanged drug.
- Phenytoin follows Michaelis-Menten or saturable pharmacokinetics. This is the type of nonlinear pharmacokinetics that occurs when the number of drug molecules overwhelms or saturates the enzyme's ability to metabolize the drug.
- When this occurs, steady-state drug serum concentrations increase in a disproportionate manner after a dosage increase.



- **FIGURE 1 --If a drug follows Michaelis-Menten pharmacokinetics (e.g, phenytoin, aspirin), as steady-state drug concentrations approach Km serum concentrations increase more than expected due to dose increases.**

- In this case, the rate of drug removal is described by the classic Michaelis-Menten relationship that is used for all enzyme systems:

  - **Rate of metabolism = (Vmax • C)/(Km + C)**

where:

- ✓ Vmax is the maximum rate of metabolism in mg/d
- ✓ C is the phenytoin concentration in mg/L or μg/mL
- ✓ Km is the substrate concentration in mg/L or μg/mL

- 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).**

- ➢ This is the reason concentrations increase disproportionately after a phenytoin dosage increase.
- For example, phenytoin follows saturable pharmacokinetics with average Michaelis-Menten constants of Vmax = 500 mg/d and Km = 4 mg/L. The therapeutic range of phenytoin is 10-20 μg/mL.
- ➢ **Calculate the change in clearance?**

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

  ↑t1/2 = (0.693 • V)/↓Cl.

Initial dosage determination methods:

1. Pharmacokinetic Dosing Method
2. Literature – based recommended dosing

1-Pharmacokinetic Dosing Method

Pharmacokinetic parameter

1-Michaelis-Menten Parameter Estimates **(V max & Km)**

- **6 months -6 years** (younger children)---- Vmax= 12 mg/kg/day , Km =6 µg /ml.
- **7-16 years**(older children) ---- Vmax= 9 mg/kg/day, Km=6 µg/ml
- **Adult** ----Vmax = 7 mg/kg/day , Km= 4 µg/ml

2- Multiply **V max *** weight [if obese use IBW]

3- Vd estimate

V= 0.7 L/kg [if obese use adjusted body weight]

- **V= 0.7 L/kg[IBW+ 1.33 (TBW-IBW)]**

4- ***Steady-State Concentration Selection***

- The general accepted therapeutic range(**Css average) 10-20 µg/mL**

Notes:

- **% overweight** = [100(TBW kg − IBW kg)]/ IBW kg = %}
- **IBW females** = 45 + 2.3(Ht inch − 60)

IBW males = 50 + 2.3(Ht inch − 60)

- **5- Compute dose**
- **LD = Css • V/ S**

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

$$Css = \frac{K_m \bullet (S \bullet MD)}{V_{max} - (S \bullet MD)}$$

✓ **Note:** For IV you should divide MD by 2 to be given twice daily(every 12 h)

- **τ** = 24 h for adult

= 12 h for children

= 12 h if used as IV

Dosage form of phenytoin

1- phenytoin sodium IV , Capsule

S factor = 8% [92% phenytoin + 8% sodium]

2- fosphenytoin is prodrug (100% phenytoin)

S factor =1

- Salt factor(S)for capsule =92% (0.92) , for tablet & suspension S =1

- ***Note:*** If the patient has significant hepatic dysfunction (Child-Pugh score ≥8), maintenance doses computed using this method should be decreased by **25%-50%** depending on how aggressive therapy is required to be for the individual

2-*LITERATURE-BASED RECOMMENDED DOSING*

- 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). [If obese use IBW]
- Phenytoin loading doses are **15-20 mg/kg.** [For obese individuals (>30% over ideal body weight), adjusted body weight (ABW) should be used to compute loading doses]

Method to calculate individualize dose or actual dose

- 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- Graves – Cloyed method*
- *4- Vozeh- sheiner Method(Graphical Method)*

Empiric Dosing Method

- Based on the knowledge of population Michaelis-Menten pharmacokinetic parameters.
- **Empiric Phenytoin Dosage Increases Based On a Single Total Steady-State Concentration**

Measured Phenytoin Total Serum Concentration (µg/mL)	Suggested Dosage Increase[a]
<7	100 mg/d or more
7-12	50-100 mg/d
>12	30-50 mg/d

[a]Higher dosage used if more aggressive therapy desired, lower dosage used if less aggressive therapy desired. Modified from Mauro, et al.[75]

- An effective way to increase the phenytoin dose for an individual that requires an increase in dose of 50 mg/d when using the 100-mg extended phenytoin sodium capsule dosage form is to increase the dose by 100 mg every other day.
- Alternate daily dosages are possible because of the extended-release characteristics of extended phenytoin capsules and the long half-life of phenytoin.

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% [1.15-1.33]**for a dosage increase or subtract **15%-33% [0.85-0.67]** for a dosage decrease to account for Michaelis-Menten pharmacokinetics:

$$\text{Css new} = (\text{D new}/\text{D old})\text{Css old}$$

- ***Note:*** The Pseudolinear Pharmacokinetics method should never be used to compute a new dose based on measured and desired phenytoin concentrations.

Graves-Cloyd Method

- This dosage adjustment method uses a steady-state phenytoin serum concentration to compute the patient's own phenytoin clearance rate.

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

- **Note:** Dose-old should multiply by S factor, then the new dose calculated divided by S factor.

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

- ***1- Empiric Dosing Method***

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

- **For instance:** if a patient has a steady-state phenytoin concentration equal to 11.2 µg/mL on 300 mg/d of phenytoin sodium and 25.3 µg/mL on 400 mg/d of phenytoin sodium, it is obvious that a dose of **350 mg/d** of phenytoin sodium will probably produce a steady-state phenytoin serum concentration in the mid-to-upper end of the therapeutic range.

- **2-Ludden method** ---*Calculate actual pharmacokinetic parameter to calculate dose and dosage interval.*

Steps:

1. Multiply dose by S factor
2. Actual Km $-\mathbf{Km = (MD1 - MD2)/[(MD1/Css1) - (MD2/Css2)]}$

where the subscript **1** indicates the higher dose and **2** indicates the lower dose.

3. Actual Vmax $\mathbf{Vmax = MD + Km(MD/Css)}$

4. New dose calculate if Css given use either:

$$\mathbf{MD = Vmax - Km(MD/Css)}$$

Or

$$\mathbf{MD = Vmax * Css / [S (Km + Css)]}$$

Or change dose[increase or decrease] empirically then calculate Css using the equation below:

$$Css = \frac{K_m \bullet (S \bullet MD)}{V_{max} - (S \bullet MD)}$$

USE OF PHENYTOIN BOOSTER DOSES TO IMMEDIATELY INCREASE SERUM CONCENTRATIONS

- A rational way to increase the serum concentrations rapidly is to **administer a booster dose of phenytoin**, a process also known as "reloading" the patient with phenytoin, computed using pharmacokinetic techniques.
- 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**

Carbamazepine is an iminostilbene derivative related to the tricyclic antidepressants that is used in the treatment of tonic-clonic, partial, or secondarily generalized seizures.

- Although methods have been suggested to treat acute seizures with carbamazepine, lack of an intravenous dosage form has limited its use in this area, the drug is used primarily as a prophylactic agent in the chronic therapy of epilepsy .
- Carbamazepine have a non-linear relationship between the dose and the plasma concentration even within the range of therapeutic doses.

THERAPEUTIC AND TOXIC CONCENTRATIONS

- The accepted therapeutic range for carbamazepine is **4-12 µg/mL** when the drug is used for the treatment of seizures.
- Carbamazepine plasma protein binding is quite variable among individuals because it is bound to both albumin and α1-acid glycoprotein (AAG).
- In patients with normal concentrations of these proteins, plasma protein binding is **75%-80%** resulting in a free fraction of drug of 20%-25%.
- **AAG** is classified as an acute-phase reactant protein that is present in lower amounts in all individuals but is secreted in large amounts in response to certain stresses and disease states such as trauma, heart failure, and myocardial infarction. In patients with these disease states, carbamazepine binding to AAG can be even **larger** resulting in an unbound fraction as low as 10%-15%.
- Although carbamazepine is highly plasma protein bound, it is harder to displace this agent to the extent that a clinically important change in protein binding takes place.
- In comparison, phenytoin is 90% protein bound under usual circumstances resulting in an unbound fraction in the plasma of 10%. It is

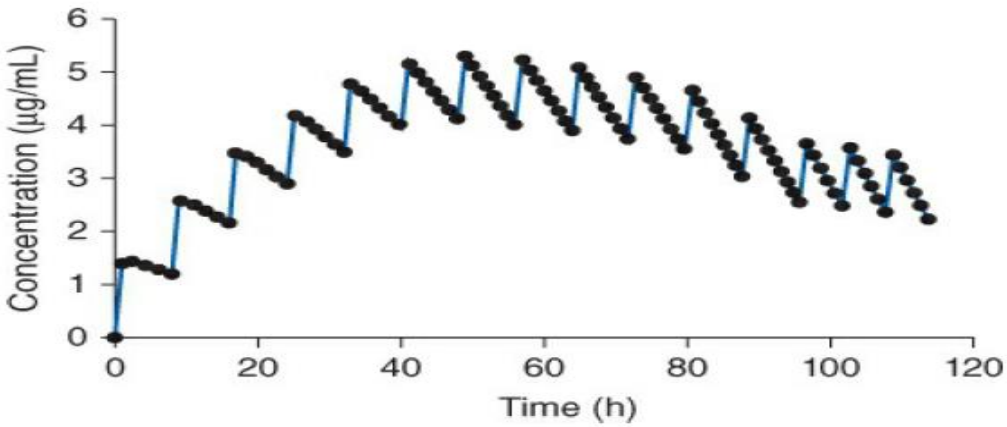
relatively easy to change the protein binding of phenytoin from 90% to 80%, under a variety of disease states or conditions, which increases the unbound fraction in the plasma from 10% to 20%.

- However, it is very difficult to change the protein binding of carbamazepine from 80% to 60% to achieve the same doubling of unbound fraction in the plasma (20%-40%).

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

- Carbamazepine is primarily eliminated by hepatic metabolism **(>99%)** mainly via the CYP3A4 enzyme system.
- Carbamazepine is a potent inducer of hepatic drug-metabolizing enzymes, and induces it's own metabolism, a process known as **auto induction**.
- As a result, patients cannot initially be placed on the dose of carbamazepine that will ultimately result in a safe and effective outcome. **At first**, patients are started on ¼-⅓ of the desired maintenance dose, This exposes hepatic drug metabolizing enzymes to carbamazepine and begins the induction process.

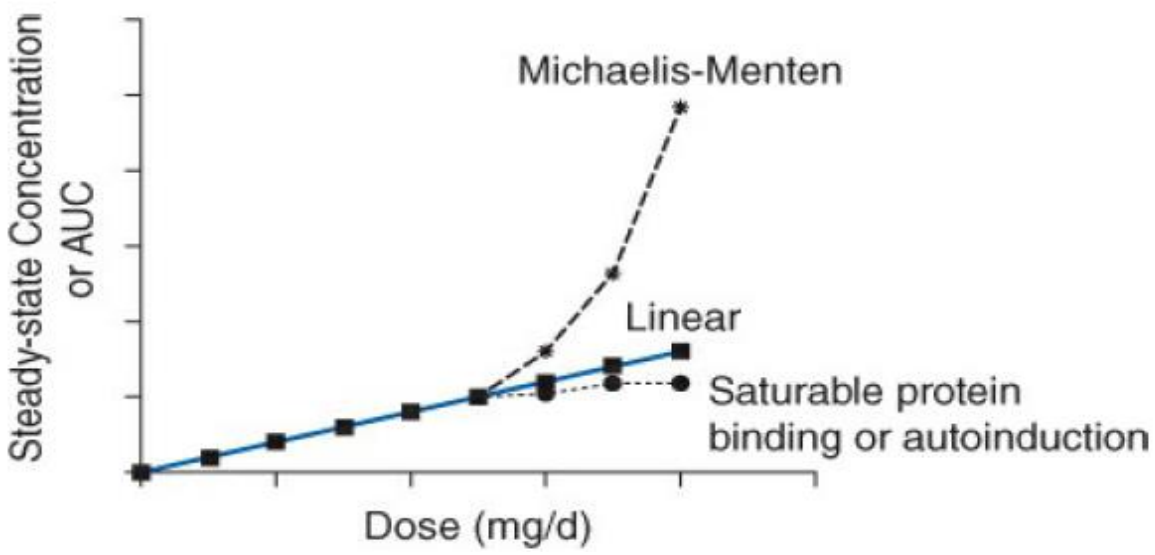
- The dose is increased by a similar amount every 2-3 weeks until the total desired daily dose is ultimately given. This gradual exposure of carbamazepine allows liver enzyme induction and carbamazepine clearance increases to occur over a 6-12 week time period.
- Therapeutic effect and steady-state carbamazepine serum concentrations can be assessed **2-3 weeks** after the final dosage increase.
- The effects of auto induction are reversible even when doses are held for as few as 6 days.



Carbamazepine Auto induction:

when dosing is initiated, serum concentrations increase according to the baseline clearance & half-life. After a few doses of carbamazepine, enough auto

induction has occurred that clearance increases, half-life decreases & drug accumulation slow down .with additional exposure of liver tissue to carbamazepine , clearance continue to increase & half-life continue to shorten.



Carbamazepine pharmacokinetics demonstrates **auto induction** ,total steady-state drug concentrations decrease less than expected as dose increases.

Pharmacokinetic parameters

- After single dose of carbamazepine:
- Oral clearance (Cl/F) is **11–26 mL/h/kg .**
- Half-life is **35 hours** for adults.
- During multiple dosing after maximal auto induction has taken place, oral clearance equals **50–100 mL/h/kg**

half-life equals is **5–27 hours**.

- Carbamazepine **volume of distribution** using immediate release tablets (V/F) is **1 -2 L/kg**.

Doses & dosage forms:

- For oral use, the drug is available as
- **Immediate-release tablets** (chewable: 100 mg, regular: 200 mg),
- **Extended-release tablets** (100, 200, 400 mg), **extended-release capsules** (100, 200, 300mg).
- **Suspension** (100 mg/5 mL).
- Peak concentrations occur about 3 hours after tablet administration.
- Peak concentrations after multiple doses of the extended release dosage forms are observed 3 to 12 hours after administration.

EFFECTS OF DISEASE STATES AND CONDITIONS ON PHARMACOKINETICS AND DOSING

- Clearance rates can be **higher** and half-lives **shorter** in patients receiving other hepatic drug-metabolizing enzyme inducers (phenytoin, phenobarbital, rifampin).

Liver Dysfunction

Patients with liver cirrhosis or acute hepatitis have reduced carbamazepine clearance **because** of destruction of liver parenchyma. This loss of functional hepatic cells reduces the amount of CYP3A4 available to metabolize the drug and decreases clearance

The volume of distribution may be larger **because** of reduced plasma protein binding. Protein binding may be reduced and unbound fraction may be increased due to hypoalbuminemia and/or hyperbilirubinemia (especially albumin ≤3 g/dL and/or total bilirubin ≥2 mg/dL).

- An index of liver dysfunction can be gained by applying the Child-Pugh clinical classification system to the patient.

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

- If child-Pugh score 8 or 9 decrease dose [25%-50%]
- If child-Pugh score 5-7 normal [dosage reduction not required]
- If child-Pugh score 10 and more decrease dose to ½

- Doses of carbamazepine do not require adjustment for patients with renal failure, and the drug is not removed by dialysis.

DRUG INTERACTIONS

- Carbamazepine is a potent inducer of hepatic drug-metabolizing enzyme systems.
- Other antiepileptic drugs that have their clearance rates increased and steady-state concentrations decreased by carbamazepine-related enzyme induction include felbamate, lamotrigine, phenytoin, primidone, tiagabine topiramate, and valproic acid.
- Phenytoin and phenobarbital can **increase** carbamazepine clearance and **decrease** carbamazepine steady-state serum concentrations.
- Cimetidine, macrolide antibiotics, azole antifungals, fluoxetine, fluvoxamine, nefazodone, cyclosporine, diltiazem, verapamil, indinavir, and ritonavir are examples of drugs that **decrease** carbamazepine clearance and **increase** carbamazepine steady-state concentrations.

DOSAGE DETERMINATION METHODS

- Because of the large amount of variability in carbamazepine pharmacokinetics, even when concurrent disease states and conditions are identified, most clinicians believe that the use of standard carbamazepine doses for various situations is warranted.
- **1-Initial dosage determination method.**
- **2-Use of carbamazepine concentrations to alter doses**

(Pseudo-Linear pharmacokinetic method)

1-Initial dosage determination methods

The expected carbamazepine steady-state serum concentrations used to compute these doses was 6-8 µg/ml.

- Usual initial maintenance doses are
  - ✓ 10-20 mg/kg/d for children under 6 years of age.
  - ✓ 200 mg/d for children 6-12 years old.
  - ✓ 400 mg/d for adults.

Notes:

- ✓ Older patients have lower carbamazepine oral clearance rates than younger adults, so lower doses (100 mg/d) may be used.
- ✓ Twice daily dosing is initially used until auto induction takes place. Dosage increases to allow for auto induction are made every 2-3 weeks depending on response and adverse effects.
- ✓ If the patient has significant hepatic dysfunction (Child-Pugh score ≥8), maintenance doses prescribed using this method should be decreased by 25%-50% depending on how aggressive therapy is required to be for the individual.
- ✓ Most adults will require **800–1200 mg/d** of carbamazepine while older children will require **400–800 mg/d.**

2-USE OF CARBAMAZEPINE SERUM CONCENTRATIONS TO ALTER DOSES

- Because of pharmacokinetic variability, the auto induction pharmacokinetics followed by the drug, the narrow therapeutic index of carbamazepine, and the desire to avoid adverse side effects of carbamazepine, measurement of carbamazepine serum concentrations is conducted for almost all patients to insure that therapeutic, nontoxic levels are present.

Pseudo linear Pharmacokinetics Method

- 1- Empirically increase or decrease the dose by 200 mg according to the required Css.
- 2-calculate the new Css from the new dose by

$$\text{Css new} = (\text{D new} / \text{D old})\ \text{Css old}$$

- 3- Then subtract 10–20% for a dosage increase or add 10–20% for a dosage decrease to account for auto induction pharmacokinetics