

Phenytoin in Critically Ill Patients: A case presentation and topic review

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Objectives

- Preview case presentation
- Outline hospital treatment regimen
- Topic review of phenytoin dosing

Case Presentation

- JS is an 88 YO AAM who presented on 12/27
- CC: weakness, fever/chills, poor appetite, and swollen groin
- HPI: Patient reports worsening anorexia that has persisted over 5 months; claims to have lost over 50 pounds over the last year. Patient saw his PCP about 1 month ago concerning a possible groin infection; since this time he has had progressive weakness and is now unable to transfer himself from his wheelchair to his bed.
- PMH: Polio, multiple myeloma, COPD, DM, h/o DVT, MI, CHF, chronic anemia, chronic seizure disorder, PUD

Case Presentation

- PE: BP 114/48, afebrile, Pulse 91, SaO₂ 98%
- Home meds:
 - Lasix 20 mg po BID
 - Folic acid 1 mg po daily
 - Phenytoin 200 mg po BID
 - Finasteride 5 mg po daily
 - Coumadin 4 mg po Tues, Thurs, Sat
 - Ranitidine 150 mg po BID
 - Simvastatin 40 mg po QHS
 - Mirtazapine 30 mg po QHS
 - Acetaminophen 650 mg po Q8H prn
 - Lenalidomide 10 mg po daily

Case Presentation

- DX: septic shock, acute renal insufficiency, epididymis, thrombocytopenia DIC, N-STEMI, acute exacerbation of HF, severe malnutrition, vent dependent respiratory failure, bilateral arm deep venous thrombosis

Case Presentation

- Micro

Strep viridans in blood 12/27

Eubacterium lentum, Strep viridans, Peptostrep.
saccharolyticus in surgical culture 1/3

- Patient was initially started on Levaquin, but was switched to Vanc and Zosyn after failing to improve clinically.

Case Presentation

Phenytoin dosing regimen:

- 200 mg PO BID 12/27-1/8
- 100 mg PO TID 1/9-D/C

Date	Albumin (3.5-5 g/dl)	WBC (4.5-10.5 x 10 ³)	AST (5-40 u/L)	ALT (5-65 u/L)	SrCr (0.53- 1.43 mg/dl)	Dilantin (10-20 µg/ml)
12/27	2.4	16.6	28	29	1.13	14.6
1/3	2.0	16.2	124	59	2.14	10.1
1/5	1.7	5.4			1.41	
1/6	1.8	11.0			1.19	
1/7	1.6	9.5			0.87	
1/8		8.1			0.76	
1/9		6.2			0.75	14.9
1/13	1.8				0.92	12.1
1/17	1.7	6.4			0.8	11.3
1/19	1.9	5.8	7	8	1.00	8.9

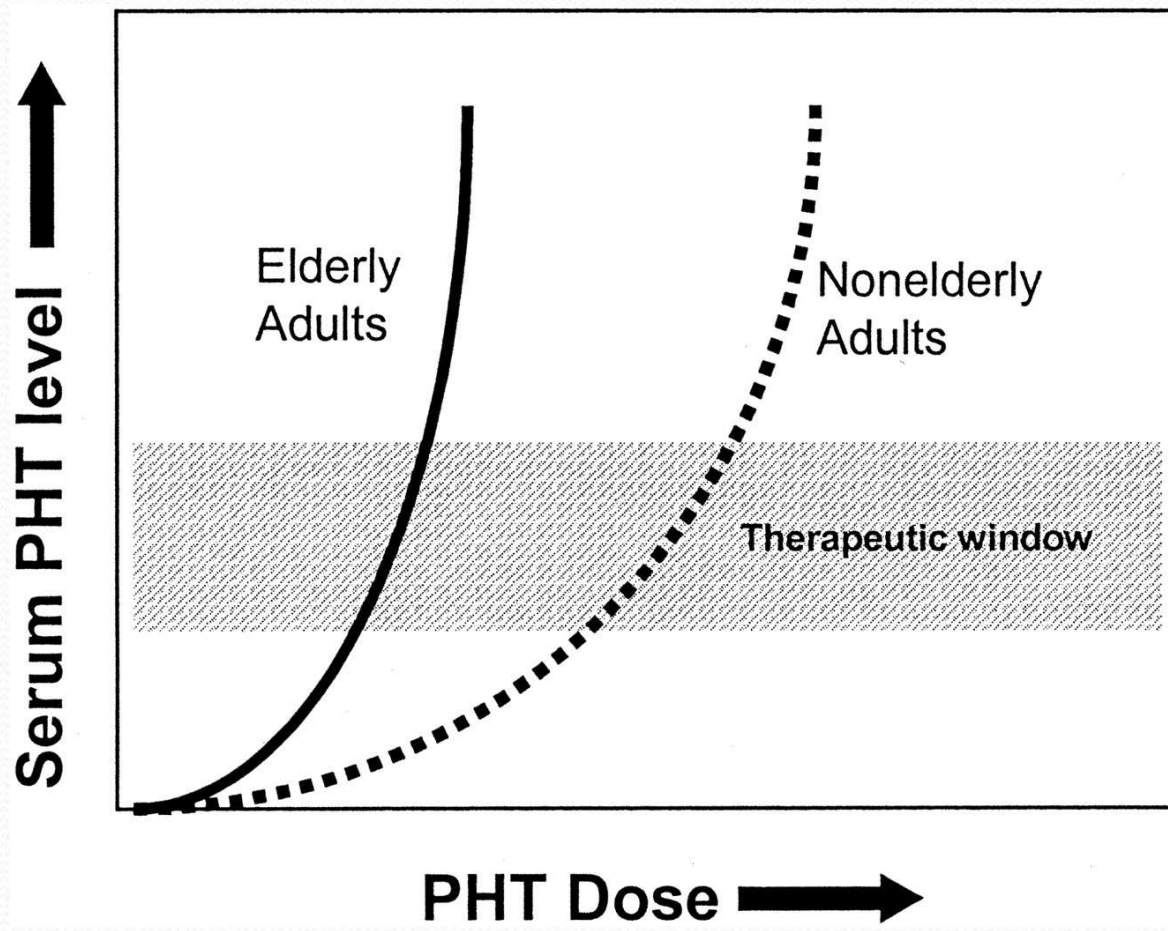
Phenytoin Kinetics Review

Metabolism

- Zero order
- Doubling dose does not result in double the concentration, could result in 4x or more
- Saturable kinetics, $T_{1/2}$ doesn't apply. As concentration increases, $T_{1/2}$ increases.

*Dose generally should not be increased by more than 50-100 mg/day. *Narrow therapeutic window*

Zero Order Kinetics



Protein Binding

- 90% protein bound, Free unbound phenytoin (f_{up}) = 0.1 in normal patients.

- **f_{up} increased in patients with hypoalbuminemia**

*Not removed by hemodialysis

Reasons for Decreased Protein Binding

- Critical Illness
- Trauma
- Burns
- Pregnancy
- Liver disease
- Age
- Renal impairment*

*It is believed that increased uremic compounds may compete for protein binding, thus increasing f_{up} ... However, there is not a good correlation between increased SrCr and free phenytoin levels.

Clearance

$$CL = V_{max} / (K_m + C) \dots$$

- V_{max} = max rate of metabolism
Increases in critically ill, trauma, burns, pregnancy
Decreases with age, hepatic impairment
 - K_m = serum conc. where metabolism is at $\frac{1}{2}$ speed
 - C = serum conc.
- *** CL is directly related to V_{max}

Volume of Distribution

- Adults: 0.6-0.8 L/kg Peds: 0.7-0.9 L/kg

*Vd increased in: pregnancy, trauma, burns, critical illness, active seizures → use $Vd=1$

“Normal” Patient Dosing

Loading Dose

- 15-20 mg/kg IV

Partial Load

- $LD = Vd \times (C_{\text{target}} - C_{\text{actual}})$

*Free therapeutic range = 10 – 20 $\mu\text{g}/\text{mL}$

“Normal” Patient Dosing

Maintenance Dose

- 4-6 mg/kg/day for adults (Q8 or Q12 for IV, daily for capsules)

Critically Ill Patients

- Increased V_{max} (hypercatabolic state) and V_d ; decreased protein binding.
- Use Q8 due to increased V_{max} , use $V_d = 1$ for calculations
- Use higher end of dosing range

“Critically Ill” Patient Dosing

Loading Dose

- 20 mg/kg IV

Partial Load

- $LD = Vd \times (C_{target} - C_{actual})$

Maintenance Dose

- 6-8 mg/kg/day

Concentration Correcting Formulas (Tozer equation)

- Hypoalbuminemia

$$C_{\text{corrected}} = C_{\text{measured}} / 0.2 (\text{serum albumin}) + 0.1$$

- ESRD

$$C_{\text{corrected}} = C_{\text{measured}} / 0.1 (\text{serum albumin}) + 0.1$$

Other proposed correcting factors:

Use 0.25 instead of 0.2 in severe head trauma or age >65.

Use what we know for JS

- Albumin on 1/5: 1.7 g/dl
- Measured dilantin level: 11.3
 11.3 $= \frac{11.3}{0.2(1.7\text{g/dl}) + 0.1}$
- Using the Tozer equation, the corrected level is: $= 25.68$

Things to Ponder...

Could JS be considered critically ill? If so...

- V_{max} and V_d will be increased.
- Protein binding will be decreased.

→ More drug is available to be metabolized due to decreased protein binding, and the rate at which the drug is metabolized is also increased.

→ Look for signs of toxicity; compare total phenytoin level to adjusted levels, do they make sense?

Signs of Toxicity

- Nystagmus
- Diplopia
- Confusion
- “Halo”
- Ataxia
- Slurred speech
- Hyperglycemia?

Be Aware of Interacting Meds!

- Highly protein bound meds
- CYP 2C9 and 2C19 inducers/inhibitors
- If in doubt, look it up

Resources

- **Anderson GD, Pak C, Doane DK, et al. Revised Winter-Tozer equation for normalized phenytoin concentrations in trauma and elderly patients with hypoalbuminemia. *Annals of Pharmacotherapy*. 1997; Mar 31(3): 279-284.**
- **Sandrina L von Winckelmann, Spriet I, Willems L. Therapeutic drug monitoring of phenytoin in critically ill patients. *Pharmacotherapy*. 2008; 28(11): 1391-1400.**
- **Image on slide 11:
http://www.neurology.org/content/63/10_suppl_4/S40/F3.large.jpg**