Harper Hospital
Detroit Medical Center / Wayne State University

4WS
Neurology

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CLINICAL PEARLS FOR 4 WS
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GUIDELINES FOR EMPIRIC PHENYTOIN DOSING

AVAILABLE FORMULARY PREPARATIONS			
Dosage From	**Strength**	**Chemical Form**	**Phenytoin Content & Salt Factor**
Capsules (ER)	**30mg, 100mg**	**Phenytoin Sodium**	**92% & 0.92**
Suspension (IR)	**125mg/5ml**	**Phenytoin Acid**	**100% & 1**
Chewable tables (IR)	**50mg**	**Phenytoin Acid**	**100% & 1**
Injectable (IR)	**50mg/ml**	**Phenytoin Sodium**	**92% & 0.92**

ER = extender release, may be given once daily after divided dose regime is established
IR = immediate release, should not be used for once daily dosing

MONITORIN PARAMETERS

- Vital sings and electrocardiogram (with IV use), plasma phenytoin level, CBC, liver function tests

THERAPEUTIC RANGE

- Total phenytoin plasma concentration: 10 – 20 mcg/ml (protein bound plus unbound phenytoin levels)
- Free phenytoin plasma concentrations: 1- 2 mcg/ml

LOADING DOSES

- Determine total body weight (TBW in kg)
- In obese patients loading doses should be calculated on adjusted body weight
- Sample phenytoin plasma concentration for patients already receiving phenytoin

Patients not receiving phenytoin

Intravenous

- Dose mg = $\frac{\text{Vd (0.7 L/kg) x weight in kg x plasma C desired}}{\text{S x F}}$
- 15 – 20 mg/kg (TBW) at rate ≤ 50mg/min as direct IV injection or infusion
- Start maintenance dose within 12 to 24 hours of the loading dose

Oral

- 18 – 20mg/kg in 2 to 4 divided doses given 2 hours apart
- Start maintenance dose 24 hours after the loading dose

Patients with suboptimal phenytoin plasma concentration

Intravenous

- Dose mg = $\frac{\text{0.7L/kg x weight in kg x (plasma C desired – plasma C observed)}}{\text{S x F}}$

Oral

- Dose mg = intravenous dose (mg/kg) + 10 %

MAINTENANCE DOSE

- 5mg/kg/day up to 300 mg - 400 mg a day
- Start low and anticipate to adjust upwards

SAMPLING TIMES

Loading dose

- Intravenous — >1 hr after end of infusion after distribution phase **OR** sample 18 to 24 hours after the completition loading dose
- Oral — About 24 hours after the loading dose

Maintenance dose

- Intravenous (divided doses) — Trough
- Oral (divided dose) — Trough not critical; trough suggested
- Oral single daily dose — Trough recommended

- After a regimen is started, the first sample should be drawn within n 3 to 4 days (not steady state) to ensure that concentrations are not too low or high for a prolonged period. Sampling should be performed with decreased frequency thereafter if levels are acceptable and stable
- Flowing change in: maintenance dose or dosage form, route of administration, declining or increasing of phenytoin levels or addition of drugs known to alter metabolism or absorption sample should be drawn every 3 to 4 days
- At steady state the sampling interval should be done every 7 to 14 days in the acute care setting and every 1 to 6 months in ambulatory patients

DOSE ADJUSTMENT

- Because of penytoin dose-dependent kinetic phenytoin dosage should be adjusted in small increments in dose to avoid toxicity. Sufficient time should be allowed for the new steady state to be achieved before further increasing the dose.

"Clinical Rules for Phenytoin Dosing" by Privitera:

Initial plasma phenytoin concentrations	Increase the dose by
<7 mcg/ml	**100 mg/day**
7 to < 12 mcg/ml	**50 mg/day**
≥ 12 mcg/ml	**30 mg/day**

These increases will result in less than 10% of patients achieving a phenytoin serum concentration greater than 25 mcg/ml

Patients with Low Serum Albumin

Measured Total Phenytoin Concentration (mcg/ml)	Patient's Serum Albumin (gm/dl)			
	3.5	3	2.5	2
	Adjusted Total Phenytoin Concentration (mcg/ml)			
5	6	7	8	10
10	13	14	17	20
15	19	21	25	30

Adjusted serum concentration = Measured total concentrations + [(0.2 x albumin) + 0.1]

Patients with Renal Failure (Clcr ≤ 10 ml/min)

Measured Total Phenytoin Concentration (mcg/ml)	Patient's Serum Albumin (gm/dl)				
	4.0	3.5	3	2.5	2
	Adjusted Total Phenytoin Concentration (mcg/ml)				
5	**10**	**11**	**13**	**14**	**17**
10	**20**	**22**	**25**	**29**	**33**
15	**30**	**33**	**38**	**43**	**50**

Adjusted serum concentrations = Measured total concentration + [(0.1 x albumin) + 0.1]

FOSPHENYTOIN (CEREBYX) ®

- Following fosphenytoin administration, it is recommended that phenytoin concentrations not be monitored until a conversion to phenytoin is essentially complete. This occurs within approximately 2 hours after the end of IV infusion and 4 hours after IM injection
- Equimolar doses of IM phosphenytoin may be substituted for oral phenytoin sodium with no dosage adjustments needed when initiating IM or returning to oral therapy
- Phenytoin capsules are approximately 90% bioavavailable by the oral route. Fosphenytoin is 100% biovailable by both the IM and IV routes. For this reason, plasma phenytoin concentrations may increase modestly when IM or IV fosphenytoin is substituted for oral phenytoin sodium therapy
- IM fosphenytoin should not be used in the treatment of status epilepticus because therapeutic phenytoin concentrations may not be reached as quickly as with IV administration
- In controlled trials, IM fosphenytoin was administered as a single daily dose utilizing either 1 or 2 injection sites. Injection of 10 to 20 ml at a single site was well tolerated
- **Loading dose on 4 WS is administered as up to 5 ml per single injection site**

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE - drugs first as cause:

- Antiepileptic drugs (e.g. carbamazepine sodium valproate)
- Antineoplastic agents(e.g. vincristine, vinblastine)
- Nonsteroidal anti-inflammatory drugs
- Chlorpropamide
- Tricyclic antidepressants and selective serotonin reuptake inhibitors
- Narcotics
- Angiotensin converting enzyme inhibitors
- Clofibrate
- Oxytocin

- ADH analogs (desmopressin, vasopressin)
- Antiphysotic agents

EPIDURAL BLOOD PATCH – is used to treat refractory post – dural puncture headache. Blood obtained from venepuncture is injected into the epidural space outside of the spinal canal.

WHAT ARE THE DRUGS TO BE USED WITH CAUTION WITH MYASTHENIA GRAVIS?

Antibiotics	Other Drugs
• Aminoglycosides • Polymyxin B • Colystin • Oxytetracycline • Rolitetracycline • Lincomycin • Clindamycin • Erythromycin • Ampicillin **Neuromuscular Blockers, Cardiac and other drugs** • Quinine • Quinidine • Procainamide • Trimethaphan • Lidocaine beta-adrenergic blockers	• Phenytoin • Chloroquine • Trimethadione • Lithium carbonate • Magnesium salts • Methxyflurane • Oxytocin • Aprotinin • Diazepam • Ketamin • D-penicillamine • Carnitine

THALIDOMIDE
Thalidomide use is closely regulated by the manufacturer. The regulatory program involves mandatory pregnancy testing and contraceptive measures that are acknowledged in writing by the patient and the prescribing physician. Pharmacist may dispense the drug in amounts sufficient for only 1 month of therapy and only with appropriate patient registries and consents. Prior to dispensing authorization number must be obtained:
1-888-423-5436.
Patient has to have own medication while in hospital. You may be asked to direct medical staff on how to acquire medication on outpatient basis.

INTRAVENOUS IMMUNOGLOBULIN THERPY (IVIG) 0.4gm/kg – complete preprinted order form

- Chronic immune-related demyelinating polyradiculopathy (CIPD)
- Myasthenia Gravis
- Multifocal neuropathy
- Dermatomyosis
- Polymyositis
- Stiff man syndrome

All patients, unless obese, should be dosed based on total body weight (TBW). Obese patients should be dosed using adjusted body weight.

CARBAMAZEPINE

- No need to adjust does-rate in renal impairment
- Caution liver disease. Changes in enzyme activity affect the unbound serum concentration of carbamazepine, resulting in changes in response. Changes in liver blood flow (e.g. CHF) do not affect serum concentrations of carbamazepine
- An increase in dose-rate could cause a further increase in carbamazepine clearance, and the effect would be less than expected: less than proportional increase in Css, avg
- Carbamazepine is 75 to 80% protein bound
- Total carbamazepine concentrations must be interpreted with great caution whenever altered serum protein binding is suspected
- First order behavior is generally assumed

PHENOBARBITAL

- There is a definite need to adjust dose-rate in liver disease. Changes in liver blood flow (i.e. CHF) do not affect serum concentrations of carbamazepine
- Phenobarbital is 50% protein bound, fu (fraction unbound) will not be affected much by a decreased albumin concentrations
- First order behavior
- You can use proportionality to adjust dose rate – 2 x the dose-rate produces 2 x the Cu (concentration unbound) and Css, avg
- You can trust total levels

VALPROIC ACID

- Several oral products are available: solution (sodium salt), liquid-filled capsules (acid), enteric-coated delayed-release tablets & extender release tablets (divalproex sodium), sustained release Sprinkle® (capsules containing coated particles (divalproex sodium). Parenteral injection for IV uses (sodium salt). Divalproex sodium is a 1:1 ratio of valproic acid and valproate sodium, which dissociates into valproate in the GI tract. All of these products are "labeled" according to the active acid
- No need to adjust dose - rate in renal impairment
- Caution in liver disease. Changes in enzyme activity affect the unbound serum concentration of carbamazepine, resulting in changes in response. Changes in liver blood flow (i.e. CHF) do not affect serum concentrations of
- Valproic acid is very highly protein bound
- The fu of valproic acid is increased in renal insufficiency (uremia), cirrhosis and acute viral hepatitis. The fu also progressively increases when higher dose-rates are given **(nonlinear protein binding)**
- In these situations total levels do not predict response and cannot be fully trusted to reflect changes in unbound levels. Total levels may be misleading predictors of response to valproic acid at **high dose rates**
- Not the first order behavior with regard to **total** valproic acid levels
- First order behavior with regard to **free** valproic acid levels. If you double the dose-rate, you will see double the average free level at steady state