Phenytoin Introduction

Phenytoin is the drug of choice for generalized and partial tonic-clonic seizures and is widely used in patients of all ages. It exhibits complex saturable kinetics and variable protein binding which complicate dosing and interpretation of serum levels.

Dosage: Maintenance dose are generally in the range of 5 - 7 mg/kg/d for both adults and children, but vary greatly between patients. In newborns, 3 mg/kg is more usual due to hepatic immaturity.

Time to Steady State: 7 - 10 days (occasionally up to 30 days)

Bioavailability: 85% to 95%

Time to peak: 4 - 7 hours with Dilantin brand capsules, but may be greatly delayed in massive acute overdoses. Peaks may occur at 1.5 - 3 h with normal doses of other formulations.

Half Life: 7 - 42 hours (concentration dependent as it switches from linear to non-linear or saturated pharmacokinetics in the middle of the therapeutic range), may be longer in children or those with polytherapy.

Toxicities: Most of phenytoin's major toxicities involve the CNS. Disturbances of behaviour (concentration, judgment) and of cerebello-vestibular integration (nystagmus, ataxia, incoordination) are most common at toxic and even therapeutic levels. Autonomic disturbances occur at higher levels, and coma may be observed at serum levels above 40 µg/mL. Toxicity is accentuated by rapidly rising levels and blunted by gradual accumulation of drug. An assortment of idiosyncratic and hypersensitivity effects also occur. With prolonged treatment, other toxic effects may occur, including permanent cerebellar dysfunction, peripheral neuropathy, gingival hyperplasia, and osteomalacia.

When to draw levels: The best time to draw levels is at trough. Other times are acceptable, but it is most important to draw levels at consistent and reproducible times.

Therapeutic range: 1.0 – 2.0 µg/mL free phenytoin or 10 – 20 µg/mL total phenytoin.

Routes of elimination: Phenytoin is eliminated primarily by hepatic metabolism. The primary metabolite, 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH), is conjugated to a glucuronide and excreted in urine.

Active Metabolites: Not thought to be significant.

Protein binding: Phenytoin is extensively protein bound (~90% in normal individuals). Decrease in albumin and increases in protein-bound inactive metabolites can both cause decreased protein binding and increases in the pharmacologically active free phenytoin fraction.

Volume Distribution (total phenytoin): 0.64 + 0.04 L/kg

Free Phenytoin Basics

Most drug assays measure total drug in the serum, but both the efficacy and the toxicity are generally dependent on the free drug concentration. Thus, the concentration of free drug is especially important for drugs that are highly bound to protein, since small changes in the extent of binding may result in large changes in the free concentration.

At a normal albumin levels, circulating phenytoin is ~90% bound to albumin. Only the free or unbound phenytoin is pharmacologically available. Hence, both the efficacy, toxicity and the rate of elimination depend ONLY on the free level. However, our routine assay measure total phenytoin, but it is usually possible to predict the free concentration.

Phenytoin binds to albumin with an affinity which causes approximately 10% of the total drug to be free at normal albumin concentration (4.0 g/dL). Thus, a therapeutic range of 10 – 20 μg/mL in a normal patient corresponds to a free concentration of 1 – 2 μg/mL. We define a quantity, alpha, as the ratio of free to total phenytoin. Binding of phenytoin to albumin is low affinity (μm – mm), but there are a large excess of binding sites (100 – 1000x). This creates a situation where across a relatively wide range of phenytoin concentrations (5 – 40 μg/mL) the percent free is relatively constant and stays near 10%. In contrast, the percent free is very sensitive to the albumin concentration. If the albumin level decreases, the percent free has an approximately proportional increase, such that at an albumin of 2 g/dL, the percent free is closer to 20%.

Imagine a patient with an albumin of 4.0 g/dL, a total phenytoin level of 10 μg/mL and a free level of 1 μg/mL. He will have 9 μg/mL bound to his albumin or 2.25 μg per g albumin. Now let's remove 1 g of albumin, including its bound drug. Free level will not change, since remaining albumin is just as saturated as before (approximation but holds over this range). The patient's new values will be 1 μg/mL free, 6.75 μg/mL bound and 7.75 μg/mL total (calculate on your own to confirm). By extrapolation, the patient's new therapeutic range will be 7.75 – 15.5 μg/mL total. Remove another gram of albumin, and free should still be approximately 1.0 μg/mL, but bound is now 4.5 μg/mL and total is 5.5 μg/mL. The new therapeutic range will be 5.5 – 11.0 μg/mL. Hence, therapeutic range can be approximated by 10 x (albumin/4) to 20 x (albumin/4). This approximation would have given therapeutic ranges of 7.5 – 15 and 5 – 10, respectively, which do not differ significantly from 7.75 – 15.5 and 5.5 – 11. Some conditions may change the value of alpha: drugs such as valproic acid and aspirin in high doses and excessive bilirubin compete with phenytoin for binding to albumin. In complete renal failure, accumulated waste products compete for binding as well, raising alpha. For a patient with normal albumin and total renal failure, alpha is usually about 0.2 (20%), but rarely may be as high as 0.3. Thus, in renal failure with alpha of 0.2, a normal albumin and a total phenytoin level of 10 μg/mL, we would predict a free level of 2 μg/mL. This patient would have a therapeutic range of 5 – 10 μg/mL. If his albumin were also low, a further reduction in therapeutic range would be expected. The therapeutic range for a patient in complete renal failure can be approximated by halving the values obtained by computing the therapeutic range calculated from the patient's albumin level.

Note that because phenytoin pharmacokinetics are determined by the free level, a patient on a given dose at steady state will maintain the same free concentration, even though total concentration may change drastically. For example, a patient on 400 mg/day with a steady state level of 15.0 μg/mL (free level = 1.5 μg/mL) who subsequently developed hypoalbuminemia (new albumin, 2.0 g/dL) would drop his total level to 4.5 μg/mL, but his free level would remain at 1.5 μg/mL. He is still effectively therapeutic, with a revised therapeutic range of 3-6 μg/mL. It is not necessary to change his dose (assuming there has been no change to the rate of metabolism of phenytoin).

Why measure total phenytoin levels? This is a good question. There would be no reason to measure them at all if the assay for measuring free phenytoin was as easy and as accurate as total phenytoin, but it isn't. Basically, to measure free phenytoin we centrifuge plasma in a filtration device that retains plasma proteins but allows the small, soluble components to pass through leaving a protein-free filtrate containing only the free drug. When analyzed using essentially the same assay as used for total phenytoin, we get the free value. However, because the free level is so much smaller than the total level and the error in the measurement is about the same, the error in the free as a percentage of the real value is much larger. The goal is to only measure free levels to assist in interpretation of the total level (since the total level is the more accurate one). Hence, each free level should include a corresponding total level, an albumin, an assessment of renal function (e.g. Cr or lack of history of renal insufficiency), and concentrations of displacing agents such as drugs or bilirubin, if clinically relevant.

General guidelines for free phenytoin consultation/interpretation

1. For patients showing signs of toxicity when total levels are low or normal.
    a. Confirm total level.
    b. Predict therapeutic range from albumin and renal status (see procedure). If patient is outside his therapeutic range, dose should be reduced to bring him into this range. Free level is probably not needed.
    c. If patient is in his predicted range already, do free level.
2. For patients with renal failure or low albumin. (request was made because normal range is not applicable).
    a. Assist physician in calculating appropriate therapeutic range for patient.
    b. A free level determination is needed when patient has partial renal failure (creatinine clearance >10 mL/min).
    c. Calculate the percent of free phenytoin from the measured free and total concentrations. Knowing the percent of the total that is free will allow for the measurement of only total phenytoin as long as the renal status remains the same.
3. For patients with high aspirin intake, high valproate levels, high bilirubin, etc.
    a. Do a free level.
    b. Calculate the percent free and expected therapeutic range.
    c. Patient can subsequently be managed with total concentrations as long as other levels remain the same. (A free level is probably not indicated in patients with low valproate levels unless patient is toxic with a normal phenytoin level).
4. For patients with normal total level, but inadequate seizure control
    a. Check albumin. If significantly different from 4.0 g/dL, predict therapeutic range.
    b. If patient has a total phenytoin level with the normal range (10 to 20 μg/mL) the free phenytoin level is likely to be adequate. It is easy to decrease phenytoin binding but very hard to increase it.
5. For patients with low total phenytoin levels on normal dosing regimens.
    a. The patient may have decreased binding of phenytoin (i.e. increased percent free), because of low albumin, renal failure or drugs, resulting in a normal free level but low total level.
    b. Predict patient's therapeutic range. If measured total level is in this range, a free level is not indicated (but can be valuable for confirmatory purposes).
    c. If patient does not show a reason for decreased binding, other possibilities for a low total phenytoin with adequate dosing are: non-compliance, incomplete absorption (nasogastric feedings, antacids, increased GI motility, etc), rapid metabolism. A free level is still not likely to be helpful (but, again, can be reassuring).

An Alternative Generic Protocol for Free Phenytoin Consultation

1. Always get an albumin. If the albumin is less than 4.0, calculate the correction factor for low albumin:

    $f = (0.2 * Alb) + 0.1$ (Sheiner-Tozer Equation, gives a correction factor for alpha)

2. Need an estimate for the degree of displacement of phenytoin from albumin due to an increase in circulating substances that compete for binding to albumin, which we call the displacement correction factor or "g". If the patient has normal renal function, a normal bilirubin and is not taking any medication that binds strongly to albumin, then "g" is simply 1.0. For end stage renal disease, "g" reaches a maximum of around 2.0. In most cases, g is somewhere in between and should be estimated from a simultaneous measurement of the total phenytoin concentration (Ctot), the free phenytoin concentration (Cfree) and the serum albumin:

    $g = (Cfree/Ctot)*(f/0.1)$, where $f = (0.2 * Alb) + 0.1$

3. Once the displacement correction factor (g) is known, then clinicians should monitor phenytoin therapy with serial Ctot and albumin levels as long as the expected level of displacing substances is constant. There are three ways to "correct" these measurements. The goal is always to provide a way to interpret the Ctot. Remember there is never any need to change dosing based upon a change in albumin concentration or displacement. It only requires a change in how the Ctot is interpreted.
    a. Provide a "corrected Ctot": Ctot,corr = Ctot * g/f. This value should be compared the original reference range, i.e. either 10 – 20 μg/ml or whatever was previously established clinically for the patient.
    b. Provide a "corrected" reference range (RR): RRcorr = RRorig * f/g. In this case the uncorrected Ctot should be compared to this adjusted reference range. RRorig is again either 10 – 20 μg/ml or whatever was previously established clinically for the patient.
    c. Provide a predicted Cfree: Cfree,pred = 0.1 * g/f * Ctot. Cfree,pred should be compared to the standard reference range of 1 – 2 μg/ml or whatever was previously established clinically for the patient.

Example 1: A patient was provided an appropriately calculated loading dose of phenytoin. However, the Ctot was unexpectedly low at 6 μg/ml.

1. Albumin measured at 1.5 g/dl; correction factor, f = (0.2 * 1.5) + 0.1 = 0.4.
2. Note that the fraction free can now be calculated based on 0.1/f = 0.1/0.4 = 0.25.
3. Patient has normal renal function, normal bilirubin and not on any other medications expected to displace phenytoin from albumin; hence, g assumed to be 1.0.
4. Three consultative approaches:
    a. Ctot,corr = Ctot / f = 6 / 0.4 = 15 μg/ml. Hence, this patient is in the middle of the standard reference range of 10 – 20 μg/ml.
    b. Alternatively, RRcorr = [10 – 20 μg/ml] * 0.4 = [4 – 8 μg/ml]. Hence, this patient is in the middle of their corrected reference range.
    c. The Cfree,pred = (0.1/0.4) * 6 = 0.25 * 6 = 1.5 μg/ml. Again, this is in the middle of the standard reference range for Cfree of 1 – 2 μg/ml.

Example 2: A severly ill patient in the ICU with renal insufficiency has signs of phenytoin toxicity at an unexpectedly low Ctot = 14 μg/ml.

1. Albumin = 2.5 g/dl; f = (0.2 * 2.5) + 0.1 = 0.6.
2. Patient has a Cr = 2.0. Hard to predict the actual free fraction as it is influences by both low albumin and displacement. Need to measure a Cfree, which comes back at 2.9 μg/ml. This is high and consistent with the patient's toxicity. Now need to provide guidance on how to interpret future Ctot in terms of the decreased albumin and the renal insufficiency: g = (2.9 / 14) * (0.6 / 0.1) = 1.2
3. Ctot,corr = 14 * 1.2 / 0.6 = 28 μg/ml. Hence, this patient is actually well above the standard reference range of 10 – 20 μg/ml.
4. Alternatively, RRcorr = [10 – 20 μg/ml] * 0.6 / 1.2 = [5 – 10 μg/ml]. Again, this patient is above their corrected reference range.
5. One recommendation is for the clinicians to dose the patient according to the corrected reference range (5 – 10 μg/ml), unless there is a significant change in serum albumin or renal function. A change in albumin will only require recalculation of the recommended reference range. A change in renal function will require a new estimate of the displacement correction factor or "g".

Optional proof why the centrifugation to remove protein does not change free phenytoin.

It is reasonable to be concerned whether separation of free from bound phenytoin changes the concentration of free phenytoin. It doesn't, only because the

Consider the equilibrium: M + D <==> B, where

M is if the free albumin concentration,

D is the free phenytoin concentration, and

B is the concentration of phenytoin bound to albumin.

We can define an equilibrium constant, K, for this reaction: K = B / (M * D)

This can be rearranged to give: D = (B / M) * (1/K)

In the above equation, 1/K is a constant. Hence, the free drug concentration (D) only depends on the ratio of the bound drug concentration (B) divided by the free albumin concentration (M). Since both B and M refer to the same **total volume**, the ratio is really independent of volume. As the sample is concentrated and a solution volume is removed containing free drug, the bound drug and albumin stay behind in the same total volume.

Let's show an example. We need to define the total albumin concentration at Mt = M + B.

Similarly, the total drug concentration Dt = D + B.

Assume that in the patient's serum, Mt = 0.5 mM = 500 uM, Dt = 10 uM, and we use a 1 ml aliquot.

In this case, the free drug should start out (before concentration) as 1 uM, which implies B = 9 uM and M = 491 uM.

We can calculate from this scenario a K = 9 / (491 * 1) = 0.0183 uM^-1.

Now imagine that 1/2 of the total volume is instantaneously removed along with its amount of free drug, but leaving behind ALL of the bound drug and the albumin. This is what happens during centrifugation (but slowly).

Now, the big question is after both the free and bound drug "re-equilibrate" is the free drug concentration changed?

In the original 1 ml aliquot of serum there was 0.001 uMoles of free drug (1 uM * 1 mL * 10^-3 L/mL) and

0.01 uMoles of total drug (10 uM * 1 mL * 10^-3 L/mL).

In removing 1/2 of the volume and only taking the free drug, we reduce the total amount of free drug to 0.0005 uMoles in 0.5 ml, which is still 1 uM.

The concentration of bound drug and of free albumin has doubled: B = 2*9 uM = 18 uM; M = 2*491 uM = 982 uM.

But all the ratios are still maintained, K = B / (M * D) = 982 / (18 * 1) = 0.0183 uM^-1.

Thus, the constituents are still at equilibrium even though half of the free drug was removed.