Antiepileptics

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5

Outline

- Introduction
- Phenytoin
- Valproic Acid
- Phenobarbital
- Carbamazepine
- Levetiracetam
- Lacosamide
- Conclusion
- Sample Calculation: Phenytoin for Loading Dose
- Summary Table: Antiepileptic Agents

Introduction

Antiepileptic medications like phenobarbital and phenytoin have been used for decades while a plethora of new agents have come to the market in the past 20 years. Some antiepileptic medications have a narrow therapeutic index or nonlinear pharmacokinetics (PK) that require therapeutic drug monitoring. Phenytoin and valproic acid (VPA), for example, exhibit nonlinear PK that can make dosing challenging. Some antiepileptic agents are metabolized, inhibited, or induce the cytochrome (CYP) P450 isoenzymes, leaving the potential for drug interactions to occur. The International League Against Epilepsy released a special report regarding requirements for therapeutic monitoring. Unfortunately, no guidance was given to the use of these antiepileptic medications in obese patients.[1] This chapter will focus on the current knowledge that exists for dosing phenytoin, VPA, phenobarbital, carbamazepine, levetiracetam, and lacosamide in obese patients.

Phenytoin

Phenytoin is used for partial and generalized seizures and is one of the first-line therapies for status epilepticus.[2] It demonstrates nonlinear (Michaelis-Menten) PK and is ~90% protein bound, mainly to albumin. Hypoalbuminemia and uremia can cause an altered free fraction, leading to possible toxicity if the dose is not corrected. Some institutions have free phenytoin levels to aid

in assessing patients with these factors.[2] The normal therapeutic range of total phenytoin is defined as 10 to 20 mg/L.

Equation 5-1, Table 5-1 shows the maintenance dosing equation based on the Ludden method.[3] There are several PK parameters that need to be understood specifically when managing phenytoin. These include V_{max}, which is the maximum rate or velocity of metabolism, and K_m, which is the concentration at which metabolism is occurring at half the maximum rate.[3] Normal population estimates for adults is a V_{max} of 7 mg/kg/day and K_m of 4.3 mg/L (some texts recommend using 5.8 mg/L for geriatrics >59 years old).[3] Please note these are population parameters and can vary greatly among individual patients. It is also important to remember which formulation of phenytoin you are using as there are two salt (S) forms that exist. The intravenous (IV) and extended-release formulation of phenytoin contains sodium, and they have an S correction factor of 0.92. The chewable tablets and oral suspension are formulated as just phenytoin and have an S = 1. The population estimate for the volume of distribution (V_d) is 0.65 L/kg. (See Table 5-1.)

Special Note: Fosphenytoin is a prodrug of phenytoin and will be combined into the below discussion.

Table 5-1. Phenytoin Equations

Equation 5-1[3]	$\text{Dose} = \frac{(V_{max})(C_{ss})(\tau)}{(K_m + C_{ss})(S)(F)}$
Equation 5-2: Adjusted body weight equation for loading phenytoin in obese patients	Adjusted body weight for phenytoin = IBW+1.33 (TBW– IBW)
Equation 5-3: Calculating a loading dose	$\text{LD} = \frac{(C_{desired})(V_d)}{(S)(F)}$
Equation 5-4: Calculating a loading dose (Method #2)	Loading dose (mg) = [14 mg/kg × (IBW)] + [19 mg/kg × (TBW– IBW)]

$C_{desired}$ = mg/L; C_{ss} = concentration at steady state; F = bioavailability (1 for phenytoin sodium); IBW = ideal body weight; K_m = concentration when metabolism is at half the maximum rate; LD = loading dose (mg); S = salt (0.92 for phenytoin sodium); τ = dosing frequency; TBW = total body weight; V_d = volume of distribution (0.65 L/kg); V_{max} = maximum rate or velocity of metabolism.

Calculating a Loading Dose

The best evidence for calculating a loading dose of phenytoin in obese subjects comes from a study by Abernethy and Greenblatt.[4] They investigated the PK effects of a single IV dose of 300 mg phenytoin over 10 minutes in 14 obese individuals (mean weight of 124 kg) and 10 control patients (mean weight of 67 kg). When adjusted based on percentage of ideal body weight (IBW), they found that phenytoin distributed greater into adipose tissue by a factor of 1.33, and thus a correction should be used (**Equation 5-2, Table 5-1**). To explain this, recall that clearance (Cl) = $k \times V_d$, where k is an elimination rate constant and inversely proportional to half-life ($t_{½}$). It may be easier to think of the equation as $Cl = V_d / t_{½}$. In the above study, there was not a statistical difference in total mean Cl. There was, however, a significant increase in mean elimination half-life with 19.9 versus 12 hours in the obese and control groups, respectively (p <0.025). Because the half-life was increased but Cl was not changed significantly, V_d must then have been affected. This was the case as the total V_d was greater in the obese group compared to the control group (82.2 versus 40.2 L, respectively; p <0.001). Thus, an adjusted body weight is used for the dosing weight (Equation 5-2, Table