Seizure Management: Pharmacokinetics and Pharmacodynamics

James C. Cloyd, PharmD, Professor, Department of Experimental and Clinical Pharmacology, University of Minnesota College of Pharmacy
Lisa Coles, MS, PhD, Associate Director, Clinical Pharmacology and Pharmacometrics, University of Minnesota College of Pharmacy

1. Introduction

Drugs are the cornerstone of epilepsy therapy. Hence, it is incumbent on those treating this disorder to have a sound understanding of the principles of pharmacokinetics (PK) and pharmacodynamics (PD), which underlie antiseizure pharmacotherapy.

A central tenant of therapy is the selection of the optimal drug and attainment and maintenance of a therapeutic dose/drug concentration for a given patient (Figure 1). The drug and dose may vary as a function of age, sex, type of epilepsy, disorder progression, genomics, medical conditions, and co-medications; but the principles of therapy apply across all epilepsies and antiseizure drugs (ASD).

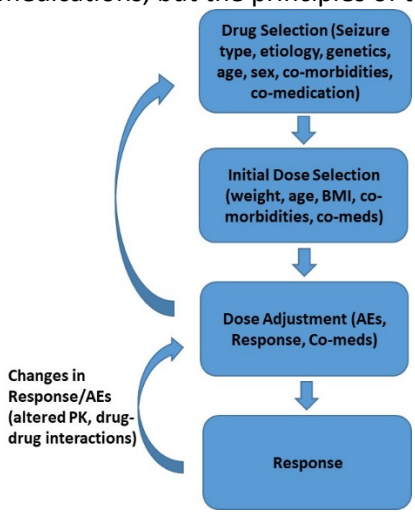

Figure 1. Scheme for Selection and Management of Anti-Seizure Drugs (ASD) Based on Drug Pharmacokinetics

As a general rule, the intensity and duration of drug effect is related to the concentration at the site of action, also known as the effect site. In most cases, measurement of drug concentration at the site of action is impossible. Hence, measurement of concentrations in an accessible site, most commonly, plasma or serum, is employed as a surrogate. Plasma/serum ASD concentrations are essential in characterizing pharmacokinetics and linking concentration to response.

This section of the curriculum will provide an introduction to the principles of PK and PD that guide ASD therapy using case examples to illustrate how these principles apply to clinical care. As an introduction on this section, consider the effect of pregnancy on response to lamotrigine therapy, which highlights PK and PD principles. Several reports have shown that women previously well controlled on lamotrigine have an increase in seizure activity during pregnancy[1,2], which is associated with decreased lamotrigine concentrations and increased clearance. This example illustrates that effective management of ASD therapy requires clinicians to anticipate alterations and prescribe dosage adjustments that maintain effective concentrations of the drug.

Pharmacokinetics is the branch of pharmacology concerned with the movement of drugs within the body or "what the body does to the drug". In this module, we describe the processes of drug absorption, distribution, metabolism, and excretion. Commonly used analyses intended to characterize PK include model independent (non-compartmental analysis) and empirical (compartmental) and physiologically-based models. Physiological factors such as saturation of drug elimination mechanisms or protein binding may be incorporated into these models.

Conversely, PD is the study of "what the drug does to the body". Here we are dealing with the reactions between drugs and living systems where we relate dose (or concentration) with response often using empirical (linear, Emax, logistical regression) or mechanistic models. A powerful approach is to utilize combined PK/PD models, which allows the prediction of response over time given a particular dose and dosing regimen.

Population modeling is an increasingly applied approach, which includes sources and correlates of variability in drug concentrations and/or response. Such models seek to identify the measurable patient-specific physiologic and pathophysiologic factors that cause changes in the dose-concentration or exposure-response relationships and the extent of these changes so that dosing can be appropriately modified.

2. Absorption

Absorption refers to the passage of drug molecules across tissues into the bloodstream. It is described by both the rate and extent of drug movement. Drug physiochemical characteristics affecting absorption include lipid and aqueous solubility; molecular size; and degree of ionization. Physiological characteristics such as absorptive surface area, membrane thickness, blood flow, pH, and tissue composition also play an important role. When considering a solid dosage form, the drug must first undergo disintegration, then dissolution in order to be absorbed. Drugs, such as ASDs, which exert their affect in the central nervous system, must possess a balance of water solubility to be dissolved and lipid solubility to cross the blood-brain-barrier. The rate of absorption is influenced by several formulation factors: 1) dosage form - an ASD drug in solution is more rapidly absorbed than the same drug given as a suspension>capsules>tablets, and 2) formulation modifications - for example, immediate- and

extended-release products. With regard to the later, the product is modified to slow the rate of absorption to minimize oscillation between peak and trough concentrations and extend dosing intervals. It is important to note that extended-release formulations do not affect the rate of drug elimination. Absorption of some drugs may also be affected by active transport mechanisms (efflux or influx). For example, gastrointestinal efflux transporters can decrease the amount of drug that is absorbed across the intestinal mucosa. As a case in point, P-glycoprotein (P-gp) and multidrug resistance transporters (MRPs) transport a number of drugs including some ASDs from the epithelium tissue back to intestine. However, due to the high permeability of ASDs, these efflux transporters do not play a major role in limiting drug absorption.

The extent of absorption describes the amount of a given drug that reaches the blood stream. The bioavailability, F, a measure of absorption, is the fraction of the administered dose that reaches systemic circulation relative to a reference. This is typically determined by comparing the total exposure (area under the concentration-time curve) following administration by a given route divided by the AUC of the same drug given intravenously. Bioequivalence is a regulatory term that is used to compare the rate and extent of two products of the same drug.

3. Distribution

Once a drug enters into systemic circulation by absorption or direct administration, it can then be reversibly distributed into tissues including the brain. Factors that govern distribution include physiochemical properties such as drug lipophilicity, size, and charge as well as blood flow and tissue composition. For example, water-soluble, but poorly lipid soluble drugs tend to remain within the blood and interstitial space resulting in relatively smaller volumes of distribution. Most ASDs, however, are relatively lipid-soluble, thus allowing distribution into tissues such as the brain. These drugs show multi-exponential decreases in plasma drug concentrations, which is due to differential distribution into body tissues.

The quantitation of drug distribution throughout the body is a theoretical construct. As calculated, the volume (Vd) describes the volume that would be necessary to contain the total amount of an administered drug at the same concentration that it is observed in the plasma. This is computed by dose / area under the concentration-time curve (AUC) x elimination rate constant (kel). Volume of distribution can be used to calculate IV loading doses where dose = target concentration x Vd. Physiological factors that can affect volume of distribution include obesity, protein concentration, and fluid volumes.

In order for drugs to reach the brain, they must first cross the blood-brain-barrier (BBB). The BBB is formed by a bi-layer of endothelial cells joined by tight junctions, which restrict the diffusion of drugs and other substances into the brain. Transport proteins are also highly expressed at the BBB to help regulate movement of molecules into and out of the brain. In general, ASDs have the requisite properties such as small molecular weight and high lipid-solubility that allow for distribution into the

brain. The ASDs with the greatest lipid-solubilities, such as benzodiazepines, are particularly useful for seizure emergencies because they rapidly distribute into the CNS. Several ASDs are substrates for efflux transporters such as P-gp, but the impact of P-gp activity on efficacy is unknown. Gabapentin is an example of an ASD that is a substrate for an influx L-type amino acid transporter at therapeutic concentrations.[3]

Protein Binding. Most drugs bind to some extent to plasma proteins such as albumin, alpha 1-acid glycoprotein (AAG), etc. In most cases, the relationship between total and unbound drug concentrations remains constant. This relationship is often expressed as the free fraction. When changes in protein binding occur, they can have complex effects on pharmacokinetics resulting in altered relationship between total and unbound concentrations as well as the exposure at the site of action. Such changes are often misunderstood and can lead to inappropriate management of drug therapy. Whether total or unbound drug concentrations are affected by altered protein binding is determined by the drug's intrinsic clearance and volume of distribution; route of administration; and the degree of binding. For ASDs that are highly bound (>90%), such as phenytoin and valproic acid, changes in protein binding can have clinical implications.

In some situations, the unbound concentrations will be higher than expected relative to the total concentrations. The protein binding of valproic acid is saturable within the therapeutic range (50-150 mg/L total) resulting in a non-linear relationship between concentration and protein binding.[4] For example, in a typical patient a total drug concentration of 50 mg/L would have an unbound drug concentration of 2.5 mg/L (free fraction = 5%), whereas, a total concentration of 150 mg/L would have an unbound drug concentration of 30 mg/L (free fraction = 20%). AAG, which is often elevated in trauma or inflammatory processes, may increase free fraction but changes in free drug concentration may be counteracted by changes in clearance.

For drug administered orally, while unbound concentrations are unchanged with altered protein binding, total concentrations may change. For example, during pregnancy, total concentration of phenytoin are significantly decreased.[5] This is the result of increased clearance due to increased free fraction of phenytoin. However, the unbound steady-state concentrations remain largely unchanged. Valproic acid may also displace phenytoin from plasma protein binding sites, thereby increasing phenytoin clearance.

Higher than expected free fractions of valproic acid and phenytoin can also occur in patients with hypoalbuminemia, and hepatic and renal diseases. Hence, monitoring of total drug concentrations can be unreliable. For highly bound drugs, unbound concentrations should be measured.

4. Elimination

Drugs are eliminated via multiple processes, which include renal, metabolic, pulmonary, intestinal, etc. They can be excreted either unchanged or metabolized. Metabolism often results in a more water-soluble compound that is inactive or less active than the parent drug allowing elimination via renal

excretion. However, in some instances the metabolic product is the active drug as is the case for fosphenytoin, oxcarbazepine and eslicarbazepine acetate. Alternatively, some metabolites are associated with adverse effects (e.g. valproic acid). Total body clearance (CL) is the primary measure of drug elimination and describes the rate at which the active drug is removed from the body. It is defined as the volume of blood from which the drug is eliminated per unit of time (for example L/hr or L/kg/hr). CL can be calculated by dividing the dose by the area under the concentration-time curve (AUC), is useful in characterizing and comparing drug elimination, and can be used to calculate appropriate doses. As an example, the dose for a constant IV infusion can be determined by multiplying the target steady-state concentration (Css) by CL. An oral dose can be calculated by the target Css x CL x dosing interval / F. These calculations assume that clearance remains constant so that at steady-state drug input equals output. Although this is true for many drugs, it is not the case for phenytoin whose metabolism is saturable at therapeutic drug concentrations. As a result, total and unbound steady-state concentrations will disproportionately increase with dose (e.g., when the dose is doubled, plasma concentrations may increase three- to five-fold or more).

Clearance is the combination of renal and hepatic elimination. Gabapentin, pregabalin, and vigabatrin are examples of ASDs that are primarily excreted renally as unchanged drug without metabolism. In most cases, an indication of renal function such as creatine clearance can be used to direct dosing of ASDs eliminated by this pathway. Renal dysfunction may require a change in dose or use of another ASD.

The majority of ASDs are metabolized to some extent by the cytochrome P450 (CYP) superfamily as Phase I reactions (oxidation) followed by Phase II reactions which include glucoronidation and sulfation. As originally coined these terms were intended to convey a sequential process; Phase I followed by Phase II. However, several ASDs, such as lamotrigine, are primarily metabolized by glucuronidation. Introduction or discontinuation of medications can affect ASD pharmacokinetics, most importantly drug clearance. Drugs or pathophysiological changes can alter clearance. In the case of drugs, metabolizing enzymes either can be induced or inhibited possibly affecting response by decreasing or increasing ASD concentrations. Such interactions are both time- and concentration-dependent. In the case of inhibitory interactions, the full effect does not occur until the inhibitor reaches steady state. Simultaneously, the affected drug's clearance will decrease and its new steady-state concentration will occur thereafter (later than inhibitor). The concentration of the inhibitor will affect the inhibition. This relationship tends to follow an Emax model and is often described by the inhibitor concentration that decreases the rate of the enzyme-catalyzed reaction by 50% and the maximum inhibition attained. Typically, inhibitory interactions require a few days to a week to produce new, higher steady-state concentrations of the affected ASD. However, an alteration in response (positive or negative) can occur within a few hours depending on the drugs half-lives and sensitivity of patient to the drug. Discontinuation of an inhibitor will follow a similar time course.

Enzyme induction interaction are also time- and concentration-dependent. The additional on an inducer triggers upregulation of one or more metabolizing enzymes. The full effect of which occurs when the inhibitor concentration reaches steady state followed by the new state-state of the induced enzyme. The time course for induction and de-induction reactions typically occurs over a few weeks.
When describing elimination, a more commonly used term is elimination half-life ($t_{1/2}$) which is a secondary pharmacokinetic parameter. It is a function of both V and CL where $t_{1/2} = CL/V$. Half-life is useful to determine the time required to reach steady state (~ 5 half-lives) and can be used to determine the optimal dosing interval.

Drug-drug Interactions. Several review articles summarize potential enzyme-mediated drug-drug interactions with ASDs.[6-9] Carbamazepine, phenytoin, phenobarbital, primidone, rifampin, and oxcarbamazepine can induce select cytochrome P450s (CYP) and glucuronyl transferase (GT) enzymes, resulting in clinically significant reductions in plasma concentration of drugs that are substrates of the same enzymes. Further, carbamazepine can induce its own metabolisms (autoinduction) resulting in decreased drug concentrations with time. At high doses, topiramate may induce CYP 2C19 and effect the metabolism of its substrates including oral contraceptive steroids. Conversely, valproic acid, rufinamide, and stiripentol and felbamate are enzyme inhibitors that may result in increased plasma concentrations of ASDs metabolized by those enzymes. Importantly, ASDs which induce or inhibit enzymes may themselves be affected by other inhibitors/inducers including other ASDs.

Lamotrigine concentrations can be decreased substantially when given with known GT enzyme inducers. Lacosamide, levetiracetam, vigabatrin, gabapentin and pregabalin have the least potential to be involved in clinically relevant enzyme-mediated drug-drug interactions. Increased monitoring of drug and concomitant drug concentrations and dosage adjustment are indicated whenever enzyme inducing or inhibiting drugs are introduced or withdrawal.

5. PK/PD

Understanding the PK of a drug is critically important in relating drug concentration to effects as combination (PK-PD) modeling is a powerful tool for optimizing doses and dosing regimens as well as guiding the design of research studies. PK/PD models allow you to predict response as a function of time given a dose or dosing regimen or conversely determine the dose or dosing interval needed to attain a given response. Drug exposure-response models are commonly used during drug development. For example, population PK models and PK/PD models were developed that describe plasma brivaracetam concentrations in adult patients with partial onset seizures and the relationship with daily seizure counts in well-controlled efficacy trials [10]. Simulations were then used to help determine dosages associated with maximal response. Rufinamide is another example in which steady-state plasma concentrations were positively correlated with a reduction in seizure frequency [11].

6. Genetic Considerations

Certain genetic-based epilepsies may dictate which drug(s) you prescribe. The most well established example is HLA testing in patients, particularly those of Asian ethnicity, who are candidates for carbamazepine [12]. Polymorphisms in transport and hepatic metabolizing enzymes may also be of relevance [13]. For example, polymorphisms in *CYP2C9* and/or *CYP2C19 have been shown to effect the PK of* phenobarbital, valproic acid, zonisamide, and clobazam. Understanding these genetic variances help clinicians in terms of drug selection, dosing, and monitoring. The importance of genomics in epilepsy drug therapy will likely grow as we learn more.

7. Special Populations

Both PK and PD are affected by a number of patient factors including age, sex, pregnancy, and concomitant medical problems. With regard to pharmacokinetics, organ maturation affects both renal and metabolic elimination. For example, newborns have a reduced rate of drug metabolizing activity with expression of various CYP 450 isoenzymes changing within the first 2 years of life. Drug distribution also changes in concert with body composition and blood proteins. In contrast, advanced age can result in diminished renal clearance of drugs and variable metabolic clearance, although this is not always the case. Women of childbearing age may have increased CYP3A4 activity. Both renal and hepatic disease can alter protein binding and clearance.

A PD example in special populations, PB causes hyperactivity in some children, whereas in older patients it causes sedation. Another example is patients taking other CNS depressants. ASDs with sedation potential taken in combination with other CNS drugs such as antidepressants and antipsychotics may have an additive or supra-additive effect.

8. References

1 Pennell, P. B. *et al.* Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. *Neurology* **70**, 2130-2136, doi:10.1212/01.wnl.0000289511.20864.2a (2008).
2 Reisinger, T. L., Newman, M., Loring, D. W., Pennell, P. B. & Meador, K. J. Antiepileptic drug clearance and seizure frequency during pregnancy in women with epilepsy. *Epilepsy Behav* **29**, 13-18, doi:10.1016/j.yebeh.2013.06.026 (2013).
3 Dickens, D. *et al.* Transport of gabapentin by LAT1 (SLC7A5). *Biochem Pharmacol* **85**, 1672-1683, doi:10.1016/j.bcp.2013.03.022 (2013).
4 Cramer, J. A. & Mattson, R. H. Valproic acid: in vitro plasma protein binding and interaction with phenytoin. *Ther Drug Monit* **1**, 105-116 (1979).
5 Tomson, T., Lindbom, U., Ekqvist, B. & Sundqvist, A. Disposition of carbamazepine and phenytoin in pregnancy. *Epilepsia* **35**, 131-135 (1994).

6 Johannessen, S. I. & Landmark, C. J. Antiepileptic drug interactions - principles and clinical implications. *Curr Neuropharmacol* **8**, 254-267, doi:10.2174/157015910792246254 (2010).
7 Patsalos, P. N. Drug interactions with the newer antiepileptic drugs (AEDs)--Part 2: pharmacokinetic and pharmacodynamic interactions between AEDs and drugs used to treat non-epilepsy disorders. *Clin Pharmacokinet* **52**, 1045-1061, doi:10.1007/s40262-013-0088-z (2013).
8 Patsalos, P. N. & Perucca, E. Clinically important drug interactions in epilepsy: interactions between antiepileptic drugs and other drugs. *Lancet Neurol* **2**, 473-481 (2003).
9 Tanaka, E. Clinically significant pharmacokinetic drug interactions between antiepileptic drugs. *J Clin Pharm Ther* **24**, 87-92 (1999).
10 Schoemaker, R., Wade, J. R. & Stockis, A. Brivaracetam Population Pharmacokinetics and Exposure-Response Modeling in Adult Subjects With Partial-Onset Seizures. *J Clin Pharmacol* **56**, 1591-1602, doi:10.1002/jcph.761 (2016).
11 Perucca, E., Cloyd, J., Critchley, D. & Fuseau, E. Rufinamide: clinical pharmacokinetics and concentration-response relationships in patients with epilepsy. *Epilepsia* **49**, 1123-1141, doi:10.1111/j.1528-1167.2008.01665.x (2008).
12 Leckband, S. G. *et al.* Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and carbamazepine dosing. *Clin Pharmacol Ther* **94**, 324-328, doi:10.1038/clpt.2013.103 (2013).
13 Saruwatari, J., Ishitsu, T. & Nakagawa, K. Update on the Genetic Polymorphisms of Drug-Metabolizing Enzymes in Antiepileptic Drug Therapy. *Pharmaceuticals (Basel)* **3**, 2709-2732, doi:10.3390/ph3082709 (2010).