Pharmacology for the Audiologist

Tracy Offerdahl, PharmD, BPharm[1] and Vallabhi Mishra, PharmD candidate[2]

ABSTRACT

The purpose of this article is to provide a brief introduction and review regarding basic principles of pharmacology, including terminology and colloquialisms, as well as pharmacokinetic and pharmacodynamic principles of ototoxic agents. As an audiology practitioner, it is more important than ever to have a working knowledge regarding the known and proposed mechanisms of action for drugs and chemicals with known ototoxicity potential. Additionally, this article provides a discussion regarding the biochemistry behind distribution, which is a major step in determining ototoxic potential of known and potential ototoxins.

KEYWORDS: pharmacokinetics, pharmacodynamics, ototoxicity, distribution, ADMET

The study and evaluation of drugs and chemicals for the audiology practitioner is more important now than ever. A review that integrates pharmacokinetics (PK), pharmacodynamics (PD), terminology, colloquialisms, and ototoxicity is warranted. As an integral part of the healthcare team, audiologists are a valuable resource to patients and other practitioners, who seek their in-depth knowledge and skills regarding whether an audiologic manifestation may be caused by a chemical. Even more significant is the potential for this review to provide the knowledge and skills necessary for an audiologist to recognize and prevent an ototoxic effect (or other adverse reaction) of a chemical.[1–3]

Some points of clarification: pharmacology as a discipline sometimes uses many terms to describe the same thing. For the purposes of this article, you will see chemical, drug, and medication used to describe a compound that may have therapeutic or toxic effects. Generally, one may refer to a drug or medication as a product that has been studied in animals and/or humans and is used for therapeutic purposes, whereas the term chemical is sometimes used to describe a compound that is in clinical trials or that has no known therapeutic beneficial effects in humans (e.g., insecticides). Since pharmacology is biochemistry at its core, all these terms will be used.

[1]Osborne College of Audiology, Salus University, Elkins Park, Pennsylvania; [2]Temple University School of Pharmacy, Philadelphia, Pennsylvania.

Address for correspondence: Tracy Offerdahl, PharmD, BPharm, Osborne College of Audiology, Salus University, 8360 Old York Road, Elkins Park, PA 19027 (e-mail: tofferdahl@salus.edu).

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Biotransformation and metabolism will be used interchangeably to indicate the breakdown step in the PK process. Clearance, elimination, and excretion will be used interchangeably to describe the removal of the drug from the body, as the terminal step in the PK process. Lastly, side effect and adverse effect/event will be used interchangeably to describe the risks associated with giving a drug, whereas toxic effect will predominantly describe a more severe event following the administration of a drug or chemical.

The study of pharmacology is an extension of chemistry. There is no way to separate the two concepts. However, a practitioner need not be adept at chemistry to effectively discuss and utilize basic pharmacology skills in patients. Having a working knowledge about basic pharmacology is a major key to becoming a proactive practitioner.

Two important subclasses include PK and PD. PK consists of four steps: absorption, distribution, metabolism (biotransformation), and clearance (elimination, excretion), and is sometimes abbreviated as the acronym ADME. It specifically refers to the evaluation of a drug or chemical's timeframe as it moves through these four steps and is defined as what the body does to the drug or chemical as it goes from input (absorption) to output (excretion/elimination/clearance).[2,4–8]

Author John Hodgson references a slightly different acronym, ADMET, where T (i.e., toxicological potential/problem) is added to the original acronym. Hodgson states, "A chemical cannot be a drug, no matter how active nor how specific its action, unless it is also taken appropriately into the body (absorption), distributed to the right parts of the body, metabolized in a way that does not instantly remove its activity, and eliminated in a suitable manner – a drug must get in, move about, hang around, and then get out."[4] This is an interesting addition, as Hodgson says that drugs that make it to market and drugs that never make it to market all have a potential for dangerous toxicologic manifestations. How very true. PD refers more specifically to what the drug or chemical does to the body. In other words, it refers to the mechanism of action that produces the efficacy and toxicity of the agent. From an audiologic perspective, one tends to spend more time in the PD arena, as ototoxicity lies squarely under the umbrella of this definition. This article will describe how this is possible from an anatomic, physiologic, and pathophysiologic perspective.[2,4–8]

Absorption is the first step in the PK process. When a PO drug is swallowed and lands in the stomach, the major event that must take place is dissolution of the drug from the dosage form. In other words, a drug must be liberated or freed from its dosage form to be absorbed (e.g., capsule, tablet). This liberation step is the major factor in determining the *RATE* and even the *EXTENT* of absorption of a PO drug. For example, if a drug is meant to be taken on an empty stomach, then taking it with food will likely slow down the absorption (i.e., decrease the rate) and/or decrease the amount (i.e., decrease the extent) of the drug that will end up in the bloodstream. This may result in subtherapeutic blood levels.[3–8]

Looking at it from the opposite perspective, the rate and extent of a PO medication may be drastically increased if taken with a hot liquid (e.g., swallowing a morphine tablet with hot coffee or tea). This example may result in supratherapeutic blood levels that may be deadly. Additionally, chewing or splitting a PO drug that is intended to be swallowed whole may result in loss of activity due to destruction by stomach acid or a deadly load of the drug being absorbed all at once. This last example is particularly true of long-acting PO drugs that are taken once per day. In general, a drug should be taken according to manufacturer directions, as they are meant to optimize absorption of an agent in an individual patient. Parenterally administered drugs (e.g., IV, IM, SC) are generally unaffected by the stomach contents and will be addressed later in this article.[3,5–8]

When a drug is given orally (PO), it must cross the biologic membranes of the gut (usually the beginning of the small intestine) where it then dumps into the liver via the portal vein. Here, the drug compound may undergo hepatic extraction (first pass effect) and/or biliary excretion before reaching the systemic circulation. The main purpose of this extraction is to begin the breakdown process (metabolism/biotransformation) to prepare the drug for clearance/elimination.[3,5–9]

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The first pass effect has no impact on parenterally administered agents, as they enter the venous circulation without going through the portal vein, which is one of the main reasons why oral drug doses are many times higher than a parenteral dose of the same agent. Once absorbed, the fraction of drug reaching the systemic circulation is known as bioavailability (F). Bioavailability (Fig. 1) describes how much of a PO dose is biologically available to exert an effect in the body, both therapeutically and as an adverse effect. In other words, F represents the fraction of drug given (i.e., absorbed) that reaches the bloodstream. For example, IV medications have an F = 1, as they circumvent absorption all together because they are injected directly into the systemic circulation. Conversely, most PO medications have an F that is less than 1, as the body has already begun the metabolism/biotransformation (e.g., first pass effect) and clearance/elimination steps by the time the medication reaches the systemic circulation. Most other routes of administration have a bioavailability that is somewhere in between the bioavailability of PO and IV medications, with most parenteral routes and sublingual (SL) administration having an F close to 100%. Once a drug is systemic, it can be distributed to the therapeutic site of action and to potential sites that produce side effects, including ototoxicity.[3,5–9]

When a drug or chemical reaches the systemic circulation, there are several detours that a drug may take; so, a discussion that looks at the PD process of the drug-receptor complex is warranted. Why do some drugs improve symptoms like vertigo or motion sickness, whereas other drugs cause adverse effects like ototoxicity, hepatotoxicity, or nephrotoxicity? More specifically, why do some antibacterials treat meningitis, endocarditis, or pneumonia, while other antibiotics do not treat these infections? The simple answer to these questions is because the drugs *get there*. They distribute to these areas (which will be discussed in the next section) and once they get to these areas, they have the ability to exert an effect. That effect might be therapeutic (i.e., benefit the patient) or it might cause a side effect (i.e., risk of taking a drug). This is precisely why a practitioner

F = amount of drug reaching the systemic circulation

amount of drug given (in a single dose)

Example 1: "drug A" is given to a patient as a 500mg PO capsule; after the patient swallows the drug, blood samples are drawn at 0.5, 1, 2, 4, 6, 8, 10 hours after ingestion of the drug. The average of the 7 samples is put into the equation:

F = 195mg (average of the amount of "drug A" in blood samples) = 0.39

500mg (the PO dose of "drug A" given to patient

Explanation: "F" of a PO dose of "drug A" is 39%

Example 2: "drug B" is given to a patient as a 1,000mg IV bolus dose; 8 blood samples are drawn at 5, 10, 20, 30, 45, 60, 75, and 90 minutes after the dose is injected. The average of the 8 samples is put into the equation:

F = 1.000mg (average of the amount of "drug B" in blood samples) = 1

1,0000mg (The IV dose of "drug B" given to patient

Explanation: "F" of a IV dose of "drug B" is 100%

Figure 1 Bioavailability ("F").[5,6,16]

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must always think in terms of risk versus benefit and efficacy versus toxicity when any agent is used. When a drug enters the systemic circulation, it finds a place to fit, and this is many times onto a receptor.[1–3,5–7,9–14]

When a drug binds to a receptor to activate it or produce a biologic response, it is known as an agonist. On the contrary, some drugs bind to a receptor to simply block a response or reverse a response and are known as antagonists. A competitive antagonist can be overcome by increasing the dose of the agonist, whereas a noncompetitive antagonist interferes with an agonist differently and therefore simply increasing the dose of the agonist would have no effect. While there are multiple types of drug-receptor responses, a detailed explanation for all of them is beyond the scope of this discussion. In general, the strength of the drug-receptor complex can be described graphically as a dose–response curve and as a higher or lower affinity. This drug-receptor complex is vital in the clinical trial evaluation of drugs, where minimum doses, maximum doses, and dosing intervals are generally determined.[1–3,5–7,9–14]

Once a drug is absorbed into the systemic circulation, consideration is given in terms of how subsequent doses are to be given. To have predictable serum concentrations, distribution, and even efficacy, drug dosing should follow recommendations for dosing amounts and dosing intervals.

Serum concentrations refer to blood levels of a drug in this particular discussion. Blood flow to the target tissue or organ is a very significant consideration, as highly perfused areas (e.g., lungs) allow the body to clear a drug faster and therefore may need to be dosed with higher amounts and/or more often. Additionally, two concepts play a vital role in absorption, distribution, and dosing: serum half-life ($t_{1/2}$) and concentration steady-state (Css). $T_{1/2}$, as a unit of time, represents the time it takes for drug plasma concentrations to decrease by 50%. While the $t_{1/2}$ typically is referring to measurement in the plasma, terminal $t_{1/2}$ refers to secondary (i.e., deep) body tissues or compartments where a drug may be distributed other than the plasma. Terminal $t_{1/2}$ typically takes a longer amount of time for a drug to clear. For example, gentamicin generally has a serum $t_{1/2}$ of 2 to 3 hours, whereas its terminal $t_{1/2}$ may be 50+ hours because the drugs accumulate and sit in the inner ear and in renal parenchyma. This is a major issue in the nephrotoxicity and ototoxicity associated with gentamicin and other aminoglycoside antibiotics.[1,3,5,6,8,15,16]

Css indicates that concentrations of drug in plasma will be steady, and is achieved when drugs are administered at a constant rate, which is typically determined by $t_{1/2}$. Most PK models suggest that a drug can be considered to be at Css after five $t_{1/2}$s have passed. Some drugs can be given as a loading dose, which bypasses the five $t_{1/2}$ rule, as a loading dose can typically bring the plasma drug concentrations to Css after a single dose. Maintenance doses are repetitive doses that are typically given in the same amounts and in the same intervals to maintain Css. Css relies on an important assumption, which is for each dose of drug given, another dose of drug is being eliminated at an equal rate and amount. Therefore, if a patient is unable to eliminate a drug, then Css will not be maintained as serum levels will begin to increase and potentially cause toxicity.[1,3,5,6,8,15,16]

Another important term that is evaluated once a drug has been absorbed is called the therapeutic index, which is an indication (represented as a ratio) of the safety of a drug. This ratio represents the ratio between the lowest systemic concentration associated with toxicity and the lowest systemic concentration associated with therapeutic benefit or efficacy. In short, a drug with a high therapeutic index is considered to be safer than a drug with a low therapeutic index. This term is generally used along with therapeutic range, which is an extension of therapeutic index and refers specifically to plasma drug concentrations. It evaluates and quantifies the range of plasma concentrations between therapeutic and toxic blood levels.[1,3,5,6,8,15,16]

Similar to the therapeutic index, drugs with a large therapeutic range are generally considered to be safer than those with a small/narrow therapeutic range, as there is more distance between plasma levels that are therapeutic versus toxic. For practical application, this generally means that drugs with a narrow therapeutic range tend to be potentially more toxic and intense monitoring and follow-up is generally required. With some drugs, measuring plasma drug concentrations helps

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ensure efficacy while limiting toxicity. Additionally, with medications like aminoglycosides and vancomycin, practitioners measure peak and trough levels. Peak refers to the highest concentration of a drug in the bloodstream, usually measured shortly after administration of an IV medication. Trough or pre-dose concentration refers to the concentration of a drug in the bloodstream, usually measured a short time before the next dose of an IV medication is given. Theoretically, these terms would also hold true for other routes of administration (e.g., IM, PO, SL); however, there are currently no drugs available that routinely require this type of monitoring.[1,3,5,6,8,15,16]

Throughout the body, PK distribution describes the movement of drugs and chemicals into areas outside of the blood stream and is therefore a very important PK parameter in terms of describing drug delivery. Distribution is, however, described as apparent in pharmacology, as it is referring to an apparent volume that the drug is occupying inside of the body. The volume of distribution (Vd) seeks to relate the amount of drug inside the body compartment(s) to the concentration (C) of drug in the bloodstream. In other words, it gives an estimated value that describes/quantifies how a drug partitions between the plasma and tissues. Vd is apparent because these volumes are estimated/extrapolated based on the chemical characteristics of the drug as well as the chemical characteristics of every tissue and compartment in the body.[5,6,9]

Once a drug reaches the systemic circulation, it is distributed throughout various fluids (e.g., intracellular and extracellular) in the body on its way to reach target tissues. Target tissues refer to areas where drugs/chemicals exert an effect, either therapeutically or as a toxicity. Although this may seem like a simple process, the vasculature is quite distinct depending on location, and multiple physicochemical properties of molecules and membranes are involved. In many cases, drugs leave the systemic circulation and move into local tissues from postcapillary venules. This basic distribution is frequently a passive diffusion. Another more complicated diffusion principle of a drug is traversing biologic membranes which tend to be hydrophobic, and there are layers of mechanisms for how some drugs are able to complete this process.[5,6,9,13,14,16]

When comparing the various passive or active diffusion models, a common theme boils down to biochemistry principles of the drug and the biologic membranes. Chemical properties of drugs that impact distribution include molecular weight, lipophilicity (fat soluble), and hydrophilicity (water solubility). Distribution of a drug is not a random, unpredictable process. On the contrary, distribution is fairly predictable once a practitioner understands the basic biochemistry that helps determine it. For example, aminoglycoside antibacterials (e.g., tobramycin, gentamicin, amikacin) are predominantly hydrophilic. Hydrophilic chemicals tend to have a smaller distribution as they do not tend to move out of the bloodstream into other tissues as much as a lipophilic chemical. On the contrary, lipophilic drugs like some opioids (fentanyl) deposit into adipose tissue and then slowly seep out over a long period of time. In terms of molecular weight, smaller chemical compounds tend to distribute outside of the bloodstream more than very large, heavier chemicals. When both concepts are put together, we see that a small, fat-soluble drug has a wider distribution than a large, water-soluble drug. While this is generally a correct and reliable assumption, a brief discussion regarding how distribution is determined is helpful.[5,6,9,13,14,16]

It is important to keep in mind that distribution refers to all areas of the body, including tissues/organs that may help eliminate a drug (e.g., liver and kidney) or noneliminating tissues or organs (e.g., brain, muscles, and lungs). PK studies and academic writings tend to represent Vd in compartments such as total body water, extracellular water, blood plasma, and adipose tissue (i.e., fat). Additionally, the concept that certain areas of the body receive no drug (e.g., blood–placenta barrier, blood–brain barrier (BBB), blood–testicular barrier) is a historic and disproven theory. While these tissues or organs may have a small amount of a chemical when compared with other areas of the body, the concept of a complete "barrier" is no longer valid. Looking at the body from a two-compartment model helps explain this "barrier" concept by evaluating the rate and duration of drug distribution. The central compartment includes well-

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perfused tissues and organs like the heart, kidney, brain, and liver. Due to increased blood flow in this compartment, drugs are able to perfuse and equilibrate within a relatively short period of time. Even though the central compartment is well perfused, drug distribution into the central nervous system (CNS) is slightly more complicated due to the BBB. In general, the BBB contains very tight junctions that are specifically there to protect the CNS from foreign substances, including drugs. From a biochemistry perspective, small, hydrophobic drugs can most easily pass through the biologic membranes of the BBB. If this does not work, then a drug must use existing transport proteins in the BBB to try to penetrate into the central compartment.[1–3,5–14,16,17]

The second compartment is the peripheral compartment and is composed of less-perfused organs like the adipose tissue and skeletal muscles. Due to decreased blood flow, drugs generally take longer to equilibrate. In addition, the adipose tissues can act as a storage site. In short, drugs that tend to stay in the blood stream have a relatively low Vd, whereas drugs that move into fat, muscle, and other fairly nonvascular sites have a relatively high Vd. One last drug/biochemical concept that can decrease Vd is plasma protein binding to albumin, which is the most abundant protein in human plasma. While drug binding to albumin is considered to be a drug interaction, it is a distribution concept. Highly protein-bound drugs tend to stay in the blood stream which can impact their ability to distribute to a tissue binding site outside of the vasculature. While this is significant on paper, PK and PD studies have shown this to be fairly predictable and the dose of highly protein-bound drugs generally takes this into consideration. What may be significant and applicable in patients is the competitive nature of highly protein-bound drugs. When two (or more) highly protein-bound drugs are present in the blood stream at the same time, they compete for albumin-binding sites. The danger is that a highly protein-bound drug like warfarin can be "bumped" off of albumin when a second highly protein-bound drug is ingested (e.g., aspirin). This allows more free warfarin in the blood stream (because it has been "bumped" off of albumin) and a potential bleeding disaster may ensue. Interestingly, scientists have discovered that many times the drug that has been bumped off of the albumin and present in much higher serum concentrations is not always the disaster that one would expect, as the body has the unique capability of increasing the metabolism and elimination of this sudden increase in free drug. Appropriate monitoring for efficacy and toxicity is crucial when patients are simultaneously taking more than one highly protein-bound drug.[1–3,5–14,16,17]

Drugs also can be distributed into several other special compartments which often have poor access due to the structure of the organ or tissue, such as the inner ear. Unlike the rest of the body, the PK and delivery of drugs in the inner ear is unclear. The PK of drug delivery and distribution into the inner ear is a complex and intricate process. Accumulation of data in the past has shown that drugs given both systemically or topically can slowly diffuse through the fluid spaces throughout the different regions of the ear. Some of the commonly used antibiotics such as aminoglycosides have been shown to be acutely ototoxic to the auditory and vestibular regions of the ear, often leading to irreversible damage to hearing. The method of drug delivery can play a crucial part for the distribution of the drug to the target tissue. From a therapeutic perspective, adequate delivery of medication to the inner ear has been a challenge for physicians due to the intricate physiology of the ear. Drugs can be distributed within the inner ear from three different entry points: round window membrane, oval window, and cochlear bone via application in the middle ear. A blood–cochlear barrier (similar to the BBB) can limit the concentration of the drug actually being delivered to the inner ear and therefore systemic drug delivery may be inadequate for many inner ear disorders.[1,3,5,6,8,17–19]

Almost immediately after a dose of a drug is given, irrespective of route of administration, the body begins the process of drug clearance for hydrophilic drugs, or the preparation of a drug for clearance if it is chemically more hydrophobic/lipophilic. This can be a stressful physiologic process for the body, whose view of homeostasis is myopic at best. In other words, the human body's main goal is to maintain homeostasis from millisecond to millisecond,

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and it essentially has no capacity to understand why a drug would be inserted into its systems or tissues that it views as running perfectly fine at all times. This includes illness, as our bodies have sophisticated systems and mechanisms in place to handle every potential scenario (e.g., allergic reaction, cancer, bacterial infection), and the body is never happy that a drug has come along to take one of its jobs. Our bodies always think that dysfunction is better handled endogenously rather than exogenously (i.e., drug); so, the physiologic and anatomic stress that ensues when multiple drugs are taken each day is likely immeasurable over time, and every dose of a drug likely induces an internal panic as the body works to get rid of the drug or drugs as fast as possible.

This is the essence of drug metabolism/biotransformation: to terminate any pharmacologic/biologic activity of a drug and/or to make a drug more water soluble for elimination via the kidneys. As such, it is not surprising that drugs tend to leave the body from the blood stream first, then muscle, and then adipose tissue (i.e., hydrophilic to lipophilic, respectively). To reach the last stop in the body (i.e., elimination/clearance/excretion), drugs that are more lipophilic and/or have a high molecular weight must be metabolized/biotransformed first. Because of the human body's rigid desire to maintain homeostasis and eliminate a drug that it never wanted in the first place, it has several systems and mechanisms in place to make ready a drug or drugs for renal elimination. Multiple tissues/organs have some ability (usually enzymatic) to biotransform drugs into more urine-friendly structures, including the liver, lungs, skin, gut, and kidneys. However, the liver is the primary organ for metabolism/biotransformation, particularly those drugs that are hydrophobic/lipophilic.[1,4–7,16,17,20]

Metabolism and biotransformation is not a one-size-fits-all scenario; so, the body is prepared to handle many different types of compounds. Enzymatic degradation and/or conversion of the drug structures are the major events that take place, typically through hydrolysis, oxidation, or reduction. For example, Phase I reactions are many times referred to as oxidation or reduction reactions, as the primary purpose of these reactions is to terminate any pharmacologic activity.

A Phase I reaction takes a parent compound and breaks it down into metabolites that are more hydrophilic. A metabolite, which is the breakdown chemicals of a drug, can either be pharmacologically inert or it can have modified activity (e.g., active metabolite). If these metabolites are still not sufficiently hydrophilic enough to leave in the urine, one or more additional metabolic reactions/steps may be required. Phase II reactions are known as conjugating or hydrolysis reactions as it takes a parent compound (i.e., it has not been broken down) or a metabolite from a Phase I reaction and converts it to a water-soluble compound to make the drug or metabolite more likely to meet the hydrophilic-only requirements of the urine.[1,4–7,16,17,20]

A well-known system that exists under the Phase I category is known as the cytochrome P450 (CYP450) enzyme system (Fig. 2). This enzymatic system is categorized as a metabolic drug interaction because it occurs as drugs are being biotransformed and readied for elimination in the blood stream. Drugs that utilize the CYP450 system are categorized as a substrate (i.e., the targeted drug), an inhibitor, or as an inducer. An inhibitor will inhibit the biotransformation of a substrate, resulting in an increase in the blood concentrations of the substrate, potentially causing a toxic blood level of the substrate. An inducer will increase the biotransformation of a substrate, resulting in a decrease in the blood concentrations of the substrate, and a potential unanticipated failure in therapy. A couple of common isoenzymes that break down individual agents include 3A4/5, 2C9, 2C19. It is a competitive drug interaction, and two or more drugs must be using the same isoenzymes (e.g., 3A4/5) for biotransformation for the metabolic drug interaction to occur. In other words, if one drug utilizes CYP450 3A4/5 isoenzymes and a second drug utilizes 2C19 isoenzymes for biotransformation, there will not be an interaction.[1,4–7,16,17,20]

One additional consideration in the metabolism or biotransformation of drugs is the type of PK reaction that is occurring. If it is a fairly predictable reaction where a doubling of a dose results in the doubling of blood or serum concentrations, then it is termed first-order kinetics and is, in essence, linear. Most medications

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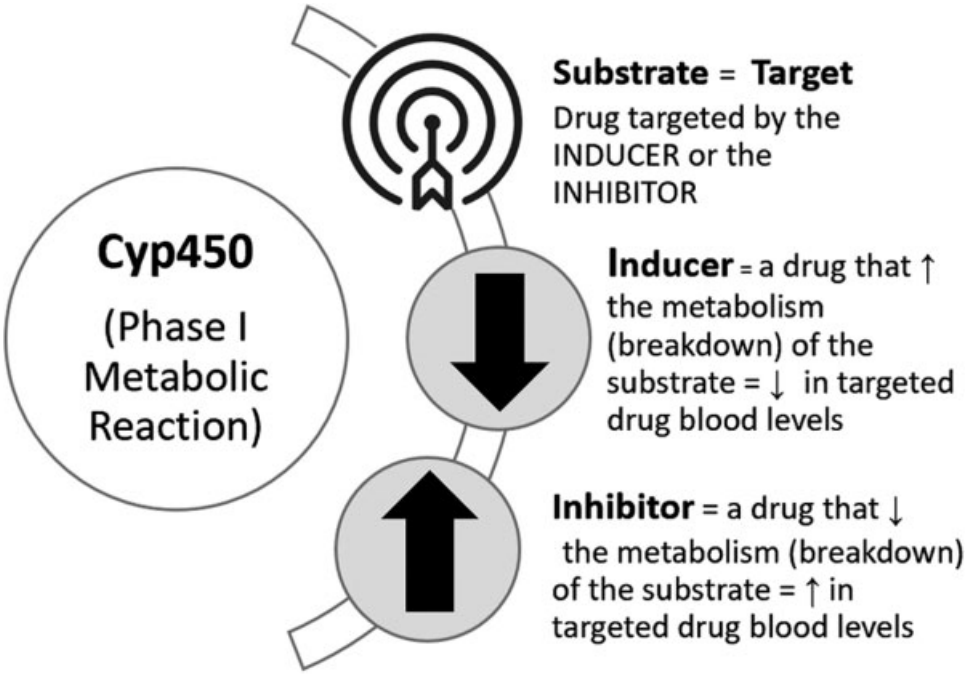

Figure 2 Cytochrome P450 enzyme system drug interactions.

follow first-order/linear kinetics, which makes these agents fairly predictable, as the amount of drug that is biotransformed or excreted per unit of time is proportional to the amount of drug in the serum concentration at that time. In short, as a drug dose increases, blood concentrations increase at the same concentration and rate, and metabolism/elimination occurs at the same rate. When plotted on a semilogarithmic graph, this results in a straight line which is why this common PK metabolism/elimination is most well known as linear. Zero-order kinetics are much less common. The best example under this model is alcohol. When alcohol is initially ingested, it follows first-order (i.e., linear) kinetics. Once the metabolic capacity of the enzymes that biotransform alcohol is saturated, then blood/serum concentrations may quickly become toxic because the body continues to remove a constant amount of the alcohol (or any zero-order kinetic drug) per unit of time; however, the amount of alcohol in the blood stream continues to rise.[1,4–7,12,16,17,20,21]

The final, terminal step of this long journey of a drug through the body is clearance/elimination. While the purest definition of elimination is the sum of any organ involved in the elimination of drug from the body, the vast majority of drugs leave the body as a terminal step in the urine, with a small number leaving via biliary extraction and then in the stool. Biochemically, drugs that leave in the urine are water soluble (hydrophilic) and have a small molecular weight, either as the original (parent) compound or as a metabolite. Because most drugs follow the first-order kinetic model, the simple definition of clearance refers to the volume of plasma fluid that is cleared of drug or metabolite per unit of time. Many times the clearance is estimated and this is called estimated creatinine clearance (estClCr). This simple calculation utilizes patient-specific information, including serum creatinine, because it is a by-product of skeletal muscle metabolism that is cleared at a constant rate via the kidneys. Once calculated, the estClCr estimates the glomerular filtration rate of the kidneys, which also estimates the ability of the body to renally clear a drug. The clearance of the drug is the single most important step in the PK process in determining Css. In other words, if the clearance of a drug is impaired, then Css is not steady and blood and tissue concentrations can

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rise to dangerous or even deadly levels. For some patients, particularly the elderly or those with chronic kidney disease, a small decrease in renal elimination can result in large increases in drug exposure. Most ototoxic agents fall into this category, as they are known/presumed to have an increase in ototoxic potential when renal function is diminished. This list includes the aminoglycosides, vancomycin, cisplatin, aspirin, and loop diuretics. If a body cannot clear a drug, then that drug will hang around and do nothing good. This is where many of our toxic drug concentrations occur. Relating back to $t_{1/2}$ and Css, it is of interest to note that if a drug is at Css, then when the last dose is given the "wash-out" period occurs. Assuming the drug follows first-order kinetics, then it will take approximately five $t_{1/2}$ for the drug to completely leave the body. This concept is useful in a situation where a patient is experiencing an adverse drug reaction or toxicity (e.g., ototoxicity), as it allows the practitioner to predict when the drug will be completely cleared from the body.[2,5,6,9,12,21,22]

The gravity of utilizing ADMET is an extremely complicated and important set of tasks; however, as practitioners with unique skills and experiences, we have the tools necessary to make good decisions for our patients. As long as we remember that our first job is truly *primum non nocere* (i.e., first do no harm), which Hippocrates so boldly stated in the 5th century, then we will make excellent decisions as practitioners. The use of a drug can sometimes seem to the patient and the practitioner like a random lottery ticket or rolling the dice regarding our choices. Every time a drug is used, there is the real chance of unpredictability, which is why it is so important to understand the basics of how a drug moves through the body, the unique biochemical characteristics of an individual drug, and how a patient, their habits, and comorbidities have an impact on that drug. We must do our part to control the controllable, rather than our patient care and drug use becoming completely random.[4–6,23]

CONFLICT OF INTEREST
None.

REFERENCES

1. Hitchings AW. Monitoring drug therapy. Medicine (Baltimore) 2016;44(07):427–432
2. Mouton JP, Njuguna C, Kramer N, et al. Adverse drug reactions. Medicine (Baltimore) 2016;95(19): e3437
3. Maxwell SRJ. Pharmacodynamics for the prescriber. Medicine (Baltimore) 2016;44(07):401–406
4. Hodgson J. ADMET–turning chemicals into drugs. Nat Biotechnol 2001;19(08):722–726
5. Fan J, de Lannoy IA. Pharmacokinetics. Biochem Pharmacol 2014;87(01):93–120
6. Buxton IO. Pharmacokinetics: the dynamics of drug absorption, distribution, metabolism, and elimination. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13th ed. New York, NY: McGraw-Hill; 2007
7. Rey JA. Pharmacodynamics and pharmacokinetics. In: Winter ME, ed. Basic Clinical Pharmacokinetics. Vancouver, WA: Applied Therapeutics, Inc; 1994:1–18
8. Abdel-Rahman SM, Kauffman RE. The integration of pharmacokinetics and pharmacodynamics: understanding dose-response. Annu Rev Pharmacol Toxicol 2004;44:111–136
9. Lee DH. One-compartment open model: intravenous bolus administration. In: Shargel L, Yu AC. eds. Applied Biopharmaceutics & Pharmacokinetics, 7th ed. New York, NY: McGraw-Hill. Available at: http://accesspharmacy.mhmedical.com.ezproxy.pcom.edu:2048/content.aspx?bookid=1592&sectionid=100669650. Accessed October 7, 2018
10. Daneman R. The blood-brain barrier in health and disease. Ann Neurol 2012;72(05):648–672
11. Buck TP, Trahan HP, Wendel OT. Pharmacotherapeutics and patient factors. In: Campbell KCM, ed. Pharmacology and Ototoxicity for Audiologists, 1st ed. Clifton Park, NY: Thompson Delmar Learning; 1997
12. Récoché I, Rousseau V, Bourrel R, et al. Drug-drug interactions with imatinib: an observational study. Medicine (Baltimore) 2016;95(40):e5076
13. Sun H, Zhao H. Physiologic drug distribution and protein binding. In: Shargel L, Yu AC, eds. Applied Biopharmaceutics & Pharmacokinetics, 7th ed. New York, NY: McGraw-Hill; 2012
14. Schmidt S, Gonzalez D, Derendorf H. Significance of protein binding in pharmacokinetics and pharmacodynamics. J Pharm Sci 2010;99(03): 1107–1122
15. Receptor theory. In: Stringer JL, ed. Basic Concepts in Pharmacology: What You Need to Know for Each Drug Class, 5th ed. New York, NY: McGraw-Hill. Available at: http://accesspharmacy.mhmedical.com.ezproxy.pcom.edu:2048/

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content.aspx?bookid=2147&sectionid=161350965. Accessed November 1, 2018
16. Baca QJ, Golan DE. Pharmacokinetics. In: Golan DE, Tashjian AH, Armstrong EJ, Armstrong AW, eds. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012
17. Swan EE, Mescher MJ, Sewell WF, Tao SL, Borenstein JT. Inner ear drug delivery for auditory applications. Adv Drug Deliv Rev 2008;60(15): 1583–1599
18. Salt AN. Pharmacokinetics of drug entry into cochlear fluids. Volta Review 2005;105(03):277–298
19. Liu H, Hao J, Li KS. Current strategies for drug delivery to the inner ear. Acta Pharm Sin B 2013; (02):86–96
20. Taniguchi C, Guengerich P. Drug metabolism. In: Golan DE, Tashjian AH, Armstrong EJ, Armstrong AW, eds. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012
21. Pirmohamed M. Pharmacogenetics for the prescriber. Medicine (Baltimore) 2016;44:412–415
22. Rischel WA, Kearns GL, eds. Pharmacogenetics and pharmacogenomics. In: Handbook of Basic Pharmacokinetics…Including Clinical Applications, 7th ed. American Pharmacists Association; 2009
23. Furberg BD, Furberg CD. What are the strengths of randomized controlled trials? In: Furberg BD, ed. Evaluating Clinical Research: All That Glitters Is Not Gold, 2nd ed. New York, NY: Springer Science; 2007

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