Practical Pharmacokinetics and Pharmacodynamics

41

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Abbreviations

α	Distribution half-life
AUC	Area under the curve
β	Terminal half-life
Cl	Clearance
Cmax	Maximum concentration
Cmaxss	Steady-state maximum concentration
Css	Steady-state concentration
CYP	Cytochrome P450
F	Bioavailability
*f*T>MIC	Free concentration time above minimum inhibitory concentration
ICU	Intensive care unit
Ke	Elimination constant
LD	Loading dose
LOS	Length of stay
MIC	Minimum inhibitory concentration
PD	Pharmacodynamics
PK	Pharmacokinetics
PK/PD	Pharmacokinetics and pharmacodynamics
TDM	Therapeutic drug monitoring
T1/2	Half-life
T>MIC	Time above mean inhibitory concentration
Vd	Volume of distribution

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Introduction

The physiological responses to surgery, critical illness, and subsequent resuscitation can alter both pharmacokinetics (PK) and pharmacodynamics (PD) [1]. As a result of these changes, pharmacotherapy may need to be altered to produce the desired outcomes. A basic understanding of the principles of pharmacokinetics, or the movement of drugs in the body, and pharmacodynamics, the cells responses to drugs, is needed to maximize pharmacotherapy [2]. This chapter will review basic pharmacokinetic and pharmacodynamic principles and some changes in the critically ill surgical patient.

Pharmacokinetics

Pharmacokinetics is the process by which drugs are absorbed, distributed, metabolized, and eliminated by the body. It relates to the concentration of drug in the blood and various body parts and how drug moves through the body over time. These principles dictate drug dose and dosing interval, and understanding them will aid the clinician in medication selection, dosing, and appropriate monitoring. The four main pharmacokinetic parameters used in PK models are bioavailability (F), volume of distribution (Vd), half-life (t1/2), and clearance (Cl). In simple PK modeling, the one-compartment model assumes a drug enters into a compartment with a given volume of distribution to achieve a homogenous concentration and is subsequently eliminated based on an elimination rate constant (ke). Vasoactive catecholamines such as epinephrine and norepinephrine follow one-compartment PK model. The two-compartment model aligns better with what actually occurs in the body clinically. It accounts for a second compartment mimicking tissues and organs. A drug enters into a central compartment and distributes between the central and peripheral compartments [3]. For some very lipid soluble drugs, such as amiodarone, there are three or four compartment PK models that also account for adipose tissue. Despite underlying assumptions to simplify these

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Table 41.1 Basic pharmacokinetic equations

	Equation
Half-life	0.693/ke
Elimination constant	$(\ln C1 - \ln C2)/(t1 - t2)$
Maximum concentration	C1/[ê - ke(t1)]
Minimum concentration	$Cmax\left[\hat{e} - ke(\tau - t')\right]$
Volume of distribution first dose	Dose/Cmax
Volume of distribution steady state	$D\left(1 - \hat{e} - ke(t')\right)/\left[t'ke\left(Cmax - Cmin * \hat{e} - ket'\right)\right]$
New maximum concentration steady state	$D\left(1 - \hat{e} - ket'\right)\right]/\left[t'keVd\left(1 - \hat{e} - ke\tau\right)\right]$

C1 concentration one, *C2* concentration two, *Cmax* maximum concentration, *Cmin* minimum concentration, *ke* elimination constant, *t1* time one, *t2* time two, *t'* infusion duration, τ (*tau*) dosing interval

models, they are clinically useful in predicting drug concentrations (Table 41.1).

The bioavailability of a drug is the fraction of the administered dose that reaches systemic circulation of the patient. A drug with 100 % oral bioavailability achieves a systemic concentration comparable to that of the intravenous route when the drug is administered at the same dose. Drug properties such as the chemical and dosage form impact absorption as well as patient factors. An oral solution, for example, may have greater bioavailability than a solid formulation such as a capsule or tablet as it has already undergone the dissolution phase. The first-pass effect, metabolism by enzymes in the liver or gut wall occurring prior to the drug entering systemic circulation, will also affect bioavailability. Medications which undergo extensive first-pass metabolism will have a lower bioavailability, although it could also be increased in the setting of liver impairment [4]. Sublingual administration of some medications, such as tacrolimus, has enhanced bioavailability since first-pass metabolism is bypassed. Medications with low oral bioavailability either need to be dosed higher or administered using alternate routes. Physiologic factors such as ileus may be another reason for use of alternate routes in the critically ill population. These alternate routes including rectal, subcutaneous, or transdermal administration are not without disadvantages such as unpredictable serum concentrations. Dosing conversions between intravenous and alternate formulations depend on the bioavailability. Medications with high bioavailability such as levetiracetam have a one-to-one conversion from intravenous to oral, whereas it is generally accepted to dose oral furosemide twice that of the intravenous form because of its lower bioavailability. Most PK studies are conducted in young healthy males, and as a result there are little data on how bioavailability may or may not be affected in critically ill surgical patients.

Volume of distribution (Vd) is a theoretically derived PK parameter that corresponds to the lipophilicity of a specific drug. Typically, drugs with higher Vd are more fat-soluble. The amount of bound and unbound (free) drug in the plasma versus tissues relates not only to bioavailability but also to Vd. Only the unbound drug has a pharmacologic effect. It is a hypothetical volume relating the total amount of drug in the body to plasma concentration, but is not associated with a true physiologic space. Apparent Vd could be a greater value than what is physiologically reasonable. A large Vd thus indicates extensive tissue distribution [3]. For example, amiodarone has a Vd of 60 L/kg due to it being extremely fat-soluble. A small volume indicates that a large proportion of drug is confined to the plasma and does not readily distribute to tissues. Vasoactive catecholamines are examples of drugs with small Vd. The degree and rate of distribution depends on tissue perfusion and protein binding among other factors. For example, amiodarone is typically loaded when used for atrial arrhythmias because it has a large volume of distribution. A continuous infusion is typically started after the loading infusion because amiodarone rapidly distributes out of the plasma into tissues. Another example of extensive distribution is midazolam. Although it readily crosses the blood-brain barrier and therefore has a quick onset of action, it also has a shorter duration of action rendering it useful for procedures. On the other hand, aminoglycosides are hydrophilic and have a small volume of distribution and the VD may be affected by total body water. Volume of distribution should be considered when determining dosing weight for weight-based medications, especially in obese patients where there is a large disparity between actual body weight and ideal body weight. There are numerous factors affecting Vd, and some factors include age, total body water, acid-base imbalances, and protein binding [5].

Medications with a large Vd may warrant a loading dose (LD) in order to achieve adequate serum concentrations. Amiodarone is one such example as well as vancomycin. Typically loading doses are used to quickly fill up the volume of the space. They do not need to be altered due to problems with elimination such as renal failure with vancomycin [4]:

$$LD = Css \times Vd$$

Digoxin is the exception to the "rule." A typical loading dose is 15 mcg/kg, but in critically ill patients or those with renal insufficiency, there is altered protein binding leading to a decreased volume of distribution and thus increased plasma drug concentration. Typically half the normal loading dosage is sufficient in these patients [6].

The elimination of a drug by the body is called clearance and the main routes of clearance are renal, hepatic, and biliary. Other routes of clearance include the reticuloendothelial system and plasma enzymes. Clearance is measured by the amount of drug cleared over a unit of time. In first-order kinetics, which a majority of drugs follow, clearance is proportional to drug concentration. In other words, the rate of elimination will proportionately increase with increases in drug concentration. Total drug clearance is the sum of all routes of clearance such as renal clearance, hepatic clearance, and biliary clearance. Depending on the extent of each type of elimination for a particular drug, dose adjustments may be warranted in the setting of organ impairment. For example, digoxin is primarily renally excreted, necessitating a decrease in dose with renal impairment. In contrast, diltiazem has negligible renal excretion, so the dose does not need to be adjusted in the case of renal impairment. Cisatracurium and remifentanil are considered to have organ-independent metabolism since cisatracurium relies on nonenzymatic degradation in the blood for metabolism, and remifentanil is rapidly metabolized by blood and tissue esterases.

Clearance also estimates the drug concentration over time or area under the curve (AUC) based on the dose. Dosing strategies used may have the same AUC with different peak effect. It is influenced by bioavailability, dose, dosing interval, and clearance:

$$AUC = Dose / Cl$$

For example, intravenous acetaminophen was shown to have the same AUC as oral acetaminophen despite reaching a higher peak concentration.

Half-life is the period of time required for the amount of drug in the body to be reduced to one-half of a given concentration. It is dependent on volume of distribution and clearance:

$$t1/2 = \left(0.693 \times Vd\right) / Cl$$

The half-life is directly proportional to Vd and inversely proportional to Cl. Drugs with very fast clearance such as norepinephrine have very short half-lives because they are metabolized by the blood enzymes, monoamine oxidase, and carboxy-O-methyltransaminase. It has a short half-life of 2–2.5 min and therefore has a small Vd. Amiodarone, on the other hand, is very lipid soluble and has a long half-life of approximately 60 days based on its large Vd. Half-life is clinically relevant in determining dosing interval since it indicates how quickly drug concentration decreases over time. Generally, drugs with shorter half-lives are dosed more frequently or continuously. Critically ill patients may develop renal impairment, so the dosing interval would be extended to account for the longer half-life. In some cases, drugs with short half-lives such as esomeprazole may not be dosed as frequently due to the longer pharmacodynamic effects that persist.

As a general rule, a drug is at approximately 90 % of its steady state at 3.3 half-lives and at approximately 100 % of steady-state concentration at five half-lives. A drug is completely eliminated from the body in approximately five half-lives irrespective of dosage itself. It takes this same amount of time to reach a steady-state concentration whereby peak and trough concentrations converge and the amount of drug entering the body matches the amount being eliminated over a period of time. Peak concentration is the highest concentration within one dosing interval and trough concentration is the lowest. A loading dose may be administered to maintain therapeutic concentrations prior to the steady state being reached.

Some drugs such as vasopressors follow the one-compartment model, but most drugs follow the two-compartment model including antibiotics. These drugs with more than one compartment have both a distribution phase (α), or distribution half-life, and an elimination phase (β), or terminal half-life. The distribution phase generally consists of a shorter half-life, but the drug will be nearly entirely distributed throughout the body after five half-lives also [3, 4]. In the case of amiodarone, because of its lipophilicity, a bolus dose will be distributed into the tissues rapidly in contrast to its long terminal half-life, necessitating a continuous infusion to maintain an adequate serum drug concentration.

The liver plays a major part of metabolism and drugs that are metabolized by the liver can undergo a variety of pathways. Phase 1 metabolism occurs via the cytochrome P (CYP) enzyme system and phase 2 metabolism occurs via glucuronidation. Glucuronidation is a more fundamental process than oxidation by the complex CYP enzyme system. There are numerous CYP enzymes responsible for drug metabolism. Common enzymes include CYP3A4, 2D6, 2C9, and 2C19 [7]. The CYP3A4 enzyme metabolizes over 50 % of medications [8]. Medications may be metabolized through more than one pathway. There is a higher risk of drug-drug interactions for medications that are substrates, inducers, or inhibitors of common enzymes. There is potentially a major drug-drug interaction between carbamazepine and phenytoin. Carbamazepine can induce CYP2C9- and CYP2C19-mediated phenytoin metabolism, and phenytoin can induce CYP3A4-mediated carbamazepine metabolism. Interactions based on enzyme induction may have a delayed onset

compared to inhibition because of the time needed for enzyme synthesis.

Genetic polymorphisms and other factors can also affect function of the CYP enzyme system. The resulting phenotypes are defined as poor, intermediate, extensive, and ultrarapid metabolizers [8]. In the case of patients who are deficient in CYP2D6, they would have inadequate analgesia with codeine, a prodrug whose activity is dependent on its conversion to the active metabolite, morphine. Ultrarapid metabolizers, on the contrary, may develop serious side effects from codeine based on excessive morphine plasma concentrations. Warfarin has a multitude of drug-drug interactions as well as altered metabolism based on variations of the CYP2C9 and VKORC1 genes. Genetic polymorphisms can impact response to clopidogrel therapy, a platelet P2Y12 receptor blocker, resulting in clopidogrel treatment failure. Hypo-responsiveness, or platelet resistance, may result in a patient being switched to a more potent thienopyridine such as ticagrelor or prasugrel. There are assays available to determine the degree of platelet inhibition from the use of P2Y12 inhibition drug therapies [9].

Another source of drug interactions can arise based on altered protein binding. Drugs that are highly protein bound at the same sites may compete with one another for the limited binding sites. This is the case with phenytoin and valproic acid in which concurrent use may result in altered levels. In addition this partially explains why the interaction is unpredictable.

Changes in Pharmacokinetics in Surgical ICU Patients

The physiological response to surgery and critical illness and the resultant fluid resuscitation can alter the pharmacokinetics of drugs in critically ill surgical patients [1]. The resultant trauma from surgery and response to critical illness may lead to changes in renal, hepatic, and cardiovascular systems and significant changes in protein binding and intravascular volume. As a result, patients are often fluid resuscitated and may require many liters of fluid. In these patients there may be an increase in total body fluid and for drugs that have small volumes of distribution and distribute to the extracellular space, such as aminoglycoside and beta-lactam antibiotics, a result increase in Vd with a decrease in concentrations [1]. Therefore larger dosages may be required during this acute phase. As the patients get better and mobilize the fluids and diuresis, the volume of distribution will return to normal and the dosage may need to be modified especially with the aminoglycosides. In addition there are changes in plasma protein homeostasis that may affect distribution especially of unbound drug. Albumin in particular is decreased during critical illness, and drugs that are highly protein bound such as phenytoin may have altered pharmacokinetics. Conversely there can be a relative increase in acute phase proteins such as alpha-glycoproteins which may affect drugs such as morphine and lidocaine [1].

There are little data describing the absorption of drugs in critically ill surgical patients. Changes in gastric motility, intestinal permeability, and motility are thought to affect drug absorption. Critically ill surgical patients are affected by these and surgical complications such as fistula development or short gut syndrome. In general, most drugs are absorbed in the small bowel but a few drugs such as warfarin are absorbed in the stomach and can be administered to patients with short gut. As it is hard to determine if the gut is working, one may have to determine this based on clinical response. For example, a patient that is both tachycardic and on high end of normal blood pressure, the addition of enteral diltiazem to intravenous metoprolol may result in a significant decrease in heart rate and signify that the diltiazem is being absorbed.

The clearance of drugs may also be significantly altered in the critically ill. Most drugs are eliminated either hepatically or renally, and in states of shock blood is shunted away from these organs potentially decreasing elimination. Furthermore, hypoxia can decrease hepatic enzyme activity, especially the cytochrome P450 system. Finally the use of renal replacement therapies, which are common in the ICU setting, can increase clearance of some drugs.

Pharmacodynamics

The relationship of the drug concentration and pharmacologic responses is termed pharmacodynamics [2]. It is also been defined as *what the drug does to the body* [10]. Although this is somewhat similar to pharmacokinetics, it differs in that the change in drug effect is usually not proportional to the change in drug dose or concentrations [2]. Since pharmacokinetics and pharmacodynamics are related, it may be difficult to explain the difference. Using loop diuretics, such as furosemide, as an example, there can be both a pharmacokinetic and pharmacodynamic reason to diuretic resistance [11]. Furosemide is secreted into the nephron by the organic acid pathway. To be actively secreted into the nephron, a threshold concentration of furosemide needs to be achieved, and if there is significant gut edema present, this may not occur with oral administration of furosemide. This is the pharmacokinetic reason for diuretic resistance and it can be overcome by giving intravenous furosemide that should result in diuresis. In cases where intravenous furosemide does not achieve adequate diuresis, there may be a pharmacodynamic change in the patient that may be the cause of diuretic resistance. With chronic use of loop diuretics, there is a higher sodium concentration than normal in the distal tubules, and as a result there is hypertrophy of the distal tubules causing more sodium and in turn water reabsorption than normal. This pharmaco-

dynamic response can be overcome by administration of concomitant thiazide diuretic that works in the distal tubules.

The most basic pharmacodynamic concept is the pharmacologic response produced by a drug as a result of the drug's binding to the receptor. This explains why a pharmacologic response may lag behind the drug pharmacokinetic concentrations. Take the sedative dexmedetomidine as an example. Dexmedetomidine is an alpha-2a agonist that produces "cooperative sedation" in the critically ill patient by decreasing norepinephrine concentrations [12]. Dexmedetomidine has a half-life of 2–3 h. Although the product labeling suggests the use of a loading infusion followed by a continuous infusion, clinical studies have shown that the use of loading infusion does not increase onset of sedation. By understanding the pharmacology of dexmedetomidine and its pharmacodynamics this makes sense. As dexmedetomidine binds to the alpha-2a receptor, it blocks norepinephrine reuptake, and thus the norepinephrine is inactivated by plasma enzymes to produce a decrease in norepinephrine concentrations. Since the half-life of norepinephrine is between 2 and 5 min, it will take four to five half-lives for the norepinephrine to be metabolized or approximately 20 min, which happens to be the onset of dexmedetomidine. As dexmedetomidine does not by itself metabolize norepinephrine, it does not matter if initially there is a high or low concentration of dexmedetomidine at the alpha-2a receptor; it is the pharmacodynamic response that is needed.

Pharmacodynamics is often applied by the use of sophisticated models, especially during the development phase to help determine drug-dosing regimens [2, 13]. These models are often complex and may contain many linked mathematical sub-models [13]. Although used in the drug development process, these models are often not used in clinical practice. The use of complex pharmacokinetic and pharmacodynamic (PK/PD) modeling is being increasingly used to help maximize and individualize pharmacotherapy. Basically PK/PD models have been developed to combine both principles of PK and PD to describe the effect-time course directly resulting from administration of a fixed dose of the drug [13]. The main value of the PK/PD modeling is to extrapolate relation between the effect-time course from existing data [13]. Many studies are now using complex PK/PD modeling, most notable with antibiotics to help improve efficacy in this time of increasing antibiotic resistance [14]. Pharmacokinetic and pharmacodynamic modeling is also being applied to other classes of medications such as antifungals and analgesics [13, 15, 16].

The ultimate goal of PK/PD is maximize a drug-induced effect or changed in physiologic parameter [13]. Especially in critically ill surgical patients, the physiologic baseline values are not constant. It is often difficult to quantify efficacy based on PK/PD models and surrogates often are used [13]. As a result it is necessary that the surrogate parameter needs to correlate with the desired effect. Using dexmedetomidine again as an example, the sedation effect is a result of decreased norepinephrine concentrations in the synaptic cleft between the presynaptic and postsynaptic neuron. As it is very difficult to measure this, so surrogates are often used, most notably mean arterial pressure and heart rate. Although heart rate typically correlates with the decrease in norepinephrine concentrations, mean arterial does not. As the concentration of dexmedetomidine increases, it loses selectivity for the alpha-2a receptor, a vasodilator, and also binds to the alpha-2b receptor, a vasoconstrictor. As it is very difficult to measure this, surrogates are often used, most notably mean arterial pressure and heart rate. Although heart rate typically correlates with the decrease in norepinephrine concentrations, mean arterial does not. As the concentration of dexmedetomidine increases, it loses selectivity for the alpha-2a receptor, a vasodilator, and also binds to the alpha-2b receptor, a vasoconstrictor. This results in higher mean arterial blood pressure from baseline so use of mean arterial as a surrogate of efficacy would not be useful in PK/PD modeling for dexmedetomidine.

There are four common PD modes used based on steady-state concentrations [13]. They are fixed effect model, linear model, log-linear model, and E_{max} model. In the fixed effect model, it relates a certain concentration of a drug with the statistical likelihood of a predefined effect (Table 41.2). An example of this model would be the development of ototoxicity with gentamicin therapy when the trough concentration exceeds 4 mcg/mL for greater than 10 days [13, 17]. In the linear model, there is a direct correlation between the drug concentration and drug effect. In this model doubling the dosage of a drug and thus the concentration would double the effect seen. The linear model is most intuitive, but it rarely applies to most drugs [13]. More common than the linear model is the log-linear model where the desired effect is linear when compared to the logarithm of the drug concentration. With all things being constant, this was used to relate synthesis of prothrombin complex activity with the concentration of warfarin [13, 18]. When the curve produced by the log-linear model is hyperbolic in shape, then one has the E_{max} model. This model is based on the receptor theory relationship and explains when a concentration of a drug is below the EC50; increasing the dosage typically increases the effect. An example of this is increasing the dosage of amlo-

Table 41.2 Pharmacodynamic model equations

Model	Equation
Fixed effect model	$E = E_{\text{fixed}} \text{ if } C > C_{\text{threshold}}$
Linear model	$E = m \times C + E_0$
Log-linear model	$E = m \times \log C + b$
E_{max} model	$E = (E_{max} \times C)/(E_{50} + C)$

C concentration, E effect, E_0 baseline effect without any drug, E_{50} 50 % of the maximal effect, E_{max} maximal effect of drug

dipine from 5 to 10 mg and then seeing an increase in the blood pressure-lowering effect. When the concentration exceeds the EC50, increasing the concentration of the drug only produces small changes in the effect. This can be seen when increasing amlodipine from 10 to 20 mg, as the changes in blood pressure are minimal.

Pharmacokinetic/Pharmacodynamic Modeling

With the decrease in new and novel antibiotics being developed and available for use worldwide, complex PK/PD modeling is increasing being used to help maximize antibiotic therapy (Table 41.3) [14]. The PK/PD modeling takes into account the concentration-time response achieved in a patient and the effect in this case is on the bacteria [14]. With antibiotics the minimum inhibitory concentration (MIC) is used to determine susceptibility to an antibiotic. It is the minimum concentration that inhibits visible growth of a microorganism. Although the use of broth dilution is the gold standard for determining MIC, it is labor intensive and not routinely used in clinical practice. Automated systems such as Vitek-2 or Microscan are commonly used. Since these are commercially available, they cannot be modified and may estimate the MIC. *E*-test is a less labor-intensive method than broth dilution to assess exact MIC by using a test strip that is impregnated with an exponential gradient of the antibiotic. Use of *E*-test is restricted to those antibiotic strips supplied by the *E*-test manufacturer, and since the MIC is based on ocular inspection it may be subjective. As a result, there may be differences in reported MIC by various testing methods, therefore the MIC may not be a good PD parameter to characterize concentration-effect relationships.

In general antibiotics are bactericidal or bacteriostatic [14]. Bactericidal antibiotics kill bacteria, while bacteriostatic agents stun bacteria to prevent growth and allow the patient's immune system to kill the bacteria. Beta-lactams and aminoglycoside are examples of bactericidal agents, while linezolid is an example of a bacteriostatic agent. Bactericidal agents can also be broken into two subgroups: time-dependent killing and concentration-dependent killing. Time-dependent antibiotics effectively kill bacteria at the same rate as long as the concentration is above the MIC. Beta-lactam antibiotics are an example of time-dependent killing, and it does not matter if the concentration is at the MIC or 1,000 times the MIC. For concentration-dependent antibiotics, there is more effective or faster killing of the bacteria with high concentrations of antibiotics. Examples of antibiotics that are concentration dependent include the aminoglycoside or fluoroquinolones. Area under the curve, AUC, and maximum concentrations, Cmax, are often used with these concentration-dependent antibiotics and are represented by AUC/MIC and Cmax/MIC [14].

The use of simulations with PK/PD modeling is a potential powerful tool to select the optimum dosing regimen to maximize the efficacy of antibiotics [14]. In 2001, Drusano and colleagues introduced Monte Carlo, a stochastic, simulation to antibiotic PK/PD modeling [19]. In these simulations the probability of target attainment above the MIC is simulated from a large population and is simulated, and the proportion of subjects above the identified target is computed form a range of MIC and dosing regimens [14, 19]. Based on the results, the probability of target attainment based on the MIC and dosing regimen is determined. The use of simulation with PK/PD modeling, such as Monte Carlo, has increased dramatically since the turn of the century, and it is even used by the European Committee on Antibiotic Susceptibility Testing to set clinical breakpoints for antibiotics susceptibility [14, 20].

Based on these PK/PD models and simulation changes, many alternative antibiotic dosing regimens have been developed [21]. For time-dependent antibiotics, such as beta-lactams, efficacy is optimized when the free concentration above the MIC (*f*T>MIC) for 60–70 % of the dosing regimen (Table 41.4) [22]. In most cases antibiotics are either administered as a loading infusion followed by continuous infusion (e.g., nafcillin 2 g over 60 min followed by 0.5 g/h) or extended infusion (e.g., cefepime 2 g over 3–4 h every 8 h). Although these alternative regimens are based on population parameters, it is unknown if they truly improve clinical outcomes. In 87 patients with *Pseudomonas aeruginosa* bacteremia or pneumonia where 63 % were in the ICU at the onset set of infection, Bauer and colleagues reported the use of extended-interval cefepime regimen (2 g over 4 h every 8 h) versus traditional cefepime (2 g over 30 min every 8 h) was associated with significant lower mortality (3 % versus 20 %, $p = 0.03$) and median ICU length of stay (8 versus 18.5 days,

Table 41.3 Basic pharmacokinetic and pharmacodynamic models for antibiotics and antifungals

Model	Equation
Area under the inhibitory curve (AUIC)	AUC/MIC
Concentration-dependent model	Cmax/MIC
Time-dependent model	$T >$ MIC
Free concentration time-dependent model	fT > MIC

AUC area under the curve, *Cmax* maximum concentration, *fT* free concentration over time, *MIC* minimum inhibitory concentration, *T* time

Table 41.4 Pharmacokinetic and pharmacodynamic effects of beta-lactam antibiotics

Drug class	Time > MIC for bacteriostatic effect	Time > MIC for bactericidal effect
Penicillins	30 %	50 %
Cephalosporins	40 %	70 %
Carbapenems	20 %	40 %

MIC minimum inhibitory concentration

$p = 0.04$) [22]. More studies are needed especially with pathogens with higher MIC organisms and ICU patients to determine the true efficacy of these alternative dosing regimens.

For concentration-dependent antibiotics such as aminoglycosides (amikacin, gentamicin, and tobramycin), the use of high-dose extended-interval dosing (i.e., 7 mg/kg tobramycin q24–28 h based on renal function) has been promoted [23]. This is based on the PK/PD models with the goal to obtain a Cmax/MIC >10 with the first dose. This parameter has been demonstrated to have a quicker resolution of infection in the general population with less nephrotoxicity than traditional dosing. In ICU patients due to changes in volume of distribution and variability in clearance, the target attainment (Cmax/MIC > 10) may be difficult to achieve. In addition it will be harder to attain this goal for pathogens with higher MICs, and they are more likely to occur in the ICU than the general units.

Not only has PK/PD modeling been used to maximize antibiotic therapy, it also is being used to maximize antifungal therapy [16]. Most of the data are with the triazole antifungals (e.g., fluconazole) with *Candida* infections. Studies have demonstrated that triazole have time-dependent killing that is optimized at one to two times the MIC and that there is a prolonged suppression of growth following therapy. The best PK/PD model for the triazole is AUC/MIC [24–26]. In this case for *Candida* species with higher MICs, a higher dosage is required [24–26]. As AUC is the concentration over time curve, increasing the dose will increase the AUC, and dose/MIC has been used when describing the effect of triazole on candidemia as the AUC/MIC and dose/MIC correlate to each other. In a study of 77 patients with candidemia including 29 ICU patients, treated with fluconazole, those that survived had significant higher dose/MIC ratio and a trend to higher AUC/MIC ratio suggesting that maximizing them improves mortality [26]. This explains why higher dosages, such as 800 mg a day, are used in *Candida* infections in which there is a higher MIC (e.g., 8–16 mg/L). It is also thought that for triazoles active against *Aspergillus* species, such as voriconazole, the PK/PD is best described by AUC/MIC [16]. In a study of 51 patients with invasive mycoses, there was a significant reduction in lack of response when the trough level exceeded 1 mg/L compared to those with a trough less than 1 mg/L (12 % versus 46 %, $p = 0.02$) [27].

Similar to aminoglycosides, the echinocandins (anidulafungin, caspofungin, and micafungin) and amphotericin B formulations exhibit concentration-dependent killing. They are also best described by Cmax/MIC in which large doses are given less frequently [16]. These agents also produce a significant prolonged suppression of growth. Unlike the triazoles, there is little PD data with these agents in humans. With amphotericin B studies have demonstrated that there is increased killing when concentrations are two to ten times above the MIC. Unfortunately infusion-related adverse effects and toxicities are a problem with amphotericin B formulations, especially the deoxycholate formulation.

Drug Classes

Nondepolarizing Neuromuscular Blockers

Nondepolarizing neuromuscular blocking agents are used during procedures and as continuous infusion in the critically ill [28]. They are competitive antagonist of the nicotinic receptor and block acetylcholine from binding to the nicotinic receptors. They are divided into two classes the aminosteroid compounds and the benzylisoquinoliniums. The aminosteroid compounds include pancuronium, vecuronium, and rocuronium. These agents have significant renal and hepatic elimination and can accumulate in renal or hepatic insufficiency [28]. The benzylisoquinoliniums include atracurium and cisatracurium which are eliminated in by plasma hydrolysis and Hofmann elimination. These agents are the preferred agents for continuous infusions in critically ill with hepatic or renal insufficiency [28].

Opiates

Intravenous opioids are the mainstay for analgesia in the surgical ICU and are considered first-line therapy [29]. The most commonly used opiates include morphine, hydromorphone, and fentanyl, while methadone and remifentanil are occasionally used. With the exception of remifentanil that is metabolized by ester hydrolysis in the plasma, all opioids are metabolized in the liver and some have active metabolites. Morphine and hydromorphone are glucuronidated, but morphine has active metabolites that are eliminated renally. Morphine can accumulate in hepatic or renal insufficiency. Meperidine has an active metabolite that is eliminated renally, normeperidine, and is known to lower seizure threshold and limits it use. Fentanyl has no active metabolites but undergoes dealkylation and accumulates in hepatic failure. With prolonged use fentanyl can accumulate in adipose tissue and have prolonged elimination. Methadone has dual mechanism of action on both the mu and N-methyl-D-aspartate receptors. It also has unpredictable PK/PD and elimination half-life of 15–60 h. Conversely due to its rapid clearance, remifentanil has an elimination half-life of 3–10 min.

Sedatives

Sedatives are also commonly used medications in the surgical ICU, and like opioids there are PK differences among them [29]. The most commonly used agents are propofol,

benzodiazepines, and dexmedetomidine. Propofol is a sedative-hypnotic that is highly lipid soluble. As a result it is has an extremely short onset of action, 1–2 min, as it readily crosses the blood-brain barrier. It has a large Vd due to its lipid solubility and therefore a prolonged half-life. With short use its half-life is 3–12 h and with prolonged use it has a half-life of over 50 h.

The common used benzodiazepines include lorazepam and midazolam and to a lesser extent diazepam. Both midazolam and diazepam are highly lipid soluble, oxidized via the cytochrome P450 system, and have a quick onset of action of 2–5 min [29]. They also have active metabolites, which are eliminated renally. Midazolam has a shorter half-life of 3–11 h, while diazepam is 20–120 h. Due to accumulation from their high VD, the half-life is longer with prolonged use. Conversely, lorazepam is less lipid soluble and has a longer onset of action of 15–20 min. It is glucuronidated in the liver and does not have any active metabolites. It has a half-life 4–15 h. Similar to lorazepam, dexmedetomidine is glucuronidated and does not have any active metabolites. Its half-life is 2–3 h [12].

Anticoagulants

Heparin and low molecular weight heparins, such as enoxaparin and dalteparin, are commonly used anticoagulants for both prophylaxis and treatment of venous thromboembolism in the surgical ICU [30]. Heparin is a large molecular and is eliminated by the reticuloendothelial system with a volume of distribution closely mirrors that of total blood volume [31]. Obese and morbidly obese critically ill patients required higher dosages of therapeutic heparin than the non-obese critically ill patients [31]. Conversely low molecular weight heparins and fondaparinux, a pentasaccharide, are smaller than heparin and eliminated predominately renally [30]. Their use in patients with renal insufficiency may lead to accumulation and increased bleeding. Recently, newer oral anticoagulants are available in the United States and include the direct thrombin inhibitor, dabigatran, and the anti-Xa inhibitors, apixaban, edoxaban, and rivaroxaban. Dabigatran cannot be crewed or crushed. At the time of writing, there are not good laboratory markers for anticoagulation or a reversal agent available. All these newer anticoagulants are eliminated between 25 and 40 % unchanged in the urine, and clinical studies excluded the use in patients with creatinine clearance less than 30 ml/min. Therefore the agents should be used with extreme caution or not at all in most surgical ICU patients.

The parenteral direct thrombin inhibitors, argatroban and bivalirudin, are often used as anticoagulants for patients with suspected or confirmed heparin-induced thrombocytopenia [32, 33]. Argatroban is mainly metabolized in the liver and eliminated in the feces through the biliary system, although the half-life is short in healthy males (39–51 min) but is unpredictably prolonged in patients with hepatic or renal insufficiency and during critical illness [33]. In a study of 73 critically ill patients, 21.9 % developed bleeding complications including 9.6 % with major bleeding. Risk factors included major surgery, total bilirubin 3 mg/dl, weight >90 kg, and baseline platelet <70,000/mcL [33]. Bivalirudin has a half-life of 25 min in healthy volunteers and is eliminated predominately through serum proteases (80 %) and unchanged in the urine (20 %) [32]. Studies have demonstrated that as renal function worsens, the dosing of bivalirudin decreases linear fashion, and it is removed by hemodialysis by approximately 25 % [34, 35]. The use of a bivalirudin nomogram in 65 critically ill patients demonstrated a similar rate of bleeding as the argatroban study of 30 % with 10.7 % developing a major bleeding [32]. Caution should be used with the use of either agent in critically ill surgical patients. Initial dosages may need to be decreased, and frequent monitoring may be required.

Proton Pump Inhibitors

Proton pump inhibitors are commonly used medications in the ICU for both prevention and treatment of gastric bleeding. Critically ill patients typically have more acid secretion than healthy patients and have potential for altered pharmacokinetics such as gut edema, luminal stasis, and decreased blood flow [36, 37]. The half-life of proton is relatively short, 2–3 h, but they bind irreversibly to gastric proton pump, which allow daily dosing for prevention of stress-related mucosal bleeding. Olsen and Devlin demonstrated that the use of enteral lansoprazole compared to IV was associated with lower bioavailability (76 %); probably for the reasons above, the PD effects demonstrated significantly higher average gastric pH over 24 h and average time for pH to be greater than 4 [37].

Levetiracetam and Lacosamide

In recent years, the use of levetiracetam and lacosamide for the treatment of seizures has increased. This is partially due to some favorable effects such as minimal drug interaction and linear pharmacokinetics, unlike fosphenytoin or phenytoin [38]. Levetiracetam and lacosamide are both relatively small molecular weight that have small Vd and low protein binding. They have excellent bioavailability and are eliminated unchanged in the urine. In a PK study in 12 neurocritical care patients, levetiracetam was demonstrated to have faster clearance and shorter half-life than studies in healthy volunteers. Therefore higher dosages administered every

12 h (1,500–2,000 mg) or smaller dosages (100 mg) every 8 h may be needed [39]. Although PK studies with lacosamide are currently lacking, it is expected to have similar PK profile as levetiracetam. In addition both of these medications are expected to be significantly removed by continuous renal replacement therapy.

Therapeutic Drug Monitoring

The therapeutic range of a drug is based on the minimum therapeutic concentration and the minimum toxic concentration observed. Not all drugs have an established therapeutic range, limiting drug monitoring using drug levels in some cases. Drugs with an established narrow therapeutic window such as phenytoin may be more closely monitored to ensure safety compared to those with a wider therapeutic window. In fact, some drugs with narrow therapeutic windows such as theophylline, a methylxanthine, are no longer used in favor of ones with wider therapeutic windows, such as caffeine for apnea of prematurity. Selective serotonin reuptake inhibitors (SSRIs) may be favored over tricyclic antidepressants for this same reason.

Therapeutic drug monitoring (TDM) can be used both for efficacy and safety purposes. It is the monitoring of medication concentration in the plasma. Most drug levels measure total drug concentration, including both bound and unbound drug. Some drugs that are highly protein (albumin) bound, such as phenytoin, may also be measured as an unbound or free level. In many cases TDM is relevant for medications with narrow therapeutic windows to ensure efficacy and prevent toxicity. There may be an increased need for TDM in critically ill patients due to physiologic changes such as acute kidney injury as well as fluid shifts that would affect medication concentrations differently than expected.

Not all medications have interpretable levels. For example, it is not clear at what level levetiracetam has optimal efficacy and may differ among patients. Some levels may take time to return if the assay is not available at the particular institution. Monitoring of low molecular weight heparin involves drawing an anti-Xa level 4 h following dosage administration. However, it may take several days for the result to return, at which time a clinical decision may be made whether a dosage change is needed.

Therapeutic drug monitoring does not replace overt clinical monitoring such as signs and symptoms of bleeding or clotting. Most drugs require peak and/or trough levels for TDM. Vancomycin is a commonly monitored antibiotic that requires trough levels to be drawn. It is important to recognize that TDM relating to pharmacokinetics does not necessarily correlate with the pharmacodynamics. Regardless of therapeutic vancomycin trough levels, if a patient is exhibiting persistent signs and symptoms of infection despite perceived adequate therapy, vancomycin therapy failure should be considered in the differential.

Conclusion

A basic understanding of PK and PD principles is necessary in critically ill surgical patients to help maximize efficacy and minimize adverse effects. In the complex environment of the surgical ICU, alterations in PK parameters can be multifactorial and be constantly changing. Likewise PD changes frequently occur. As a result of these alterations in PK and PD parameters, development of alternative dosing methods may be needed to optimize drug therapy.

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