



Pharmacologic issues in the critically ill

Vidya Krishnan, MD^a, Patrick Murray, MD^{b,*}

^aDepartment of Internal Medicine, West Suburban Hospital Medical Center, 3 Erie Court, L700, Oak Park, IL 60302, USA

^bDepartments of Clinical Medicine, Anesthesia and Critical Care, and Clinical Pharmacology, Section of Nephrology, MC 5100, University of Chicago Hospitals, 5841 South Maryland Avenue, Chicago, IL 60637, USA

Individualization of therapeutic interventions is the cornerstone of critical care medicine. Application of pharmacologic principles can guide the design of a rational drug regimen to achieve rapid and beneficial effects while minimizing adverse events (Fig. 1). Choosing a drug and dosing regimen is particularly challenging in critically ill patients, who have changes in drug disposition and effect resulting from drug-patient, drug-disease, and drug-drug interactions. After a rational drug regimen is implemented, therapeutic drug monitoring is necessary to ensure maintenance of the desired outcome while monitoring for potential toxicity and adverse events. Finally, tools to reduce medication errors in the intensive care unit (ICU) should be considered to maximize patient safety.

Drug disposition and dosing in the critically ill

Bioavailability and route of administration

The chosen route and delivery system for administration of a drug to a critically ill patient are determined by factors such as the onset, reliability, and titratability of available preparations. Gut dysfunction and the contrasting reliability of the intravenous (IV) route commonly result in parenteral administration of

drugs in the ICU, but with increased emphasis on enteral feeding, oral administration is increasingly an option. There are two major factors to consider with respect to drug absorption, the extent and the rate of absorption by various routes. The extent of absorption, or bioavailability (F), describes the fraction of administered drug that reaches the central circulation unchanged. Drugs that are administered by the IV route have complete bioavailability (F = 1.0). For all other routes of administration, F is less than or equal to 1.0 because of incomplete absorption, and, for some enterally-administered drugs, because of pre-systemic metabolism. Specifically, enterally-administered drugs that are absorbed between the stomach and the colon may be subjected to presystemic metabolism (or “first pass metabolism”) before entrance into the systemic circulation. Gastrointestinal flora, intestinal enzymes, and hepatic enzymes can alter parent drugs and render them inactive (as in the case of morphine or propranolol), or activate prodrugs (enalapril to enalaprilat). It is important to appreciate the effects of incomplete oral bioavailability on dose adjustments when switching between oral and IV dosing. In the case of cyclosporine, the conversion factor for changing an oral dose to intravenous is one-third, because of the bypassing of the first-pass metabolism by intestinal and hepatic enzymes. These first-pass metabolism pathways can be affected by drug-drug and drug-disease interactions. For example, the oral bioavailability of cyclosporine is increased by coadministration of ketoconazole, which inhibits intestinal and hepatic presystemic metabolism by the cytochrome p450 enzyme CYP 3A4 (see later discussion).

For non-IV parenteral routes, such as topical, subcutaneous, or intramuscular, variability in local

This work was supported by grants from the Pharmaceutical Research and Manufacturers of America Foundation and the National Institutes of Health (1K23GM00713-01A1), both to Dr. Murray.

* Corresponding author.

E-mail address: pmurray@medicine.bsd.uchicago.edu (P. Murray).

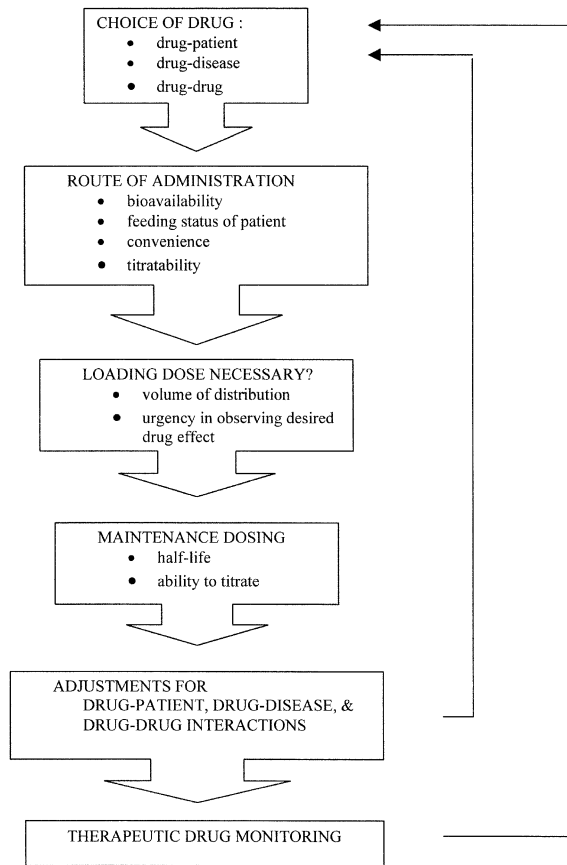


Fig. 1. Approach to pharmacotherapy in the ICU.

perfusion, changes in local pH, and site-specific factors, such as edema and scar tissue may alter the extent of absorption. Drugs that are administered by an enteral route are dependent on gut absorptive function and motility for adequate absorption. In the critically ill population, disorders, such as bowel wall edema or ileus, commonly alter the normal function of the gastrointestinal tract. Other routes of administration, such as inhalation or intracavity, are usually intended for local effects only, but may have systemic manifestations. For example, β -blocking eyedrops for glaucoma can be absorbed into systemic circulation and cause bradycardia.

The rate of absorption may be an important factor for determining the route of administration. Medications are often prescribed and administered in the ICU with the intent of producing immediate effect. The IV route is the most rapid, and, therefore, is the preferred route of administration. Biodelivery systems that cause a slow, sustained release of medication are convenient in the outpatient setting,

but lack the titratability that is desirable in the critically ill patient (eg, IV esmolol rather than oral long-acting metoprolol preparations for rate control of supraventricular tachycardia [SVT] in a patient who has congestive heart failure [CHF]).

Drug distribution and loading dose selection

After a drug has reached the central circulation, distribution throughout the body is determined by a variety of factors, including active and passive transport mechanisms, drug polarity, ambient pH of blood and tissues, and tissue perfusion. In a healthy patient, the drug distribution may be predictable; small, lipophilic drugs will distribute extensively, whereas large, protein-bound drugs will remain in the vascular space. In a critically ill patient, the distribution may be altered by the disease. In a patient who has meningitis, the inflamed meninges render the blood-brain barrier less effective and allow large antibiotics, such as vancomycin, which otherwise have poor

central nervous system (CNS) penetration, access to the cerebrospinal fluid to achieve therapeutic concentrations. Acidemia, as seen with sepsis, respiratory failure, and toxic ingestions, favors a shift of weak acids to the nonionic form; this allows for increased penetration into the brain and accounts for the greater CNS side effects of tricyclic antidepressants and salicylates in acidemia.

The pharmacokinetic parameter of volume of distribution (Vd), which describes the extent of distribution, is determined by amount of drug in the body (D) and the corresponding plasma concentration that is achieved (C).

$$Vd = D/C \quad (1)$$

For example, a large, hydrophilic drug, such as amphotericin B, will be retained within the vascular compartment, and Vd will approximate the volume of the intravascular space (0.04 L/kg). Vd does not describe an anatomical space; rather, it is a theoretical volume that represents the volume that the drug would occupy if it were distributed in a single homogenous compartment. To illustrate this, consider drugs such as digoxin, amitriptyline, and amiodarone, which have massive Vd, as a result of extensive distribution and avid tissue binding (6–7 L/kg, 7–22 L/kg, 18–148 L/kg, respectively), which greatly exceed the volume of any anatomic body compartment.

Vd is clinically significant because it can be used to determine an appropriate loading dose (LD) of drug. Usually a drug is prescribed with the intent of causing a rapid therapeutic action. If a drug has a long half-life, the time that is required to achieve steady-state might result in an unacceptable delay in the onset of drug action (see later discussion). A loading dose can be administered to rapidly achieve therapeutic plasma drug levels without affecting the time that is necessary to achieve steady-state. If we rearrange Equation 1, we can determine the required loading dose to achieve a target plasma concentration:

$$D = Vd \times C \text{ or} \\ LD = Vd \times \text{desired plasma concentration} \quad (2)$$

To calculate the required loading dose, we need to know a drug's Vd and the desired plasma level. The Vd for a drug under normal physiologic conditions and its target plasma concentration can be obtained from several references [1]. Vd is usually expressed in terms of volume per unit of weight (usually liters per kilogram). The calculation of body weight introduces another variable in the calculation of the loading dose. For nonobese patients, the lesser of the lean (or ideal) and actual body weight (ABW) is usually used. Ideal

body weight (IBW) can be calculated from the patient's height:

$$\text{Men: IBW (kg)} = 50 + (2.3 \\ \times [\text{height in inches} \\ \text{greater than 5 feet}]) \quad (3)$$

$$\text{Women: IBW (kg)} = 50 + (2.3 \\ \times [\text{height in inches} \\ \text{greater than 5 feet}]) \quad (4)$$

Adjustments to the total Vd can be made according to certain clinical features. For obese patients, the additional weight above the IBW may affect the total Vd. For lipophilic drugs, such as many sedatives, the entire excess body weight should be included in the calculation of loading dose; for hydrophilic drugs, such as aminoglycosides, a factor of 10% x (ABW – IBW) should be added to the Vd to account for the water in the excess weight compartment. Critical illness can rapidly change total body weight, particularly when septic shock requires multiple liters of volume resuscitation, and the additional fluid weight increases the Vd of hydrophilic drugs. For hydrophilic drugs, the net increase in body weight secondary to fluid resuscitation should be added to the total Vd.

Let us consider an example to further illustrate this point. A man who has pseudomonas sepsis requires aminoglycoside therapy. He is 64 inches tall, weighs 80 kg on admission, and after fluid resuscitation, weighs 100 kg. By using Equation 3, we can calculate his IBW to be approximately 60 kg. Given that the Vd of tobramycin is 0.25 L/kg and the desired plasma concentration of tobramycin is 8 mg/L, we can calculate the LD based on IBW using Equation 2 to be: 60 kg (0.25 L/kg) (8 mg/L) = 120 mg.

This is approximately the same loading dose that would be prescribed using standard weight-based dosing (1.5–2 mg/kg LBW). However, neither the use of standard Vd data nor the use of mg/kg dosing will provide an adequate loading dose in this patient; 120 mg does not come close to achieving the target plasma concentration. Because tobramycin is a hydrophilic drug, its Vd is influenced by the additional hydrophilic component in the excess adipose tissue, as well as the extra third-spaced volume following resuscitation from shock. A more accurate calculation of Vd would include the following:

$$\begin{aligned} &(\text{Vd using IBW}) \\ &+ (10\% \text{ of excess adipose weight, in kg}) \\ &+ (\text{excess third-spacing weight, in kg}) \\ &= (0.25 \text{ L/kg} \times 60 \text{ kg}) + (0.10 \times 20 \text{ kg}) \\ &+ (100 \text{ kg} - 80 \text{ kg}) = 37 \text{ L} \end{aligned}$$

The corresponding calculation of loading dose using the adjusted Vd is $37 \text{ L} \times 8 \text{ mg/L} = 296 \text{ mg}$.

If the volume of distribution is not adjusted for the massive increases that are observed with sepsis and (to a lesser extent) obesity, then the calculated loading dose would be grossly underestimated and the observed peak plasma concentration of aminoglycoside would be inadequate for optimal concentration-dependent bacterial killing at the time of greatest urgency. Studies indicate that loading doses of aminoglycosides are routinely underestimated using standard dosing strategies; adjustments for increased Vd are crucial to successful initiation of therapy in this setting [2].

Factors that influence maintenance dosing

Most drugs' dispositions can be described by a linear pharmacokinetic profile (Fig. 2). Following a single IV bolus (and assuming instantaneous complete distribution), plasma drug concentration declines following first-order elimination process (biotransformation or excretion), so that a plot of the logarithm of plasma drug concentration ($\log C_p$) versus time (t)

yields a linear graph. Back-extrapolation of this graph to time zero permits estimation of the plasma drug concentration immediately following the bolus (C_{p0}), and thus an estimate of Vd, because $Vd = D/C$. The slope of the plot is referred to as the elimination rate constant, k_e .

The elimination of drug from the plasma is a combination of biotransformation of the drug, primarily by the liver, and excretion of the drug, primarily by renal and gastrointestinal routes. The clearance of a drug is defined as the amount of plasma removed of the drug per unit time. The rate of drug clearance (CL) is based upon the balance of elimination and distribution rates:

$$CL = -k_e \cdot Vd(\text{min}^{-1} \cdot \text{mL}) \quad (5)$$

This relationship is more meaningful when we consider it in the context of drug half-life ($t_{1/2}$). From Fig. 2 we can calculate the time that is required for elimination of 50% of the administered drug ($t_{1/2}$), as follows:

$$t_{1/2} = \ln 2/k_e \text{ or approximately } t_{1/2} = 0.693/k_e \quad (6)$$

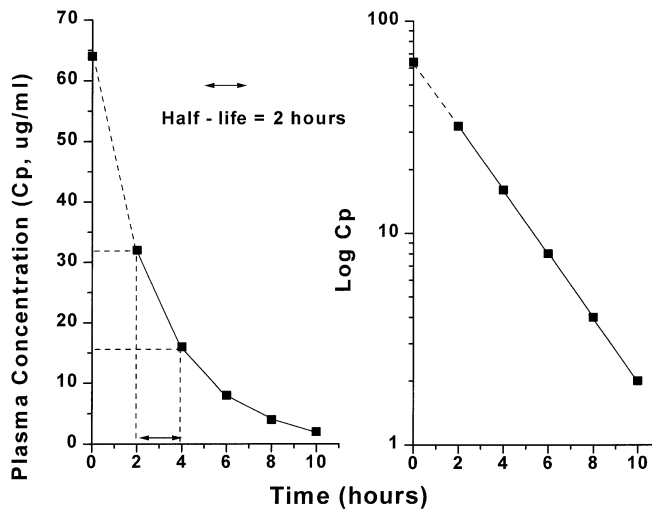


Fig. 2. Linear pharmacokinetic profile with a single compartment model. The left panel depicts the plasma concentration curve following IV administration of an 800 mg drug dose to a 100 kg adult. The first plasma sample, obtained 2 hours after bolus administration, contains a measured drug concentration of 32mg/ml. Subsequent samples reveal that the plasma drug concentration declines by 50% every two hours, which is consistent with an elimination half-life of 2 hours. The right panel shows the semi-log plot of the same data that were plotted in the left panel. Log transformation of the plasma concentration values yields a linear plot, which is consistent with first-order elimination. Back-extrapolation to time 0 suggests that the plasma concentration at this time was 64 $\mu\text{g/mL}$ (C_{p0}); assuming instantaneous complete distribution, Vd is estimated ($Vd = \text{dose}/C_{p0} = 800 \text{ mg}/64 \text{ mg/L} = 12.48 \text{ L}$ or 0.1248 L/kg). The slope (k_e) of the log-linear plot is $0.3465 \cdot \text{hr}^{-1}$, which is consistent with the known half-life of 2 hours ($k_e = 0.693/t_{1/2}$). CL may be estimated by using the equation $CL = k_e \cdot Vd = 0.3465 \times 12.48 = 4.32 \text{ L/hr} = 72 \text{ mL/min}$. (From Murray P, Corbridge T. Critical care pharmacology. In: Hall JB, Schmidt GA, Wood LDH, editors. Principles of critical care. 2nd edition. New York: McGraw-Hill Health Professions Division; 1998. p. 1530; with permission.)

Table 1

Number of half-lives that is required to eliminate a drug bolus by a first-order process

Number of half-lives	Percentage of original concentration
0	100.0
1	50.0
2	25.0
3	12.5
4	6.25
5	3.125

From Murray P, Corbridge T. Critical care pharmacology. In: Hall JB, Schmidt GA, Wood LDH, editors. Principles of critical care. 2nd edition. New York: McGraw-Hill Health Professions Division; 1998. p. 1529; with permission.

By substituting Equation 5 into Equation 6:

$$t_{1/2} = 0.693 \times Vd/CL \quad (7)$$

Conceptually, this equation expands our understanding of drug elimination. The half-life of a drug is directly proportional to the volume of distribution and inversely proportional to the rate of clearance (ie, the process of elimination is slower [and half-life is longer] when the extent of distribution is high so that the fraction of drug available for elimination in the plasma is decreased, and also when the rate of clearance is slow). Plasma drug concentration declines by 50% during each half-life, so that little of a bolus dose remains after four or five half-lives (Table 1). Critical illness may alter volume of distribution, clearance, or both, and these alterations may have additive or

opposing effects on drug elimination and half-life. Extracorporeal routes of elimination, such as renal replacement therapy or “liver dialysis,” are regarded as playing a significant role in drug elimination if they augment drug clearance by 30% or more (see later discussion).

If the same drug given above as a bolus to estimate simple (single compartment) pharmacokinetic (PK) parameters is instead administered as a continuous IV infusion, and the rate of infusion exceeds the rate of simultaneous (first-order) elimination, then the plasma drug concentration will increase as accumulation occurs. Because the amount of drug that is excreted per unit time increases with increasing plasma drug concentration, the elimination rate eventually becomes equal to the rate of administration; the plasma drug concentration at this time, which from that point on remains constant (unless the rates of administration or elimination change), is termed the steady-state concentration (C_{pss}) (Fig. 3, upper panel). Accumulation of intermittently-administered drugs differs from constant IV infusion only in the presence of peak and trough plasma drug concentration fluctuations; steady-state still develops over the same number of half-lives, with peak-to-trough fluctuations around a mean C_{pss} (Fig. 3, lower panel). Accumulation of an agent that exhibits linear pharmacokinetics proceeds in a fashion which is the mirror image of its elimination following a single intravenous bolus (Table 2). It is therefore possible to use the concept of half-life to estimate the time to attainment of a steady-state plasma drug level (and pharmacologic effect) following initiation of

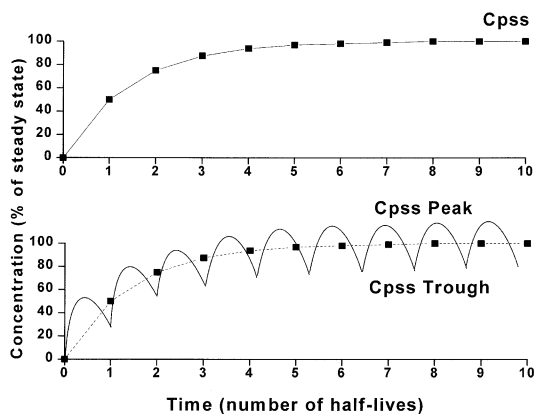


Fig. 3. Drug administration by continuous IV infusion (upper panel) or intermittent IV bolus (lower panel). Attainment of steady state plasma concentration (C_{pss}) occurs after three to five half-lives, irrespective of the dosing regimen. Peak and trough fluctuations around C_{pss} are aimed to each be within the therapeutic range (therapeutic but subtoxic plasma levels). (From Murray P, Corbridge T. Critical care pharmacology. In: Hall JB, Schmidt GA, Wood LDH, editors. Principles of critical care. 2nd edition. New York: McGraw-Hill Health Professions Division; 1998. p. 1529; with permission.)

Table 2
Number of half-lives that is required to attain steady-state plasma concentration ($C_{p_{ss}}$)

Number of half-lives	Percentage of $C_{p_{ss}}$
0	0.0
1	50.0
2	75.0
3	87.5
4	93.75
5	96.875

From Murray P, Corbridge T. Critical care pharmacology. In: Hall JB, Schmidt GA, Wood LDH, editors. Principles of critical care, 2nd Edition. New York: McGraw-Hill Health Professions Division; 1998 p. 1529; with permission.

therapy, and the time to offset of drug effect following discontinuation of the agent, irrespective of the dosing regimen in use.

A practical consequence of the kinetic principles of clearance and half-life is that we can calculate the dosing regimen that is necessary to maintain a desired plasma drug concentration. The amount and rate of the maintenance dose (MD) is based on the rate of clearance of the drug:

$$MD = CL \times C_p \quad (8)$$

where C_p is the desired plasma concentration of the drug. Because clearance is determined by distribution and elimination (Equation 7), it is logical that these factors also affect the amount and rate of the maintenance dose. Many disease states, including renal failure and hepatic disease, will affect clearance or volume of distribution.

A maintenance dose can be administered by continuous infusion or by intermittent boluses. To choose the appropriate maintenance dose regimen, one must consider half-life of the drug, therapeutic index, patient characteristics, desired effect, and cost or staffing factors. Continuous infusion is appropriate for drugs with short half-lives, such as nitrovasodilators, esmolol, heparin, propofol, and cis-atracurium, to take advantage of the properties of titration of the drug to the desired effect and also to ease nursing responsibilities that are associated with frequent doses. Continuous infusion also may be appropriate to achieve the desired drug effect by enhancing the drug effect while minimizing the peak and trough effects that are observed with intermittent dosing. Fluctuations in plasma level may be deleterious if the therapeutic index is narrow or if physiologic rebound mechanisms are induced by subtherapeutic levels. Effects of loop diuretics and histamine (H_2)-receptor antagonists are enhanced when administered as an infusion, because there is increased cumulative exposure of drug at the receptor

site, as well as the minimization of physiologic rebound mechanisms of salt retention and acid production, respectively. Intermittent bolus regimens are appropriate when the half-life is long and frequency of dosing is reasonable. Intermittent dosing is also appropriate to allow for drug-free intervals. Drugs such as nitroglycerin, dobutamine, and opiates can elicit tolerance during uninterrupted administration, and may require escalating doses to achieve a constant physiologic effect. Recent evidence concerning sedation of intubated patients indicates that sedation-free intervals allow for adequate monitoring of neurologic status and decreases the time required to liberate the patient from the ventilator, probably by preventing the undetected accumulation of sedative drugs, or other clinically inapparent causes of CNS depression [3].

The preceding description of drug disposition applies to drugs that exhibit linear/first-order pharmacokinetics, as applies to most agents. Zero-order pharmacokinetics are required to describe the elimination of drugs by a saturable or capacity-limited pathway, in which case a constant amount of drug, rather than a constant fraction, is eliminated per unit time. The “half-life” of elimination of these agents is concentration-dependent, because of capacity-limited clearance. Small dose escalations may result in disproportionately large plasma concentration increments when the maximum metabolic capacity is exceeded. Common drugs, such as ethanol, salicylates, and phenytoin, observe zero-order kinetics, although many drugs may develop saturation of metabolic pathways in overdose.

Variability of drug disposition and effect

Selection of a dosing regimen is additionally influenced by a variety of drug-patient, drug-disease, and drug interactions; many of them are common in the critically ill (Table 3). Although these interactions commonly affect maintenance dosing, they are relevant to all aspects of drug disposition and effect, as discussed below. Drug-patient interactions include the effects of genetics, age, gender, and immune system (allergy) on drug disposition and response. Drug allergy will not be discussed further in this article, but is an important source of preventable adverse drug events; patient histories should include broad inquiries regarding any adverse drug events and documentation of specific details, including whether the event was believed to represent a true allergic response. Cross-reactivity to related agents (eg, cephalosporins or carbapenems in penicillin-allergic patients) should also be considered. Drug-disease interactions are common in the ICU, where renal, hepatic, and circulatory dysfunction are frequently encountered. Finally, be-

Table 3
Interactions that cause variability of drug disposition and effect

Drug–patient	Drug–disease	Drug–drug
Race / Pharmacogenetics	Renal insufficiency	Pharmacokinetics
Age	Liver disease	Pharmacodynamics
Sex	Circulatory failure	
Allergy	Sepsis/SIRS	

Abbreviation: SIRS, systemic inflammatory response syndrome.

cause polypharmacy is the rule in the ICU, it is not surprising that potential drug-drug interactions are common; maximal use of available resources to prevent these interactions is advised to prevent associated adverse drug events. Available resources include the drug packaging insert as well as electronic resources, such as Physicians' Desk Reference Online (available at PDR.net), Epocrates Pro, Micromedex, MD Consult, and American Hospital Formulary Drug Information, to name a few.

Pharmacogenetics and race

The liver is the primary site of drug biotransformation, whereas the kidneys, skin, and lungs play a lesser role. Drug biotransformation reactions are classified as phase I (functionalization reactions, exposing or introducing a functional group) or phase II (biosynthetic) reactions. Phase II reactions form a covalent linkage between a drug's functional group and one of several: glucuronic acid, sulfate, glutathione, acetate, or amino acids. These conjugates are highly polar, usually inactive, and undergo urinary or fecal excretion [4]. Phase I reactions are predominantly oxidations, reductions, or hydrolytic reactions, and are usually catalyzed by enzymes of the cytochrome P450 system that is located in the endoplasmic reticulum. The cytochrome P450 system, comprising at least 12 families (in humans) of heme-containing endoplasmic reticulum enzymes, is the major catalyst of hepatic drug biotransformation reactions [5]. Three families (CYP 1, CYP 2, and CYP 3) are responsible for most drug biotransformations, through phase I reactions. The importance of the major cytochrome P450 enzymes in the metabolism of commonly-administered drugs is depicted in Fig. 4.

Cytochrome P450 nomenclature is based upon amino acid sequence homology: families (designated by numbers, such as CYP 3) contain at least 40% homology; subfamilies (designated by capital letters, such as CYP 3A) are greater than 55% homologous; individual P450 enzymes are again designated by Arabic numbers (for example, CYP 3A4). The CYP 3A subfamily accounts for greater than 50% of phase I drug metabolism, predominantly by the CYP 3A4

subtype. Most other drug biotransformations are performed (in decreasing order of frequency) by CYP 2D6, CYP 2C, CYP 2E1, and CYP 1A2 (see Fig. 4) [5]. More than one enzyme may metabolize a particular drug, but metabolism of many drugs is dependent upon a single enzyme. Because the cytochrome P450 nomenclature is based upon structural criteria, rather than biotransformation function, isozymes of a particular class often lack any common substrates.

Drug biotransformation may be enhanced or impaired by multiple factors, including age, gender, enzyme induction or inhibition, pharmacogenetics, and the effects of hepatic dysfunction or other disease states (including CHF or shock with decreased hepatic perfusion). Conditions that impair drug biotransformation may result in type A adverse drug reactions, that are caused by accumulation of toxic concentrations of parent drug or metabolites (see later discus-

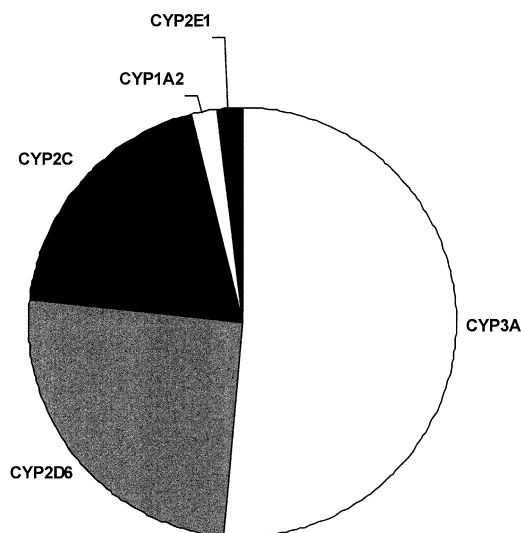


Fig. 4. The proportion of drugs that is metabolized by the major cytochrome P450 enzymes. (From Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG. The pharmacological basis of therapeutics. New York: McGraw Hill Health Professions Division; 1996. p. 14; with permission.)

sion). Many adverse drug reactions that were formerly termed type B (dose-independent, “idiosyncratic”) are now recognized to be caused by genetic polymorphisms of expression (through autosomal recessive traits) of hepatic drug metabolizing enzymes (phase I or phase II) in particular individuals and racial groups [6]. The absence of expression of the relevant genotype results in the existence of a “poor metabolizer” phenotype subpopulation, in contrast to the more prevalent “extensive metabolizer” phenotype. Expression of the cytochrome P450 enzymes, the best studied class of metabolizing enzymes, has been found to vary between race and gender, although it must be remembered that pharmacogenetic factors that control drug disposition and response also vary between individuals of the same race and gender. Frequency of expression of certain polymorphisms of drug metabolizing enzymes, such as CYP2C9, CYP2C19, and CYP2D6, varies by patient ethnicity or race [7,8]. The most common P450 polymorphism in white persons is of CYP2D6 expression; 63% carry some variant allele of the enzyme, whereas the incidence of CYP2C9 polymorphism is only 1% in white persons. The most prevalent P450 polymorphism in Asians is of CYP2C19 expression; 15% to 17% of Chinese patients and 18% to 23% of Japanese patients (but only 2% to 6% of white patients) lack expression of this isozyme and are poor metabolizers of substrates such as *s*-mephenytoin, phenytoin, diazepam, and omeprazole [9]. In contrast, approximately 3% to 10% of the white population, but less than 2% of Chinese, Japanese, and African subjects lack expression of the CYP2D6 enzyme, and are “poor metabolizers” of substrates of this enzyme (see later discussion) [10]. Genetic polymorphism of phase II enzymes is also well known; for example, acetylation of procainamide, hydralazine, isoniazid, and sulfa drugs underlies the “slow acetylator” phenotype that is seen in more than 50% of American blacks and whites but only 17% of Japanese subjects [11,12]. The more commonly known metabolic polymorphisms are discussed below.

CYP2D6 polymorphism. CYP2D6 is responsible for the metabolism of approximately 30 to 40 commonly used drugs, about half of which are psychoactive agents (antidepressants, including all tricyclic antidepressants and selective serotonin reuptake inhibitors, and antipsychotics, including haloperidol) [13]; many of the remaining agents are β -blockers (all except atenolol and sotalol, which are renally-excreted, not metabolized) and other antiarrhythmic drugs. Patients who have variant alleles of CYP2D6 are prone to develop profound bradycardia during standard β -blocker therapy or severe drowsiness when receiv-

ing psychoactive drug therapy; in each case the adverse event is due to accumulation of parent drug. Conversely, these individuals derive little analgesic effect from codeine, which must be metabolized by CYP2D6 to its more potent metabolite, morphine, to achieve therapeutic efficacy.

CYP2C9 polymorphism. Important substrates include *s*-warfarin, phenytoin, diclofenac (and other hepatically-metabolized nonsteroidal anti-inflammatory drugs), and losartan. As a result of decreased metabolism rate, patients who have particular polymorphisms of CYP2C9 (and CYP2A6) result in significant reduction of warfarin dose compared with the subpopulation who has the wild-type allele [14].

CYP2E1 polymorphism. CYP2E1 metabolizes acetaminophen and many volatile anesthetics, and is induced by isoniazid and ethanol. Ten percent of subjects who have alcoholic liver disease have a CYP2E1 rapid metabolizer phenotype, and metabolize CYP2E1 substrates to a greater extent than most of the population.

The lack of a clinically-apparent CYP3A polymorphism has been attributed to the wide range of expression of activity of this enzyme in normal populations, although emerging data demonstrate the existence of a CYP3A5 polymorphism [12,15].

Many phase II reactions are similarly subject to pharmacogenetic variation [16] that results in polymorphic expression of the metabolic capacity for specific agents; examples include: acetylation, glucuronidation (Gilbert’s syndrome, irinotecan metabolism), and the activities of glutathione-S-transferase (acetaminophen metabolism), thiopurine methyl transferase (azathioprine metabolism), glucose-6-phosphate dehydrogenase (drug-induced hemolysis), pseudocholinesterase (prolonged paralysis following succinylcholine), and dihydropyrimidine dehydrogenase (5-fluorouracil toxicity).

Age

Age has a variety of effects on drug disposition and effect (Box 1). Some changes observed are due to the process of aging and are variable in the population; other changes are caused by the additional influences of drug-disease and drug-drug interactions, which are more likely in the aged population who commonly have multiple comorbid conditions and are treated with multiple medications [17]. CYP1A2 activity is increased in children compared with adults which causes the well-known increased theophylline dosage requirement in this population. In contrast, CYP3A4 activity seems to decrease in elderly patients; age-related decreases in hepatic size, hepatic blood flow, or

Box 1. Effects of aging on drug disposition and effect in the elderly

Bioavailability - decreased gastrointestinal (GI) motility and absorption, decreased splanchnic blood flow, increased GI pH; little clinical significance with these changes. Increased likelihood of drug-drug interactions because of polypharmacy.

Protein binding - decreased albumin affects protein binding of acidic drugs; increased *B*-1-glycoprotein affects protein binding of basic drugs.

Volume of distribution - increased for some drugs (eg, acetaminophen, diazepam, salicylates); decreased for some drugs (eg, digoxin, ethanol, gentamicin, phenytoin, theophylline).

Biotransformation - decreased phase I metabolism, reduced hepatic blood flow, and reduced hepatic mass cause decreased first-pass and systemic metabolism of some drugs.

Excretion - decreased renal blood flow, GFR, and tubular secretion impair elimination of some drugs and their metabolites.

Pharmacodynamic (PD) effects - alterations in receptor number and affinity change "sensitivity" to some agents.

drug binding and distribution may underlie this phenomenon because *in vitro* enzyme activity is unchanged with age. Aging is also associated with a decline in renal function, which is often clinically-inapparent because of the associated age-dependent decrease in muscle mass, and has a variety of effects on drug disposition (Box 2). Declining muscle mass lowers daily creatinine production and prevents the elevation of serum creatinine which would make the glomerular filtration rate (GFR) loss of aging detectable by progressively increasing serum creatinine concentration. This problem may, to some extent, be overcome by the use of formulas to calculate GFR from serum creatinine values, to account for the effects of age, size, gender, and (in recent years) race and other laboratory variables, or measurement of creatinine clearance with timed urine collections (Table 4).

Gender

In 1993, the National Institute of Health mandated the inclusion of women in clinical trials, largely as a

Box 2. Effects of renal failure on drug disposition and effect

Bioavailability - absorption of specific drugs may be impaired by increased gastric pH (because of gastric urease-produced ammonia), chelation by orally-administered phosphate-binding agents, or by bowel wall edema. Conversely, bioavailability may be increased by uremia-induced impairment of first-pass metabolism. Uremic effects on intestinal motility (ileus) affect the rate, rather than the extent, of drug absorption, unless emesis results in loss of ingested drug.

Protein binding - binding of acidic drugs to albumin is decreased, because of competition with accumulated organic acids, and because of uremia-induced structural changes in albumin, which decrease drug-binding affinity (eg, barbiturates, cephalosporins, penicillins, phenytoin, salicylate, sulfonamides, valproate, warfarin).

Volume of distribution - *V*_d may be altered in the presence of renal failure. Drugs which are acidic, are highly protein-bound, and have a small volume of distribution are likely to be significantly affected. Other drugs may also be affected (eg. aminoglycosides, volume status effects; digoxin, displacement from tissue sites by "uremic substances").

Biotransformation - nonrenal (ie, hepatic) clearance may be impaired. This phenomenon is best characterized in chronic renal insufficiency (rather than acute renal failure) and affects oxidative metabolism (phase I enzymes). Conversely, phenytoin clearance is augmented.

Excretion - drugs for which more than 30% occurs as unchanged in the urine are likely to have significantly diminished CL in the presence of renal insufficiency. This results in a prolonged half-life for elimination of drugs such as digoxin, aminoglycosides, insulin, and others. The renal excretory route may assume increased importance in clearance of some drugs in the presence of hepatic impairment. Other drugs have toxic or active metabolites that require renal elimination (see Table 4). If

dialysis or hemofiltration is required, drug removal may be significant.

PD effects - some drugs, such as sedative agents, may have enhanced effect in combination with the uremic milieu. Electrolyte abnormalities and acidosis may alter the effects of drugs such as antiarrhythmic agents.

From Murray P, Corbridge T. Critical care pharmacology. In: Hall JB, Schmidt GA, Wood LDH, editors. Principles of critical care, 2nd edition. New York: McGraw-Hill Health Professions Division; 1998. p. 1534; with permission.

result of the increasing amount of data that showed gender differences in drug disposition. Differences in oral bioavailability may be caused by gender differences in the activity of hepatic and intestinal enzymes that are important in the first-pass metabolism of certain drugs. Gender-based variability in distribution of drugs is attributable to differences in body composition, physiologic changes during the menstrual cycle, or differences in plasma protein binding secondary to hormonal effects [18]. Increasingly, gender differences in hepatic drug biotransformation are being recognized, such as sex-specific expression of hepatic enzymes like CYP3A4 and CYP1A2, and may be as subtle as sex-related differences in the metabolism of specific stereoisomers of a particular drug formulation, as is observed with metoprolol and ketoprofen [19,20]. In addition, sex-related differences in drug effect have been observed, and may be caused by pharmacodynamic, rather than pharmacokinetic, phenomena; for example, women have a higher incidence of hemorrhagic stroke after treatment with thrombolytic therapy for myocardial infarction [7].

Renal insufficiency

Renal insufficiency is a common problem in the critically ill population, either as a pre-existing comorbidity that contributes to the critical illness (chronic renal insufficiency) or as a result of acute or acute-on-chronic renal failure. In either case, renal impairment has significant implications for the prescription of drug therapy (see Box 2). If dosing is not accurately adjusted to account for the effects of renal dysfunction, suboptimal therapy or serious adverse drug reactions may occur. Additionally, renal replacement therapy

may augment drug elimination. The practical approach to these problems requires estimation of degrees of renal dysfunction to account for the effects of renal replacement therapy, appropriate adjustment of drug dosaging, and careful monitoring of drug therapy.

Most elimination by the kidneys is accomplished by glomerular filtration; therefore, estimation of the GFR has traditionally served as an approximation of renal function. Normal glomerular filtration averages 100 to 130 mL/min, which represents 4% to 5% of the cardiac output. Glomerular filtration of plasma constituents is primarily limited by size (<50,000 Da), water solubility, plasma protein binding (only free drug is filtered), and volume of distribution (extensively-tissue bound substances are less likely to be renally-excreted). Many methods are available to estimate GFR, each with its own usefulness and limitations (see Table 4). There are certain circumstances that might confound the measurement of GFR. Many methods of GFR estimation require the steady-state level of plasma creatinine, which is not possible in the early stages of acute renal failure. The accuracy of interpretation of serum creatinine for assessment of renal function is compromised in the setting of muscle wasting, such as in patients who have cirrhosis, spinal cord injury, or cachexia, which are common in the intensive care setting. Additionally, some drugs that are commonly used in critically ill patients, such as trimethoprim and cimetidine, impair tubular creatinine secretion which increases plasma creatinine concentration without a corresponding decrease in GFR. Despite these limitations, an attempt to estimate GFR is the critical step in proper dosing of renally-eliminated drugs.

Many drugs are dosed according to published guidelines based upon categories of degree of renal impairment: mild (creatinine clearance [CrCL] > 50 mL/minute), moderate (CrCL 10–50 mL/minute), or severe (CrCL < 10 mL/minute). For many commonly-used ICU drugs, there are standard published interval or dose adjustments for patients who have graded levels of renal impairment. Consider our example of the patient who is receiving tobramycin for pseudomonas sepsis. His serum creatinine is 2.0. Using the Cockcroft-Gault equation (see Table 4), we can calculate his GFR to be approximately 30 mL/minute. The standard interval adjustment for this degree of renal insufficiency is to dose the aminoglycoside every 24 hours, rather than every 8 hours in the absence of renal dysfunction. Theoretically, there may be drugs that are known to be predominantly renally-excreted with no published adjustment information for renal insufficiency that require empiric adjustment of dosing that is proportional to the level

Table 4
Methods of estimation of glomerular filtration rate

Method	Formula	Limitations / comments
Inulin clearance	$U(\text{inulin}) \times V/P(\text{inulin})$	Requires infusion of inulin
Creatinine clearance (CrCL)	$U(\text{Cr}) \times V/P(\text{Cr})$	Overestimates GFR because of effects of tubular secretion of creatinine Requires steady-state of P(Cr)
Urea clearance (UCL)	$U(\text{urea}) \times V/P(\text{urea})$	Underestimates GFR because of tubular reabsorption of urea Requires steady-state of P(urea)
Average of CrCL and UCL	$(\text{CrCL} + \text{UCL})/2$	Requires steady-state conditions
Estimation of CrCL by 2-hour urine collection	$U(\text{Cr}) \times V/P(\text{Cr})$	Practical for ICU Reasonable correlation with 24-hour results
Cockcroft and Gault formula	$\frac{(140 - \text{age}) \times (\text{IBW}) (\times 0.85 \text{ in females})}{72 \times P(\text{Cr})}$	Requires steady-state of P(Cr) Requires estimation of IBW Empiricism of age and sex estimates used to develop formula Effects of some medications on tubular creatinine secretion
Aminoglycoside clearance	Calculated from therapeutic drug monitoring of peak and trough plasma levels	Often need GFR estimation before dosing of aminoglycoside Requires empiric information to calculate true half-life of drug Useful additional GFR estimate in patients receiving aminoglycosides
Modified diet in renal disease equation (MDRD)	$198 \times P(\text{Cr})^{-0.858} \times \text{age}^{-0.167} \times (0.822 \text{ if patient is female}) \times (1.178 \text{ if patient is black}) \times P(\text{urea})^{-0.293} \times U(\text{urea})^{+0.249}$ OR $170 \times P(\text{Cr})^{-0.999} \times \text{age}^{-0.176} \times (0.762 \text{ if patient is female}) \times (1.180 \text{ if patient is black}) \times P(\text{urea})^{-0.170} \times P(\text{albumin})^{+0.318}$	Most accurate method of estimating GFR in chronic kidney disease Requires steady-state conditions

Abbreviations: Cr, creatinine; P(X), plasma concentration of X; TBW, total body weight; U(X), urinary concentration of X; V, volume.

of renal impairment. This can be done by proportional dose reduction, interval prolongation, or a combination of both techniques.

$$\text{Adjusted total dose} = \text{calculated total dose} \times (\text{patient's estimated GFR/normal GFR})$$

where the normal GFR is 100 mL/min (9)

For drugs with a narrow therapeutic window (eg, antiseizure drugs), wide variations in plasma drug concentration with interval extension may be detrimental, and a decrease in the amount of each dose

would be more appropriate. For drugs with peak concentration-dependent effects, for which periods of “subtherapeutic” plasma level are not problematic, interval extension is ideal; aminoglycoside dosing with interval extension has the additional benefit of decreasing trough levels and associated toxicity. For some drugs, such as digoxin, a combination of dose and interval adjustment is required.

The effects of renal replacement therapy should also be accounted for in the dosing regimen. The extent of “dialyzability” of a given drug can be predicted by drug characteristics and renal replacement therapy

Box 3. Factors that predict removal of drug by renal replacement therapy

Water solubility
 Low protein-binding (<90%)
 Small size (<500 d for traditional membranes; <5000 d for high-flux membranes)
 Small volume of distribution (<250 L or <4 L/kg)
 Intrinsic clearance of the substance (<500 mL/70kg/min)
 Blood and dialysate flow rates (for hemodialysis)

technique (Box 3). For drugs that may have an increased clearance as a result of dialysis, additional doses after dialysis may be necessary to maintain therapeutic plasma levels, as is the case for vancomycin (using modern, porous, “high flux” membranes) and aminoglycosides. In the absence of specific data regarding the influence of dialysis on drug clearance, it is prudent to administer doses postdialysis in patients who receive intermittent dialytic therapy, assuming a GFR of less than 10 mL/minute for the maintenance regimen. This is not feasible in patients who receive continuous renal replacement therapy (CRRT). The membranes that are used for CRRT are highly porous and the small molecule clearance that is achieved approximates an equivalent GFR of 20 to 30 mL/minute. In the absence of data on the required supplementation to account for drug removal by CRRT, one approach is to empirically increase the maintenance dose of drugs to that required for a GFR of 20 to 30 mL/minute. Of course, for drugs with availability of plasma drug level assays, therapeutic drug monitoring guided by plasma concentrations is the preferred approach to guide adjustment of maintenance dosing in this situation.

Liver disease

Although some drugs may be entirely cleared by renal excretion, most drugs are too lipophilic to avoid reabsorption by proximal tubules or intestinal membranes after glomerular filtration or biliary excretion, respectively. These drugs require modification to allow for more efficient excretion. Drugs can be categorized based on the rate-limiting factor of biotransformation: flow-limited, enzyme-limited, or a combination. Enzyme-limited drugs are metabolized by saturable enzymes and the pharmacokinetics can be described by first-order or zero-order models, de-

pending on the available concentration of free (unbound) drug. The metabolism of highly-extracted, flow-limited drugs is limited only by the hepatic blood supply and follows first-order kinetics.

Unlike renal function, liver function is difficult to quantitate. Derangements in common liver function tests indicate the presence of disease, but not necessarily the extent of disease. Although several disease states, such as ischemic injury, neoplasm, infections, or toxic injury, may be common in the critically ill population, the effect on liver function is not clearly definable. Most liver functions can be maintained with some degree of liver injury (production of urea from ammonia requires only 60% of liver function; blood glucose maintenance requires 20% of total liver function; bilirubin elimination requires less than 10% of liver function) [21], so liver pathology can exist without affecting liver function. At best, one can guess at the level of liver dysfunction (mild, moderate, or severe) based on available information on synthetic function (albumin, coagulation factors), enzyme concentrations (transaminases, γ -glutamyl transferase), and pathology.

Liver dysfunction alters drug disposition and response in a variety of ways (Box 4). The volume of distribution is affected by multiple factors. Synthesis of many proteins, including albumin and α -1-glycoprotein, affects the protein-binding properties of acids and bases, respectively. Additionally, accumulation of endogenous compounds can displace drugs from protein binding sites. For example, bilirubin has a high affinity for albumin and can displace phenytoin, which increases the free-to-bound phenytoin ratio. Third-spacing of fluid into the peritoneal cavity and extremities can also increase the volume of distribution for numerous drugs. For example, the presence of ascites doubles the normal volume of distribution for propranolol. In essence, liver dysfunction has opposing effects on the extent of drug distribution; decreased protein-binding increases the free drug fraction and allows for increased clearance (if not saturated), whereas third-spacing of volume can increase V_d directly. Drug biotransformation is not predictably altered by liver disease. As general rules, higher grades of cirrhosis are more likely to have impaired metabolism than lesser degrees and phase II pathways tend to be better preserved than phase I reactions. The approach to drug dosing in the presence of hepatic dysfunction should be based on several factors including: (1) extent of liver damage; (2) degree of hepatic elimination of drug; (3) degree of protein binding; (4) class to which drug belongs (enzyme-limited; flow-limited, or both); and (5) route of

Box 4. Effects of liver dysfunction on drug disposition and effect

Bioavailability - drugs that undergo extensive “first-pass” metabolism may have a significantly higher oral bioavailability in cirrhotics than in normal subjects. Impaired drug absorption, because of bowel wall edema, has not been found in studies of cirrhotic subjects. GI hypomotility may delay peak response to enterally-administered drugs in these patients.

Protein binding - hypoalbuminemia or altered glycoprotein levels may affect the fractional protein binding of acidic or basic drugs, respectively. Monitoring of “free” drug levels may be indicated. In addition, drug-drug interactions by displacement from plasma protein binding sites may become important when biotransformation is concomitantly impaired.

Volume of distribution - altered plasma protein concentrations may affect the extent of tissue distribution of drugs that are normally highly protein-bound. The presence of significant edema and ascites may alter the Vd of highly water-soluble agents (eg, aminoglycosides).

Biotransformation - the presence of cirrhosis may result in some decrease in drug clearance, although not predictably so. Specific information regarding the use of each agent prescribed in patients who have a type and severity of liver disease similar to the patient in question should be sought, if possible.

Excretion - renal elimination of drug or metabolites may be impaired by concomitant renal insufficiency, which may be unsuspected based upon an “inappropriately” low serum creatinine in patients who have severe liver disease.

PD effects - sedative effects (and side-effects) of drugs may be augmented in patients who have liver disease.

From Murray P, Corbridge T. Critical care pharmacology. In: Hall JB, Schmidt GA, Wood LDH, editors. Principles of critical care, 2nd edition. New York: McGraw-Hill Health Professions Division; 1998. p. 1535; with permission.

administration (steady-state plasma levels may increase markedly for oral agents that are normally subject to extensive first-pass metabolism, because of increased bioavailability and then subsequent impaired systemic clearance). If possible, drug doses should be reduced and titrated upward slowly in the presence of liver disease (“start low and go slow”), but therapeutic urgency often precludes this approach in the ICU. Pharmacodynamic monitoring, such as daily assessment of time-to-awakening following sedation withdrawal, may permit safe and effective use of hepatically-metabolized drugs in the presence of liver disease [3]. If therapeutic drug monitoring of plasma levels is available, this is the preferred method to guide adjustments in dosing of low therapeutic index drugs in patients who have liver dysfunction.

Circulatory failure and systemic inflammatory response syndrome

Circulatory failure from a variety of causes, including CHF and sepsis, is common in critically ill patients. CHF can alter disposition and effects of drugs (Box 5). Secondary decrements in hepatic and renal blood flow result in impaired clearance of some drugs that are eliminated by these routes. Clearance of hepatically-

Box 5. Effects of congestive heart failure on drug disposition and effect

Bioavailability - impaired drug absorption because of bowel wall edema. Passive hepatic congestion may alter “first-pass” metabolism. Peripheral edema inhibits absorption by non-IV parenteral routes.

Protein binding is not specifically altered by congestive heart failure

Volume of distribution - the balance of tissue hypoperfusion versus increased total body water with edema may unpredictably alter Vd.

Biotransformation - hypoperfusion of liver may alter drug metabolizing enzyme function, especially flow-dependent drugs (eg, lidocaine)

Excretion - prerenal azotemia may impair elimination of some drugs.

PD effects - increased sensitivity to negative inotropes at therapeutic doses. Increased arrhythmic potential with antiarrhythmic drugs. Patients who have CHF are more prone to radiocontrast nephropathy.

eliminated drugs is more likely to be impaired by CHF if their metabolism is flow-limited (ie, characterized by a high extraction ratio, such as lidocaine). It is doubtful that most information, even from populations who have “decompensated” CHF, is applicable to the setting of cardiogenic shock.

Even less data is available regarding the disposition of most agents in patients who have septic shock, sepsis syndrome without frank hypoperfusion, or even systemic inflammatory response syndrome. Just as is the case in CHF, septic hypoperfusion may disproportionately involve the renal or splanchnic circulations, which results in impairment of renal or hepatic perfusion to a degree that would not be expected based upon global hemodynamic data. The net effect of these derangements on drug disposition is a grossly neglected area of investigation. For example, standard antimicrobial dosing regimens are based on research with patients who, for the most part, were not critically ill [2]. Standard IV dosing of ceftriaxone with 2 g daily in a patient who has sepsis may result in inadequate plasma concentrations in patients who have normal renal function and excess accumulation in septic patients who develop renal insufficiency. These differences are attributed to alterations in V_d from third-spaced volume and altered clearance [22]. Additionally, antibiotics poorly penetrate abscesses and other compartmentalized tissue, so direct therapy, such as intraperitoneal fluoroquinolone for bacterial peritonitis, or increases in standard dosing of antibiotics may be necessary to achieve adequate minimum inhibitory concentrations. Experimental evidence suggests that endotoxemia impairs hepatic drug metabolizing-enzyme function [23] and that nitric oxide probably mediates much of this inhibition [24,25].

Other factors

Many other factors may contribute to the variability in drug disposition between individuals. In the critically ill population, institution of therapies, such as radiation and therapeutic pheresis, and conditions such as hormone imbalances and nutritional depletion, may contribute to alterations of drug metabolism. Whole body or head radiation can alter drug metabolism, possibly as a result of decreased corticotropin secretion by the pituitary gland. Corticosteroid concentration is inversely proportional to the rate of metabolism. Other hormone imbalances, including thyroxine, estrogen, and progesterone levels, may be similarly influential [26]. Nutritional status can also affect drug disposition. Patients with a diet that is deprived of fat or protein have a reduced rate of metabolism. Vitamins are also essential to the rate of metabolism. Iron deficiency does not seem to affect the rate of drug metabolism,

although the major hepatic enzymes that are involved in drug metabolism contain iron [21].

Drug-drug interactions

Drug-drug interactions can occur at each stage of drug disposition (Table 5). Bioavailability of certain drugs will be altered by changes in gastric pH or intestinal motility. Distribution and clearance of drugs may be altered with competitive plasma protein binding and subsequent changes in free drug concentrations. Additionally, common substrates of the P450 enzyme that are responsible for metabolism of a particular drug may be inhibitors or inducers of its metabolism, and, therefore, create the potential for drug interactions. For example, because cyclosporine and tacrolimus are metabolized by CYP 3A4, biotransformation of both agents is predictably affected by known inhibitors and inducers of this enzyme. Substances that are not substrates of a P450 isozyme may also be inhibitors or inducers of its activity (eg, fluconazole and CYP2C9, quinidine and CYP2D6). Ketoconazole is a particularly potent inhibitor of CYP 3A4 and has been used to deliberately lower cyclosporine dosage requirements as a cost-saving measure [27]. Many novel antiretroviral HIV drugs are inducers and inhibitors of the P450 enzymes. Coadministration of antibiotics with a variety of drugs with low therapeutic index may result in toxic effects (eg, ciprofloxacin with theophylline, fluconazole with phenytoin, erythromycin with cyclosporine; Table 6). By contrast, some antituberculous drugs and antiepileptic drugs commonly induce all of the cytochrome P450 enzymes and can result in subtherapeutic drug levels. For a more comprehensive and frequently updated table of drug interactions, please refer to websites, such as Dr. David

Table 5
Potential drug-drug interactions according to pharmacokinetic and pharmacodynamic principles

Absorption	Alterations in gastric pH Effects on intestinal absorption Alterations in gastrointestinal motility Alterations in first-pass metabolism
Distribution	Competitive binding to plasma proteins (albumin, α -1-glycoprotein)
Biotransformation	Induction Inhibition
Elimination	Alterations in renal and biliary function
Pharmacodynamics	Alterations at site of drug action Alterations in receptor number and function Physiologic interactions between drugs

Table 6
Examples of cytochrome P450 substrates, inhibitors, and inducers

Enzyme	Substrates	Inhibitors	Inducers
CYP 1A2	Theophylline	Ciprofloxacin	Omeprazole, hydrocarbons (smoking)
CYP 2C9	Phenytoin, warfarin	Fluconazole	Rifampin
CYP 2C19	Phenytoin, warfarin	Cimetidine	Carbamazepine, rifampin
CYP 2D6	Metoprolol, haloperidol	Fluoxetine, quinidine	Rifampin
CYP 3A4	Cyclosporine, tacrolimus	Erythromycin, ketoconazole	Phenytoin, rifampin

Flockhart's [28] from Indiana University, as an example. Inducers and inhibitors of phase II enzymes have been less extensively characterized, but some clinical applications of this information have emerged; examples include the use of phenobarbital to induce glucuronyl transferase activity in icteric neonates, and the use of phenobarbital and valproate to modulate chemotherapeutic agent glucuronidation and toxicity [29]. The potential for such an interaction is increasingly predictable, because specific information regarding metabolic pathways and potential biotransformation interactions is routinely included in medication packaging inserts.

Therapeutic drug monitoring

Although pharmacokinetic principles may aid in the construction of a logical dosing regimen for a drug, therapy requires frequent monitoring and titration to optimize the desired effect. Using pharmacologic principles, we can approximate the time that is required to achieve steady-state or the time that is required to observe a cessation of drug effect after discontinuation; we can use these estimates to interpret clinical events. Often in the course of a patient's critical illness, there are dramatic and sudden changes in the patient's condition, sometimes as a result of the patient's disease state and sometimes from adverse events from therapy. Whenever an adverse event occurs with a critically ill patient and the cause is unknown, the primary question to ask is "Is this a result of an adverse drug event?" The list of medications administered should be carefully reviewed and unnecessary drugs should be discontinued. Monitoring of adverse drug events can consist of indirect measurements, such as degree of sedation or analgesia, blood pressure, or heart rate, or direct monitoring, such as plasma levels of drug or metabolites. Although direct plasma drug level monitoring is possible for some drugs, it is not available for most. Despite the best efforts to individualize a patient's drug regimen, the constantly evolving nature of a critically ill patient's disease may prohibit precise modeling of

the disposition of the drugs given. Irrespective of critical illness, complex groups, such as transplant patients who require immunosuppressants, have a large interindividual variation in drug dose-to-effect ratio and require frequent drug level monitoring to balance efficacy and toxicity.

There are many considerations involved in choosing to obtain a plasma drug level. First, what form of drug is to be measured? Many drugs have a high affinity to plasma proteins and the difference between free and bound drug may be significant. For example, phenytoin has a high affinity for plasma proteins, but only the free form is clinically active. Free phenytoin levels must be monitored in hypoalbuminemic patients or in uremic patients in whom endogenous substances displace phenytoin from albumin binding sites. Second, what is the timing of the plasma drug level in relation to the time of the last dose? For some drugs (eg, chloramphenicol), measurement of the peak plasma concentration is suggested, whereas for others (eg, cyclosporine, tacrolimus), only the plateau drug concentration is required to assess effective dosing. Other drugs may require peak and trough levels to adequately monitor efficacy and potential toxicity; aminoglycosides are commonly dosed to aim for a peak plasma concentration of 6 to 8 mg/L, because this optimizes bactericidal activity; trough levels of less than 2 mg/L are desired to minimize the risk of oto- and nephrotoxicity. Existing data suggest that once-daily administration of high-dose aminoglycoside may maximize the benefit of high-peak levels for bacterial killing while minimizing the potential for high trough levels, drug accumulation, and nephrotoxicity [30].

Prevention of adverse drug reactions

"Primum non nocere." Despite the first edict of medical practice to do no harm to patients, medical errors account for a significant percentage of morbidity and mortality. Estimates from the Institute of Medicine indicate that 98,000 deaths per year are attributable to medical errors; a significant portion of those is related to medication errors [31]. Classes of medications that

were most often administered incorrectly included vasoactive medications, sedatives, and analgesics [32]. These errors heavily impact the intensive-care population, where patients are likely to receive low therapeutic index drugs, are subject to routine poly-pharmacy, and lack physiologic reserve to tolerate drug-induced insults.

There are basically two types of medical errors — “mistakes” and “accidents.” Mistakes are errors in applying knowledge, such as an inappropriate antibiotic choice or anticoagulation of a patient who is bleeding. Accidents are skill-based errors, such as administration of a drug at the wrong time or at the wrong infusion rate. Most research that studies medication errors focuses on accidents and probably underestimates the true incidence of error. Medication administration involves multiple stages which allow for opportunity for error, both mistakes and accidents, at every juncture: prescription, transcription, preparation, and administration [33]. The first step is the actual prescription of medication by the physician. Notoriously poor physician handwriting and errors in medication choice or dosage are examples of errors that can occur at this stage. Next is the transcription of the physician order to the pharmacist. Errors in copying the actual physician order into the form that is received by the pharmacist and delays in sending the physician order to the pharmacist are potential pitfalls at this stage. The third stage of medication administration is preparation of the medication. The pharmacist and the nurse are involved in preparation of the medication in the form that can be administered to the patient. Finally, the medication is actually administered to the patient. Errors in medication administration involve a failure at one or more of these four stages. Interventions to decrease the frequency of errors are, in general, more beneficial when targeted at multiple stages of drug delivery [33].

Medical error reporting

The first step in reducing medical errors is to collect data regarding when and where errors occur to identify patterns of occurrence. Mechanisms for reporting errors vary by institution and often depend on voluntary reporting. This process likely does not capture the full extent of medical errors because of the barriers in the voluntary reporting system, which include: the fear of admitting guilt and creating new malpractice suits, the fear of waiver of peer review immunity in discovery, and the differences in definitions of errors that result in over- and underreporting. Departmental morbidity and mortality conferences can sometimes be conducted in a punitive format, instead of being a

constructive educational experience. The medical community needs to cultivate a culture that is dedicated to patient safety and promotes open discussion of adverse events for the purpose of improving medical practice. Mandatory reporting systems have been advocated by many, including the Agency for Health Care Research and Quality, the Joint Commission, and by Congress through federal and state initiatives. Although this may be a necessary first step, further improvements will require a change in the negative perceptions of error reporting within the medical community.

Protocols

There are many common processes in the ICU that can be standardized to minimize the opportunity for error. Events such as sedation, pain management, and anticoagulation are so frequent that many units have opted for protocols that provide a checklist of diagnostic and therapeutic steps that should be performed for each event. For example, a protocol for anticoagulation with heparin should include: consideration of any potential blood loss; a check of baseline levels of hemoglobin, platelets, prothrombin time, partial thromboplastin time, and serum potassium to effectively monitor for expected effects of the heparin and potential idiosyncratic effects; and a systematic titration of the heparin infusion based on coagulation tests. Protocols are an effective way to ensure thorough consideration of a comprehensive strategy for a common event.

Dedicated pharmacist in the intensive care unit

Many studies have investigated the benefits of a dedicated team of professionals in the ICU. The Leapfrog Initiative advocates dedicated intensivists caring for critically ill patients to improve mortality and reduce adverse drug events [34]. This advantage is theorized to be a result of specialized training in particular issues that arise in critically ill patients, a broader perspective of issues that pertain to critically ill patients, and improved continuity of care. This same rationalization can be used to justify the role of a dedicated ICU pharmacist. The traditional role of a pharmacist to accept and clarify orders and dispense medications is antiquated. A study by Anderson et al [33] showed that during a 9-month study period, having a pharmacist who participated in clinical rounds as a full member of the patient care team in the ICU decreased adverse drug events from 10.4 to 3.5 per 1000 patient-days and decreased the costs of hospitalization by \$270,000. The benefits are explained by improved communication between the

health care professionals, optimization of therapy, and improved monitoring and management of adverse drug events. Bond et al [35] showed that pharmacist-conducted review of drug and allergy history alone can reduce adverse drug events by more than 50%, perhaps as a result of their focus on optimization of drug therapy. For example, for the treatment of an infection in a critically ill patient, the ICU pharmacist may contribute specialized knowledge in selecting the narrowest spectrum antibiotic, in selecting an appropriate drug to minimize antibiotic resistance based on patterns of organism resistance in the hospital, in minimizing potential adverse drug reactions, and in selecting the most cost-effective agent. Barriers to implementing the dedicated ICU pharmacist model include the initial investment of money and time to create a new staff position; however, preliminary data show that these initial costs are easily overcome by savings in drug costs and prevention of adverse drug events.

Computer technology in the intensive care unit

The application of computer technology to medical care can improve efficacy and decrease errors at every step of drug administration. Computers can serve as a repository for references. The availability of textbooks, journals, review services and formularies may be valuable at the time of drug prescription. Although the availability of all references by print may be prohibitive, online references are easily accessible (eg, Medline, MDConsult, Physician Drug References [1], UpToDate).

Most institutions in the United States use computers to store patient medical records. A further step in the integration of computer technology into medical practice is patient information capture. Real-time capture of patient data, such as vital signs, pulse oximetry, and laboratory results, aid in the dissemination of information and more informed decisions for drug prescription and drug effect monitoring. Therapeutic drug monitoring can be more effectively regulated with integration of patient data and drug administration.

Physician order entry systems (POES) may also aid in reducing medical errors. Prescription of medications through a computer system may reduce errors in interpretation of the handwritten order by nurses and pharmacists and allow for a check of cross-reactions with other drugs and with the patient's condition. POES are additionally beneficial in decreasing the delay time between physician prescription and actual administration of the medication, because orders may be received by the pharmacist instantaneously. The benefit of POES is recognized by the Leapfrog

Initiative as a necessary measure to improve patient safety [34].

Recent advances in handheld devices make all of the aforementioned systems even more convenient and portable. Software for handheld devices, such as Epocrates Rx (Epocrates Inc. Corp., San Mateo, California) and Medcalc, allow for quick and convenient references for patient data interpretation. While computer technology continues to advance, the major barriers to incorporation of these systems into the medical practice include the initial costs of the computer devices and software, the time to install the appropriate software, the education and willingness of health care professionals to use the technology, and the real possibility of technical malfunction. Future trends in computer technology in the ICU involve expert systems that can simulate human judgment to aid in diagnostic and therapeutic decision making and data mining that can analyze large amounts of data to recognize relationships that have not been otherwise discovered. For example, Clinical-HINTS (Health Intelligence systems) is a horizontally-integrated decision support system that was designed to meet the requirements for clinical information management in an ICU setting in London [36,37].

Summary

The pharmacotherapy of critically ill patients poses numerous challenges to the ICU team. Polypharmacy and alterations in drug disposition are common in the ICU; critically ill patients have limited physiologic reserve to deal with adverse drug events. Careful prescribing, based upon sound pharmacologic principles, decreases the potential for preventable adverse events and maximizes the opportunity for successful therapy. A systematic approach to reporting, analysis, and prevention of errors is a further step in our ultimate goal to provide optimal care for the vulnerable patients whom we support in our ICUs.

References

- [1] Physicians' Desk Reference. 57th edition. Montvale (NJ): Economics Company; 2002.
- [2] Summer WR, Michael JR, Lipsky JJ. Initial aminoglycoside levels in the critically ill. *Crit Care Med* 1983; 11(12):948–50.
- [3] Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *New Engl J Med* 2000;342(20):1471–7.

- [4] Tukey RH, Johnson EF. Molecular aspects of regulation and structures of the drug-metabolizing enzymes. In: Pratt WB, Taylor P, editors. Principles of drug action. 3rd edition. New York: Churchill Livingstone; 1990. p. 423–68.
- [5] Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG. The pharmacological basis of therapeutics. 9th edition. New York: McGraw Hill; 1996.
- [6] Lennard MS. Genetically determined adverse drug reactions involving metabolism. *Drug Saf* 1993;9(1): 60–77.
- [7] Anthony M, Berg MJ. Biologic and molecular mechanisms for sex differences in pharmacokinetics, pharmacodynamics and pharmacogenetics: part I. *J Womens Health Gen Based Med* 2002;11(7):601–15.
- [8] Burroughs VJ, Maxey RW, Levy RA. Racial and ethnic differences in response to medicines: towards individualized pharmaceutical treatment. *J Natl Med Assoc* 2002;94(10 Suppl):1–26.
- [9] Flockhart D. Drug interactions and the cytochrome P450 system: the role of cytochrome P450 2C19. *Clin Pharmacokinet* 1995;29:45–52.
- [10] Relling MV, Cherrie J, Schell MJ, et al. Lower prevalence of the debrisoquin oxidative poor metabolism phenotype in American black versus white subjects. *Clin Pharmacol Ther* 1991;50:308–13.
- [11] Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W. Potential role for pharmacogenomics in reducing adverse drug reactions: a systematic review. *JAMA* 2001; 286(18):2270–9.
- [12] Weinshilboum R. Inheritance and drug response. *N Engl J Med* 2003;348(6):529–37.
- [13] Lerena AL, Alm C, Dahl ML, et al. Haloperidol disposition is dependent on debrisoquine hydroxylation phenotype. *Ther Drug Monit* 1992;14:92–7.
- [14] Freeman BD, Zehnbauser BA, McGrath S, Borecki I, Buchman TG. Cytochrome P450 polymorphisms are associated with reduced warfarin dose. *Surgery* 2000; 128(2):281–5.
- [15] Watkins PB. Drug metabolism by cytochrome P450 in the liver and small bowel. *Gastroenterol Clin N Am* 1992;21(3):511–25.
- [16] Vessel ES. Therapeutic lessons from pharmacogenetics. *Ann Intern Med* 1997;126:653–5.
- [17] Beyth RJ, Shorr RI. Principles of drug therapy in older patients: rational drug prescribing. *Clin Geriatr Med* 2002;18:577–92.
- [18] Beierle I, Meibohm B, Derendorf H. Gender differences in pharmacokinetics and pharmacodynamics. *Int J Clin Pharmacol Ther* 1999;37(11):529–47.
- [19] Luzier AB, Killian A, Wilton JH, Wilson MF, Forrest A, Kazierad DJ. Gender-related effects on metoprolol pharmacokinetics and pharmacodynamics in healthy volunteers. *Clin Pharmacol Ther* 1999;66(6):594–601.
- [20] Rudy AC, Liu Y, Brater C, Hall S. Stereoselective pharmacokinetics and inversion of (r)-ketoprofen in healthy volunteers. *J Clin Pharmacol* 1998;38:3S–10.
- [21] Morgan DJ, Smallwood RA. Clinical significance of pharmacokinetic models of hepatic elimination. *Clin Pharmacokinet* 1990;18:61–76.
- [22] Joynt GM, Lipman J, Gomersall CD, Young RJ, Wong EL, Gin T. The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients. *J Antimicrob Chemother* 2001;47(4):421–9.
- [23] Shadklofsky SI, Israel BC, McClain CJ. Endotoxin administration to humans inhibits hepatic cytochrome P450-mediated drug metabolism. *J Clin Invest* 1994; 94(6):2209–14.
- [24] Muller CM, Scierka A, Stiller RL. Nitric oxide mediates hepatic cytochrome P450 dysfunction induced by endotoxin. *Anesthesiology* 1996;84(6):1435–42.
- [25] Blobner M, Kochs E, Fink H, Mayer B, Veihelmann A, Brill T, et al. Pharmacokinetics and pharmacodynamics of vecuronium in rats with systemic inflammatory response syndrome: treatment with NG-monomethyl-L-arginine. *Anesthesiology* 1999;91(4):999–1005.
- [26] Katzung BG. Basic and clinical pharmacology. 8th edition. New York: Lange Medical Books/McGraw Hill; 2001.
- [27] Keogh A, Spratt P, McCosker C, et al. Ketoconazole reduces the need for cyclosporine after cardiac transplantation. *N Engl J Med* 1995;333:628–33.
- [28] Flockhart D. Cytochrome P450 Drug Interaction Table. Available at: <http://medicine.iupui.edu/flockhart/>. Accessed on May 29, 2003.
- [29] Gupta E, Wang X, Ramirez J, Ratain MJ. Modulation of glucuronidation of SN-38, the active metabolite of irinotecan, by valproic acid and phenobarbital. *Cancer Chemother Pharmacol* 1997;39(5):440–4.
- [30] Prins JM, Buller HR, Kuijper EJ, Tange RA, Speelman P. Once versus thrice daily gentamicin in patients with serious infections. *Lancet* 1993;341(8841):335–9.
- [31] Pronovost P, Wu AW, Dorman T, Morlock L. Building safety into ICU care. *J Crit Care* 2002;17(2):78–85.
- [32] Calabrese AD, Erstad BL, Brandl K, Barletta JF, Kane SL, Sherman DS. Medication administration errors in adult patients in the ICU. *Intensive Care Med* 2001;27: 1592–8.
- [33] Anderson JG, Jay SJ, Anderson M, Hunt TJ. Evaluation of the capability of information technology to prevent adverse drug events: a computer simulation approach. *J Am Med Inform Assoc* 2002;9:479–90.
- [34] Delbanco S. Leaping into patient safety. *Mich Health Hosp* 2001;37(2):28–30.
- [35] Bond CA, Raehl CL, Franke T. Clinical pharmacy services, hospital pharmacy staffing, and medication errors in United States hospitals. *Pharmacotherapy* 2002;22(2):134–47.
- [36] Kalogeropoulos D, Carson ER, Collinson PO. Clinical-HINTS: integrated intelligent ICU patient monitoring and information management system. *Medical Informatics Europe* 1997;22:906–10.
- [37] Murray P, Corbridge T. Critical care pharmacology. In: Hall JB, Schmidt GA, Wood LDH, editors. Principles of critical care. 2d edition. New York: McGraw-Hill Health Professions Division; 1998. p. 1527–51.