Handbook of Drug Monitoring Methods
Handbook of Drug Monitoring Methods

Therapeutics and Drugs of Abuse

Edited by

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To my wife Alice
Starting from the 1970s, therapeutic drug monitoring has evolved from monitoring concentrations of a few antiepileptic drugs to a major discipline in today’s laboratory practice. For a drug with a narrow therapeutic range, therapeutic drug monitoring becomes an essential part of patient management, especially because of the development of immunoassays for measuring concentrations of drugs in a biological matrix. In current practice, 15–20 therapeutic drugs are routinely monitored even in medium-size clinical laboratories, and a list of well over 50 therapeutic drugs can be found in the laboratory test guides of major medical centers in the United States, academic medical centers, and reference laboratories. These centers not only employ immunoassays but also take advantage of sophisticated analytical techniques such as gas chromatography/mass spectrometry and high-performance liquid chromatography coupled with mass spectrometry for therapeutic drug-monitoring services.

Similarly, in the past two decades, drugs of abuse testing became a routine part of emergency room testing and clinical laboratory service. Federal and state governments, as well as the private sector, now recognize the necessity of a drug-free work environment. Moreover, drug testing is a routine part of law enforcement activity in crime and forensic laboratories. Strict laws are also enforced throughout the United States against driving under the influence of alcohol. Therefore, alcohol and drug testing is an important component of most toxicological laboratory services.

Hand book of Drug Monitoring attempts to bridge different analytical techniques used in today’s practice of therapeutic drug monitoring and drugs of abuse as well as alcohol testing with relevant theory, mechanism, and in-depth scientific discussion on each topic. As a handbook at the bench of a clinical laboratory the book serves as a quick reference to find the potential source of a false-positive or a false-negative result. At the same time, this book is a reference for medical technologists, supervisors, laboratory directors, clinical chemists, toxicologists, and pathologists looking in-depth for the cause of a potential interference, as well as a guide to the tests that can be ordered to circumvent such problem.

The book has 22 chapters, 13 focusing on various issues of therapeutic drug monitoring, one on analysis of heavy metals, one on alcohol testing, and seven on issues of drugs of abuse testing. Chapters are written by experts in their relative subspecialties and also by the editor. I am grateful to this outstanding group of contributors because without their generosity and dedication this book would never have been written.

The chapters on therapeutic drug monitoring cover a wide range of topics from clinical utility of free drug monitoring to interferences in digoxin assay, and include issues in monitoring anticonvulsant drugs, immunosuppressants, tricyclic antidepressants, and antiretrovirals used in treating AIDS patients. One chapter is focussed on common interferences from endogenous substances such as bilirubin, hemoglobin, and lipids in immunoassays for therapeutic drugs. Another chapter is dedicated to
interferences from heterophilic antibodies in therapeutic drug monitoring. Pharmacogenomics and personalized medicine is the future frontier of therapeutic drug monitoring. Chapter 11 is dedicated to this subject.

Use of complementary and alternative medicines by the general population is increasing steadily not only in the United States but also worldwide. Unexpected concentrations of therapeutic drugs because of use of complementary and alternative medicine have been well documented in the literature; for example, low concentrations of many therapeutic drugs because of self-medications with St. John’s Wort, an herbal antidepressant. Chapter 13 is dedicated to important issues of drug–herb and drug–food interactions and their impact on therapeutic drug monitoring.

People try to beat drug tests to avoid consequences of a failed test. Chapter 17 discusses common household adulterants, as well as other adulterants such as nitrite, pyridinium chlorochromate, and glutaraldehyde, which people add in vitro to their urine to cheat on drug tests. Routine specimen integrity testing may not detect some adulterants, and practical tips are given in Chapter 17 to identify such adulterated specimens. There is much interference with drugs of abuse testing of the amphetamine class. Therefore, Chapter 20 addresses this important issue. Designer drugs and rave party drugs may escape detection in routine laboratory procedures for drugs of abuse testing. This topic and how to avoid such pitfalls are addressed in Chapter 19. Alternative specimens for drugs of abuse testing such as hair, saliva, sweat, and meconium are the topics of Chapter 18.

An analytic true positive may be a clinically false positive, for example, positive opiate test because of ingestion of poppy seed product. This important issue is addressed in Chapter 21 which will be helpful to medical review officers as well as to any toxicologist. Another chapter is dedicated to the topic of expert witness testimony by technologists performing alcohol and drugs of abuse testing and toxicologists supervising such tests, when often called as factual or expert witnesses in a court of law.

I express my sincere thanks to Robert L. Hunter, MD, PhD, Professor and Chairman, Department of Pathology and Laboratory Medicine, University of Texas-Houston Medical School, for his continued support for the last one-and-half years as I worked on this project. In addition, he critically read all chapters I wrote and made excellent recommendations for improvement. Alice Wells, MT(ASCP), read the entire manuscript and checked whether references were put in correct order and number and also helped me in editing this book. John Mohr, PharmD, assistant professor of internal medicine at our institution, reviewed therapeutic ranges and helped me with important suggestions. I also thank him. I also thank two of our pathology residents, Michelle Rodriguez, MD, and Anna Richmond, MD, for critically reading several chapters and making helpful suggestions. Last but not least, I express my thanks to my wife Alice for tolerating the long hours spent on this project and her continued support. Finally, readers will be the judge of the final success of this project. If they find this book helpful, we will feel our effort is well rewarded.

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<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Authors</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Drug–Herb and Drug–Food Interactions: Impact on Therapeutic Drug Monitoring</td>
<td>Amitava Dasgupta</td>
<td>235</td>
</tr>
<tr>
<td>14</td>
<td>Toxic Element Testing with Clinical Specimens</td>
<td>Gwendolyn A. McMillin and Joshua A. Bornhorst</td>
<td>263</td>
</tr>
<tr>
<td>15</td>
<td>Alcohol Testing</td>
<td>Steve C. Kazmierczak and Hassan M. E. Azzazy</td>
<td>283</td>
</tr>
<tr>
<td>16</td>
<td>Introduction to Drugs of Abuse Testing</td>
<td>Tai C. Kwong</td>
<td>297</td>
</tr>
<tr>
<td>17</td>
<td>Urinary Adulterants and Drugs of Abuse Testing</td>
<td>Amitava Dasgupta</td>
<td>317</td>
</tr>
<tr>
<td>18</td>
<td>Hair, Oral Fluid, Sweat, and Meconium Testing for Drugs of Abuse:</td>
<td>Uttam Garg</td>
<td>337</td>
</tr>
<tr>
<td>19</td>
<td>Abused and Designer Drugs and How They Escape Detection</td>
<td>Barry Levine and Rebecca Jufer-Phipps</td>
<td>365</td>
</tr>
<tr>
<td>20</td>
<td>Interpretation of Amphetamines Screening and Confirmation Testing</td>
<td>Larry Broussard</td>
<td>379</td>
</tr>
<tr>
<td>21</td>
<td>Clinical False-Positive Drug Test Results</td>
<td>Tai C. Kwong</td>
<td>395</td>
</tr>
<tr>
<td>22</td>
<td>Providing Expert Witness for Alcohol and Positive Drugs of Abuse Test Results</td>
<td>Andrea Terrell, William Clarke, Michael Evans, and Jennifer Collins</td>
<td>407</td>
</tr>
</tbody>
</table>

Index                                                                 |                                                                                             | 421  |
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Introduction to Therapeutic Drug Monitoring

Amitava Dasgupta, PhD

Contents

1. Introduction
2. Implications of Therapeutic Drug Monitoring
3. Characteristics of Drugs Require Monitoring
4. Factors Affecting Serum Drug Concentrations
5. Effect of Disease on Serum Drug Concentrations
6. Drug Metabolism and Clearance in Neonates, Children, and Elderly
7. Therapeutic Drug Monitoring of Individual Drugs
8. Conclusions

Summary

Therapeutic drug monitoring is defined as measuring serum concentrations of a drug in a single or multiple time points in a biological matrix after a dosage. The purpose of therapeutic drug monitoring is to individualize the dosage to achieve maximum efficacy of a drug and at the same time minimize adverse drug reactions. Therapeutic drug monitoring has clinical importance for drugs with a narrow therapeutic window, such as various anticonvulsants, cardioactive drugs, theophylline, immunosuppressants, tricyclic antidepressants, antiretroviral drugs, certain antibiotics, and neoplastic drugs. Altered pharmacokinetic parameters are observed for many drugs in disease states including hepatic and renal impairment, cardiovascular disease, thyroid dysfunction, and cystic fibrosis. Altered drug disposition also occurs in pregnant women. Therapeutic drug monitoring helps to identify such altered drug disposition, and dosage adjustment can be made for proper management of the patient to avoid adverse reactions. Therefore, therapeutic drug monitoring is cost effective in health care.

Key Words: Anticonvulsants; antineoplastic drugs; cardioactive drugs; immunosuppressants; pharmacokinetics; therapeutic drug monitoring; tricyclic antidepressants.

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1. INTRODUCTION

Pharmacological response of a drug given in a selected dosing regimen depends on several factors, including compliance of the patient, bioavailability of the drug, rate of drug metabolism (depending on the genetic make up of the patient) as well as the protein-binding ability of the drug. It is well established that only unbound (free) free drug can bind with the receptor and produce the desired effect. For certain drugs, a good correlation exists between serum drug concentrations and pharmacological response. Therefore, monitoring serum concentrations of these drugs is beneficial for patient management especially if the drugs have very narrow therapeutic ranges. Moreover, for these drugs, adjustment of dosing may be more useful based on serum drug concentration rather than routine assessment of a patient. For example, adjusting phenytoin dosing in patients based on their serum phenytoin concentrations rather than seizure frequencies not only decrease the morbidity but also prevent unnecessary toxicity of phenytoin in these patients. Peterson et al. (1) reported that in their study with 114 patients, total phenytoin concentrations provided as good an indication of the clinical response as the free phenytoin concentrations in most patients, but in 14.2% patients, free phenytoin concentrations were better correlated with clinical picture than total phenytoin concentrations. Another report indicated that quality of life improved in a group of patients with congestive heart failure where digoxin dosing was based on target therapeutic concentrations (2).

Therapeutic drug monitoring has been used in clinical practice to individualize drug therapy since the beginning of the 1970s. The goal of therapeutic drug monitoring is to optimize pharmacological responses of a drug while avoiding adverse effects. Usually for drugs that are routinely monitored in clinical laboratories, serum concentrations are a better predictor of desired pharmacological effects than the dose. Moreover, therapeutic drug monitoring is also utilized to monitor a patient’s compliance with a drug regimen and to identify potential drug–drug or food–drug interactions.

Therapeutic drug monitoring not only consists of measuring the concentration of a drug in a biological matrix but it also involves the proper interpretation of the value using pharmacokinetic parameters, drawing appropriate conclusion regarding the drug concentration and dose adjustment. The International Association for Therapeutic Drug Monitoring and Clinical Toxicology adopted the following definition, “Therapeutic drug monitoring is defined as the measurement made in the laboratory of a parameter that, with appropriate interpretation, will directly influence prescribing procedures. Commonly, the measurement is in a biological matrix of a prescribed xenobiotic, but it may also be of an endogenous compound prescribed as a replacement therapy in an individual who is physiologically or pathologically deficient in that compound” (3).

Only a fraction of drugs currently used worldwide require routine monitoring. For a drug in which the gap between therapeutic and toxic concentration is wide, therapeutic drug monitoring is not indicated unless in the case of intentional overdose, for example with salicylate or acetaminophen. In an Italian collaborative study on the utilization of therapeutic drug monitoring, it was noted that only 16.3% of the population was given drugs for which therapeutic drug monitoring was available in the hospital. Digoxin was the most frequently ordered drug in their study population (4).
Chapter 1 / Therapeutic Drug Monitoring

2. IMPLICATIONS OF THERAPEUTIC DRUG MONITORING

When appropriate, patients gain both medically and economically from therapeutic drug monitoring. Many reports in the literature indicate that therapeutic drug monitoring can decrease hospital stay and have important implications on the cost of medical care. Reduced drug-related toxicities are beneficial for patients and also diminish the liability of physicians. Ried et al. (5) evaluated the effectiveness of therapeutic drug monitoring in reducing toxic drug reactions by meta-analysis of 14 studies. The authors concluded that patients monitored for appropriate drugs suffered fewer toxic drug reactions than patients for whom therapeutic drug monitoring was not undertaken. Another study reported that determination of serum drug concentrations and evaluation of such results by clinical pharmacists resulted in significant cost savings (6). Crist et al. evaluated the impact of therapeutic drug monitoring of aminoglycoside (gentamicin or tobramycin) using 221 patients on the length of hospital stay, cost effectiveness, and related factors. The mean length of hospital stay was 8.4 days in the patient group that received individualized aminoglycoside doses (study group) versus 11.8 days in the control group. In addition, the hospital cost was lower by $725 per patient in the study group which would produce a savings of $640,000 at the author’s institution (7).

3. CHARACTERISTICS OF DRUGS REQUIRE MONITORING

Drugs that are candidates for therapeutic drug monitoring have several characteristics. A list of commonly monitored and less frequently monitored therapeutic drugs is given in Table 1. The following are the characteristics of a drug where monitoring is beneficial:

1. Narrow therapeutic range where the dose of a drug that produces the desired therapeutic concentrations is near the dose that may also produce toxic serum concentration.
2. There is no clearly defined clinical parameter that allows dose adjustments.
3. There is an unpredictable relationship between dose and clinical outcome. For example, a certain dose may produce a desirable pharmacological response in one patient but the same dose may cause toxicity in another patient.
4. Toxicity of a drug may lead to hospitalization, irreversible organ damage, and even death.
5. There is a correlation between serum concentration of the drug and its efficacy as well as toxicity. For strongly protein-bound drugs (protein binding >80%), a better correlation may be observed between unbound (free) drug concentration and clinical outcome rather than between traditionally monitored total drug concentration (free + protein bound) and clinical outcome. This is particularly applicable to a special patient population with hepatic or renal impairment. Moreover, elderly patients and critically ill patients may also demonstrate elevated concentrations of free drugs. Therefore, for these patients, monitoring free drug concentrations (free phenytoin, free valproic acid, free carbamazepine etc) is strongly recommended instead of monitoring total drug concentrations. Clinical utility of free drug monitoring is discussed in detail in Chapter 2.
Table 1  
Commonly and Less Frequently Monitored Therapeutic Drugs in Clinical Laboratories

<table>
<thead>
<tr>
<th>Class of Drug</th>
<th>Commonly Monitored</th>
<th>Less Frequently Monitored</th>
</tr>
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<tbody>
<tr>
<td>Anticonvulsants</td>
<td>Phenytoin&lt;sup&gt;a&lt;/sup&gt;, carbamazepine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Diazepam, clonazepam</td>
</tr>
<tr>
<td></td>
<td>Valproic acid&lt;sup&gt;a&lt;/sup&gt;, phenobarbital&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Felbamate, methsuximide</td>
</tr>
<tr>
<td></td>
<td>Primidone&lt;sup&gt;a&lt;/sup&gt;, ethosuximide&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Gabapentin, zonisamide</td>
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<tr>
<td></td>
<td>Lamotrigine</td>
<td></td>
</tr>
<tr>
<td>Cardioactive</td>
<td>Digoxin&lt;sup&gt;a&lt;/sup&gt;, quinidine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Flecainide, verapamil</td>
</tr>
<tr>
<td></td>
<td>Disopyramide&lt;sup&gt;a&lt;/sup&gt;, lidocaine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mexiletine, tocaimide</td>
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<td></td>
<td>Procainamide&lt;sup&gt;a&lt;/sup&gt;, NAPA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Propanol, amiodarone</td>
</tr>
<tr>
<td></td>
<td>Lamotrigine</td>
<td></td>
</tr>
<tr>
<td>Antiasthmatic</td>
<td>Theophylline&lt;sup&gt;a&lt;/sup&gt;, caffeine&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<tr>
<td></td>
<td>Mycophenolic acid&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Immunosuppressants</td>
<td>Cyclosporine&lt;sup&gt;a&lt;/sup&gt;, tacrolimus&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Sirolimus, Everolimus</td>
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<tr>
<td>Antidepressants</td>
<td>Amitriptyline, nortriptyline</td>
<td>Fluoxetine/norfluoxetine</td>
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<td></td>
<td>Doxepin, imipramine</td>
<td>Paroxetine, sertraline</td>
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<td></td>
<td>Desipramine, clomipramine</td>
<td>Haloperidol</td>
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<tr>
<td></td>
<td>Trimipramine, lithium&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Antibiotic</td>
<td>Amikacin&lt;sup&gt;a&lt;/sup&gt;, gentamicin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Ciprofloxacin, cefazolin</td>
</tr>
<tr>
<td></td>
<td>Tobramycin&lt;sup&gt;a&lt;/sup&gt;, vancomycin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Chloramphenicol, nafcillin</td>
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<tr>
<td>Antiviral</td>
<td>Indinavir, nelfinavir</td>
<td>Ritonavir, saquinavir</td>
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<td></td>
<td>Ritavirin, nevirapine</td>
<td>Delavirdine, nevirapine</td>
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<tr>
<td>Antineoplastic</td>
<td>Methotrexate&lt;sup&gt;a&lt;/sup&gt; cisplatin</td>
<td>Doxorubicin, tamoxifen</td>
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<tr>
<td></td>
<td></td>
<td>Cyclophosphamide, 5-fluorouracil</td>
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<tr>
<td>Analgesic</td>
<td>Acetaminophen&lt;sup&gt;a&lt;/sup&gt;, salicylate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Ibuprofen, pentobarbital</td>
</tr>
</tbody>
</table>

<sup>a</sup> Immunoassay commercially available.  
<sup>b</sup> Automated assay commercially available.

4. FACTORS AFFECTING SERUM DRUG CONCENTRATIONS

The serum concentration of a particular drug is determined by absorption, distribution, metabolism, and excretion of a drug. Major characteristics that affect serum drug concentrations include genetic make up of a patient as well as age, gender, weight, habits (such as smoking), and diet. Elderly and newborns may metabolize a particular drug more slowly than others. Some drugs, for example theophylline, distributes to lean weight only where other drugs, such as phenytoin, distributes to total weight. Diseases may alter serum drug concentrations dramatically. Hepatic disease may alter metabolism of a drug where a patient with renal failure may clear a drug in urine more slowly than a patient with normal renal function. Pregnancy alters metabolism of several drugs while drug–drug interactions may also significantly alter serum drug concentrations.

4.1. Pharmacokinetics and Serum Drug Concentrations

When a drug is given orally, it undergoes several steps in the body and its concentration in serum or whole blood is affected by certain steps.
1. **Liberation:** The release of a drug from the dosage form (tablet, capsule, extended release formulation)

2. **Absorption:** Movement of drug from site of administration (for drugs taken orally) to blood circulation

3. **Distribution:** Movement of a drug from the blood circulation to tissues. This distribution in most cases is reversible. Certain drugs also cross the blood brain barrier.

4. **Metabolism:** Chemical transformation of a drug to the active and inactive metabolites. Cytochrome P450 enzyme system is the major drug-metabolizing agent of body.

5. **Excretion:** Elimination of the drug from the body through renal, biliary, or pulmonary mechanism.

Liberation of a drug after oral administration depends on the formulation of the dosage. Immediate release formulation releases the drugs at once from the dosage form when administered. On the contrary, the same drug may also be available in sustained release formulation. The rationales for specialized oral formulations of drugs include prolongation of the effect for increased patient convenience and reduction of adverse effects through lower peak plasma concentrations. Local and systematic adverse effects of a drug can also be reduced by use of controlled release delivery systems (8). Over the past decade, there has been a significant growth in the introduction of these new formulations of existing drugs designed to improve patient management (9). Controlled release dosage formulations include osmotic pumps and zero-order kinetics system to control the release rate of a drug, bio-adhesive systems and gastric retention devices to control gastrointestinal transit of a drug, bio-erodible hydrogels; molecular carrier system such as cyclodextrin-encapsuled drugs; externally activated system; and colloidal systems such as liposomes and microspheres (8).

The effect of food intake on bioavailability of a drug is more apparent on a single unit non-disintegrating dosage form, although controlled release formulations are not completely immune from the food intake. Polymers occupy a major portion of materials used for controlled release formulations and drug-targeting systems because this class of substances presents seemingly endless diversity in chemistry and topology (10). Microparticles are small solid particulate carriers containing dispersed drug particles either in solution or in crystalline form. The importance of microparticles is growing because of their utilization as carriers for drugs and other therapeutic agents. Microparticles are made from natural or synthetic polymers. Different materials have been used for microparticles systems, such as albumin, gelatin, starch, ethyl cellulose, and synthetic polymers, such as poly lactic acid, poly cyanoacrylates, and poly hydroxybutyrate (11). Enteric coded formulations resist gastric acid degradation and deliver drugs into the distal small intestine and proximal colon. Budesonide, a synthetic glucocorticoid with high topical anti-inflammatory activity and little or no systemic effect, has been administered through inhalation for the treatment of inflammatory airways infection. Budesonide is also manufactured into two commercially available oral control release formulations, and both the formulations are enteric coded (12). Recently, enteric coded formulation of mycophenolic acid mofetil, a prodrug of immunosuppressant mycophenolic acid is commercially available (13). Solid nanoparticles were introduced in the 1990s as an alternative to microemulsions, polymeric nanoparticles, and liposomes. These nanoparticles have several advantages such as biocompatibility and their capability of controlled and targeted drug release (14).
Oral controlled release drug delivery systems can be further classified into two broad categories; single-unit dosage forms (SUDFs) such as tablets or capsules and multiple-unit dosage forms (MUDFs) such as granules, pellets, or mini-tablets. Mini-tablets are tablets with a diameter equal to or smaller than 2–3 mm (15). Several mini-tablets can be either filled into hard capsules or compacted to a bigger tablet that after disintegration releases these subunits as multiple dosage form. Many drugs are available in sustained release formulations. For example, the immediate release venlafaxine, an antidepressant formulation, requires twice-daily administration whereas the extended release formulation is designed for once-daily administration. Another antidepressant fluoxetine is available in a sustained release dosage form, which requires once-weekly administration for continuation of therapy for depression (16). Calcium channel antagonists are a heterogenous group of drugs with different cardiovascular effects and are effective in the treatment of hypertension and angina pectoris. A number of these agents are commercially available in sustained release formulations (17). Anticonvulsants, such as carbamazepine and valproic acid, are also available in sustained release formulations (18,19). Theophylline is available in prolonged release form (20). Procainamide, a class IA antiarrhythmic drug, is also administered as sustained release formulation (21). McCormack and Keating (22) recently reviewed the use of prolonged release nicotinic acid in treating lipid abnormality.

Absorption of a drug depends on the route of administration as well as drug formulation. Generally, an oral administration is the route of choice in the practice of pharmacotherapy, but under certain circumstances (nausea, vomiting, convulsions etc), rectal route may present a practical alternative for drug administration. Rectal administration is now well accepted for delivering anticonvulsants, non-narcotic and narcotic analgesics, theophylline, and antibacterial and antiemetic agents. This route can also be used for inducing anesthesia in children. The rate and extent of rectal drug absorption are often lower compared with oral absorption possibly because of small surface area available for drug absorption. The composition of rectal formulation (solid vs. liquid, nature of suppository) also plays an important role in the absorption of a drug. However, for certain drugs, rectal absorption is higher compared with absorption of the same drug given orally. This phenomenon may be due to avoidance of the hepatic first-pass metabolism after rectal delivery. These drugs include lidocaine, morphine, metoclopramide, ergotamine, and propranolol. Local irritation is a possible complication of rectal drug delivery (23).

When a drug is administered by direct injection, it enters the blood circulation immediately. Sometimes, a drug may be administered by the intravenous or intramuscular route as a prodrug if the parent drug has potential for adverse drug reactions at the injection site. Fosphenytoin is a phosphate ester prodrug of phenytoin developed as an alternative to intravenous phenytoin for acute treatment of seizure. However, the bioavailability of derived phenytoin from fosphenytoin relative to intravenous phenytoin administration is almost 100% (24).

There is considerable interest to deliver a drug through the transdermal route. However, the skin, particularly the stratum corneum, poses a formidable barrier to drug penetration, thus limiting topical and transdermal bioavailability of a drug (25). As early as in 1967, it was demonstrated that the bioavailability of topically applied hydrocortisone alcohol was only 1.7% (26). For a drug to be delivered passively
through the skin, it should have adequate lipophilicity and a molecular weight <500 D (27). Penetration enhancement techniques are usually used to improve bioavailability following transdermal delivery of a drug. This enhancement technique is based on drug/vehicle optimization such as drug selection, prodrug and ion pairs, supersaturated drug solutions, eutectic systems, complexation, liposome vesicles, and particles. Enhancement through modification of stratum corneum by hydration, and chemical enhancers acting on the lipids and keratin of stratum corneum are also utilized for transdermal drug delivery (25). Major routes of administration of drugs in a patient and its advantages and disadvantages are summarized in Table 2.

When a drug enters the blood circulation, it is distributed throughout the body to various tissues. The pharmacokinetic term most often used to describe distribution is called volume of distribution (V\textsubscript{d}). This is the hypothetical volume to account for all drugs in the body and is also termed as the apparent V\textsubscript{d}

\[
V_d = \text{Dose/plasma concentration of drug}
\]

The amount of a drug at a specific site, where it exerts its pharmacological activity or toxicity, is usually a very small fraction of the total amount of the drug in the body because of its distribution in tissue and blood. Even in a target tissue, only a fraction of the drug binds with the receptors and exerts its pharmacological activity. Protein binding of a drug also limits its movement into tissues. Muscle and fat tissues may serve

<table>
<thead>
<tr>
<th>Route</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Oral</td>
<td>Route of choice because of ease of administration</td>
<td>Longer time to peak level; Food, alcohol may affect levels</td>
</tr>
<tr>
<td></td>
<td>Sustained release formulation prolonged effect</td>
<td>Gastric-emptying time, First-pass metabolism affect levels</td>
</tr>
<tr>
<td>Rectal</td>
<td>Can be used if patient has nausea, vomiting, convulsion Inducing anesthesia in children Few drugs show higher absorption compared with oral route because of avoidance of first-pass metabolism such as lidocaine</td>
<td>Absorption may be low; Local irritation</td>
</tr>
<tr>
<td>Intravenous</td>
<td>Rapid peak concentration and action</td>
<td>Need a intravascular access for administration/discomfort</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>No first-pass metabolism 100% Bioavailability</td>
<td></td>
</tr>
<tr>
<td>Sublingual</td>
<td>Ease of application</td>
<td>Poor systematic absorption</td>
</tr>
<tr>
<td></td>
<td>Rapid absorption and action</td>
<td>First-pass metabolism</td>
</tr>
<tr>
<td></td>
<td>Ease of application</td>
<td></td>
</tr>
</tbody>
</table>
as a reservoir for lipophilic drugs. For central nervous system drugs (neurotherapeutics), penetration of blood brain barrier is essential. Usually, moderately lipophilic drugs can cross the blood brain barrier by passive diffusion, and hydrogen-bonding capacity of a drug can significantly influence the central nervous system uptake. However, drugs may also cross the blood brain barrier by active transport (28). When a CNS drug is given as a prodrug, a delay may be observed in the accumulation of the drug in the brain because of the time required for conversion of the prodrug to the original drug. Walton et al. (29) reported that when fosphenytoin, the prodrug of phenytoin, was administered in rats, lower brain levels of phenytoin were typically observed compared with brain phenytoin levels when phenytoin was directly administered in rats. Many drugs do not effectively penetrate the blood brain barrier. Ningaraj et al. (30) recently commented on challenges in delivering new anticancer drugs to brain tumors because most new anticancer drugs that are effective outside the brain have failed in clinical trials in treating brain tumors, in part because of poor penetration across the blood brain barrier and the blood brain tumor barrier. However, there are also advantages when a drug does not effectively penetrate the blood brain barrier. Second generation antihistamines have a low tendency to cross the blood brain barrier and thus reduce sedation and impairment in patients (31).

Drugs usually undergo chemical transformation before elimination, and the process is termed as metabolism. Drug metabolism may occur in any tissue including the blood. For example, plasma cholinesterase, a glycoprotein synthesized in the liver metabolizes drugs such as cocaine and succinylcholine. Hoffman et al. (32) reported that decreased plasma cholinesterase activity is associated with the increasing risk of life-threatening cocaine toxicity. However, the liver is the main site for drug metabolism. The role of metabolism is to convert lipophilic non-polar molecules to more polar water-soluble compounds for effective excretion in urine. The drug molecule can be modified structurally (oxidation, reduction, or hydrolysis), or the drug may undergo conjugation (glucuronidation, sulfation) that increases its polarity. The rate of enzymatic process that metabolizes most drugs is usually characterized by the Michaelis–Menten equation and follows first-order kinetics (rate of elimination is proportional to drug concentration). However, for certain drugs for example, phenytoin, the metabolism is capacity-limited.

The half-life of a drug is the time required for the serum concentration to be reduced by 50%. The fraction of a drug that remains in the body after five half-lives is approximately 0.03 (Fig. 1). However, after multiple doses, usually a drug reaches a steady state after five to seven half-lives. Half-life of a drug can be calculated from elimination rate constant (K) of a drug.

\[
\text{Half-life} = \frac{0.693}{K}
\]

Elimination rate constant can be easily calculated from the serum concentrations of a drug at two different time points using the formula where \(Ct_1\) is the concentration of drug at a time point \(t_1\) and \(Ct_2\) is the concentration of the same drug at a later time point \(t_2\):

\[
K = \frac{\ln Ct_1 - \ln Ct_2}{t_2 - t_1}
\]
A drug may also undergo extensive metabolism before fully entering the blood circulation. This process is called first-pass metabolism. The drugs that are eliminated by conjugation (estrogen, progesterone, morphine, etc.) undergo significant first-pass metabolism because the gut is rich in conjugating enzymes. Factors such as gender, disease state, enzyme induction and inhibition, genetic polymorphism, and food may cause significant variability in pharmacokinetics of a drug undergoing first-pass metabolism. Drug concentrations obtained from individuals given the same dose may vary even sevenfold (33).

Renal excretion is a major pathway for the elimination of drugs and their metabolites. Therefore, impaired renal function may cause accumulation of drugs and metabolites in serum, thus increasing the risk of adverse drug effect. This may be particularly important for drugs that have active metabolites, such as procainamide and carbamazepine. Moreover, other pathological conditions such as liver disease, congestive heart failure, and hypothyroidism may also decrease clearance of drugs. Drugs may also be excreted through other routes, such as biliary excretion. The factors that determine elimination of a drug through the biliary track include chemical structure, polarity, and molecular weight as well as active transport sites within the liver cell membranes for that particular drug. A drug excreted in bile may be reabsorbed from the gastrointestinal track or a drug conjugate may be hydrolyzed by the bacteria of the gut, liberating the original drug, which can return into the blood circulation. Enterohepatic circulation may prolong the effects of a drug. Cholestatic disease states, in which flow of normal bile flow is reduced, will reduce bile clearance of a drug and may cause drug toxicity (34). Moreover, drug–drug interaction may involve bile clearance pathway of
a drug. For example, quinidine not only reduces renal clearance of digoxin but also causes an average reduction of 42% in bile clearance of digoxin (35).

### 4.2. Genetic Factors Affecting Serum Drug Concentrations

There are wide variations in a patient’s response to drug therapy. One patient may demonstrate desirable pharmacological effect after administration of a particular dose of a drug whereas another patient may show only subtle effects. Although such variability may be related to renal disease or liver disease or due to drug–drug interactions, alteration of drug-metabolizing capacity caused by hereditary enzymatic deficiency or over-expression may also lead to an altered response of a patient to a drug. As early as in 1964, Kurt et al. (36) reported that phenytoin toxicity in a patient receiving the usual dose of phenytoin was probably related to a rare genetic deficiency in phenytoin hydroxylation.

Although over 15 different enzymes have been identified in the liver, in practice the cytochrome P450 isoenzymes that mediate the oxidative metabolism of many drugs include CYP1A2, CYP2C9, CYP2D6, CYP2E1, and CYP3A4. These enzymes show marked variations in different people. Some of these enzymes also exhibit genetic polymorphism (CYP2C19, CYP2D6), and a subset of the population may be deficient in enzyme activity (poor metabolizer). Therefore, if a drug is administered to a patient who is a poor metabolizer, drug toxicity may be observed even with a standard dose of the drug. Phenotyping procedures commonly involve administration of a probe drug and calculation of the urine or plasma metabolic ratio. CYP3A4 is the most abundant hepatic oxidative enzyme in the liver, and it accounts for almost 30% of the cytochrome P450 enzyme system (37). This isoenzyme is also present in significant amounts in the epithelium of the gut, and orally administered drugs, which are substrate of CYP3A4, may undergo significant metabolism before entering circulation. CYP3A4 exhibits significant inter-individual variation that may be as high as 20-fold. The knowledge that a drug is metabolized by a certain cytochrome P450 enzyme is indicative that this drug can competitively inhibit the metabolism of other drugs, which are also substrates of this enzyme. Often the cytochrome P450 can be induced by another drug or a herbal supplement, such a St. John’s wort resulting in a lower plasma concentration of a drug because of increased metabolism of the drug. Drug interactions with St. John’s wort are discussed in detail in Chapter 13.

Pharmacogenomics approach to personalized medicine is based on the utilization of genetic information data in pharmacotherapy and drug delivery thus ensuring better drug efficacy and safety in patient management. Currently, the concept of personalized medicine and pharmacogenetics are likely to improve the areas of pharmacokinetics and pharmacodynamics because genetic polymorphisms have already been detected and analyzed in genes coding drug-metabolizing enzymes, transporters as well as target receptors. The potential of applying genotyping and haplotype analysis in future medical care could eventually lead to pharmacotyping referring to individualized drug delivery profiling based on genetic information (38). The United States Federal Drug Administration (FDA) has granted market approval for the first pharmacogenetic testing using a DNA microarray, the AmpliChip CYP450, which genotypes cytochrome P450 (CYP2D6 and CYP2C19). The test uses software to predict phenotypes and tests for 27 CYP2D6 alleles (39). Pharmacogenomics issues are discussed in Chapter 11.
4.3. Gender Differences and Serum Drug Concentrations

Biological differences between men and women result in differences in response to drug therapy. Both pharmacokinetic and pharmacodynamic differences exist between men and women. In general, men have a larger body size than women, which results in larger distribution volumes and faster total clearance of many drugs in men compared with that in women. Moreover, greater body fat in women may lead to increases in distribution of lipophilic drugs in females (40). Slower gastric emptying of women can significantly delay the onset of effectiveness of entericoated dosage form as well as differences in gastric pH between men and women may also affect dissolution of a drug between genders (41). Hepatic metabolism of drugs by Phase I (oxidation, reduction, and hydrolysis through cytochrome P450’s 1A, 2D6, and 2E1) and Phase II (conjugative metabolism by glucuronidation, glucuronyl transferase, methyltransferases, and dehydrogenases) mechanism and by combined oxidation/conjugative mechanism may result in faster drug clearance in men compared with that in women. However, metabolism of drugs by CYP2C9, CYP2C19, and N-acetyltransferase appears to be similar in both males and females. In contrast, metabolism of certain drugs that are substrates for CYP3A4 appeared to be mildly or moderately faster in women compared with that in men. Clearance of drugs that are substrates to P-glycoprotein appears to be comparable in both genders (40). Additional gender-related factors, such as intake of hormonal contraceptives, may also have further modulating effects on CYP2D6, CYP2C19 as well as phase II metabolism of drugs (42).

Women experience more adverse reactions to treatment with drugs than men. A Bayesian statistical analysis of sex difference in adverse drug reactions indicated that although about same numbers of adverse events were reported for both men and women, those reported for women were more serious. One example of a sex difference in toxicity of drugs is the drug-induced cardiac arrhythmia, torsades de pointe (43). The efficacy of antiretroviral therapy in HIV-infected patients appears to be similar between men and women, but women may experience higher toxicity profiles (44). Fleisch et al. recently commented that because of gender differences in pharmacokinetic and pharmacodynamic responses in drugs, more women should be recruited in clinical trials for new drugs. Traditionally, women are underrepresented as participants in clinical drug trials (45).

Theophylline is metabolized by CYP1A2. In one study involving 24 subjects, it was observed that theophylline metabolism is faster in women than in men (6h in female non-smoker vs. 9.3 h in male non-smokers) (46). Phenytoin and naproxen are mainly metabolized by CYP2C9. Rugstad et al. (47) reported that there was an increase in plasma naproxen concentrations with age and that females also had higher plasma concentrations of naproxen compared with males. Although women showed slightly lower concentration of phenytoin compared with men when corrected for body weight and height, the difference was not statistically significant (48). The activity of CYP2C19 may be higher in males than in females. The metabolism of mephobarbital was significantly faster in males than in females when compared after a single oral dose of 400 mg of the drug. The sex difference was more significant with the R-enantiomer (49). Clomipramine, which is metabolized by CYP2D6 and CYP2C19, has a higher clearance rate in males compared with that in females (50).
Propranolol metabolism is also faster in males than in females (51). The metabolism of methylprednisolone is mediated by CYP3A4, and in one report, metabolism was higher in women than in men (52). Many other drugs are also metabolized by CYP3A4, the major isoenzyme of human cytochrome P450 enzyme system. Higher clearance of a drug that is a substrate of CYP3A4 in women has been reported. Wolbold et al. found twofold higher CYP3A4 levels in women compared with that in men based on their analysis of 94 well-characterized surgical liver samples. Higher expression in women was also observed in CYP3A4 messenger RNA (mRNA) transcripts, suggesting a pre-translational mechanism. Expression of pregnane X receptor (PXR), which plays a major role in induction of CYP3A4, was also correlated with CYP3A4 in mRNA level, but no sex difference was observed in the expression of PXR mRNA. No sex difference was also observed in P-glycoprotein expression (53). In contrast, Bebia et al. observed no sex difference in phenotype of CYP2C19, CYP3A4, and CYP2D6 based on a study of 161 normal subjects. CYP2E1 showed an age-associated increase, which developed earlier in male subjects than in female subjects (54). Many drugs are metabolized by conjugation. In one study, acetaminophen (paracetamol) clearance was 22% greater in young males compared with that in age-adjusted young females. This difference was entirely because of increase in activity of the glucuronidation pathway in males, and no sex difference was observed in other pathways of paracetamol metabolism (55).

4.4. Food Intake and Serum Drug Concentrations

It has long been recognized that food alters absorption and metabolism of many drugs. Grapefruit juice, Seville orange juice, orange juice, and cranberry juice alter pharmacokinetics of many drugs. Food–drug interactions are discussed in detail in Chapter 13.

4.5. Alcohol and Drug Interactions

Fatal toxicity may occur from alcohol and drug overdoses. In many instances, in the presence of alcohol, a lower concentration of drug may cause fatality because of drug–alcohol interactions. In a Finnish study, it was found that median amitriptyline and propoxyphene concentrations were lower in alcohol-related fatal cases compared with cases where no alcohol was involved. The authors concluded that when alcohol is present, a relatively small overdose of a drug may cause fatality (56). Although alcohol is mostly metabolized in the liver by hepatic alcohol dehydrogenase, long-term intake of large amount of alcohol induces other pathways of metabolism, in particular, the microsomal alcohol-oxidizing system involving CYP2E1. In contrast, acute ingestion of alcohol is likely to cause inhibition of this enzyme (57). CYP2E1 also metabolizes and activates many toxicological substrates to more active products, and induction of CYP2E1 plays an important role in oxidative stress and toxicity in ethanol-induced liver injury (58).

There are two types of interactions between alcohol and a drug: pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions occur when alcohol interferes with the hepatic metabolism of a drug. Pharmacodynamic interactions occur when alcohol enhances the effect of a drug, particularly in the central nervous system. In this type of interaction, alcohol alters the effect of a drug without changing its concentration in the
blood (59). The package insert of many antibiotics states that the medication should not be taken with alcohol although only a few antibiotics have reported interactions with alcohol. Erythromycin may increase blood concentration of alcohol by accelerating gastric emptying (59). Histamine H₂ receptor antagonists, such as cimetidine, ranitidine, nizatidine, and famotidine, reduce the activity of alcohol dehydrogenase (60). DiPadova et al. studied the interactions between alcohol and cimetidine, ranitidine as well as famotidine using human subjects. Relative to baseline, ranitidine increased the mean peak concentration and area under the curve (AUC) of blood alcohol by 34% and 41%, respectively. First-pass metabolism of ethanol was also decreased significantly with an increase in bioavailability from 79.6 to 92.6%. Cimetidine showed a greater effect on blood alcohol levels compared with ranitidine, but famotidine showed no significant effect. The authors concluded that patients taking cimetidine or ranitidine should be warned of possible impairments after consumption of alcohol in quantities usually considered as safe in the absence of therapy with these medications (61). However, another study contradicted these findings and concluded that under real life conditions, the concomitant administration of alcohol and cimetidine, ranitidine, or omeprazole is unlikely to have significant physical, social, or forensic implications because no significant difference was found between percentage of first-pass metabolism, peak blood alcohol concentration, or AUC following administration of cimetidine, ranitidine, or omeprazole (62). Another report also found no significant interaction between alcohol and lansoprazole or omeprazole (63).

The effect of alcohol, even low-dose alcohol, on the enhanced antithrombotic effect of warfarin is of clinical significance. A 58-year-old Caucasian man was receiving long-term anticoagulation therapy with warfarin and had a stable International Normalization Ratio (INR). His INR increased when he started taking low-dose beer for cardiovascular protection. After he stopped the alcohol, his INR returned to normal (64). This excessive warfarin activity from low alcohol consumption may be related to the inhibition of warfarin metabolism by cytochrome P450. Conversely, in people who chronically drink alcohol, long-term alcohol consumption activates cytochrome P450 and may increase warfarin metabolism (59).

Alcohol increases sedative effect of tricyclic antidepressants (TCAs) through pharmacodynamic interactions. In addition, alcohol can also cause pharmacokinetic interactions. Alcohol appears to interfere with first-pass metabolism of amitriptyline, thus increasing serum levels of this drug. Alcohol has pharmacodynamic effects with antihistamines, increasing the sedative effects of these over the counter and prescription drugs. Alcohol also increases the sedative effect of phenobarbital and may also increase its serum concentration through pharmacokinetic interactions. Interactions between benzodiazepines and alcohol have also been reported. Alcohol consumption may result in accumulation of toxic breakdown products of acetaminophen (59).

4.6. Smoking and Serum Drug Concentrations

Approximately 4800 compounds are found in tobacco smoke including nicotine and carcinogenic compound, for example polycyclic aromatic hydrocarbons (PAHs) and N-nitroso amines. Compounds in tobacco smoke can induce certain cytochrome P450 enzymes responsible for metabolism of many drugs. PAHs induce CYP1A1, CYP1A2, and possibly CYP2E1. Smoking may also induce other drug metabolism
pathways such as conjugation (65). Cigarette smoke is responsible for pharmacokinetic drug interactions, not nicotine. Therefore, nicotine replacement therapy does not cause hepatic enzyme induction (66).

Theophylline is metabolized by CYP1A2. In one study, the half-life of theophylline was reduced by almost twofolds in smokers compared with that in non-smokers (65). Lee et al. (67) reported that theophylline clearance was increased by 51.1% and that steady state serum concentrations were reduced by 24.5% in children who were exposed to passive smoking. Clinically significant drug interactions with smoking have also been reported for caffeine, chlorpromazine, clozapine, flecainide, fluvoxamine, haloperidol, mexiletine, olanzapine, propranolol, and tacrine. With all medications, serum concentrations of drugs are significantly reduced in smokers because of increased metabolism of drugs. Smokers may therefore require higher doses than non-smokers to achieve pharmacological responses (66). Warfarin disposition in smokers is also different compared with that in non-smokers. One case report described an increase in INR to 3.7 from a baseline of 2.7–2.8 in an 80-year-old man when he stopped smoking. Subsequently, his warfarin dose was reduced by 14% (68). Another report also demonstrated an increase in INR in a 58-year-old male after cessation of smoking. His warfarin dose was lowered by 23% (69).

Pharmacodynamic drug interactions in smokers may be due to nicotine, which may counteract the pharmacological effects of a drug. The half-life of nicotine is approximately 2 h, and the pharmacological effects of nicotine, such as heart rate increases, blood pressure, diminishes rapidly after cessation of smoking. On the contrary, if nicotine replacement therapy is initiated in a hospitalized patient, heart rate may increase by 10–15 beats/min and blood pressure may increase by 5–10 mmHg (70). The transdermal nicotine patch may have a lesser effect on blood pressure and heart rate (71). Smokers taking benzodiazepines, such as diazepam and chlordiazepoxide, experience less drowsiness than non-smokers, and this interaction appears to be pharmacodynamic in nature because several studies did not find any significant difference between metabolism of benzodiazepines between smokers and non-smokers. Therefore, larger doses may be needed to sedate a smoker (66). Smokers may also need higher doses of opioids (codeine, propoxyphene, and pentazocine) for pain relief (65). In one study, to determine whether smokers require more opioid analgesic, it was found that 20 smokers (10 cigarettes a day or more for at least 1 year) required 23% more (when adjusted for body weight) and 33% more (when adjusted for body mass index) opioid analgesics compared with 69 non-smoking patients (72).

5. EFFECT OF DISEASE ON SERUM DRUG CONCENTRATIONS

Several pathophysiological conditions affect metabolism and excretion of drugs. Altered drug metabolism and excretion have been reported in patients with hepatic disease, renal impairment, thyroid disorder, cardiovascular disease, and pregnancy. Moreover, critically ill patients often metabolize or excrete drugs differently compared with ambulatory patients.

5.1. Effect of Hepatic Disease on Drug Metabolism

Severe hepatic disease alters the metabolism of many drugs. Mild to moderate hepatic disease causes an unpredictable effect on drug clearance. Hepatic cytochrome
P450 enzyme activities and gene expression can be profoundly altered in disease states. In general, the levels of affected cytochrome P450 enzymes are depressed by diseases causing potential and documented impairment of drug clearance causing drug toxicity (73). In one study, it was reported that hepatocellular carcinoma decreased expression of CYP2E1 (74). Trotter et al. reported that total mean tacrolimus dose in year one after transplant was lower by 39% in patients with hepatitis C compared with that in patients with no hepatitis C infection. The most likely explanation for these findings is decreased hepatic clearance of tacrolimus caused by mild hepatic injury from recurrent hepatitis C virus (75). Zimmermann et al. reported that oral dose clearance of sirolimus (rapamycin) was significantly decreased in subjects with mild to moderate hepatic impairment compared with that in controls, and authors stressed the need for careful monitoring of trough whole blood sirolimus concentrations in renal transplant recipients exhibiting mild to moderate hepatic impairment (76).

The liver is responsible for producing albumin and other proteins, and hepatic impairment diminishes this process by decreasing concentrations of serum albumin and other proteins. Many drugs are bound to serum protein, and elevated concentration of strongly protein-bound drugs such as phenytoin and valproic acid in patients with hepatic impairment is well documented in the literature. Because free fraction of a drug is responsible for pharmacological action as well as toxicity monitoring, free drug concentrations and dose adjustment based on free drug levels is required in patients with liver disease. This issue is discussed in detail in Chapter 2.

5.2. Renal Impairment and Drug Clearance

Renal disease causes impairment in the clearance of many drugs by the kidney. Correlations have been established between creatinine clearance and clearance of digoxin, lithium, procainamide, aminoglycoside, and many other drugs. The clearance of a drug is closely related to glomerular filtration rate (GFR), and creatinine clearance is a valid way to determine GFR. Serum cystatin C is another marker of GFR. In clinical practice, the degree of renal impairment is widely assessed by using the serum creatinine concentration and creatinine clearance predicted using Cockcroft–Gault formula (77). However, creatinine clearance may be a poor predictor of GFR under certain pathological conditions. Caution should be exercised when medications are prescribed to elderly patients because they may have unrecognized renal impairment. Serum creatinine remains normal until GFR has fallen by at least 50%. Nearly half of the older patients have normal serum creatinine but reduced creatinine clearance. Dose adjustments based on renal function is recommended for many medications in elderly patients even with medications that exhibit large therapeutic windows (78). Dosage adjustments are made for amikacin, gentamicin, tobramycin, and vancomycin based on GFR. Schuck et al. (79), based on a study with 126 patients, concluded that no significant differences exist between serum concentrations of creatinine or its predicted creatinine clearance by Cockcroft–Gault formula, cystatin C, and predicted GFR with regard to dose adjustments. O’Riordan et al. (80), using 22 healthy volunteers who received a single dose of intravenous digoxin, concluded that serum cystatin C is no better than serum creatinine concentration in predicting renal clearance of digoxin. In contrast, Hoppe et al. (81) reported that serum cystatin C is a better predictor of drug clearance than serum creatinine concentrations.
Renal disease also causes impairment of drug protein binding because uremic toxins compete with drugs for binding to albumin. Such interaction leads to increases in concentration of pharmacologically active free drug concentration, which is clinically more important for strongly protein-bound drugs. This topic is addressed in Chapter 2.

### 5.3. Thyroid Disorder and Drug Metabolism

Patients with thyroid disease may have an altered response to drugs. Thyroxin is a potent activator of the cytochrome P450 enzyme system, and hypothyroidism is associated with inhibition of hepatic oxidative metabolism of many drugs. Croxson et al. \((82)\) measured serum digoxin concentration using a radioimmunoassay in 17 hyperthyroid and 16 hypothyroid patients and observed significantly lower levels of digoxin in patients with hyperthyroidism and significantly higher levels of digoxin in patients with hypothyroidism. Although there is a general conception that serum phenytoin clearance is not affected by thyroid function state, Sarich and Wright \((83)\) reported a case where a 63-year-old female, who developed decreased serum level of free \(T_4\), showed phenytoin toxicity that may be related to decreased cytochrome P450-mediated hydroxylation of phenytoin. Another case report also indicated phenytoin intoxication induced by hypothyroidism. A 42-year-old woman with a 29-year history of hypothyroidism and 18-year history of epilepsy was treated with phenytoin, meprobamate, valproic acid, and thyroid replacement therapy. However, 1 month after sudden withdrawal of the thyroid powder, she was sick and was admitted to the hospital. Her serum phenytoin and phenobarbital levels were significantly elevated over the therapeutic range (26.4 \(\mu\)g/mL for phenytoin and 36.4 \(\mu\)g/mL for phenobarbital), but her valproic acid concentration was low. The endocrinological examination revealed hypothyroidism. Thyroxine administration was started and her phenytoin concentration was decreased to a sub therapeutic level even with the same dose of phenytoin \((84)\).

Hypothyroidism also affects the metabolism of immunosuppressants. A 25-year-old man with a renal transplant had a therapeutic trough whole blood cyclosporine concentration (108–197 ng/mL) after transplant. On the 105th day, his trough cyclosporine concentration was elevated to 1060 ng/mL. His cholesterol was also elevated from 254 to 422 mg/dL, and the patient has an onset of hypothyroidism after transplantation. The authors concluded that elevated cyclosporine concentration may be due to a decrease in cyclosporine clearance resulting from decreased cytochrome P450 activity in hypothyroidism. Moreover, decreased thyroid hormone level and increased plasma lipoprotein level may have affected the distribution of cyclosporine \((85)\). Haas et al. reported a case where a patient developed hypothyroidism 6 months after single lung transplantation and was admitted to the hospital for anuric renal failure. The patient showed a toxic blood level of tacrolimus, which was resolved with the initiation of thyroxine replacement therapy and dose reduction of tacrolimus \((86)\).

The iodine-rich amiodarone affects the thyroid gland causing thyroid disorder, which may affect warfarin sensitivity. Kurnik et al. \((87)\) described three cases where patients developed amiodarone-induced thyrotoxicosis, resulting in a significant decrease in
warfarin requirement. Mechanism of interaction of thyroid hormone with warfarin is complex. One proposed mechanism is the alteration of kinetics of the clotting factors with an increase in catabolism of vitamin K-dependent factors in patients with hyperthyroidism. This interaction increases sensitivity to warfarin in patients with hyperthyroidism but decreases sensitivity of warfarin in patients with hypothyroidism (88).

5.4. Cardiovascular Disease and Serum Drug Concentration

Cardiac failure is often associated with disturbances in cardiac output, influencing the extent and pattern of tissue perfusion, sodium and water metabolism as well as gastrointestinal motility. These factors affect absorption and disposition of many drugs requiring dosage adjustment. \( V_d \) and clearance of lidocaine are decreased in cardiac failure. For drugs that are metabolized by the liver, decreased blood flow in the liver accounts for reduced clearance, but impaired hepatic metabolism in these patients also plays a role. Accumulation of active metabolites of lidocaine and procainamide in these patients are clinically significant. Theophylline metabolism, which is largely independent of hepatic blood flow, is reduced in patients with severe cardiac failure and dose reduction is needed. Digoxin clearance is also decreased. Quinidine plasma level may also be high in these patients because of lower \( V_d \) (89). Elimination half-life is directly related to the \( V_d \) and inversely related to clearance. Pharmacokinetic changes are not always predictable in patients with congestive heart failure, but it appears that the net effect of reduction in \( V_d \) and impairment in metabolism usually results in higher plasma concentrations of a drug in a patient with congestive heart failure compared with that in healthy subjects. Therefore, therapeutic drug monitoring is crucial in avoiding drug toxicity in these patients (90). Recently, Kotake et al. (91) reported that heart failure elevates the serum level of the drug cibenzoline, which is used in the treatment of arrhythmia.

Physiological changes in critically ill patients can significantly affect the pharmacokinetics of many drugs. These changes include absorption, distribution, metabolism, and excretion of drugs in critically ill patients. Understanding these changes in pharmacokinetic parameters are essential for optimizing drug therapy in critically ill patients (92). Moreover, usually free fractions of strongly protein-bound drugs are elevated in the critically ill patients because of low serum albumin concentrations. This issue is discussed in Chapter 2.

5.5. Drug Metabolism and Clearance in Pregnancy

Epidemiologic surveys have indicated that between one-third and two-thirds of all pregnant women will take at least one medication during pregnancy. Drug therapy in pregnant women usually focuses on safety of the drug on the fetus. However, pharmacokinetics of many drugs is altered during pregnancy. Therapeutic drug monitoring during pregnancy aims to improve individual dosage improvement, taking into account pregnancy-related changes in drug disposition (93). Physiological changes that occur during pregnancy alter absorption, distribution, metabolism, and elimination of drugs thus affecting efficacy and safety of the drugs toward pregnant women unless careful dosage adjustments are made. During third trimester, gastrointestinal function may be prolonged. Moreover, the amount of total body water and fat increase
throughout pregnancy and are accompanied by increases in cardiac output, ventilation, and renal and hepatic blood flow. In addition, plasma protein concentrations are reduced, increasing the unbound fraction of a drug. Therefore, careful therapeutic drug monitoring of the free (unbound) concentration of strongly protein-bound drugs, such as phenytoin, is recommended in pregnant women. Moreover, changes occur in the drug-metabolizing capacity of the hepatic enzymes in pregnancy. Renal absorption of sodium is increased. Placental transport of a drug, compartmentalization of a drug in the embryo/placenta, and metabolism of a drug by the placenta and the fetus also play important roles in the pharmacokinetics of a drug during pregnancy (94).

The increased secretion of estrogen and progesterone in normal pregnancy affects hepatic drug metabolism differently depending on the specific drug. A higher rate of hepatic metabolism of certain drugs, for example phenytoin, can be observed because of the induction of the hepatic drug-metabolizing enzymes by progesterone. On the contrary, the hepatic metabolism of theophylline and caffeine is reduced secondary to the competition of these drugs with progesterone and estradiol for enzymatic metabolism by the liver. Cholestatic effect of estrogen may interfere with the clearance of drugs, for example, rifampin (93). By the end of pregnancy, total and unbound phenobarbital concentrations are reduced up to 50% of the original concentration, but primidone concentrations are altered marginally. Total phenytoin concentrations may fall by 40% compared with serum phenytoin levels before pregnancy. Total and free carbamazepine values may also alter because of pregnancy, but reports are conflicting (95). Significant increases in clearance of lamotrigine have been reported in pregnancy. Apparent clearance seems to increase steadily during pregnancy until it peaks approximately at 32nd week when 330% increases in clearance from baseline values can be observed (96). Another study involving 11 pregnant women also demonstrated significant decreases in the ratio of plasma lamotrigine concentration to dose (65.1% during second trimester and 65.8% in third trimester) compared with pre-pregnancy values. Five patients experienced seizure deterioration during pregnancy, and there were significant inter-patient variations in the pharmacokinetics of lamotrigine (97).

Lower serum concentrations of lithium have been reported in pregnancy, and this may be related to an increase in the GFR in pregnancy. Altered pharmacokinetics of ampicillin can be observed in pregnancy where serum concentrations may be lower by 50% in pregnant women compared with that in non-pregnant women because of altered pharmacokinetics. Faster elimination of phenoxyethylpenicillin (Penicillin V) in pregnant women has also been demonstrated (93).

Combined antiretroviral therapy can reduce transmission of the human immunodeficiency virus (HIV) from mother to fetus significantly. However, pregnancy may alter the pharmacokinetics of the antiretroviral drugs. Available data indicate that pharmacokinetics of zidovudine, lamivudine, didanosine, and stavudine are not altered significantly during pregnancy. However, nevirapine half-life is significantly prolonged in pregnancy. For protease inhibitors, reduction of maximum plasma concentration of indinavir was observed in pregnancy. This may be due to induction of cytochrome P450. Standard adult doses of nelfinavir and saquinavir produced lower drug concentration in HIV-infected pregnant women compared with that in non-pregnant women (94).
During pregnancy, the thyroid is hyper-stimulated resulting in changes in thyroid hormone concentrations. Gestational age-specific reference intervals are now available for thyroid function tests. Knowledge of expected normal changes in thyroid hormone concentrations during pregnancy allows individual supplementation when needed (98). Hypothyroidism is common in pregnancy, and therapeutic drug monitoring of antithyroid drugs is important. Consistently lower serum concentrations of propylthiouracil were observed in pregnant women compared with that in non-pregnant women (99).

6. DRUG METABOLISM AND CLEARANCE IN NEONATES, CHILDREN, AND ELDERLY

In the fetus, CYP3A7 is the major hepatic cytochrome responsible for steroid metabolism. Variably expressed in the fetus, CYP3A5 is also present in significant level in half of the children. However, in adults, CYP3A4 is the major functional hepatic enzyme responsible for metabolism of many drugs. CYP1A1 is also present during organogenesis whereas CYP2E1 may be present in some second trimester fetuses. After birth, hepatic CYP2D6, CYP2C8/9, and CYP2C18/19 are activated. CYP1A2 becomes active during the fourth to fifth months after birth (100).

In general, age is not considered to have a major influence on the absorption of drugs from the gut except for the first few weeks of life when absorption steps may be less efficient. Neonates and infants demonstrate increased total body water to body fat ratio compared with adults whereas the reverse is observed in the elderly. These factors may affect $V_d$ of drugs depending on their lipophilic character in infants and elderly compared with that in adult population. Moreover, altered plasma binding of drugs may be observed in both neonates and some elderly because of low albumin, thus increasing the fraction of free drug. Moreover, drug-metabolizing capacity by the liver enzymes is reduced in newborns particularly in premature babies but increases rapidly during the first few weeks and months of life to reach values which are generally higher than adult-metabolizing rates. In contrast, efficiency of cytochrome P450 enzymes declines with old age. Renal function at the time of birth is reduced by more than 50% of adult value but then increases rapidly in the first 2–3 years of life. Renal function then starts declining with old age. Oral clearance of lamotrigine, topiramate, levetiracetam, oxcarbazepine, gabapentin, tiagabine, zonisamide, vigabatrin, and felbamate is significantly higher (20–120%) in children compared with that in adults depending on the drug and the age distribution of the population. On the contrary, clearance of these drugs is reduced (10–50%) in the elderly population compared with that in the middle-aged adults (101).

Clearance of aminoglycoside is dependent on the GFR, which is markedly decreased in neonates, especially in premature newborns. These drugs appear to be less nephrotoxic and ototoxic in neonates compared with that in the adult population. The $V_d$ of aminoglycoside increases in neonates, which may also contribute to a longer half-life of aminoglycoside in neonates. Decreased renal clearance in neonates is responsible for decreased clearance of most beta-lactam antibiotics (102). Higher $V_d$ and lower clearance of gentamicin was also observed in neonates (103). Conversion of theophylline to caffeine in human fetuses has been reported (104). Kraus et al. studied maturational changes in theophylline disposition in 52 infants and observed
Table 3
Factors and Diseases Affecting Disposition of Drugs

<table>
<thead>
<tr>
<th>Factor or disease</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender difference</td>
<td>Men may have faster clearance of drugs than women except for drugs cleared by CYP3A4. Women may be more susceptible to drug toxicity.</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>Pharmacodynamic interactions with many drugs causing significant toxicity with lower amounts of drugs when alcohol is present. Cimetidine and ranitidine may increase blood alcohol level. Alcohol may increase International Normalization Ratio (INR) in patients taking warfarin. Alcohol increases serum levels of amitriptyline.</td>
</tr>
<tr>
<td>Smoking</td>
<td>Theophylline serum concentrations reduced in smokers. Reduced serum concentrations of many other drugs. Interaction with warfarin.</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>Decreased clearance of tacrolimus and sirolimus requiring dosage reduction. Elevated free concentrations of strongly protein-bound drugs.</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>Decreased clearance of drugs where renal excretion is the major pathway. Elevated free concentrations of strongly protein-bound drugs.</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>Elevated concentration of certain drugs (cyclosporine, phenobarbital etc.) in hypothyroidism. Thyrotoxicosis may reduce warfarin requirement.</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Reduced metabolism of many drugs because of decreases in hepatic blood flow. Reduced clearance of digoxin, theophylline, and other drugs.</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Elevated free concentrations of drugs because of reduced plasma proteins. Increased metabolism of certain drugs (phenytoin, indinavir), but clearance of some drugs (theophylline) may also be reduced. Lower serum concentration of lithium.</td>
</tr>
<tr>
<td>Children</td>
<td>Increase oral clearances of many antiepileptic drugs. Conversion of theophylline to caffeine in children.</td>
</tr>
</tbody>
</table>

that postconceptional age was an import factor in describing theophylline metabolism in neonates. Disappearance of serum caffeine concentrations and maturation of theophylline clearance were primarily related to the demethylation pathway that produced 3-methylxanthine. Theophylline clearance and urine metabolite pattern reached adult values in infants 55 weeks after postconceptional age (105). Major factors affecting drug distribution and metabolism are summarized in Table 3.
7. THERAPEUTIC DRUG MONITORING OF INDIVIDUAL DRUGS

Usually, concentration of a therapeutic drug is measured in the serum or plasma. However, whole blood concentration of immunosuppressant drugs such as cyclosporine and tacrolimus is usually measured for therapeutic drug monitoring. Obtaining blood for measurement of a drug during the absorption or the distribution phase may lead to misleading information. Moreover, to measure the peak concentration of a drug, timing of the sample will depend on the route of administration. After intravenous administration, the peak concentration of a drug may be achieved in a few minutes. On the contrary, for a sustained release tablet, the mean time to reach the peak plasma concentration of theophylline was 7.9 h in one study (106). The trough concentration is clinically defined as the serum drug concentration just before the next dose. Usually, trough concentrations are monitored for most drugs, but for aminoglycosides and vancomycin, both peak and trough concentrations are monitored. For a meaningful interpretation of a serum drug concentration, time of specimen collection should be noted along with the time and date of the last dose and route of administration of the drug. This is particularly important for aminoglycoside because without knowing the time of specimen collection, the serum drug concentration cannot be interpreted. Information needed for proper interpretation of drug level for the purpose of therapeutic drug monitoring is listed in Table 4.

Table 4

<table>
<thead>
<tr>
<th>Patient Information</th>
<th>Other Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of the patient</td>
<td>Dosage regimen</td>
</tr>
<tr>
<td>Hospital identification number</td>
<td>Time of taking dosage</td>
</tr>
<tr>
<td>Age</td>
<td>Type of specimen (serum, urine, saliva, other body fluid) Number of specimens (if more than one) and type of drug concentration requested (total vs. free) Time of specimen collection (peak vs. trough)</td>
</tr>
<tr>
<td>Height and weight</td>
<td></td>
</tr>
<tr>
<td>Gender (if female pregnant?)</td>
<td>Time of last dose</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Concentration of the drug</td>
</tr>
<tr>
<td>Albumin level, creatinine clearance</td>
<td>Pharmacokinetic parameters of the drug</td>
</tr>
</tbody>
</table>

*a Optional information.*

7.1. Therapeutic Drug Monitoring of Anticonvulsants

Phenytoin, phenobarbital, ethosuximide, valproic acid, and carbamazepine are considered as conventional anticonvulsant drugs. Many people with epilepsy suffer from side effects of anticonvulsants as well as suboptimum seizure control, which can be minimized by regular medication review and dosage adjustments based on serum drug levels (107). All these antiepileptic drugs have a narrow therapeutic range. Phenytoin, carbamazepine, and valproic acid are strongly bound to serum proteins.