Drug Dosage and Administration

Modern Theory and Practice

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University Park Press
Baltimore

UNIVERSITY PARK PRESS
International Publishers in Medicine and Human Services
300 North Charles Street
Baltimore, Maryland 21201

Typeset by Maryland Composition Company, Inc.

Manufactured in the United States of America by The Maple Press Company

Library of Congress Cataloging in Publication Data
Wartak, Joseph.
Drug dosage and administration.

Bibliography: p. 165
Includes index.
1. Drugs—Dosage. 2. Drugs—Administration. I. Title.
[DNLM: 1. Drugs—Administration and dosage. QV 748 W295d]
RM145.W37 1983 615'.14 82-17417
ISBN 0-8391-1786-8

Notice

The author and the publisher have exercised great care to ensure that the drug dosages, the formulas for calculating dosages, and other information presented in this book are accurate and consistent with knowledge prevailing at the time of publication. Because pharmacology is a dynamic science, readers are advised always to check the product information sheet packaged with each drug to be fully informed of changes in recommended dosages, contraindications, and the like, before prescribing or administering any drug. This recommendation is particularly applicable to new and infrequently used drugs.

Preface

The theory and practice of drug dosage and administration have changed dramatically in recent years with the introduction of new dosage forms (e.g., pressurized aerosols and sustained-release preparations), advanced drug delivery systems, analytic techniques for assaying drug levels in the blood, and pharmacokinetic studies of drug disposition in the body. The wealth of information on drug administration and dosage has expanded to such a degree that it cannot be confined any longer to a chapter in a textbook of pharmacology. A textbook coverage of this subject is not only scanty but frequently also outdated.

It is unfortunate that the need for a careful dosage adjustment in an individual patient is not adequately appreciated by practicing physicians. Too often drug dosage is selected in a rather empirical and schematic manner without due consideration of the patient's individual characteristics (including age, body mass, nutritional status, disease process, kidney and liver function, genetic makeup), environmental factors, bioavailability of the drug, and previous or concurrent drug therapy. More recently, it has been documented that the ability to detoxify or eliminate drugs may vary as much as 10-fold among individuals, so that the failure to adjust dosage may result in serious side effects or lack of efficacy.

This book provides current and detailed information on drug administration and dosage adjustment presented in a clear and systematic fashion. Whenever possible, difficult concepts have been supported by illustrations, which for most people are more comprehensible than lengthy descriptions. To achieve a logical development of the subject matter, chapters on drug dosage forms and drug concentrations in blood have been incorporated. In addition, the book is provided with a slide rule which should prove to be a valuable tool for quick and accurate dosage calculations.

The book is intended mainly for medical students and physicians, but it also should prove useful to allied health professionals such as nurses and pharmacists, whose participation in drug treatment is becoming increasingly more active. In addition, this book can be effectively used as a core text for lectures or seminars and above all for self-study aimed at utilization of modern scientific principles in therapeutics.

Acknowledgments

This book incorporates some material derived from several research projects sponsored by Astra Pharmaceuticals Canada Ltd., Ayerst Laboratories of Canada, Eli Lilly and Company (Canada) Ltd., Schering Canada Inc., and Merck, Sharp and Dohme (USA).

Computer plots appearing in Figures 9, 13, 16, 18, 24, 26, 27, 28, 29, 30, 36, and 37 have been reproduced from the author's book *Clinical Pharmacokinetics: A Modern Approach to Individualized Drug Therapy*, published by Praeger Scientific.

Contents

Part I

Dosage of Drugs

Chapter 1

Drug Dosage Scale

To produce desired therapeutic effects, drugs must be given in proper doses. These doses are initially established by clinical trials and then recommended for routine use. These recommended doses may be expected to produce therapeutic effects in most but not all subjects, because the pharmacologic action of drugs is influenced by a number of factors which include the genetic makeup and age of the individual; the functional state of the liver, kidney, and cardiovascular system; the nature and severity of the disease process; nutritional status and general health; environmental conditions; bioavailability of the drug; and prior or concomitant treatment with other drugs.

MINIMAL AND MAXIMAL DOSES

Any drug can be used safely and effectively only in a certain dosage range. Below that range a drug is ineffective, and above that range a drug is toxic or lethal. The smallest dose that is sufficient to produce therapeutic effects in most ordinary cases is called the minimal dose (Figure 1).

The largest dose that exerts therapeutic effects without producing toxic reactions is called the maximal dose. Maximal doses are sometimes given in official drug compendia or package inserts. They are not legally binding on the physician and may be exceeded if this is considered to be necessary. In such cases, however, the prescriber should indicate that the larger doses are intentional. This can be done by writing on the prescription an exclamation mark or initials after the dose or underlining the dose.

AVERAGE DOSES

Between the minimal and maximal doses lies the therapeutic dose range. A portion of the therapeutic dose range found to be most effective in clinical trials is used as the average or usual dose. Average doses are often given as ranges between the upper and lower limits. The upper limit indicates that a larger dose may enhance the risk of toxicity; the lower limit indicates that a smaller dose may not produce full therapeutic effects for most patients. These concepts are illustrated in Figure 1.

The term "average dose" refers to the dose used successfully in a large group of patients and hence recommended for the average patient. The majority of individuals can be regarded as being average because their response to a given drug is similar. On the other hand, a small fraction of the population can be regarded as not being average because their response to a given drug is very weak or very strong or completely abnormal. Because average

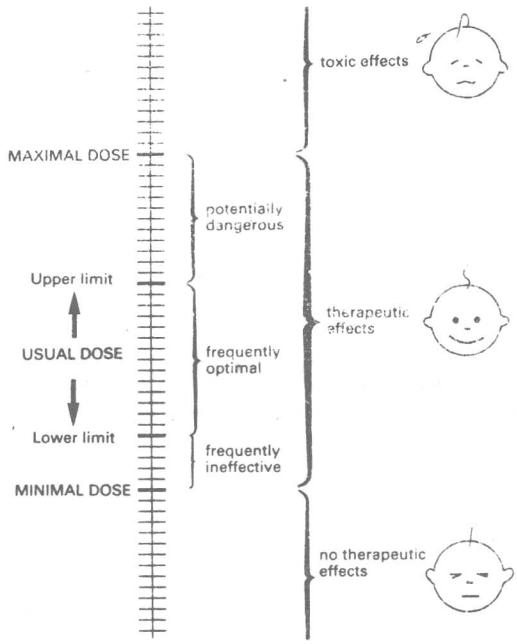

Figure 1. Drug dosage scale.

doses are determined in such a way as to maximize therapeutic effects and minimize undesirable effects in the majority of patients, and because there is no reliable method of estimating a patient's response to a given drug, the average dose is regarded as a safe dose at which to start therapy with a particular drug in an adult patient who has normally functioning kidneys and liver.

When a given drug has never been used by the patient before, it is mandatory to observe carefully the patient's response to initial doses and monitor blood levels if toxic reactions occur. The physician should keep in mind that there may be variations of 5- to 10-fold in the disposition of many commonly used drugs (e.g., phenytoin, phenylbutazone, salicylates, amobarbital) as the result of genetically determined changes in proteins which are involved in drug metabolism.

Unless otherwise stated, average doses are intended for oral administration to adult subjects on one occasion. For some drugs a period of time is specified over which the whole dose should be given, for example, "daily, in divided doses." In such cases the physician makes the decision about the number of divided doses.

Chapter 2

Individualization of Drug Dosage

Average doses are intended, unless otherwise stated, for adults weighing 70 kg (150 pounds) who have normally functioning kidneys and liver. Such doses produce satisfactory therapeutic effects in the vast majority of patients, but may be too high and may cause serious toxicity in some subjects, or may be insufficient to produce the desired therapeutic effects in others. Consequently, some patients may require modification of the usual doses to achieve optimal therapeutic effects (Figure 2).

VARIATION IN DOSAGE REQUIREMENTS

Safe and effective therapy can be achieved only with those doses which produce optimal concentrations of a drug in the plasma and target tissues. For most subjects epitomized by an idealized "average patient," there is a good correlation between the size of doses and plasma concentrations of drugs. That is, only the usually recommended average doses will produce optimal concentrations and therapeutic effects, whereas larger doses will be toxic and smaller doses will be ineffective.

In some subjects, however, the correlation between average doses and plasma concentrations or therapeutic effects is distorted because the absorption, distribution, or elimination of a given drug may be different than in an average patient. Such differences may be caused by age, body weight, disease, genetic makeup, concomitant drug therapy, environmental factors, and drug bioavailability. Therefore, the recognition of factors modifying the usual dose-response relationship is essential for drug therapy that provides optimal effects with minimal risk to the individual patient.

Individualization of dosage is especially important for drugs with a narrow therapeutic range, such as digitalis, antiarrhythmics, anticoagulants, and anticonvulsants. For example, the therapeutic dose of digoxin has been estimated by some investigators to be only 65 percent of the toxic dose. This explains why the use of digitalis is frequently accompanied by toxic reactions.

INFANTS AND CHILDREN

Infants and young children show significant differences in absorption, distribution, metabolism, and excretion of many drugs as well as an increased sensitivity of the target tissue to some drugs. Consequently, drug dosage in infants and children should be based on controlled clinical trials reported in pediatric journals or product monographs provided by drug manufacturers. Unfortunately, such infor-

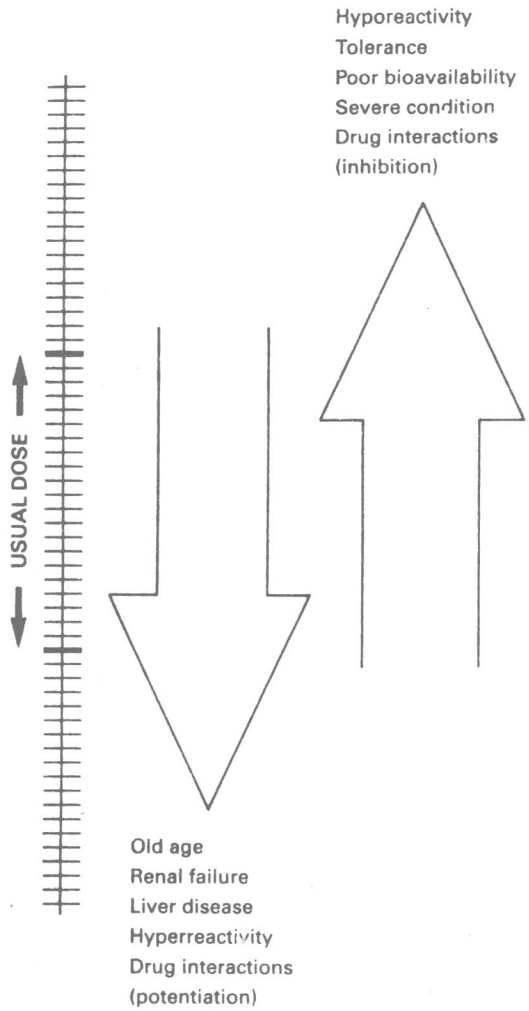

Figure 2. Principal factors requiring dosage adjustment.

mation is not always available, so that drug dosage in infants and children must be determined by reducing the adult dose proportionally to weight or body surface area of the infant or child (for details see Chapter 3).

UNDERWEIGHT AND OVERWEIGHT ADULTS

For drugs with a narrow therapeutic index, average doses are stated in milligrams or micrograms per kilogram, so that the dose for the individual patient is calculated by multiplying the patient's weight in kilograms by the recommended number of milligrams or micrograms of drug per kilogram. However, when average doses are recommended on a body weight basis, they are meant for 70-kg subjects. Obviously, when the patient is exceptionally large or small or emaciated, doses should be adjusted according to weight or body surface area. The dose required by a given subject according to body mass can be calculated by multiplying the average therapeutic dose by the subject's weight in kilograms and dividing by 70. The dose required by a given subject according to body surface area can be calculated by multiplying the average therapeutic dose by the subject's body surface area in square meters and dividing by 1.73. Dosage adjustment according to sex of the patient is usually not necessary.

For some drugs, dosage should be calculated according to the patient's lean body mass (LBM), which can be determined from the following formula

$$\text{LBM} = 0.8 \times \text{height (in cm)} - \text{X}$$

Where X is a constant whose value depends on sex and body build as follows: for large-framed men, X = 70; for medium-framed men, X = 75; for small-framed men X = 80; for large-framed women, X = 80; for medium-framed women, X = 85; and for small-framed women, X = 90.

ELDERLY PATIENTS

People over 60 years of age usually require lower dosages of most drugs because of one or more of the following factors: 1) reduced renal function with consequent impairment of drug elimination; 2) decreased concentration of serum albumin with a consequent increase of the unbound fraction of drug; 3) increased sensitivity of the target tissues to some drugs; 4) changes in body composition (less water and more

adipose tissue relative to weight) which may affect drug distribution; and 5) reduced body mass.

Dosage modifications are especially important for such drugs as aminoglycosides, anticoagulants, anticholinergics, antihypertensives, digitalis, diuretics, narcotics, barbiturates, and psychotropic drugs. As a rule of thumb, the dose for people above 60 years should be reduced to four-fifths to two-thirds the average dose, and for those above 80 years to one-half the average dose.

RENAL DISEASE

In patients with renal disease, the ability of the kidney to eliminate drugs or their metabolites is impaired to an extent determined by the severity of the condition, which may usually be assessed by the serum creatinine clearance determination. Consequently, the dose of those drugs that are predominantly excreted unchanged by the kidney must be reduced to avoid a potentially toxic accumulation of the drug. This especially applies to those drugs that have a narrow range between their therapeutic and toxic serum levels (e.g., digitalis, aminoglycoside antibiotics). The appropriate adjustment of drug dosage for patients with renal failure can be accomplished by several methods which are discussed in Chapter 4.

LIVER DISEASE

The liver is the principal site for drug biotransformation, and any disease process that results in the damage of liver cells, the slowing of hepatic blood flow, or the decrease in plasma proteins may raise the plasma concentrations of many drugs. Because the toxicity of most drugs is related to their elevated concentration in the plasma, toxic responses may be promoted with hepatic disease. Consequently, in patients with hepatic disease, it may be necessary to avoid certain drugs or to reduce their doses and monitor plasma concentrations.

The effect on biotransformation of drugs is greatest in an acute stage or in an advanced stage of liver disease. In advanced cirrhosis of the liver, the flow of blood through this organ is markedly impaired, and thus the clearance of drugs that normally are extracted from the blood by more than 70 percent during their first pass through the liver will be significantly reduced. Drugs with a high extraction ratio include lidocaine, propranolol, pethidine, nortriptyline, pentazocine, and some others.

At present, there is not enough quantitative information on how liver disease affects drug metabolism, drug distribution in plasma, and various tissues and receptor sensitivities. There is also considerable interpatient variability in response to drugs when liver impairment is present. In addition, the liver function tests correlate poorly with rates of drug metabolism and therefore have practically no value in predicting the overall effect of liver damage on drug disposition. Consequently, even though it may be suspected that drug elimination is altered in patients with liver disease, there are no specific guidelines for dosage adjustment in such cases.

Given these limitations, the use of drugs in patients with hepatic disease should be based on the following principles: 1) treatment should be limited to drugs that are essential to the patient's well-being; 2) wherever possible, one should use drugs that are eliminated by extrahepatic routes or are known to be little affected by liver disease (for example, lidocaine, which is primarily metabolized in the liver, should be substituted by disopyramide, which is excreted predominantly by the kidney); 3) dosage of drugs eliminated mainly by biotransformation should be reduced in severe liver disease; whereas in moderate liver disease dosage

adjustment is frequently not necessary; 4) for long-term therapy frequent determinations of drug plasma levels are helpful in preventing overdosage and consequent toxic effects. Ideally, the plasma level of an unbound drug should be measured and compared, especially when the albumin concentration in plasma is substantially reduced.

MISCELLANEOUS DISEASE STATES

The usual dose-response relationship for some drugs may also be altered by congestive heart failure, electrolyte imbalance, hypoproteinemia, thyroid disease, gastrointestinal disorders, and possibly some other conditions. For example, in patients with cardiac failure the hepatic clearance of lidocaine, propranolol, and some other highly metabolized drugs is reduced due to impaired blood flow, and the average dose may be toxic. In hypothyroidism and hypokalemia the sensitivity of the target cells to digitalis is increased, and the usual dose of the drug will produce toxic effects. Hypoproteinemia in patients with severe cirrhosis, nephrosis, and extensive burns can alter the distribution of drugs, especially those highly bound to plasma proteins. Consequently, high and potentially toxic concentrations of the free drug may be associated with the usual doses.

The nature and severity of the disease also plays an important role in determining the dose of some drugs. For example, the dose of aspirin for the relief of a minor pain is considerably smaller than that necessary to control the symptoms of rheumatoid arthritis. Other things being equal, the dosage of drugs (especially antiinfective agents and insulin) should be directly proportional to the severity of a disease—the more severe the disease, the higher the dose.

GENETIC DETERMINANTS

It is believed that much of the biologic variation in response to drugs may be due to genetic differences in subjects. The two most important conditions that are related to genetic factors are drug allergy and idiosyncrasy. Both are quite different from the normal reaction produced by the drug in any dosage. Two other genetically determined conditions are hyper- and hyporeactivity to the usual doses, and both occur in subjects with an abnormal rate of biotransformation of a particular drug. Although genetic factors play an important role in determining drug safety and dosage, they become evident only after the subject has been exposed to the drug.

The genetic makeup of the individual controls the rate of drug metabolism and some other processes (e.g., drug receptor synthesis and activity) which determine the response to drugs. Because of genetic differences, drug biotransformation in some subjects may be slow, resulting in high and usually toxic plasma levels with the average dose. A slow drug metabolizer may achieve plasma levels on a fixed dose that are 10 times higher than the population mean. Similarly, drug biotransformation in some other subjects may be fast, resulting in low plasma levels and high concentrations of metabolites with the usual doses. The best known example is the acetylation of isoniazid. In slow acetylators of isoniazid, usual doses of the drug may lead to dose-related toxicity. In fast acetylators of isoniazid, usual doses of the drug produce higher concentrations of a hepatotoxic metabolite which may damage the liver.

DRUG TOLERANCE

Drug tolerance refers to a decreased response that the body develops toward certain drugs if they are taken repeatedly (e.g., daily). As a result, successive increases in drug dosage are required to achieve a satisfactory therapeutic effect. Tolerance appears usually in about 2 weeks, increases thereafter for some time, and then becomes constant toward the dose employed. If the drug is discontinued

for a few weeks, the tolerance is lost. Drugs capable of producing tolerance include barbiturates, tranquilizers, narcotics, and some others. Cross-tolerance may develop between alcohol and central nervous system depressant drugs, so that alcoholics often show a marked resistance to the effects of barbiturates, benzodiazepines, or phenothiazines. The exact mechanism of tolerance is not known, but some believe that it results from a decreased reactivity of the receptor or induced synthesis in the liver of microsomal enzymes involved in drug biotransformation.

CONCOMITANT DRUG USE

Concomitant use of other drugs can influence the absorption, distribution, metabolism, or excretion of a particular drug and may require dosage adjustment. Although drug interactions are quite common, few of them have been found to be clinically significant. One such interaction is the competition for plasma protein binding between oral anticoagulants and many nonsteroid anti-inflammatory drugs (e.g., salicylates, phenylbutazone, mefenamic acid). Consequently, when patients receive warfarin together with any of these interacting drugs, some warfarin will be displaced from protein binding sites, and the usual doses will produce bleeding.

DOSAGE FORM

The dosage form may also influence the response to drugs, because formulation factors that determine to a large extent the biologic availability of the active agent from tablets and capsules may vary among different brands of the same drug. Such a variation in bioavailability should be considered especially in the case of digoxin.

ENVIRONMENTAL FACTORS

The usual dose-response relationship may be altered by food, alcohol, cigarette smoking, and numerous non-drug chemicals to which the individual may be exposed (e.g., food additives and contaminants, household cleaning products, pesticides, occupational exposure). With few exceptions, the effects of such environmental factors on drug responsiveness are largely unknown.

Food generally depresses the rate or extent of drug absorption, and to minimize this effect drugs should be taken on an empty stomach with an adequate amount of water or other fluid.

Chronic alcohol use induces microsomal oxidation enzymes participating in drug metabolism, so that the usual doses of drugs that depend upon hepatic biotransformation for excretion will produce inadequate plasma concentrations. However, when hepatic cirrhosis develops in the chronic alcoholic, the reverse will be true: the usual doses may produce toxic concentrations.

Cigarette smoking frequently enhances the rate of drug metabolism, so that the usual doses of some drugs (e.g., theophylline, tricyclic antidepressants) may be insufficient to produce therapeutic concentrations in the plasma.

METHOD OF DRUG DOSAGE ADJUSTMENT

The adjustment of drug dosage for a particular patient is aimed at producing the desired therapeutic effect with the least possible amount of the drug, so that undesirable side effects can be minimized or, ideally, avoided altogether. Such a task can be usually accomplished by one or more of the following methods: 1) a close observation of the patient's clinical response; 2) laboratory or clinical monitoring of the patient's response; 3) monitoring of the drug plasma concentration; 4) general or specific guidelines based on controlled clinical trials; and 5) mathematical formulas, nomograms, slide rules, and computer programs.

Most commonly, the dosage of drugs is adjusted according to the patient's response manifested by changes in symptoms, physical findings, and laboratory data. Using this method, one starts therapy with the average recommended dose, which, depending upon the patient's response, can be subsequently reduced or increased. This method, called titration by patient response, is obviously very inaccurate, especially when close observation of the patient cannot be accomplished. Consequently, dosage determination by titration may be hazardous and should be used only for drugs with a wide therapeutic range.

When the drug's pharmacologic effect can be measured (e.g., prothrombin time in the case of anticoagulants, blood pressure in the case of antihypertensive agents, glucose blood level in the case of hypoglycemics), the method of choice is laboratory or clinical monitoring of the patient's response. In this method one starts therapy with the lowest recommended doses and gradually increases them until optimal therapeutic results and/or mild undesirable side effects occur. The occurrence of undesirable side effects usually requires the reduction of subsequent doses unless such effects are mild and can be tolerated by the patient.

Another method of determining an individual dose is based on monitoring the concentration of the drug in the blood and maintaining it slightly above the minimal effective level, if such has been established for that drug. This is usually indicated for drugs with a low therapeutic index and when one suspects poor gastrointestinal absorption, impaired hepatic clearance, tolerance, drug interactions, or noncompliance by the patient.

Consulting the most recent guidelines for the use of drugs in renal disease and liver disease as well as the reports on controlled clinical trials with specific drugs in children and elderly patients offers a considerable help to the prescriber by enabling him or her to use a less empirical approach to drug dosage individualization. Also, various mathematical formulas and nomograms, slide rules, and computer programs based on such formulas can be utilized for more accurate drug dosage individualization. So far this approach has been applied to a limited number of drugs (e.g., digoxin, aminoglycoside antibiotics) or to a few categories of patients (e.g., children, patients with renal failure). However, its widespread application in the future is almost certain.