THIRTEENTH EDITION

HARRISON'S PRINCIPLES OF INTERNAL MEDICINE

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PRINCIPLES OF INTERNAL MEDICINE
Thirteenth Edition

1 2 3 4 5 6 7 8 9 0 DOW DOW 9 8 7 6 5 4

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FRENCH (Twelfth Edition)—Flammarion, © 1992
GERMAN (Tenth Edition)—Schwabe and Company, Ltd., © 1986
GREEK (Twelfth Edition)—Parissianos, © 1994 (est.)
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PORTUGUESE (Twelfth Edition)—Editora Guanabara Koogan, S.A., © 1992
SPANISH (Twelfth Edition)—McGraw-Hill/Interamericana de Espana, © 1992

This book was set in Times Roman by Monotype Composition Company. The editors were J. Dereck Jeffers and Stuart D. Boynton. The indexer was Irving Tullar; the production supervisor was Roger Kasunic; the designer was Marsha Cohen; R. R. Donnelley & Sons Company was printer and binder.

Library of Congress Cataloging-in-Publication Data

Harrison's principles of internal medicine—13th ed./editors, Kurt J. Isselbacher . . . [et al.]
p. cm.
Includes bibliographical references and index.
ISBN 0-07-032370-4 (1-vol. ed.) : 98.00 — ISBN 0-07-911169-6 (2 vol. ed. set) : 127.00 — ISBN 0-07-032371-2 (bk. 1). — ISBN 0-07-032372-0 (bk. 2)
1. Internal medicine. I. Harrison, Tinsley Randolph, 1900–
II. Isselbacher, Kurt J. III. Title: Principles of internal medicine.
[DNLM: 1. Internal Medicine. WB 115 P957 1994]
RC46.H333 1994
616—dc20
DNLM/DLC
for Library of Congress 93-47393
CIP

66 PRINCIPLES OF DRUG THERAPY

JOHN A. OATES / GRANT R. WILKINSON

QUANTITATIVE DETERMINANTS OF DRUG ACTION

Safe and effective therapy with drugs requires their delivery to target tissues in concentrations within the narrow range that yields efficacy without toxicity. Optimal precision in achieving concentrations of drug within this therapeutic "window" can be achieved with regimens that are based on the kinetics of the drug's availability to target sites. This chapter deals with the principles of drug elimination and distribution that form the basis for loading and maintenance regimens for the average patient and considers instances in which elimination of the drug is impaired (e.g., renal failure). The basis for optimal utilization of plasma level data is also discussed.

PLASMA LEVELS AFTER A SINGLE DOSE The levels of lidocaine in plasma following intravenous administration decline in two phases, as illustrated in Fig. 66-1; such a biphasic decline is typical for many drugs. Immediately following rapid injection, essentially all of the drug is in the plasma compartment, and the high initial plasma level reflects its confinement to this small volume. Subsequently, the drug is transferred into the extravascular compartment, and the period of time during which this occurs is referred to as the *distribution phase*. For lidocaine the distribution phase is virtually complete within 30 min; then a slower rate of fall ensues, referred to as the *equilibrium phase* or *elimination phase*. During this latter phase, the drug levels in plasma and those in the tissues change in parallel.

Distribution phase Pharmacologic events during the distribution phase depend on whether the level of drug at the receptor site is similar to that in the plasma. If this is the case, the pharmacologic effects, whether favorable or adverse, may be inordinately great during this period because of the high initial levels in plasma. For example, following a small bolus dose (50 mg) of lidocaine, antiarrhythmic effects may be evident during the early distribution phase but disappear as levels fall below those which are minimally effective and even before equilibrium between plasma and tissue is reached. Thus larger single doses or multiple small doses must be administered to achieve an effect that is sustained into the equilibrium phase. Toxicity resulting from high levels of some drugs during the distribution phase precludes administration of a single intravenous loading dose that will achieve therapeutic levels during the equilibrium phase. For example, the administration of a loading dose of phenytoin as a single intravenous bolus can cause cardiovascular collapse due to the high levels during the distribution phase. If a loading dose of phenytoin is administered intravenously, it must be given in fractions at intervals sufficient to permit substantial distribution of the prior dose before the next is given (e.g., 100 mg every 3 to 5 min). For similar reasons, the loading dose of many potent drugs that rapidly equilibrate with their receptors is divided into fractional doses for intravenous administration.

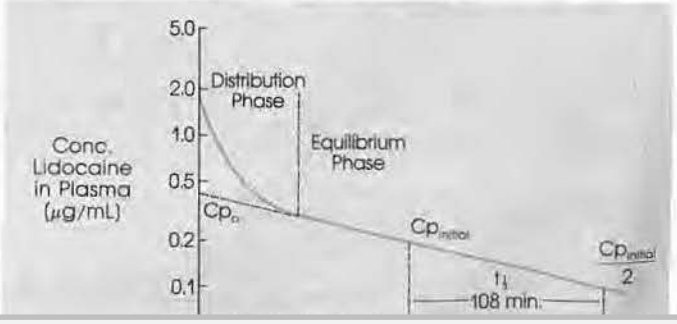
Because the drug is not absorbed instantly after oral administration and is delivered into the systemic circulation more slowly, much of the drug is distributed by the time absorption is complete. Thus procainamide, which is almost totally absorbed after oral administration, can be given as a single 750-mg loading dose with little risk of hypotension; in contrast, loading of the drug by the intravenous route is more safely accomplished by giving the dose in fractions of about 100 mg at 5-min intervals to avoid the hypotension that might ensue during the distribution phase if the entire loading dose were given as a single bolus.

In contrast, other drugs are distributed slowly to their sites of action during the distribution phase. For example, levels of digoxin at the receptor site (and its pharmacologic effect) do not reflect plasma levels during the distribution phase. Digoxin is transported (or bound) to its cardiac receptors more slowly by a process that proceeds throughout distribution. Thus plasma levels fall during a distribution phase of several hours, while levels at the site of action and pharmacologic effect increase. Only at the end of the distribution phase, when the drug has reached equilibrium with the receptor, does the concentration of digoxin in plasma reflect pharmacologic effect. For this reason, there should be a 6- to 8-h wait after administration before plasma levels of digoxin are obtained for a guide to therapy.

Equilibrium phase After distribution has proceeded to the point where the concentration of drug in plasma is in dynamic equilibrium with that in the tissues outside the vascular compartment, the levels in plasma and tissues fall in parallel as the drug is eliminated from the body. Thus the *equilibrium phase* is sometimes also referred to as the *elimination phase*. Measurement of drug concentration in plasma provides the best reflection of drug level in tissues during this phase.

Most drugs are eliminated as a first-order process. During the equilibrium phase, a characteristic of the first-order process is that the time required for the level of drug in plasma to fall to one-half the original value (the half-life, $t_{1/2}$) is the same regardless of which

FIGURE 66-1 Concentrations of lidocaine in plasma following the administration of 50 mg intravenously. The half-life of 108 min is computed as the time required for levels to fall from any given value during the equilibrium phase ($Cp_{initial}$) to one-half that level. Cp_0 is the hypothetical concentration of lidocaine in plasma at time zero if equilibrium had been achieved instantly.



point on the plasma level curve is chosen as a starting point for the measurement. Another characteristic of the first-order process is that a semilogarithmic plot of the concentrations in plasma versus time during the equilibrium phase is linear. From such a plot (Fig. 66-1) it can be seen that the half-life of lidocaine is 108 min.

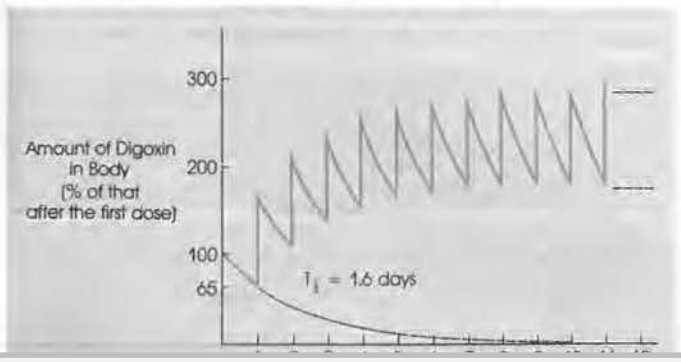
One can calculate what amount of the administered dose remains in the body at any multiple of the half-life interval following administration:

Number of half-lives	Amount of dose remaining in the body, %	Amount of dose eliminated, %
1	50	50
2	25	75
3	12.5	87.5
4	6.25	93.75
5	3.125	96.875

In principle, the elimination process never reaches completion. From a clinical standpoint, however, elimination is essentially complete when it has reached 90 percent. Therefore, for practical purposes, *a first-order elimination process reaches completion after 3 to 4 half-lives.*

DRUG ACCUMULATION—LOADING AND MAINTENANCE DOSES With repeated administration of a drug, the amount in the body accumulates if the elimination of the first dose is incomplete when the second dose is given, and both the amount of drug in the body and its pharmacologic effect increase with continuing administration until they reach a plateau. The accumulation of digoxin administered in repeated maintenance doses (without a loading dose) is illustrated in Fig. 66-2. Since digoxin's half-life is about 1.6 days in a patient with normal renal function, 65 percent of digoxin remains in the body at the end of 1 day. Thus the second dose will raise the amount of digoxin in the body (and average plasma level) to 165 percent of that following the first dose. Each subsequent dose will result in greater amounts in the body until a *steady state* is achieved. At this point, drug intake per unit of time is the same as the rate of elimination, with the fluctuation between peak and trough plasma levels remaining constant. If the rate of drug delivery is subsequently altered, a different and new steady state will be attained. Continuing infusion of a drug at constant rate also will result in progressive accumulation to a predictable steady state (Fig. 66-3). In this case, a constant plasma level (Cp_{ss}) is achieved which is between the peak and trough values attained when the same rate of drug delivery is administered in an intermittent fashion. For *all* drugs with first-order kinetics, the time required to achieve steady state levels can be predicted from the half-life because accumulation also is a first-order process with a half-life identical to that for elimination. Hence

FIGURE 66-2 The time course of digoxin accumulation when a single daily maintenance dose is given without a loading dose. Note that accumulation is more than 90 percent complete by the end of 4 half-lives.



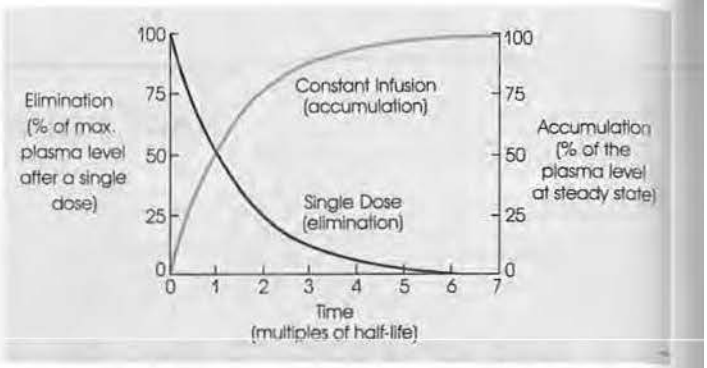


FIGURE 66-3 The time course of plasma levels of a drug following a single intravenous dose compared with those during a constant intravenous infusion. This relationship applies to all drugs that rapidly achieve equilibrium between plasma and tissues.

accumulation reaches 90 percent of steady state levels at the end of 3 to 4 half-lives. For digoxin, with a half-life of 1.6 days (with normal renal function), accumulation will be practically complete in 5 days. Continuous infusion of a drug at a constant rate also will result in progressive accumulation to a steady state with a time course predictable from the elimination curve for that drug (Fig. 66-3).

When the time required to reach steady state is longer than one wishes to wait, desired plasma levels may be achieved more rapidly by the administration of a *loading dose*. Loading entails the administration of an amount that will bring the concentration in plasma (at equilibrium) to the level present during steady state. If the desired plasma level (Cp_{ss}) is known, the loading dose can be estimated with knowledge of the extent of the drug's extravascular distribution at equilibrium, the apparent volume of distribution, or V_d:

$$\text{Loading dose} = \text{desired plasma level at steady state} \times \text{volume of distribution}$$
$$= Cp_{ss} \times V_d$$

Loading may be accomplished by the administration of the loading amount as a single dose, or in the case of drugs for which there is risk of toxicity if all the drug is introduced into the plasma compartment rapidly, the loading amount is administered in a series of fractions of the total loading amount. Since the accumulation of procainamide to 90 percent of steady state by infusion would require approximately 10 h (the $t_{1/2}$ is 3 h), a loading regimen is almost always desirable. The load required to suppress an arrhythmia, however, varies among individuals from 300 to 1000 mg, and rapid intravenous administration of the *average loading dose* causes hypotension during the distribution phase in some patients. Therefore, the intravenous loading dose of procainamide is given in fractions (e.g., 100 mg every 5 min) until the arrhythmia is controlled or adverse effects such as hypotension indicate that no further drug should be given. Dividing the loading dose into fractions is appropriate for most drugs that have a low therapeutic index (the *therapeutic index* is the ratio of toxic dose to the therapeutic dose). This permits better individualization of the loading amount and minimizes adverse effects.

The size of the loading dose required to achieve the plasma levels at steady state also can be determined from the fraction of drug eliminated during the dosage interval and the maintenance dose (in the case of intermittent drug administration). For example, if the fraction of digoxin eliminated daily is 35 percent and the planned maintenance dose is to be 0.25 mg daily, then the loading dose to achieve steady state levels should be 100/35 times the maintenance dose, or approximately 0.75 mg. Thus

The fraction of drug eliminated during any dosage interval can be determined from a semilogarithmic graph in which the total amount in the body at time zero is set at 100 percent and the fraction remaining at the end of one half-life is 50 percent.[1] Conversely, if the loading dose is known, the maintenance dose can be similarly calculated.

To calculate a loading dose designed to achieve the plasma concentration of a known infusion rate at steady state,

$$\text{Loading dose} = \frac{\text{infusion rate}}{k}$$

where k is the fractional elimination constant that describes the rate of drug elimination.[1]

Regardless of the size of the loading dose, *after maintenance therapy has been given for 3 to 4 half-lives, the amount of drug in the body is determined by the maintenance dose*. The independence of the plasma levels at steady state from the load is illustrated in Fig. 66-3, which indicates that the elimination of the loading dose would be practically complete after three to four half-lives.

DETERMINANTS OF PLASMA LEVELS DURING THE EQUILIBRIUM PHASE An important determinant of the level of drug in plasma during the equilibrium phase after a single dose is the extent to which the drug is distributed outside the plasma compartment. For example, if the distribution of a 3-mg dose of a large macromolecule is confined to a plasma volume of 3 L, then the concentration in plasma will be 1 mg/L. However, if a different drug is distributed so that 90 percent of it leaves the plasma compartment, then only 0.3 mg will remain in the 3-L plasma volume and the concentration in plasma will be only 0.1 mg/L. The *apparent volume of distribution*, or V_d, expresses the relationship between the amount of drug in the body and the plasma concentration at equilibrium:

$$V_d = \frac{\text{amount of drug in body}}{\text{plasma concentration}}$$

The amount of drug in the body is expressed as mass (e.g., milligrams), and the plasma concentration is expressed as mass per volume (e.g., milligrams per liter). Thus V_d is a hypothetical volume into which a quantity of drug would distribute if its concentration in the entire volume were the same as that in plasma. Although it is not a real volume, it is an important concept because it determines the fraction of total drug in the plasma and therefore the fraction available to the organs of elimination. An approximation of V_d in the equilibrium phase can be obtained by estimating the concentration of drug in plasma at time zero (Cp_0) by back-extrapolation of the equilibrium-phase plot to zero time, as illustrated in Fig. 66-1. Then, after intravenous administration when the amount in the body at time zero is the dose, we have

$$V_d = \frac{\text{dose}}{Cp_0}$$

For the administration of the large macromolecule mentioned above, the measured Cp_0 of 1 mg/L after a 3-mg dose indicates a V_d that is a real volume, the plasma volume. This is the exception, however, for the V_d of most drugs is larger than plasma volume; many drugs are so extensively taken up by cells that tissue levels exceed those in plasma. For such drugs, the hypothetical V_d is large, even greater than the volume of body water. For example, Fig. 66-1 indicates that the Cp_0 obtained by extrapolation after administration of 50 mg lidocaine is 0.42 mg/L, yielding a V_d of 119 L.

Since elimination is performed largely by the kidneys and liver, it is useful to consider the elimination of drugs according to the *clearance* concept. For example, in the kidney, regardless of the extent to which removal of drug is determined by filtration, secretion, or reabsorption, the net result is a reduction of the concentration of drug in plasma as it passes through the organ. The extent to which the concentration is reduced is expressed as the *extraction ratio*, or E, which is constant as long as first-order elimination occurs.

$$E = \frac{C_a - C_v}{C_a}$$

where C_a = arterial plasma concentration
C_v = venous plasma concentration

If the extraction is complete, $E = 1$. If the total plasma flow to the kidneys is Q (mL/min), the total volume of plasma from which drug is completely removed in a unit time (clearance from the body, Cl) is determined as

$$\text{Cl}_{\text{renal}} = QE$$

If the renal extraction ratio of penicillin is 0.5 and renal plasma flow is 680 mL/min, then penicillin's renal clearance is 340 mL/min. If the extraction ratio is high, as is the case for renal extraction of aminohippurate or hepatic extraction of propranolol, then clearance is a function of organ blood flow.[2]

Clearance from the body is the sum of clearance from all organs of elimination and is the best measure of the efficiency of the elimination processes. If a drug is removed by both the kidney and liver, then

$$\text{Cl} = \text{Cl}_{\text{renal}} + \text{Cl}_{\text{hepatic}}$$

Thus, if penicillin is eliminated by both renal clearance (340 mL/min) and hepatic clearance (36 mL/min) in a normal individual, total clearance is 376 mL/min. If renal clearance is reduced to half, total clearance is 170 + 36 or 206 mL/min. In anuria, total clearance equals hepatic clearance.

Only the drug in the vascular compartment can be cleared during each passage through an organ. To ascertain the effect of a given plasma clearance by one or more organs on the rate of removal of drug from the body, the clearance must be related to the volume of "plasma equivalents" to be cleared, that is, the volume of distribution. If the volume of distribution is 10 L and clearance is 1 L/min, then one-tenth of the drug in the body is eliminated per minute. This fraction, Cl/V_d, is known as a *fractional elimination constant* and is designated as k:

$$k = \frac{\text{Cl}}{V_d}$$

If the fraction k is multiplied by the total amount of drug in the body, the actual rate of elimination at any given time can be determined:

$$\text{Rate of elimination} = k \times \text{amount in body} = \text{Cl}Cp$$

This is the general equation for all first-order processes and expresses the fact that rate is proportional to the declining quantity in a first-order process.

Since half-life is a temporal expression of the exponential first-order process, half-life ($t_{1/2}$) can be related to k as follows:

$$t_{1/2} = \frac{0.693}{k}$$

$$\text{Because } k = \frac{\text{Cl}}{V_d}$$

$$\text{then } t_{1/2} = \frac{0.693 V_d}{\text{Cl}}$$

As shown in the section on drug dosage in renal failure, the linear relationship of k to creatinine clearance makes k a useful parameter

[1] Alternatively, the fraction of drug lost from the body during a dosage interval can be determined nongraphically from this equation:

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