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# Nomogram for Modification of Dosage Regimens in Patients with Chronic Renal Function Impairment

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*A nomogram is presented for modifying dosage regimens of drugs administered to patients with chronic renal function impairment. The usefulness and limitations of the nomogram are discussed in terms of the objectives of dosage regimens. The nomogram is intended to serve as a guide for drug administration in patients with renal disease. It may be particularly helpful for drugs on which little or no definitive research has been undertaken.*

**KEY WORDS:** dosage regimens—normal and in renal failure; dosage regimen nomograms; drug administration in renal failure.

## INTRODUCTION

The *usual* dosage regimens of drugs are established for individuals with *normal* metabolism and renal function. In patients with impaired renal or hepatic function, or both, the elimination of drugs may be considerably reduced. The *usual* dosage regimen in such patients will result in the accumulation of the drug in the body to levels potentially producing undesirable side-effects and toxicity.

To date, there is no hepatic function test that can be quantitatively used to estimate the reduction of metabolism of drugs in hepatic disease. On the other hand, in renal function impairment there is considerable evidence in the literature that the renal excretion of drugs can be directly correlated with common renal function tests, such as endogenous creatinine clearance, serum creatinine concentration, and blood urea nitrogen. Exogenous

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compounds, e.g., inulin and para-aminohippuric acid, have also been successfully used to correlate kidney function with renal excretion of other drugs.

Although the renal clearance of a drug may be drastically reduced in a patient with renal failure, the total rate of elimination of the drug may hardly be altered at all. It is only for those drugs whose elimination is in large part by renal excretion that large decreases in elimination and, therefore, accumulation can be expected. Serious consideration must be given to altering the dosage regimen of these drugs in cases of renal failure.

The purpose of this communication is to present a simplified and unified approach to the adjustment of dosage regimens in patients with impaired renal function. The approach involves the use of a nomogram; however, this requires an understanding of the intent and limitations of dosage regimens and other factors that may influence decisions on administering drugs to patients with decreased renal function.

## DOSAGE REGIMENS

Basically there are three kinds of considerations, as outlined in Table I, to administering drugs in a rational therapeutic dosage regimen. The first consideration includes those factors that relate to the efficacy and safety of a drug, that is, how a drug acts on the body. The second is that of the time course of a drug in the body following single or multiple administrations of a drug by any route and in any of various dosage forms. This is a consideration of how the body acts on a drug. The third is that of the clinical state of the patient and his total therapeutic regimen. All three considerations are interrelated and interdependent. Rational drug therapy requires a thera-

**Table I.** Factors That Determine a Dosage Regimen

| | | Clinical factors | |
|---|---|---|---|
| Activity–toxicity | Pharmacokinetics | Clinical state of patient | Management of therapy |
| Minimum therapeutic dose | Absorption | Age, weight, urine *p*H, etc. | Multiple drug therapy |
| Toxic dose | Distribution | Condition being treated | Convenience of regimen |
| Therapeutic index | Metabolism | Existence of other disease states | Compliance of patient |
| Side-effects | Excretion | | |
| Dose–response relationships | Pharmacogenetics–idiosyncrasy | | |
| Tolerance–dependence | Drug–drug interactions | | |
| Pharmacogenetics–idiosyncrasy | | | |
| Drug–drug interactions | | | |

peutic amount of the appropriate drug in the body at the proper time. Once the appropriate drug is chosen, the principal objective is then to properly administer it. In this respect, pharmacokinetic considerations are of paramount importance.

Depending on clinical factors and the pharmacology–toxicology of a drug, the usual dosage regimen is either one in which the drug is administered to continuously maintain therapeutic levels or one in which therapeutic levels are achieved intermittently.

Intermittent therapy may be called for if only periodic therapeutic levels are required (this has been argued as a desirable condition for antibiotic treatment of some infectious diseases), tolerance develops to the drug, or the therapeutic effects of the drug persist and accumulate even though the

**Table II.** Dosage Regimens for Continuous Maintenance of Therapeutic Levels

| Therapeutic index[a] | Half-life[b] | Ratio of initial dose to maintenance dose | Ratio of dosing interval to half-life | Comments |
|---|---|---|---|---|
| High | Very short (<20 min) | — | — | Candidate for infusion and/or short-term therapy |
| | Short (20 min–3 hr) | 1 | 3–6 | To be given any less often than every 3 half-lives, drug must have very high therapeutic index |
| | Intermediate (3–8 hr) | 1–2 | 1–3 | |
| | Long (8–24 hr) | 2 | 1 | Very common and desirable regimen |
| | Very long (>24 hr) | >2 | <1 | Once daily is practical; initial dose may need to be much greater than maintenance dose |
| Low | Very short (<20 min) | — | — | Not a candidate except under very closely controlled infusion |
| | Short (20 min–3 hr) | — | — | Only by infusion |
| | Intermediate (3–8 hr) | 1–2 | ~1 | Requires 3–6 doses per day |
| | Long (8–24 hr) | 2–4 | 0.5–1 | Requires careful control as once toxicity |
| | Very long (>24 hr) | >2 | <1 | is produced drug and toxicity decline very slowly |

[a]Toxic dose/therapeutic dose.
[b]Elimination half-life. Definitions are arbitrary.

drug rapidly disappears. The last category is that of the "hit and run" drugs, examples of which are reserpine and methotrexate.

For the maintenance of therapeutic amounts in the body, the initial and maintenance doses must be given at dosing intervals which will keep the amount above a minimum effective level and below a level producing excessive side-effects and toxicity. To design a dosage regimen to maintain therapeutic levels, the following must be considered: the minimum therapeutic dose, the therapeutic index (ratio of toxic dose to therapeutic dose), and the elimination half-life.

Dosage regimens that achieve and maintain therapeutic amounts in the body are listed in Table II for drugs with both high and low therapeutic indices and with various elimination half-lives. A more complete theoretical description of dosage regimens has been given by Rowland (1) and Krüger-Thiemer (2).

It is very difficult to maintain therapeutic levels of drugs with short to very short half-lives. This is particularly true for drugs with a low therapeutic index. Such drugs might be given by infusion or must be discarded unless intermittent therapy is desirable. Drugs with a high therapeutic index may be given less frequently, but the greater the dosing interval the greater the

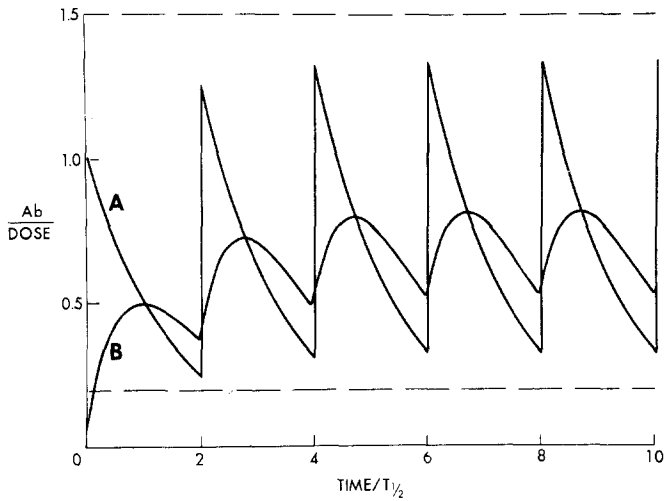



**Fig. 1.** Ratio of the amount of drug in the body to the maintenance dose with time (in elimination half-life units). The drug is administered every 2 elimination half-lives. Curve A, intravenous bolus dose; curve B, oral dose with complete absorption. The absorption is assumed to be of first order with a half-life one half that of the elimination. The dashed lines represent the minimum therapeutic level and the level at which significant toxicity commences. Analog computer simulation.

dose required to stay above a minimum effective level. Penicillin is a notable example of a drug in which the dosing interval is many times longer than the elimination half-life and in which the dose given greatly exceeds that required to yield plasma concentrations equivalent to the minimum inhibitory concentration for most microorganisms.

For drugs of short to intermediate half-life, the major considerations are therapeutic index and convenience of dosing. A drug with a high therapeutic index need only be administered every 1–3 elimination half-lives. One with a low therapeutic index will have to be given approximately every half-life or more frequently or be given by infusion.

Curve A in Fig. 1 shows the amount of drug in the body with time following an intravenous regimen in which the initial dose is repeated every 2 half-lives. The dosing interval can be greater than the half-life here because of the high therapeutic index. Absorption can play an important role in reducing the fluctuations seen after intravenous administration. Curve B

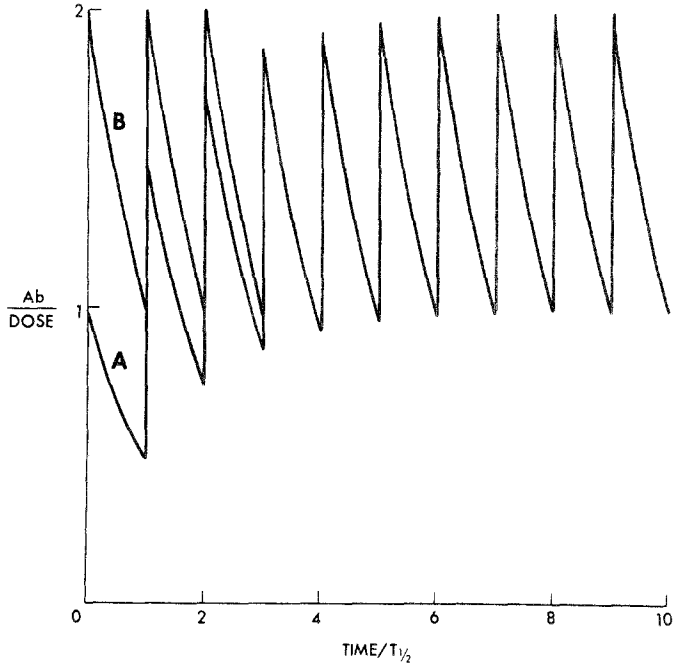



**Fig. 2.** Ratio of the amount of drug in the body to the maintenance dose with time (in elimination half-life units). The drug is administered intravenously every elimination half-life. Curve A, initial and maintenance dose are the same; curve B, initial dose is twice the maintenance dose (the curve is drawn only through the third dose; curves A and B are essentially the same thereafter). Analog computer simulation.

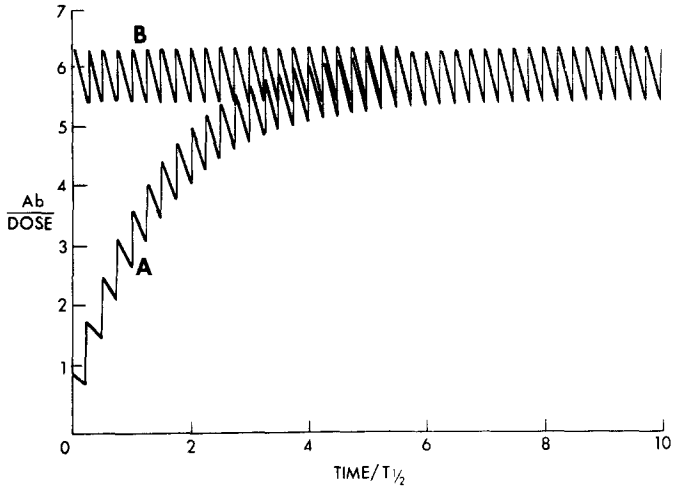



**Fig. 3.** Ratio of amount of drug in the body to the maintenance dose with time (in elimination half-life units). The dosing interval is one fourth of the elimination half-life. Curve A, initial and maintenance doses are the same; curve B, initial dose is 6.3 times the maintenance dose, this being the dose required to initially achieve the plateau level. Analog computer simulation.

represents a drug administered orally for which absorption is complete and of first order with an absorption half-life one half that of the elimination half-life. Note that by both routes of administration the average level with time is the same after several doses (4–6 elimination half-lives).

For drugs with long elimination half-lives, the most convenient regimen is to give a dose every half-life, as shown in curve A of Fig. 2 for intravenous administration. It is often desirable to achieve the maintenance levels at once instead of waiting for accumulation to occur. In this case, the initial dose (loading dose or priming dose) must be twice the maintenance dose, curve B, Fig. 2. The minimum and maximum amounts in the body are in this case equivalent to one and two maintenance doses, respectively. Administration of the drug by any nonvascular route would tend to reduce the fluctuations as shown in Fig. 2, depending on how fast absorption occurred relative to elimination. Again, the average level produced after several elimination half-lives will be the same by all routes of administration regardless of how slow the absorption, provided it is complete.

For drugs with very long half-lives, dosage regimens in which the initial dose is manyfold greater than the maintenance dose are often desirable. This is a consequence of the practical consideration of the inconvenience of taking a drug any less often than once daily. If the therapeutic effect is desired right

away, then a therapeutic dose is given initially; the smaller maintenance dose is required only to maintain the therapeutic levels as shown in curve B of Fig. 3. For some drugs with very long half-lives, the initial and maintenance doses are the same. This may require the administration of several doses to reach therapeutic levels, as seen in curve A of Fig. 3. This too is often a matter of practical consideration. Side-effects to large oral doses (gastrointestinal side-effects) or to acutely high levels in the body may necessitate a slow buildup of drug in the body.

The regimen in which the dosing interval is less than the elimination half-life is one which leads to accumulation on repeated administration of a

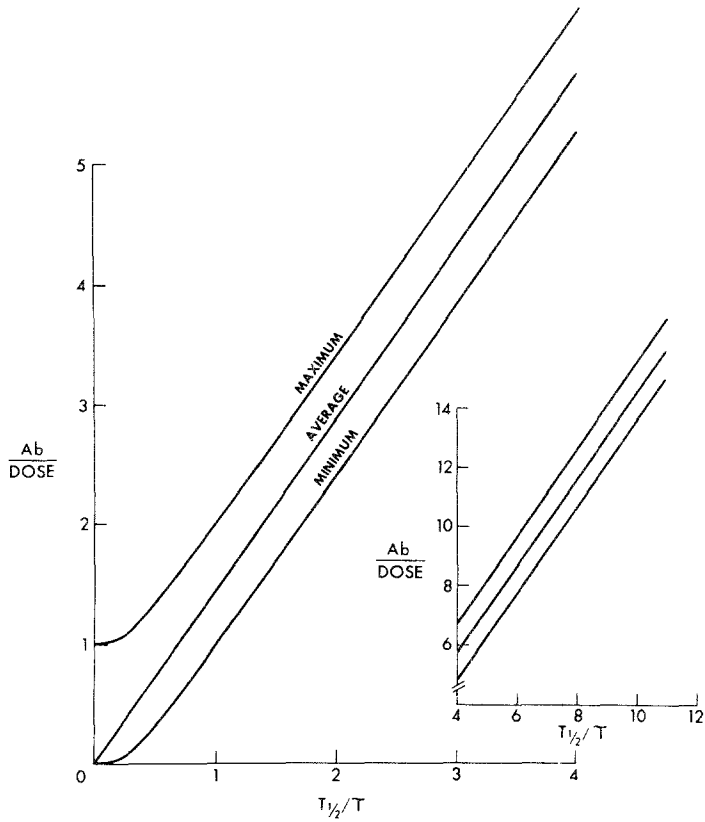



**Fig. 4.** Ratios of the maximum, average, and minimum amounts of drug in the body to the maintenance dose following chronic intravenous administration as a function of the dosing frequency. The dosing frequency is shown in units of reciprocal elimination half-lives. The graph is extended in the insert. © 1974 by author.

given dose. The greater the ratio of half-life to dosing interval, the greater the accumulation. It is this consideration that gives rise to concern for patients on usual dosage regimens that develop a failure in their ability to eliminate drugs (increased elimination half-life).

When the usual dosage regimen is one in which the dosing interval is much greater than the elimination half-life, one might think that unless the elimination is decreased to the point that the half-life approaches the dosing interval there is no cause for concern, since most of the drug from previous doses will be eliminated before the next dose. This is not necessarily true, because any increase in the half-life will increase the average level obtained in proportion to the increase in the half-life. This is graphically demonstrated in Fig. 4, in which the maximum, minimum, and average amounts of drug in the body following chronic intravenous administration of a given dose are shown. If the elimination half-life is one fifth of the dosing interval, a doubling of the half-life will double the average steady-state amount in the body, but will not significantly increase the maximum levels. If the half-life were increased beyond 50% of the dosing interval, then the maximum and minimum values would increase in rough proportion to the further increase in the half-life.

Regardless of the normal dosage regimen, renal failure may result in an increased average amount of drug in body. The increase will depend on severity of the renal failure and the normal contribution of the renal route to the total elimination of the drug.

## DOSAGE REGIMENS IN RENAL FAILURE

Various pharmacokinetic parameters have been correlated with the various tests of renal function. Half-life, daily or hourly loss of the drug in terms of the percent of drug remaining in the body, and renal clearance are the most commonly used elimination parameters. A variety of graphical representations showing the correlation of these various parameters with kidney function have been made. From these correlations, graphs for each of several drugs have been prepared to adjust the dosage regimen of these drugs in patients with renal function impairment. As the number of drugs studied has greatly increased in recent years, so have the number and kinds of correlations made and the suggestions for adjustment of dosing of these drugs in renal failure. Without the aid of a computer, it is becoming more difficult to keep abreast of the literature in the area to assure the most rational drug therapy to all patients.

For every drug for which altered regimens in renal failure have been established by experiment and of which the author is aware, there is a simpli-

fied approach based on pharmacokinetic principles (3–5) that could have been used to administer these drugs. This approach involves the use of a nomogram, the derivation of which is given in the Appendix.

The only information required to establish a dosage regimen for a patient with renal failure is (a) the *normal* dosage regimen for the patient, (b) the kidney function as a fraction of the *normal*, and (c) the fraction of the total elimination of the unchanged drug that occurs by renal excretion in the absence of hepatic or renal dysfunction.

The *normal* dosage regimen is that determined to be appropriate for the individual without renal or hepatic function impairment. The *normal* dosing schedule is determined by the patient's age, height and weight or surface area, and the condition being treated. The individual, therefore, might be an infant, a child, an adult, or a geriatric patient.

The kidney function is expressed in terms of the fraction of that which is normal for the individual. Again, the kidney function will vary with the age and weight of the patient. However, the information required is simply the kidney function as a fraction of the normal for a patient of his age, height, and weight.

The third piece of information that is needed is the fraction of the total elimination of a drug that normally occurs by renal excretion. This value, too, should be that for a normal individual of the same age, height, and weight as the patient. Of the three kinds of information, this is probably the most difficult to accurately determine. The percentage of a dose excreted unchanged is given in most good pharmacology texts; however, one has to be careful in interpreting the value given, as the figure quoted is sometimes that obtained after an oral dose, in which case the fraction of the dose absorbed is unknown. Also, the assay techniques used may not have distinguished between drug and metabolite(s), and sometimes the reported values are based on incomplete urine collection. The latter occurs by missed samples and in not continuing to obtain urine until virtually all of the drug has been eliminated from the body.

To explain how to use the nomogram, a few examples of specific drugs will be used. As a first example, consider how the dosage regimen of kanamycin, a drug that is virtually completely eliminated by excretion, should be altered in renal function impairment. The suggested dosage regimen for adult, average-sized patients with normal renal function is 7 mg/kg intramuscularly every 12 hr (6,7). Two of the three required pieces of information are now given, that is, the fraction of dose excreted unchanged, 1.0, and the normal dosage regimen. The third requirement is an estimate of kidney function.

If a patient weighing 72 kg has an endogenous creatinine clearance of 30 ml/min/1.73 $m^2$, then the following information is quickly derived:

1. *Normal* dosage regimen:
   7 mg/kg × 72 kg = 500 mg to be administered intramuscularly every 12 hr.
2. Kidney function—120 ml/min/1.73 $m^2$ is assumed to be the normal kidney function:

$$\frac{30 \text{ ml/min}}{120 \text{ ml/min}} = 0.25.$$

3. Fraction excreted unchanged = 1.0.

To determine the dosage regimen in this patient, the point on the graph of Fig. 5 at which the lines representing kidney function of 0.25 and fraction excreted unchanged of 1.0 cross is obtained. The vertical scale reading, $Q$, is 4, indicating an increase of four-fold in the half-life of the drug in the body. The dosage regimen may now be modified in any of the following ways:

A. The dosing interval may be increased by a factor of 4. Dosage regimen: 500 mg every 48 hr.
B. The maintenance dose may be decreased by a factor of 4. Dosage regimen: 500 mg initially, then 125 mg every 12 hr.
C. Both the dosing interval and the maintenance dose may be adjusted to decrease the average rate of administration by a factor of 4. Dosage regimen: 500 mg initially, then 250 mg every 24hr.

The above three dosage regimens are identical only with respect to the average rate of administration of kanamycin. In general, one would expect that a regimen that diminishes fluctuations of drug in the body would be preferred, regimen B. In this case, two arguments might be given in support of regimen A or C. In terms of convenience to the patient, regimen A necessitates an intramuscular dose only every 2 days. Regimen C both reduces fluctuations and has a convenient dosing interval. In the normal regimen, the levels may be below the minimum level for several hours in each dosing interval. Some might argue the desirability of doing so based on the theory of allowing the infectious organism to grow to a more susceptible stage. However, the 48-hr interval may allow much greater periods of potentially inadequate levels, and this may not be in phase with the growth of the microorganism. To this end, it is the author's view that regimen C, which reduces both normal fluctuations and inconvenience to the patient, is probably preferred, at least until proven to be otherwise.

As a second example, consider the dosage regimen for procainamide, a drug in which 40–50% of a parenteral dose in excreted unchanged (8) in a 50-kg patient whose renal function is only 15% of normal. Koch-Weser and Klein (8) suggest an average daily dose of 50 mg/kg of procainamide hydro-

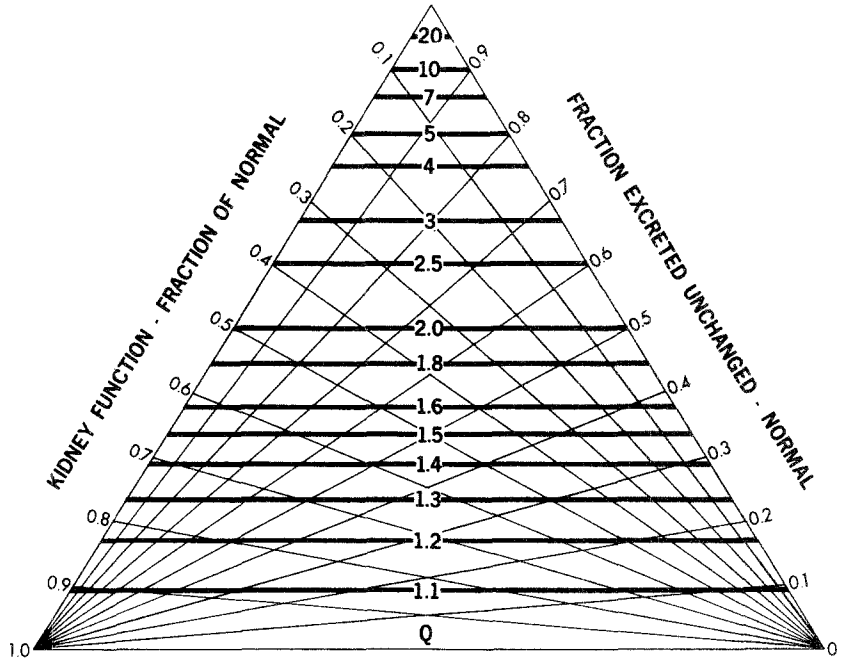



**Fig. 5**

Nomogram for modification of drug dosage regimens in chronic renal failure. To be used to determine how to change a *normal* dosage regimen. The normal dosage regimen depends on age, weight, condition being treated, etc. Activity and toxicity of metabolites are not taken into consideration. © 1974 by author.

Modification of dosage regimen.

I. Initial dose—no change.

II. Adjustment of rate of administration (using factor $Q$ of center scale)

A. Change in dosing interval, $\tau$, only

$$\tau \text{ (failure)} = Q \times \tau \text{ (normal)}$$

B. Change in maintenance dose, $D$, only

$$D \text{ (failure)} = \frac{D \text{ (normal)}}{Q}$$

C. Change in rate of administration, $D/\tau$

$$(D/\tau) \text{ (failure)} = \frac{(D/\tau) \text{ (normal)}}{Q}$$

chloride given in divided doses every 3 hr as a usually effective antiarrhythmic dosage regimen. A parenteral priming dose is suggested in urgent situations.

In this patient, the following information is obtained:

1. Normal dosage regimen:

50 mg/kg × 50 kg = 2.5 g/day in 8 divided doses or
313 mg every 3 hr.

2. Kidney function = 0.15.
3. Fraction excreted unchanged = 0.45.

To estimate the modified dosage regimen in this patient, it is necessary to interpolate. The point on the nomogram satisfying both a kidney function of 0.15 and a fraction excreted unchanged of 0.45 is 1.65. Thus the *normal* dosage regimen is to be modified by this factor. Again, this can be accomplished by increasing the dosing interval, decreasing the dose, or a combination of the two. Since the normal rate of administration is 313 mg/3 hr or 103 mg/hr, the new rate of administration should be 63 mg/hr. Practical considerations of the dose contained in the commercially available oral dosage form and of the dosing interval will determine a preferred dosage regimen. In this case, a 250-mg capsule every 4 hr or two 250-mg capsules every 8 hr might be administered. The former would probably be preferred to prevent large fluctuations in the blood levels.

A third example to show the use of the nomogram in renal failure is that of administering digoxin, 60–70% of which is excreted unchanged by the kidney (9). An elderly patient who has been maintained for a year with a 0.25-mg tablet of digoxin once a day develops signs of digitalis toxicity. Tests show that the patient has developed impaired kidney function. After several days of attempts to readjust the dose, it is apparent that the renal function has stabilized at about 20% of normal. The renal function is, of course, subsequently monitored.

The maintenance dosing rate of digoxin is determined from the nomogram by the ordinal value of the point where the lines representing a kidney function of 0.20 and a fraction excreted unchanged of 0.65 cross. Thus the *normal* rate of 0.25 mg/day is to be decreased by a factor of 2.15. The patient should require only 0.111 mg/day. This might be approximated with 0.125 mg once daily. The drug should be withdrawn until signs of toxicity are gone, then this dosage regimen instituted. Subsequent monitoring of kidney function is essential.

It should be apparent that the initial dose is not altered; the same amount in the body is required for a therapeutic response.

The decision to increase the dosing interval or decrease the maintenance dose will depend on practical considerations. The latter leads to reduced fluctuations of the level of the drug in the body. The former may make administration more convenient. A change in both the dosing interval and maintenance dose may be preferred. It is important to realize that the objective is to reduce the rate of administration to accommodate the reduction in the rate of elimination, thereby achieving the same average therapeutic amount of drug in the body.

Many other examples might be given to show the potential of the nomogram for modification of a dosage regimen in cases of impaired renal

function. There are, of course, a number of assumptions or qualifications that must be considered in applying the nomogram, such as the following:

1. The metabolites of the drug are assumed to be pharmacologically inactive and nontoxic.
2. Individual variations in metabolism or in the response to a given plasma concentration of the drug are not considered, only average values. This limitation would be obviated in the case in which the therapeutic dosage regimen for the individual is known when renal function is normal.
3. Altered distribution or metabolism of the drug brought about by the failure in renal function, for example, accumulation of a metabolite, or accumulation of endogenous compounds that displace the drug from plasma proteins, is assumed not to occur. Altered distribution in severe renal function impairment has been suggested for gentamycin (10) and digoxin (11). The significance of this has not been fully elucidated.
4. Cardiac output, hepatic function, and all other physiological functions which might affect the absorption or disposition of the drug are assumed to be normal.
5. Reasonably constant renal function with time is assumed.
6. It is assumed that nonlinear pharmacokinetics does not apply to either the metabolism or renal excretion of the drug.
7. A direct relationship is assumed between the renal clearance of the drug and the renal clearance of the compound used to determine renal function.

A note of caution should be emphasized on the last qualification. It is assumed that regardless of whether the compound is primarily eliminated by glomerular filtration or active secretion the clearance of the compound decreases in proportion to the clearance of the compound used to determine renal function. Although the author is unaware of any definitive work in this regard, there is evidence in the literature that this assumption is valid. Para-aminohippuric acid (6), procainamide (8), carbenicillin (12), and penicillin (13) are examples of actively secreted compounds whose clearances are apparently proportional to endogenous creatinine clearance and inulin clearance.

At the present time, there are a number of drugs for which no reliable estimate of the fraction excreted unchanged is available; therefore, the nomogram cannot be used. For some of these drugs, an alternative method may be available from data correlating the half-life with a parameter of kidney function. The nomogram may be useful, in this case, to estimate the fraction normally excreted unchanged.

The limitations given above should make it clear that the use of the nomogram does not take the place of nor discourage the monitoring of blood levels of drugs, especially those with low therapeutic indices. The nomogram is intended to serve as a useful guide to modify the dosage regimens in renal function impairment. It may be of particular value for a drug in which definitive research on the pharmacokinetics in renal failure is totally lacking.

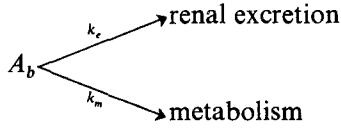
## APPENDIX

### Derivation of Nomogram

The nomogram is based on the following assumptions:

1. One body compartment for the drug.
2. The processes of renal excretion, metabolism, and other routes of elimination are first order.
3. The metabolites are inactive and not toxic in the levels that are produced in the body.
4. The renal clearance of the drug is directly proportional to the kidney function as determined by methods employed.
5. The processes of metabolism and distribution of the drug are not altered in renal failure.

The model for the elimination of the drug *normally* is




rate of elimination = $k_d A_b$

in which $A_b$ is the amount of drug in the body, $k_e$ is the first-order excretion rate constant, $k_m$ is the first-order metabolism rate constant, and $k_d$ is the first-order elimination rate constant = $k_e + k_m$.

The following abbreviations are used to describe the altered elimination in renal function impairment:

$k_e(f)$ = first-order excretion rate constant in renal failure
$k_e V_d(f)$ = renal clearance in renal failure
$k_d(f)$ = first-order elimination rate constant in renal failure
$t_{1/2}(f)$ = elimination half-life in renal failure
$k_e(n)$ = *normal* first-order excretion rate constant
$k_e V_d(n)$ = *normal* renal clearance
$k_d(n)$ = *normal* first-order elimination rate constant
$f_e$ = fraction of dose absorbed *normally* excreted unchanged

$D$ = maintenance dose
$\tau$ = dosing interval
$(D/T)(n)$ = *normal* rate of administration
$(D/T)(f)$ = rate of administration in renal failure
$K_F$ = kidney function as a fraction of *normal*

Based on assumptions 2 and 4 above,

$$k_e V_d(f)/k_e V_d(n) = k_e(f)/k_e(n) = K_F \tag{1}$$

$$k_e(n)/k_d(n) = f_e \tag{2}$$

and

$$k_d(n) = k_e(n) + k_m \tag{3}$$

Since

$$k_d(f) = k_e(f) + k_m \tag{4}$$

substitution of equations 1–3 into equation 4 gives

$$k_d(f)/k_d(n) = [1 - f_e(1 - K_F)] \tag{5}$$

Using the relationships

$$k_d(f) = 0.693/t_{1/2}(f) \tag{6}$$

and

$$k_d(n) = 0.693/t_{1/2}(n) \tag{7}$$

then

$$t_{1/2}(f)/t_{1/2}(n) = 1/[1 - f_e(1 - K_F)] \tag{8}$$

To maintain a given amount of drug in the body in renal failure, the rate of administration becomes

$$(D/\tau)(f) = k_d(f) \times A_b \tag{9}$$

The normal rate of administration is

$$(D/\tau) = k_d(n) \times A_b \tag{10}$$

therefore,

$$(D/\tau)(f) = (D/\tau)(n) \times k_d(f)/k_d(n) \tag{11}$$

If the dosing interval is not altered, then

$$D(f) = D(n) \times k_d(f)/k_d(n) \tag{12}$$

If the maintenance dose is unchanged, then

$$\tau(f) = \tau(n) \times k_d(n)/k_d(f) \tag{13}$$

From equations 5, 8, 11, 12, and 13, the following relationships are evident:

$$\frac{k_d(n)}{k_d(f)} = \frac{t_{1/2}(f)}{t_{1/2}(n)} = \frac{D(n)}{D(f)} = \frac{(D/\tau)(n)}{(D/\tau)(f)} = \frac{\tau(f)}{\tau(n)} = \frac{1}{1 - f_e(1 - K_F)} \tag{14}$$

The factor by which the half-life and dosing interval are to be increased or by which the maintenance dose, rate of administration, or elimination rate constant is decreased in renal function impairment is reciprocally related to the fraction excreted unchanged, $f_e$, and the loss of kidney function, $(1 - K_F)$. The nomogram is prepared by using a reciprocal or hyperbolic scale for the factor of change in the dosing parameter and linear scales for the fraction excreted unchanged and the loss of renal function.

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