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**ELIMINATION KINETICS AND DOSAGE OF DRUGS IN PATIENTS WITH RENAL DISEASE**

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University of Basel, Switzerland

In the present report a simple graphical method is described which allows one to estimate quantitatively individual drug elimination rates in patients with renal impairment from the subject’s creatinine clearance, ClCR, or serum creatinine concentration, CCR. Based on the estimated drug elimination parameters individually adapted dosage regimens may be calculated by means of simple dosage rules.

As far as terminology is concerned it should be noted that all symbols relating to patients with renal disease are denoted by a circumflex sign (e.g. k̂, δ̂ etc). Symbols relating to patients with normal kidney function are characterised by the subscript
N(e.g. ClN, kN). For the sake of simplicity, normal kidney function is defined by ClCr=100ml/min. Symbols without circumflex sign or subscript are of general validity, i.e. they refer to both patients with normal and with impaired kidney function.

THEORY

The assumptions underlying the theory are as follows:

**Assumption 1** It is assumed that for clinical purposes the elimination kinetics of the drug can be described with sufficient accuracy by one-compartment first order kinetics, i.e. the decrease of the drug plasma concentration per unit of time, -dc/dt, is proportional to the plasma concentration, c:

\[-\frac{dc}{dt} = \frac{ClD}{VD}.c = k . c\]  \hspace{1cm} (1)

where ClD = overall clearance, VD = distribution volume and k = overall elimination rate constant of the drug.

**Assumption 2** The elimination rate constant, k, of the drug is the sum of its extrarenal elimination rate constant, knr, and its renal elimination rate constant, kr:

\[k = knr + kr\]  \hspace{1cm} (2)

**Assumption 3** The rate of extrarenal drug elimination remains uninfluenced by the uraemic state, i.e.

\[knr = \text{const}\]  \hspace{1cm} (3)

**Assumption 4** Bricker’s ‘intact nephron hypothesis’ (Bricker et al, 1960) is valid, i.e. the diseased kidney eliminates drugs like a kidney with a smaller than normal number of nephrons. From this it follows that the renal elimination rate constant, kr, of any drug is proportional to the glomerular filtration rate as measured by the endogenous creatinine clearance, ClCr, whether or not the drug undergoes only glomerular filtration or additional tubular secretion and reabsorption. This means in mathematical terms:

\[kr = \alpha \cdot ClCr\]  \hspace{1cm} (4)

**Assumption 5** Drug absorption is identical in normal and in uraemic patients.

Introducing eq. 4 in eq. 2 results in

\[k = knr + \alpha \cdot ClCr\]  \hspace{1cm} (5)

indicating a simple linear relationship between the overall drug elimination rate
constant, \( k \), and the creatinine clearance, \( C_{lcr} \). Based on eq. 5 the individual elimination rate constant of any drug in any patient with renal disease may be estimated by graphical methods (Dettli, 1974).

In order to further simplify the graphical estimating procedure, eq. 5 was ‘normalised’ by dividing it through the elimination rate constant of the drug in patients with normal kidney function, \( k_N \) (Dettli, 1975). This results in a new parameter, the so-called elimination rate fraction, \( Q \):

\[
Q = \frac{k}{k_N} = \frac{k_{NI}}{k_N} + \frac{\alpha}{k_N} C_{lcr} = Q_0 + \frac{\alpha}{k_N} C_{lcr}
\]  

(6)

According to eq. 6, \( \hat{Q} = \frac{k}{k_N} \) describes the individual drug elimination rate, \( \hat{k} \), in patients with renal disease in terms of a fraction of the corresponding normal elimination rate constant in subjects without renal disease, \( k_N \). As can be seen, the graphical representation of eq. 6 is again a straight line — the so-called dosing line — describing the quantitative relationship between the elimination rate fraction, \( Q \), and the creatinine clearance, \( C_{lcr} \). Based on these facts a simple nomograph (see Figure 3) has been constructed (Spring, 1975) with \( Q \) plotted on the ordinate and \( C_{lcr} \) on the abscissa. The individual elimination rate fraction in a patient with renal disease, \( \hat{Q} \), may be estimated based on the following considera-

![Figure 3. Nomograph for the graphical estimation of individual elimination rate fractions, \( \hat{Q} = \frac{k}{k_N} \) (left ordinate) of drugs in patients with renal disease. The dosing line of a drug is the straight line connecting the right upper corner of the nomograph with the value of \( Q_0 \) (see Table I) at the left ordinate. The point of intersection of the subjects creatinine clearance \( C_{lcr} \) (lower abscissa) read off from the left ordinate corresponds to the individual value of \( \hat{Q} \) of the drug in the patient. For further explanation see text.](image-url)
tions: By definition, the value of the elimination rate fraction \( Q = k / k_N \) of all drugs in patients with normal renal function is \( Q = Q_N = 1.0 \). On the other hand, in anuric patients (\( C_{\text{cr}} = 0 \, \text{ml/min} \)) the value of \( Q \) predicted by eq. 6 is

\[
Q_o = \frac{k_{nr}}{k_N}
\]  

(7)

Consequently, when the value of \( Q_o \) of a drug is plotted on the left ordinate (\( C_{\text{cr}} = 0 \, \text{ml/min} \)) of the nomograph the straight line connecting \( Q_o \) with the upper right corner of the nomograph (\( C_{\text{cr}} = 100 \, \text{ml/min} \), \( Q_N = 1.0 \)) represents the dosing line of the agent. The point of intersection between the patient’s creatinine clearance (abscissa) with the dosing line read off from the ordinate is the individual elimination rate fraction, \( \bar{Q} \), of the drug in this patient. In patients with chronic and stable kidney disease \( Q \) may be estimated from the creatinine concentration, \( C_{\text{cr}} \) (upper abscissa) in the serum.

According to the theory presented above, the relative speed of drug elimination can be estimated by means of a simple nomograph when one single parameter, \( Q_o \), is known. This is readily understood by intuitive reasoning because it can be shown by kinetic analysis that \( Q_o = k_{nr} / k_N \) as described in eq. 7 is identical with the fraction of the dose which is eliminated by extrarenal pathways in subjects with normal kidney function (Dettli, 1975; Welling et al, 1973). From this it follows that a drug with a low value of \( Q_o \) is normally eliminated almost entirely by the kidneys. Its elimination rate will therefore closely depend on kidney function. Correspondingly, the dosing line of such a drug in our nomograph will be very steep. Examples are hydrophilic drugs such as the aminoglycosides and penicillin G. On the other hand, lipophilic drugs such as chloramphenicol are normally eliminated almost exclusively by metabolic transformation. As a consequence \( Q_o \) will approach unity and the corresponding dosing line in the nomograph is practically horizontal indicating that the elimination rate of the drug is independent of renal function. At present the value of \( Q_o \) is known for about sixty different drugs (see Table I).

Table I. Elimination rate fraction, \( Q_o = k_{nr} / k_N \), and normal elimination rate constants, \( k = 0.7/t_{1/2N} \) (per hour or per day) of sixty drugs (Dettli, 1974; Welling et al, 1975). Agents denoted by an exclamation mark (!) are not recommended in patients with renal disease because formation of pharmacologically active metabolites has not been excluded beyond doubt.

<table>
<thead>
<tr>
<th>Drug</th>
<th>( Q_o )</th>
<th>( k_N ) (per hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEMOTHERAPEUTIC AGENTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>0.01</td>
<td>0.4</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>0.15</td>
<td>0.7</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0.12</td>
<td>0.8 (continued)</td>
</tr>
<tr>
<td>Drug</td>
<td>IC50 (nmol/L)</td>
<td>EC50 (nmol/L)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>0.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Cefacetril</td>
<td>0.04</td>
<td>0.7</td>
</tr>
<tr>
<td>Cefalexin</td>
<td>0.04</td>
<td>0.7</td>
</tr>
<tr>
<td>Cefaloridine</td>
<td>0.08</td>
<td>0.4</td>
</tr>
<tr>
<td>Cefalothin</td>
<td>0.04 (?)</td>
<td>1.4</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>0.06</td>
<td>0.35</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>0.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Chlortetracycline</td>
<td>0.8 (1)</td>
<td>0.1</td>
</tr>
<tr>
<td>Cicacillin</td>
<td>0.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>0.25</td>
<td>1.2</td>
</tr>
<tr>
<td>Colistimethate</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Dicloxacillin</td>
<td>0.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>1.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Epicillin</td>
<td>0.06</td>
<td>0.5</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Flucyclosin</td>
<td>0.03</td>
<td>0.25</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>0.02</td>
<td>0.3</td>
</tr>
<tr>
<td>Isoniazid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Fast inactivators</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>- Slow inactivators</td>
<td>0.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>0.03</td>
<td>0.35</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>0.4</td>
<td>0.15</td>
</tr>
<tr>
<td>Methicillin</td>
<td>0.12</td>
<td>1.4</td>
</tr>
<tr>
<td>Minocycline</td>
<td>0.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>0.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>0.25</td>
<td>1.4</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>0.2</td>
<td>0.08</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>0.02</td>
<td>1.4</td>
</tr>
<tr>
<td>Pivampicillin</td>
<td>0.12</td>
<td>0.8</td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>0.12</td>
<td>0.15</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>1.0</td>
<td>0.25</td>
</tr>
<tr>
<td>Rolitetracycline</td>
<td>0.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>0.04</td>
<td>0.25</td>
</tr>
<tr>
<td>Sulfisomidine</td>
<td>0.08</td>
<td>0.15</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>0.45</td>
<td>0.07</td>
</tr>
<tr>
<td>Sulfamethizole</td>
<td>0.55 (?)</td>
<td>0.3</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>0.85</td>
<td>0.07</td>
</tr>
<tr>
<td>Tricarcillin</td>
<td>0.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0.12</td>
<td>0.08</td>
</tr>
<tr>
<td>Thiamphenicol</td>
<td>0.08 (?)</td>
<td>0.25</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>0.02</td>
<td>0.35</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>0.45</td>
<td>0.06</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.03</td>
<td>0.12</td>
</tr>
</tbody>
</table>

**MISCELLANEOUS DRUGS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>IC50 (nmol/L)</th>
<th>EC50 (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Methyldopa</td>
<td>0.2 (?)</td>
<td>0.17</td>
</tr>
<tr>
<td>Chloropropamide</td>
<td>0.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Glukidone</td>
<td>1.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>0.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Propranolol</td>
<td>0.8</td>
<td>0.2 (continued)</td>
</tr>
</tbody>
</table>
Sulfinpyrazon
0.55
0.3

CARDIAC GLYCOSIDES
(per day)

α - Acetyldigoxin
0.3
0.7
Digitoxin
0.7 (!)
0.1
Digoxin
0.3
0.45
β - Methyldigoxin
0.5
0.25
Peruvoside
0.8 (!)
0.3
Proscillaridin
1.0
0.4
Strophanthin G (Ouabain)
0.25 (!)
1.2
Strophanthin K
0.25 (!)
1.0

THE DOSAGE RULES

In the case of *intermittent drug administration*, most problems of drug dosage modification in patients with renal disease can be solved based on the graphically estimated value of \( \hat{Q} \) by using one of the two following simple dosage rules:

**Rule 1:**

\[
\begin{align*}
\hat{D}^* &= D^*_N \\
\hat{D} &= D_N \\
\hat{T} &= T_N / \hat{Q}
\end{align*}
\]

i.e. the usual loading dose, \( D^*_N \), and the usual maintenance dose, \( D_N \), are administered to all patients; the dosage interval is prolonged by dividing the usual dosage interval, \( T_N \), through \( \hat{Q} \). Rule 1 corresponds to the dosage rule originally recommended by Cutler and Orme for Kanamycin (Cutler & Orme, 1969).

Rule 1 may be inconvenient with drugs such as long-acting sulfonamides or cardiac glycosides which have a relatively long usual dosage interval. Instead of prolonging still more the dosage interval of such drugs it is often more practical to modify the dosage regimen by lowering the maintenance dose according to the following rule:

**Rule 2:**

\[
\begin{align*}
\hat{D}^* &= D^*_N \\
\hat{D} &= D_N \cdot \hat{Q} \\
\hat{T} &= T_N
\end{align*}
\]

i.e. the same usual loading dose is administered to all patients at the usual dosage interval; the maintenance dose is lowered by multiplying the usual maintenance dose by \( \hat{Q} \). With some dosage forms, such as capsules, rule 2 may occasionally prove impractical and rule 1 may be preferred. For kinetic reasons, rule 2 should only be used when the usual dosage interval is about equal to or shorter than the
normal half-life of the drug.

A special situation arises when the usual dosage interval of a drug which is normally eliminated predominantly by the kidneys is much longer than the half-life of the agent. Examples are the aminoglycosides and the cephalosporins. Rule 2 should never be used with these irreversibly acting drugs because the peak concentrations eventually reached may be too low. In patients with moderate renal impairment we advise using rule 1. In patients with severe kidney disease rule 1 is inappropriate, as illustrated by the following example: for gentamycin the half-life is about 2 hours and the usual dosage interval 8 hours. In Table I, one finds \( Q_0 = 0.02 \). When the dosage interval is prolonged according to rule 1, one obtains \( T = T/Q = 8/0.02 = 400 \) hours or about 17 days. During the second part of this absurdly long dosage interval the plasma concentration would lie far below therapeutic levels. In order to solve this problem the following procedure is recommended. According to eq. 7 one finds the individual elimination rate constant of the drug, \( \tilde{k} \) in the following way:

\[
\tilde{k} = \hat{Q} \cdot k_N \tag{8}
\]

Based on the well known relationship

\[
t_{1/2} = \frac{1 \ln 2}{\tilde{k}} = \frac{0.7}{\hat{k}} \tag{9}
\]

one calculates the individual half-life, \( \tilde{t}_{1/2} \), according to eqs. 8 and 9:

\[
\tilde{t}_{1/2} = \frac{0.7}{\hat{Q} \cdot k_N} \tag{10}
\]

When the individual half-life of the drug in the patient is longer than the usual dosage interval of the drug (\( t_{1/2} > T \)) we recommend the following modification of a dosage rule originally proposed by Kunin (1967):

**Rule 3:**

\[
\begin{align*}
\hat{D}^* &= \frac{D^*}{k_N} \\
\hat{D} &= \frac{1}{2} \frac{D^*}{k_N} \\
\hat{T} &= \frac{0.7}{\hat{Q} \cdot k_N}
\end{align*}
\]

i.e. the same usual loading dose is administered to all patients; the maintenance dose is half the loading dose, and the dosage interval is equal to the estimated individual half-life of the drug in the patient.

When the individual half-life of the drug in the patient is shorter than the
usual dosage interval \( t_{1/2} < T \) rule 3 may result in overdosage and should not be used.

In the case of continuous drug infusion the following rule solves the problem:

**Rule 4:**

\[
\hat{D}^* = D_N^* = \frac{D_N/T_N}{k_N} \\
\hat{D} = D_N \cdot \hat{Q}
\]

i.e. the same usual loading dose is administered to all patients; the maintenance dose is lowered by multiplying the usual maintenance dose with \( \hat{Q} \).

The values of \( k_N \) to be used in rule 3 and rule 4 are also listed in Table I.

**LIMITS OF VALIDITY**

The best way to characterise the possible limits of validity of the dosage rules presented above is to emphasise the assumptions underlying the theory. It should be clear that none of these assumptions hold true in the strict sense and under all circumstances. For example, assumption 1 postulates that saturation phenomena in drug elimination are non-existent and that the distribution volume of the drug is uninfluenced by renal disease. Contrary to these postulates, dose dependent saturation effects have been demonstrated beyond doubt during recent years with some drugs, and the distribution volume of a number of agents in uraemic patients has been shown to be greater or smaller than normal (Klotz, 1976) apparently due to abnormal drug binding by intravascular and extravascular macromolecules (Reidenberg, 1971). Furthermore, drug metabolites may accumulate tremendously in the uraemic patient even when the dosage regimen has been modified properly. It has been shown that these metabolites can displace the original drug from its plasma protein binding sites (Dettli & Spring, 1973) and may inhibit drug metabolism. The validity of the assumption that drug metabolism remains unaltered in uraemic subjects could be verified for some but not for all drugs (Reidenberg, 1971). Similarly it appears improbable that Bricker’s intact nephron hypothesis will hold true under all circumstances. Finally, the question of how far uraemic enteropathy influences drug absorption remains open.

In summarising, future research efforts in this field are urgently needed in order to demonstrate whether or not the simplifying assumptions underlying our dosage theory are useful approximations to clinical reality. The following papers written by outstanding experts represent a contribution to this end.

**References**