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The Kidney in Pre-Clinical
and Clinical Pharmacokinetics

L. DETTLI*

THE MODEL

The present summarizing report on the renal elimination of drugs in subjects with and without kidney disease is based on the following fundamental assumptions¹⁾²⁾:

a) The overall drug clearance, $\dot{V}$, is the sum of its extra-renal clearance, $\dot{V}_{nr}$, and its renal clearance, $\dot{V}_r$, i. e.:

$$\dot{V} = \dot{V}_{nr} + \dot{V}_r \quad (1)$$

b) The extra-renal drug clearance, $\dot{V}_{nr}$, is uninfluenced by renal disease, i. e. $\dot{V}_{nr}$ is a drug-specific constant.

c) In accordance with Bricker's intact nephron hypothesis³⁾ the renal drug clearance, $\dot{V}_r$, is proportional to glomerular filtration rate as measured by the endogenous creatinine clearance, Cl:

$$\dot{V}_r = b \cdot Cl \quad (2)$$

Eqs. 1 and 2 result in the following linear estimating equation²⁾:

$$\dot{V} = \dot{V}_{nr} + b \cdot Cl \quad (3)$$

The slope b is the renal clearance ratio which relates the renal drug clearance to creatinine clearance because it follows from eqs. 1 and 3:

$$\dot{V}_r = \dot{V} - \dot{V}_{nr} = b \cdot Cl \quad \text{or} \quad b = \frac{\dot{V}_r}{Cl} \quad (4)$$

STANDARDIZING AND NORMALIZING
THE PARAMETERS

Since Cl depends markedly on age and body weight and is different in both sexes⁴⁾, we introduce the standard creatinine clearance, $Cl_N = 100 \text{ ml/min} = 6 \text{ L./hour}$. The standard para-

Fig. 1 The linear relationship between overall drug clearance, $\dot{V}$, and creatinine clearance, Cl. — The horizontal interrupted line represents a drug eliminated completely by extra-renal mechanisms. This results in $P_o = \dot{V}_{nr} / \dot{V}_N = 1.0$ indicating that drug elimination is independent of renal function. The interrupted line going through the origin represents a drug eliminated completely by the kidneys. This results in $P_o = 0$ indicating that drug elimination depends extremely on renal function. The solid line represents a drug which is eliminated partly by the kidneys, partly by extra-renal pathways. This results in $0 < P_o < 1.0$.

* Kantonsspital Basel
Med. Universitäts-Klinik B
CH-4031 Basel, Schweiz

parameters related to Cl_N are denoted by the subscript N (e. g. $\dot{V}_N$, k_N).

Furthermore, eq. 3 is normalized by introducing the **individual drug clearance fraction**, $P = \dot{V}/\dot{V}_N$, which expresses the individual drug clearance, $\dot{V}$, of the patient as a fraction of the standard drug clearance, $\dot{V}_N$. This results in the following normalized estimating equation :

$$P = \dot{V}/\dot{V}_N = P_0 + (1 - P_0) \cdot w \quad (5)$$

The parameter $P_0 = \dot{V}_{nr}/\dot{V}_N$ is the **minimal drug clearance fraction** in the anuric patient, and $w = Cl/Cl_N$ is the **individual creatinine clearance fraction**, i. e. the individual creatinine clearance of the subject, Cl , is expressed as a fraction of the standard creatinine clearance, Cl_N . The individual drug clearance, $\dot{V}$, may be calculated from $\dot{V}_N$ based on eq. 5 :

$$\dot{V} = \dot{V}_N \cdot P \quad (6)$$

When drug elimination can be described by **one-compartment kinetics**, $\dot{V}$ in eq. 3 may be replaced by the elimination rate constant, $k^{(5)(6)(7)}$. This results in the estimating equation

$$k = k_{nr} + a \cdot Cl \quad (7)$$

where k_{nr} is the **extra-renal elimination rate constant**. Normalization of eq. 7 results in

$$Q = k/k_N = Q_0 + (1 - Q_0) \cdot w \quad (8)$$

$Q = k/k_N$ and $Q_0 = k_{nr}/k_N$ are the **individual** and the **minimal elimination rate fraction**, respectively. Furthermore, from eqs. 5 and 8 it follows

$$Q_0 = P_0 \quad (9)$$

The **overall elimination rate constant**, k , and the **half-life**, $t_{1/2}$, in the individual patient are calculated as follows :

$$k = k_N \cdot Q = k_N \cdot P \quad \text{or} \quad t_{1/2} = t_{1/2N} / Q = t_{1/2N} / P \quad (10)$$

It is evident that the elimination of a drug depends the more on renal function the smaller the value of P_0 or Q_0 , and vice-versa. Since $\dot{V}$ is less model dependent than k the parameter P_0 will usually be preferred in the following discussion.

The values of P_0 and of the dominant **standard half-life** of about 500 drugs are listed in Tab. 1. These values are updated and published in yearly intervals in the Swiss Drug Compendium⁽⁸⁾.

NOMOGRAPHIC ESTIMATION OF DRUG ELIMINATION IN RENAL PATIENTS

Since the normalized linear estimating equation 5 is defined by a single parameter, namely the minimal drug clearance fraction, P_0 , the relative drug elimination rate in the individual patient as described by the individual drug clearance fraction, P , can be determined graphically at the bed-side by means of the simple nomogram⁽⁹⁾ depicted in Fig. 2 : P_0 is plotted on the left ordinate and connected with the upper right corner of the nomogram by a straight estimating line. The point of intersection between the patient's creatinine clearance, Cl , (lower abscissa) and the estimating line, read-off from the left ordinate, corresponds to the individual drug clearance fraction, P , in the patient.

THE DOSAGE RULES IN RENAL PATIENTS

From the **standard dosage regimen** of a drug (loading dose, D_N^* , maintenance dose, D_N , dosage interval, τ_N) the corresponding **individual dosage regimen** (D^* , D , τ) for renal patients is calculated by means of one of the following rules :

Rule 1	Rule 2	Rule 3
$D^* = D_N^*$	$D^* = D_N^*$	$D^* = D_N^*$
$D = D_N \cdot P$	$D = D_N$	$D = d \cdot D^*$
$\tau = \tau_N$	$\tau = \tau_N / P$	$\tau = \varepsilon \cdot t_{1/2} = \varepsilon \cdot t_{1/2N} / P$

Rules 1 and 2 are self-explanatory : the dosage regimen is adjusted either by reducing the maintenance dose, D (**Rule 1**), or by prolonging the dosage interval, τ (**Rule 2**).

Rules 1 and 2 are appropriate for all reversibly acting drugs. In contrast, **Rule 3** should be used

with drugs such as the aminoglycosides and most cephalosporins and penicillins, which have in common the following characteristics¹⁾:

- a) The therapeutic effect is irreversible (bactericidal).
- b) The value of P_0 is extremely small, i.e. drug elimination depends extremely on renal function.
- c) The standard dosage interval, τ_N , is much longer than the standard half-life, $t_{1/2N}$, of the drug. For example, in the case of aminoglycosides τ_N is 8-12 hours and $t_{1/2N}$ is only about 2 hours.

In Rule 3, $d=1-2^{-\epsilon}$ is the **decay fraction** i.e. the fraction of the absorbed dose eliminated during one dosage interval, and $\epsilon=\tau/t_{1/2}$ is the **relative dosage interval** i.e. the dosage interval, τ , expressed in half-lives, $t_{1/2}$. The dotted curvilinear estimating line in Fig. 2 describes the non-linear relationship between ϵ and d : the point of intersection between the patient's creatinine clearance, Cl (lower abscissa), and the estimating line, read-off from the right ordinate, corresponds to the decay fraction, d .

In addition, the following relationships may be of interest and can be determined by means of the nomogram: The **residual fraction** of the drug at the end of the dosage intervals is $r=1-d$, and the well known **accumulation factor** is $R=1/d^5$.

The following calculation illustrates the dosage adjustment according to Rule 3 using gentamicin in a renal patient with $Cl=12$ ml/min as an example: First, one has to define the **standard dosage regimen** of gentamicin, e.g. loading dose $D_N^*=100$ mg, maintenance dose $D_N=100$ mg, dosage interval, $\tau_N=8$ hours. In Tab. 1 one finds for gentamicin the kinetic parameters $P_0=0.02$ and $t_{1/2N}=1.9$ hours. With $P_0=0.02$ at the left ordinate and $Cl=12$ ml/min at the abscissa of the nomogram the point of intersection at the straight estimating line corresponds at the left ordinate to the **individual drug clearance fraction** $P=0.14$.

According to eq. 10, the **half-life** of gentamicin in this patient is $t_{1/2}=t_{1/2N}/P=1.9/0.14=14$ hours.

Next, the therapist has to decide on the desired **length of the dosage interval**, τ . For example, when he chooses $\tau=24$ hours, the corresponding **relative dosage interval** is $\epsilon=\tau/t_{1/2}=24/14=1.7$. In the nomogram the point of intersection of $\epsilon=1.7$ (lower abscissa) with the dotted estimating line results in the **decay fraction** $d=0.7$ (right ordinate). According to Rule 3 the **individual dosage regimen** for this patient reads now as follows:

$$D^*=D_N^*=100 \text{ mg}$$

$$D=D_N \cdot d=100 \cdot 0.7=70 \text{ mg}$$

$$\tau=24 \text{ hours}$$

It should be noted that our dosage rules derive the adjusted dosage regimen from the corresponding standard dosage regimen; in other words, it is assumed that the optimal standard dosage regimen in patients without renal disease is known. For a discussion of the problems associated with this assumption in the case of the aminoglycosides the reader is referred to the literature¹⁰⁾¹¹⁾¹²⁾.

ESTIMATING RENAL FUNCTION

For practical reasons the determination of the creatinine clearance, Cl , is often not possible. In patients with chronic and stable kidney disease Cl is therefore estimated from the serum creatinine concentration, c_{cr} . The values of c_{cr} plotted on the upper abscissa of the nomogram (Fig. 2) should only be used for this purpose in young adults with normal body weight. In all other cases we use the following estimating equation⁸⁾ which considers the influence of age, A (years), and body weight, G (kg), on the relationship between Cl (ml/min), and c_{cr} (μ mol/Liter):

$$Cl = \frac{(150-A) \cdot G}{C_{cr}} \quad (11)$$

Fig. 2 Nomogram for the graphical determination of individually adjusted dosage regimens in renal patients. — The use of the nomogram is explained in the text.

In males 10% are added to, and in females 10% are subtracted from, the value estimated according to eq. 11. In neonates, infants and children, and in obese patients Cl should be normalized to lean body mass¹²⁾. For patients with unstable or acute renal impairment several estimating equations have been published in the literature¹⁰⁾¹³⁾¹⁴⁾.

THE RENAL DOSE FRACTION

The **individual renal dose fraction**, f_i , is the fraction of the effectively absorbed (or intravenously administered) dose eliminated **unchanged** in the urine of any subject with or without renal disease. The **standard renal dose fraction**, f_{iN} , is the renal dose fraction in the **standard subject**, characterized by the standard creatinine clearance $Cl_N=100$ ml/min or by the standard creatinine clearance fraction, $w_N=Cl/Cl_N=1.0$. Ac-

cordingly, the corresponding **extra-renal dose fractions** are $f_{er}=1-f_i$, and $f_{erN}=1-f_{iN}$.

As shown elsewhere¹⁾ f_{iN} is calculated from f_i in the following way :

$$f_{iN} = 1 - \frac{w}{w + \frac{f_i}{1-f_i}} \quad (12)$$

On the other hand, f_i as a function of the individual creatinine clearance fraction, $w=Cl/Cl_N$, may be calculated in the following way from f_{iN} :

$$f_i = \frac{\frac{w}{1-f_{iN}} - w}{\frac{w}{1-f_{iN}} - w + 1} \quad (13)$$

Based on simple kinetic reasoning the following relationships between P_0 and f_{iN} are found :

$$P_0 = \dot{V}_{ur}/\dot{V}_N = f_{iN} = 1 - f_{er} \quad \text{or}$$

$$f_{rN}=1-P_o \quad (14)$$

Accordingly, in the case of one-compartment kinetics one finds :

$$\begin{aligned} Q_o &= k_{nr}/k_N = f_{nrN} = 1 - f_{rN} \text{ or} \\ f_{rN} &= 1 - Q_o \end{aligned} \quad (15)$$

Eqs. 14 and 15 express the fact that the elimination of a drug depends the more on renal function the larger its standard renal dose fraction, f_{rN} , and vice versa, as would be expected intuitively.

Eqs. 12-15 are of considerable importance in pre-clinical and clinical pharmacokinetics. Examples are as follows :

Prediction of Drug Elimination in Renal Disease

In our experience about 20 normal subjects and patients with renal disease of widely differing degree are needed to determine experimentally the estimating equation 3 or 7. In contrast, as we have shown elsewhere¹⁹, P_o or Q_o may be calculated according to eqs. 12-15 from the individual dose fractions, f , determined in pre-clinical kinetic studies using healthy volunteers¹¹. Since, according to eq. 5, the individual drug clearance fraction, P , in patients with renal impairment depends solely on P_o the influence of kidney disease on drug elimination may be predicted from these pre-clinical data and only a few additional experiments in renal patients may be needed to corroborate the prediction.

Furthermore, for obvious reasons the elimination kinetics of many drugs has not been investigated in renal patients. However, the value of f , determined in subjects without renal disease is known for most drugs and may be used to predict quantitatively the influence of renal disease on drug elimination. Many of the P_o values presented in Tab. 1 have been calculated in this way from literature data.

Estimating Absolute Oral Bio-Availability, Drug Clearance, and Distribution Volume without Intravenous Administration of the Agent

With oral drug administration eq. 3 reads as follows :

$$\begin{aligned} \dot{V} &= \frac{\dot{V}}{F'} = \frac{\dot{V}_{nr}}{F'} + \frac{b}{F'} \cdot Cl \\ &= \dot{V}'_{nr} + b' \cdot Cl \end{aligned} \quad (16)$$

where F' is the absolute oral bioavailability of the drug. In eq. 16 and in the following equations the prime signs (') denote symbols of apparent parameters determined with oral drug administration (e. g. $\dot{V}'$, b').

After normalization eq. 16 results in the following relationships between P_o , P'_o , and the standard renal dose fraction, f'_{rN} :

$$\begin{aligned} P'_o &= \frac{\dot{V}_{nr}/F'}{\dot{V}_N/F'} = \frac{\dot{V}_{nr}}{\dot{V}_N} = P_o = f_{nrN} \\ &= \frac{f'_{rN}}{F'} = 1 - \frac{f'_{rN}}{F'} \end{aligned} \quad (17)$$

Eq. 17 predicts

$$F' = \frac{f'_{rN}}{1 - P'_o} \quad (18)$$

i. e. in a sample of patients with differing renal functions absolute oral drug bioavailability can be calculated without intravenous injection of the agent based on the apparent standard renal dose fraction, f'_{rN} , and on the apparent minimal drug clearance fraction, P'_o , determined with oral drug administration.

Since the elimination rate constant, k , is independent of bioavailability the corresponding relationships in the case of one compartment kinetics read as follows :

$$\begin{aligned} Q'_o &= \frac{k'_{nr}}{k'_N} = \frac{k_{nr}}{k_N} = Q_o = P_o = P'_o \\ &= f_{nrN} = \frac{f'_{nrN}}{F'} = 1 - \frac{f'_{rN}}{F'} \end{aligned} \quad (19)$$

$$F' = \frac{f'_{rN}}{1-P_0} = \frac{f'_{rN}}{1-P'_0} \quad (20)$$

Furthermore, from eq. 16 it follows that $F' = b/b'$ and $b = \dot{V}_r/Cl$. Since $\dot{V}_r$ is independent of bioavailability, one may write $\dot{V}_r = \dot{V}'_r$ and obtains

$$F' = \frac{\dot{V}'_r}{b' \cdot Cl} = \frac{f'_{rN} \cdot D}{b' \cdot AUC' \cdot Cl} \quad (21)$$

Another method to estimate F' is as follows: Suppose two different doses, D_1 and D_2 , are orally administered to two patients with different creatinine clearances, Cl_1 and Cl_2 , respectively. From eq. 16 it follows:

$$\dot{V}'_{r1} + b' \cdot Cl_1 = \dot{V}'_1 = F' \cdot \frac{D_1}{AUC'_1} \quad (22)$$

$$\dot{V}'_{r2} + b' \cdot Cl_2 = \dot{V}'_2 = F' \cdot \frac{D_2}{AUC'_2} \quad (23)$$

Subtracting eq. 23 from eq. 22 results in:

$$\begin{aligned} \dot{V}'_1 - \dot{V}'_2 &= b' \cdot (Cl_1 - Cl_2) \\ &= F' \left(\frac{D_1}{AUC'_1} - \frac{D_2}{AUC'_2} \right) \end{aligned} \quad (24)$$

$$\text{and } F' = \frac{b' \cdot (Cl_1 - Cl_2) \cdot (AUC'_1 \cdot AUC'_2)}{D_1(AUC'_2) - D_2(AUC'_1)} \quad (24)$$

With $D_1 = D_2 = D$ one obtains

$$F' = \frac{b' \cdot (Cl_1 - Cl_2) \cdot (AUC'_1 \cdot AUC'_2)}{D(AUC'_2 - AUC'_1)} \quad (25)$$

Since $b' \cdot Cl = \dot{V}'_r = f'_{rN} \cdot D / AUC'$ eq. 24 is redundant with respect to b' and Cl . It follows

$$F' = \frac{(D_1 \cdot f'_{r1} \cdot AUC'_2) - (D_2 \cdot f'_{r2} \cdot AUC'_1)}{(D_1 \cdot AUC'_2) - (D_2 \cdot AUC'_1)} \quad (26)$$

and with $D_1 = D_2 = D$ one obtains:

$$F' = \frac{f'_{r1} \cdot AUC'_2 - f'_{r2} \cdot AUC'_1}{AUC'_2 - AUC'_1} \quad (27)$$

It is evident that kinetic parameters such as drug distribution volume, V , and drug clearance, $\dot{V}$, which depend on absolute bioavailability may be estimated without intravenous administration of the agent from the value of F' determined by

means of one of the above described equations based on the well known relationships:

$$V = F' \cdot V' \text{ and } \dot{V} = F' \cdot \dot{V}' \quad (28)$$

Examples will be described elsewhere¹⁶⁾.

Estimating Renal Drug Clearance without Drug Concentration Measurements in the Urine

From eq. 4 it follows

$$\dot{V}_r = \dot{V}'_r = b \cdot Cl \quad (29)$$

This means renal drug clearance can be estimated with intravenous or oral drug administration from the slope of the straight line described by eq. 16, i. e. without drug concentration measurements in the urine.

Testing the Consistency of Experimental Results in Pharmacokinetics

The equations described in the preceding sections may be used in many ways to test the consistency of the results of pharmacokinetic experiments. A few examples are as follows:

With intravenous drug administration eqs. 18, 20, 21, 24-27 should by definition result in $F = 1.0$. However, in the case of **drug instability** in the urine one will find $F < 1.0$. Examples are many penicillins and cephalosporins. Similarly, **incomplete urine sampling** will result in $F < 1.0$. An **unrecognized slow compartment** will have the same effect. A typical example are the aminoglycosides. There is general agreement that the value of P_0 and Q_0 of these drugs is about 0.01–0.02. According to eqs. 14 and 15 one should therefore find $f_{rN} = 0.98$ –0.99. However, in the older literature values of $f_{rN} = 0.8$ –0.9 are consistently reported. The discrepancy is caused by the extremely long terminal half-life of the aminoglycosides which has been detected only in recent years. As expected, f_{rN} approaches the values predicted by eqs. 14 and 15 when the time period of urine collection is sufficiently long.

THE STANDARD RENAL DOSE FRACTION AS A PHARMACOKINETIC PREDICTOR

In the renal tubular system the standard renal dose fraction, f_{rN} , is a measure of transcellular drug permeability which in turn depends almost entirely on the **polarity** of the molecule. Since many other biological membranes of the epithelial type such as the buccal and gastrointestinal mucosa and the blood brain barrier display very similar permeability characteristics due to their

common lipid structure it is understandable that molecular polarity is by far the most important determinant of the kinetic profile of a drug. It can therefore be expected that the renal dose fraction is a clinically useful predictor of the qualitative and quantitative kinetic characteristics of a drug. This is especially true for those numerous drugs whose value of f_{rN} is extremely large ($f_{rN} \rightarrow 1.0$) or extremely small ($f_{rN} \rightarrow 0$). Examples are given in Tab. 2.

Tab. 1 Minimal Drug Clearance Fraction, P_o (or Minimal Elimination Rate Fraction, Q_o , or Standard Extra-renal Dose Fraction, f_{nrN}) and Dominant Half-life, $t_{1/2N}$ of Commonly Used Drugs

Medikament	$P_o(Q_o, f_{nrN})$	$t_{1/2N}$	Medikament	$P_o(Q_o, f_{nrN})$	$t_{1/2N}$
Acebutolol	0,85(0,4!!)	2,6(9)(11!!)	Aminocaproic acid	0,15	?
Acecaïnide	?	6	Aminoglutethimide	0,6!	7
Acenocoumarol	1,0!!	9(24!!)	Aminophylline	s.Theophylline	
Acephylline	0,5	0,8	Aminopyrin	1,0	2,5
Acetaminophen	1,0!!	2,5	p-Aminosalicylic acid	1,0	0,9
Acetazolamide	?	4	Amiodarone	1,0!!	(7) ~ 700
Acetohexamide	0,6!!	1,3	Amitriptyline	1,0(1,0!!)	24(30!!)
Acetylcysteine	0,9	0,5	Amobarbital	1,0	30
Acetyldigoxin	0,3(0,3!!)	24(36!!)	Amoxicillin	0,06	1,1
Acetylmethadol	0,95!!	7	Amphetamine	0,5	12
Acetylprocainamide	0,2	6	Amphotericin B	0,95!	30 (~ 350)
Acetylstrophanthin	?	2,1	Ampicillin	0,1	0,9
Acyclovir	0,15	2,5	Antipyrin	0,95	12
Adriamycin	0,3!!	24	Aprotinin	1,0	0,7(7)
Ajmaline (Propyl-)	0,85!	6	Ascorbic acid	0,3	3,5
Alclofenac	?	2,0	Aspirin	1,0(0,8!!)	0,25(3,0!!)
Alcuronium	?	0,25(3,3)	Atenolol	0,06	6
Alinidine	0,25(0,4!!)	3,5(8!!)	Atropin	0,45	2
Allopurinol	0,85(0,25!!)	0,8(12!!)	Azapropazone	0,4	16
Allylisobutyl-barbiturate	0,9	36	Azathioprine	1,0!	4,5
Alprazolam	0,9!!	14	Azidocillin	?	1,0
Alprenolol	1,0!!	3	Azlocillin	0,4	1,0
Amantadine	0,1!	20	Azthreonam	1,7	0,35
Amezinium	0,3	13	Bacampicillin	1,0(0,1!!)	(0,9!!)
Amidotrizoate	0,12	1,7	Baclofen	0,15!	4
Amikacin	0,02	1,8(> 100)	Bacmecillinam	1,0(0,4!!)	0,2(1,2!!)
Amiloride	0,5!	10	Bamifylline	1,0!!	1,0(18!!)

Medikament	$P_o(Q_o, f_{nrN})$	t_{V2N}
Barbital	0,2	70
Bendroflumethiazide	0,7!	3,5
Benoxaprofen	0,3	27
Benzbromarone	1,0(1,0!)	3(14!)
Bethanidine	0,05	9
Bezafibrate	0,15	2,8
Bleomycin	0,45!	?
Bretylum	0,15!	8
Bromazepam	1,0	12
Bromocryptine	1,0!	48
Buflomedil	0,85!	2,1
Buformin	?	6
Bufuralol	0,9!!	3,5
Bumetanide	0,35!	0,7(3)
Bupivacaine	0,95	2,5
Butobarbital	1,0	36
Butorphanol	1,0	3
Camazepam	1,0	21
Canrenoate	1,0!!	20
Captopril	0,55!	2
Carbamazepine	1,0!!	20
Carbenicillin	0,1	1,2
Carbimazole	1,0(0,9!)	0,5(4!)
Carfecillin	0,1	1,2
Carindacillin	0,1	1,2
Carprofen	0,95	(2)10
Cephacetrile	0,04	1,0
Cephaclor	0,3!	0,7
Cephadroxil	0,08	1,4
Cephalexin	0,04	1,0
Cephaloridine	0,08	1,7
Cephalothin	0,04	0,5
Cephmandole	0,04	0,9
Cephanone	0,05	2,5
Cephapirin	0,4	1,2
Cephatrizine	0,6	1,4
Cephazedone	0,2	1,5
Cephazolin	0,06	2,0
Cephomicin	0,03	3,5
Cephoperazone	0,75	1,6
Cephoranide	0,1	2,4
Cephotaxime	0,4	1,2
Cephotiam	0,35	0,75
Cephoxitin	0,04	0,8

Medikament	$P_o(Q_o, f_{nrN})$	t_{V2N}
Cephradine	0,15	0,7
Cephroxadine	0,05	1,0
Cephsulodin	0,25	2,2
Cephtazidime	0,05	1,8
Cephtezole	0,06	0,7
Cephtrizoxime	0,05	1,5
Cephtriaxone	0,5	8
Cephuroxime	0,07	1,1
Chloral Hydrate	1,0(1,0!)	(10!)
Chloramphenicol	0,95	2,5
Chlorazepate	1,0!!	2,0(50!)
Chlordiazepoxyde	1,0!!	15(50!)
Chlormethiazole	0,95	6(18)
Chloroquine	0,3!!	(70)~200 (~500)
Chlorothiazide	0,08	15
Chlorpheniramine	0,8!!	24
Chlorphentermine	0,8!	40
Chlorpromazine	1,0!	40
Chlorpropamide	0,2!	36
Chlortetracycline	0,8!	6
Chlorthalidone	0,5!	48
Ciclacillin	0,1	0,7
Cimetidine	0,25	1,8
Cinnarizine	?	3
Cinoxacin	0,35	1,0
Clavulanic acid	0,55	0,9
Clenbuterol	0,4!	34
Clindamycin	0,9!	2,5
Clioquinol	1,0	12
Clobazam	1,0!!	18(50!)
Clofibrate	0,8(0,1!)	(16!)
Clomipramine	1,0!!	24
Clonazepam	1,0	40
Clonidine	0,4!	8(24)
Clorazepate	1,0!!(1,0!)	(50!)(8!)
Cloxacillin	0,25!!	0,6
Cocaine	0,7	2,5
Codeine	1,0(1,0!)	3(2,5!)
Coffeine	0,8!!	5
Colchicine	?	20
Colistin	0,1	3,0
Cortisol	1,0	1,5
Cyclobarbital	1,0	12
Cyclophosphamide	(0,5!)	(7)

Medikament	$P_o(Q_o, f_{rnN})$	$t_{\sqrt{2}N}$	Medikament	$P_o(Q_o, f_{nrN})$	$t_{\sqrt{2}N}$
Cycloserine	0,4!	10	Etidocaine	1,0	2,6
Cytarabine	0,9!	2	Etilefrine	1,0	3
			Etofylline	0,8	4
Dapsone	0,9!	20	Etomidate	1,0	0,5(4)
Daunorubicin	0,9!	18			
Demeclocycline	0,6	14	Fenclofenac	?	30
Desipramine	1,0!!	15	Fenclozinc acid	1,0	30
Desmethyldiazepam	1,0(1,0!!)	50(8!!)	Fenflurac	1,0!!	1,2
Desmopressin	1,0	1,2	Fenopropfen	0,95!	2,2
Dexamethasone	1,0	3	Fentanyl	0,95	(0,02)0,2(5)
Dextran 1000	0,25	2	Flucloxacillin	0,3!!	0,9
Dextran 40 000	?	10	Flucytosine	0,03	5
Dextran 60 000	?	40	Flunisolide	0,95	1,7
Diethylcarbamazine	0,15!	3,5	Flunitrazepam	1,0!	(2)16
Diazepam	1,0!!(1,0!!)	30(50!!)	5-Fluorouracil	1,0!!	0,25(70!!)
Diazoxide	0,8	28	Flurazepam	1,0!!	1,5(50!!)
Dibekacin	0,01	1,9(>100)	Flurbiprofene	0,75!	5
Dibenzepin	?	4	Fortimicin A	0,1	1,8
Diclofenac	1,0!	1,5	Fosfomycin	0,02	2,0
Dicloxacillin	0,6	0,7	Furosemide	0,3	0,9(4)
Dicumarol	1,0	48	Gentamicin	0,02	1,9(>100)
Diflunisal	0,9	8	Gitoxin	0,85	24
Digitoxin	0,7!!	180	Glibenclamide	1,0!!	7
Digoxin	0,3	36	Glibornuride	1,0!	10
Dihydroergotamine	0,9!	2	Gliclazide	1,0!	12
Dinatriumcromoglycate	0,6	1,4	Glipizide	1,0!	4
Diphenhydramine	1,0!	6	Gliquidone	1,0!	17
Diphenoxylate	1,0!!	2,5	Glutethimide	1,0!!	12
Diphenylpyraline	0,9!	32	Griseofulvin	1,0	20
Diprophylline	0,04	2	Guanfacine	0,75	20
Disopyramide	0,35!!	6			
Domperidone	0,95!	(1,5)8	Halofenate	0,65	24(48)
Doxepin	1,0!!	18(50!!)	Haloperidol	1,0	20
Doxorubicine	0,95!	17	Harmine	1,0	3
Doxycycline	0,7	15(22)	Heparin	1,0	2,0
			Heptabarbital	1,0	8
Emepronium-bromide	0,7!	1,0	Heroin	1,0(1,0!!)	0,1(2,5!!)
Ephedrine	0,3!!	6	Hetacillin	0,1	1,2
Epicillin	0,03	1,1	Hexobarbital	1,0	5
Ergotamine	?	2	Hydrallazine	0,85!	2,5
Erythromycin	0,7	2,3	Hydrochlorothiazide	0,05	10
Ethambutol	0,2	3(15)	Hydrocortisone	1,0	1,8
Ethosuximide	0,8!	40	Hydromorphone	1,0(1,0!!)	2,5(2,5!!)
Ethylbiscoumacetate	1,0!	3,0			
Ethylchlorvynol	1,0!	1,4(25)	Ibuprofen	1,0!	1,5

Medikament	$P_o(Q_o, f_{nrN})$	t_{V2N}
Idrocilamide	1,0!!	1,0
Imipramine	1,0(1,0!!)	12(16!!)
Indapamide	0,95!!	(2)18
Indomethacin	0,9	2,0(6)
Indoprofen	0,85	2,0
Indoramin	1,0!	4
Insulin	0,4	0,25(2,0)
Iodipamate	0,07	1,2
Iodohippurate	0,45	1,3
Iodoxamate	0,9	1,1
Ioglicinate	0,15	1,5
Ioglycamate	0,8	1,9
Iothalamate	0,15	1,9
Iotroxamate	0,85	1,4
Iotroxinate	0,85	1,4
Iproniazid	0,95!!	9(20!!)
Isoniacid	0,6	2,3
Isophosphamide	0,5!!	14
Isoproterenol	0,9	5
Isosorbidedinitrate	1,0(1,0!!) (0,8!!)	0,4(2,5!!) (4,5!!)
Isosorbide-5-mono-nitrate	0,8	4,5
Isoxicam	1,0!	40
Kanamycin	0,03	2,0
Ketoconazole	1,0!	4
Ketoprofen	0,9!	1,2
Ketotifen	1,0!!	0,7
Labetalol	0,95!	4
Lamoxactam	0,05	2,5
Levamisole	?	4
Levorphanol	1,0	15
Lidocaine	0,95!!	3,5(10)
Lincomycin	0,6!	5
Lithium	0,02	(6)24
Lividomycin	0,02	3,5
Loperamide	1,0!	12
Lorazepam	1,0	15
Lorcainide	1,0!!	6(20!!)
Lormetazepam	1,0	(2)10
Maprotiline	1,0!!	40
Mebendazole	?	1,2

Medikament	$P_o(Q_o, f_{nrN})$	t_{V2N}
Mecillinam	0,4	1,2
Meclofenamate	0,95	3
Medazepam	1,0!!	20
Mefloquine	?!!	~ 600
Melphalan	0,9!!	1,5
Meperidine	0,9(1,0!)	4(10)(18!!)
Mepivacaine	0,95	3
Meprobamate	0,9!	8
Meproscillarlin	1,0!	36(48)
Meptazinol	0,95	3
Mercaptopurine	0,8!	0,5
Metacyclin	0,3	11
Metformin	0,1	1,5(9)
Methadone	0,9	15(55)
Methapyrilen	1,0!	1,6
Methaqualone	0,9!	(2)24(75)
Methicillin	0,12	0,8
Methimazole	0,9	4
Methohexital	1,0	1,5
Methotrexate	0,06!!	12(70)
β -Methyl digoxin	0,35(0,3!!)	40(70) (36!!)
α -Methyldopa	0,4!!	2(8)
Methylergonovine	0,95!	2
Methylphenidate	0,95(0,1!!)	1,0(7!!)
Methylsalicylic acid	?	18
Methyltestosterone	?	4
Metipranolol	(0,9!!)	(2,5!!)
Metoclopramide	0,3	4
Metolazone	0,2	20
Metoprolol	0,95!!	3,5(8)
Metronidazole	0,9!!	7(10!!)
Mexiletine	0,8!	10
Mezlocillin	0,25	0,8
Mianserine	1,0!!	18
Miconazole	1,0!	24
Midazolam	1,0(1,0!!)	(0,5)2,5 (1,0!!)
Minocycline	0,85	17(21)
Minoxidil	0,9!!	1,5
Morphine	1,0	2,5
Moxalactam	s. Lamoxactam	
Muzolimine	0,9!	14
Nadolol	0,4	17

Medikament	$P_o(Q_o, f_{nrN})$	$t_{1/2N}$	Medikament	$P_o(Q_o, f_{nrN})$	$t_{1/2N}$
Nafcillin	0,6	0,6	Phenylbutazone	0,9(0,3!!)	70(48)
Nalbufine	1,0	5	Phenylephrine	0,85	2,5
Nalidix acid	0,8!!	1,5	Phenytoin	1,0	20
Naloxone	1,0	1,5	Pinazepam	1,0(1,0!!)	15(50!!)
Naproxen	0,9	14	Pindolol	0,5	3,5(8)
Nefopam	0,95!	4	Piperacillin	0,25	1,4
Neostigmine	0,3	1,2	Pirenzepin	0,5	10
Netilmicin	0,01	2,6(>100)	Piretanide	0,45	0,6
Nicotine	0,9	2	Piroxicam	0,9!	36
Nifedipine	1,0	2	Pirprofen	0,95!	6
Niflumic acid	0,85!	2	Pivampicillin	1,0(0,1!!)	0,2(0,9!!)
Nitrazepam	1,0	30	Pivmecillinam	1,0(0,4!!)	0,2(1,2!!)
Nitrofurantoin	0,7!!	0,3	Polymyxin B	0,12	4,5
Nitroglycerin	1,0!!	0,5(2,0!!)	Polythiazide	0,75	26
Nitroprusside	1,0(0,01!!)	0,1(170!!)	Pralidoxime	0,8	1,3
Nomifensine	0,6!	5	Prazepam	1,0!!	1,2(50!!)
Noradrenaline	1,0	0,03	Praziquantel	0,8!	1,7
Norethisterone	?	6	Prazosin	0,95	2,5
Nortriptyline	1,0!!	30	Prednis(ol)one	1,0	3
			Prenalterol	0,4	2
Ornidazole	0,95!!	14	Primidone	0,6(0,8!!)	8(80!!)
Oxacillin	0,6	0,5	Probenecid	1,0	4
Oxandrolone	0,7	9	Procainamide	0,9(0,2!!)	3(6!!)
Oxazepam	1,0	8	Procetofen	0,7!	24
Oxisurane	1,0!!	1,2(55)	Propafenone	?	3,6
Oxmetidine	0,95!	2,5	Propantheline	0,85!	2,9
Oxprenolol	0,95	1,5	Propoxyphene	0,5!!	5(35!!)
Oxyphenbutazone	0,3	48	Propranolol	1,0!!	3,5(6)
Oxytetracycline	0,2	9	Propylthiouracil	0,9	1,5
			Proquazone	1,0!!	1,0(10!!)
Pancuronium	0,4	2,0	Proscillaridin	1,0	40
Papaverine	1,0	1,8	Protriptyline	1,0!!	75
Penbutolol	0,95!	(2)27	Proxiphylline	0,75	8
Penicillin G	0,08	0,5	Pyrazinamide	0,9!	12
Pentazocine	0,8	2,5	Pyridostigmine	0,1	1,6
Pentobarbital	1,0!	(0,2)20(80)	Pyridylcarbinol	1,0	0,8
Pentoxifylline	1,0!!	1,5			
Peruvoside	0,8!	55	Quinidine	0,8!!	7
Phenacetin	1,0(1,0!!)	1,0(2,5!!)	Ranitidine	0,3!!	2,5
Phenazone	s.Antipyrin		Reserpine	1,0	150
Phenbutolol	0,95!!	26	Rifampicin	0,8!!	2,8
Pheneturide	1,0	40	Ritodrine	?	2,0(15)
Phenformin	0,6	10	Rolitetracycline	0,3	12
Phenobarbital	0,7	80			
Phenprocoumon	1,0	150			

Medikament	$P_O(Q_O, f_{nrN})$	t_{V2N}	Medikament	$P_O(Q_O, f_{nrN})$	t_{V2N}
Salbutamol	0,8	?	Thyroxine	1,0	130
Secobarbital	1,0	20	Tiapride	0,25	2,3
Sisomicin	0,01	2,9(> 100)	Tiaprofen	0,55!	1,4
Sobrerol	0,5	20	Ticarcillin	0,05	1,2
Sotalol	0,1	7(15)	Tilidine	0,9!:	0,5(10)
Sparteine	0,7!	3	Timolol	0,8!	5
Spectinomycin	0,08	1,7	Tinidazole	?	13
Spironolactone	s.Canrenoat		Tinoridine	1,0	8
Streptomycin	0,04	2,8	Tobramycin	0,02	2,0(> 100)
Strophanthin G	0,25!:	14	Tocainamide	0,6	12
Strophanthin K	0,25!:	17	Tolamolol	?	2,6
Sulbenicillin	0,15	0,7	Tolazamide	?	8
Sulfachlorpyridazine	0,2	3,6	Tolbutamide	1,0	6
Sulfacilomide	0,4	100	Tolfenamate	1,0!	50
Sulfadiazine	0,45	10	Tolmesoxide	1,0(1,0!)	2,5(12!)
Sulfadimethoxine	0,9	40	Tolmetin	0,9!	3(7)
Sulfadimidine	0,2	14	Torasemide	0,75	2,5
Sulfamerazine	0,6	24	Toxogonin	0,85	1,4
Sulfamethazine	0,3	5	Tramadol	0,7!:	7(9!)
Sulfamethizole	0,5	2,5	Tranexamate	0,03	2,3(24)
Sulfamethoxazole	0,8	10	Triameterene	0,8(0,04!)	4(3!)
Sulfamethoxy- pyridazine	0,5	36	Triazolam	1,0!:(1,0!)	2,5(4!)
Sulfametopyrazine	0,8	60	Trichlormethiazide	0,04	2,6
Sulfametrol	0,8	7	Triiodothyronine	1,0	22
Sulfamoxol	0,5	10	Trimethoprim	0,45	10
Sulfapyridine	0,4	10	TRIS-Buffer	0,15	7
Sulfinpyrazone	0,55!:	3(6)(18!)	d-Tubocurarine	0,6	3
Sulfisomidine	0,08	4,5	Valproic acid	0,95!:	15
Sulfisoxazole	0,5	8	Vancomycin	0,03	6
Sulformethoxine	0,6	~200	Vasopressin	1,0	0,1
Sulpiride	0,3	5,5(12)	Verapamil	1,0!:	5
Talampicillin	1,0(0,1!)	(0,9!)	Vinblastine	0,95!	3
Temazepam	1,0	7	Vincristine	0,95!	2,7
Terbutaline	0,45	3,5	Vinylbital	1,0	24
Tetracycline	0,12	8	Warfarin	1,0	50
Tetrahydrouridine	0,1!	7	Xipamide	0,6	7
Tetroxoprim	0,45	7	Zimelidine	1,0!:	5(18!)
Theophylline	0,9!:	8	Zomepirac	0,8	(1)4
Thiamazole	s.Methimazole				
Thiamphenicol	0,1	3			
Thiopental	1,0	0,2(10)			
Thioridazine	1,0!:	30			
Thiothixene	?	36			

— The parameters are rounded values collected from the literature. The dominant half-life is the half-life of the distribution or elimination phase which contributes the largest fractional area under the time-concentration curve, i.e. the half-life which contributes most to drug accumulation. Non-dominant initial or terminal half-lives of possible clinical significance are given in parentheses. An exclamation mark (!) indicates that the formation of pharmacologically active metabolites of potential clinical significance is not excluded. Two exclamation marks (!!) indicate that the existence of such metabolites has been proven. Whenever possible such drugs should not be used in patients with marked renal impairment.

Examples :	$P_o(Q_o f_{rN})$	$t_{1/2N}$
Aspirin	1.0(0.8!!)	0.25(3.0!!)
Gentamicin	0.02	1.9(>100)
Flunitrazepam	1.0!	(2)16

Expressed verbally this means : Aspirin is hydrolyzed with a half-life of 0.25 hours to its pharmacologically active metabolite salicylic acid, of which 80% are eliminated with a half-life of 3 hours by extra-renal path-ways. In the case of gentamicin only 2% of the dose are eliminated by extra-renal mechanisms. In the anuric patient drug clearance is 50 times smaller than in the standard individual. The drug is eliminated with a dominant initial standard half-life of 1.9 hours and with a non-dominant terminal half-life of more than 100 hours. Flunitrazepam is eliminated completely by extra-renal path-ways and the pharmacologically active metabolites are of questionable clinical significance. The drug is metabolized with a non-dominant initial half-life of 2 hours and a dominant terminal half-life of 16 hours.

No attempt has been made to quantitate intra- and inter-individual variability, and standard parameters dependent on urine pH or genetic factors are characterized by mean values.

Tab. 2 The Standard Renal Dose Fraction, f_{rN} as a Pharmacokinetic Predictor

Kinetic Process	$f_{rN} \rightarrow 1$ ($P_o, Q_o \rightarrow 0$)	$f_{rN} \rightarrow 0$ ($P_o, Q_o \rightarrow 1$)
Renal elimination	Complete	Insignificant
Non-renal elimination	Insignificant	Complete
Tubular reabsorption	Absent	Complete
CNS permeability	Poor	Excellent
G.E. absorption and bio-availability	Poor	Excellent, if not limited by dissolution rate or first-pass effect
Urine pH dependent elimination	May be marked (acids and bases)	Insignificant
Plasma albumin binding	Poor	Usually marked
Drug metabolism	Traces	Usually marked (active metabolites!!)
Renal disease:		
Abnormal elimination	Marked	Absent
Abnormal distribution	Absent	May be marked
Liver disease:		
Abnormal elimination	Absent	May be marked
Abnormal distribution	Absent	May be marked
Increased first pass effect	Absent	May be marked

Tab. 2 (Continued) The Standard Renal Dose Fraction, f_{NR} , as a Pharmacokinetic Predictor

Hypalbuminaemia		
Abnormal elimination	Absent	Usually present
Abnormal distribution	Absent	Usually present
Kinetic drug interactions		
Displacement from albumin	Absent	May be marked
Metabolic inhibition	Absent	May be marked
Enzyme induction	Absent	May be marked
Inhibition of tubular secretion	May be marked (some acids and bases)	Clinically insignificant
Genetic metabolic polymorphism	Absent	May be marked
Haemodialysis	Highly effective	Ineffective
Charcoal (e.g. haemoperfusion)	Not always effective	Usually effective
Forced alkaline diuresis	May be effective (acids)	Ineffective

References

- 1) Dettli, L. : Elimination Kinetics and Dosage Adjustment of Drugs in Patients with Kidney Disease. Progress in Pharmacology Vol. 1, No. 4. Fischer, New York (1977).
- 2) Dettli, L. : Proc. 1st Europ. Congr. Biopharm. Pharmacokin., 3 : 11 (1982). Technique et Documentation, Paris.
- 3) Bricker, N. S. et al. : Amer. J. Med., 28 : 77 (1960).
- 4) Bjornsson, T. D. : Clin. Pharmacokin., 4 : 200 (1979).
- 5) Dettli, L. : Multiple Dose Elimination Kinetics and Drug Accumulation in Patients with Normal and with Impaired Kidney Function. Advances in the Biosciences, 5 : 39 (1969). Pergamon Press, Oxford.
- 6) Dettli, L. et al. : Postgrad. med. J. 46 : Suppl., 32 (1970).
- 7) Dettli, L. et al. : Acta pharmacol. toxicol. (Kbh.), 29 : Suppl. 3, 211 (1971).
- 8) Dettli, L. : Pharmakokinetische Grundlagen der Arzneimitteldosierung, in Arzneimittel-Kompendium der Schweiz, Vol. 2, p. 1520. Documed, Basel (1983).
- 9) Spring, P. : Int. J. Clin. Pharmacol. Toxicol. Ther., 11 : 76 (1975).
- 10) Hallynck, Th. et al. : Clin. Pharmacol. Ther., 30 : 414 (1981).
- 11) Hallynck, Th. et al. : J. Antimicrob. Chemother., 8 : Suppl. A, 1 (1981).
- 12) Hallynck, Th. et al. : Br. J. Clin. Pharmacol., 11 : 523 (1981).
- 13) Chiou, W. L., Hsu, F. H. : Res. Comm. chem. Pathol. Pharmacol., 10 : 315 (1975).
- 14) Jelliffe, R. W., Jelliffe, S. M. : Math. Biosc., 14 : 17 (1972).
- 15) Dettli, L., Tschanz Chr., in Clinical Pharmacy and Clinical Pharmacology, p. 235. North-Holland Publishing Company, Amsterdam (1976).
- 16) Dettli, L. : in preparation.