As experience about the survival of type II diabetic patients with ESRD is limited, we have analysed the outcome of these patients treated at our institution within the last 10 years [3]. Analysing factors associated with survival, patients managed by renal transplantation did far better, whereas the presence of severe vascular complication and the duration of diabetes were inversely related to outcome. Whereas survival of patients with severe vascular complications was independent of mode of treatment, in patients without severe vascular complications survival depends on the mode of treatment (1- and 5-year survival: haemodialysed patients 75 and 16%: renal transplant recipients 94 and 79%, \( P < 0.0001 \)).

In conclusion, the presence of vascular complications before renal replacement therapy greatly reduces survival in diabetic patients with ESRD. Therefore patients with a history of ischaemic heart disease, stroke, or peripheral gangrene should be maintained on chronic haemodialysis treatment or continuous ambulatory peritoneal dialysis. If coronary angiography revealed a significant coronary disease which cannot be improved by percutaneous transluminal angioplasty or aortocoronary bypass surgery, renal transplantation should not be considered for these patients. The existence of a peripheral vascular disease (Fontane Class IV) is an exclusion criteria for renal transplantation. In these patients renal transplantation is not able to improve survival of type II diabetic patients compared to those maintained on haemodialysis. In contrast, renal transplantation improves the prognosis of type II diabetic patients with ESRD and without vascular complications. Thus it should be considered as the treatment of choice for this group.

References
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Pharmacokinetics and drug dosage adjustment to renal impairment

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The problem

The pharmacokinetics of two-thirds of all drugs depends on renal function [1]. Practically every nephrology department will have experienced at least one case of deafness induced by aminoglycoside overdosage. The error in the 1970s was that the drug dose was not adjusted to renal function, which resulted in toxic overdosage. The other extreme was presumably the mistake made in the 1980s: the adjusted dosage was too low and some patients died due to subtherapeutic underdosage, mainly in the intensive care units.

Elimination, distribution, metabolite clearance, plasma protein binding, or all parameters simultaneously, change in renal failure. Fortunately changes in plasma protein binding generally do not require dosage adjustments, even though intricate pharmacokinetic phenomena are to be observed [2]. The plasma-protein-bound fraction is 0.9 for phenytoin. The free fraction in plasma increases from 0.1 to 0.2 in renal failure. However, no increased side-effects are observed, since the absolute free phenytoin concentration remains unchanged.

Pharmacokinetics

A general concept of pharmacokinetics is a prerequisite to calculating individual dosage proposals from published data. Many natural processes have a half-life (\( T_1/2 \)) that, in a log-linear fashion, depends on a linear term (\( \text{Lambda} \)), where (\( \ln 2 = 0.693 \)).

\[ T_1/2 = 0.693/\text{Lambda} \]

The eliminated proportions of a dose are: after 1 \( T_1/2 \)
Quinolones
Macrolides
Dosage after haemodialysis consists of the maintenance dose and the supplementary dose (D_{HD} = D_{maint} + D_{supp}). The dosage on haemofiltration infusion in severely ill patients with a normal body weight or 65 kg (dosage maximum). The starting dose (D_{start}) corresponds to the normal dose, except for teicoplanin and aminoglycosides.

Dosage interval in hours (T_{au}). In addition the dosage after haemodialysis (D_{HD}) and for continuous haemofiltration is given (D_{CHF}). The dosage (D/T_{au}) is given in milligrams per hour (mg/h) as the dose in milligrams (D) with the elimination is calculated for an ultrafiltration rate of 3-15 litres per day (D_{CHF}). The dosage is given for intravenous bolus administration or short infusion in severely ill patients with a normal body weight or 65 kg (dosage maximum). The starting dose (D_{start}) corresponds to the normal dose, except for teicoplanin and aminoglycosides.

Table 1. Dosage of anti-infective drugs in renal insufficiency, haemodialysis (HD), and continuous haemofiltration (CHF). Dominant elimination T_{1/2} are given for selected generics. The data are given for normal renal function (norm), for a serum creatinine of 250 μmol/l (insufficiency), and for anuria (anuria). The dosage (D/T_{au}) is given in milligrams per hour (mg/h) as the dose in milligrams (D) with the dosage after haemodialysis (D_{HD}) and for continuous haemofiltration is given (D_{CHF}). The dosage after haemodialysis consists of the maintenance dose and the supplementary dose (D_{HD} = D_{maint} + D_{supp}). The dosage on haemofiltration is calculated for an ultrafiltration rate of 3-15 litres per day (D_{CHF}). The dosage is given for intravenous bolus administration or short infusion in severely ill patients with a normal body weight or 65 kg (dosage maximum). The starting dose (D_{start}) corresponds to the normal dose, except for teicoplanin and aminoglycosides.
Table 1. (continued)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Half-life (T½) (h)</th>
<th>Dosage (D/Tau) mg/h</th>
<th>Dmax (mg)</th>
<th>DClF (mg/h)</th>
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<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Anuria</td>
<td>Normal</td>
<td>Insufficiency (Crea 250)</td>
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<td>Monobactams and Carbapenems</td>
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<td>1000/12</td>
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<tr>
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<td>2.9</td>
<td>1000/8</td>
<td>1000/12</td>
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<tr>
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<td>13.3</td>
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<td>1000/12</td>
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<td></td>
</tr>
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<td>9.6</td>
<td>1400/24</td>
<td>1000/24</td>
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<td>Isoniazid</td>
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<td>5/12</td>
<td>300/24</td>
<td>300/24</td>
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<td>7.0</td>
<td>750/24</td>
<td>750/24</td>
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<tr>
<td>Pyrazinamide (oral)</td>
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<td>13</td>
<td>2000/24</td>
<td>2000/24</td>
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<tr>
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<td>4.5</td>
<td>600/24</td>
<td>600/24</td>
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<tr>
<td>Streptomycin</td>
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<td>100</td>
<td>1000/24</td>
<td>500/48</td>
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<td>Antimalarial drugs</td>
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<td></td>
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<tr>
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<td>15</td>
<td>600/12</td>
<td>600/12</td>
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<tr>
<td>Chloroquine</td>
<td>4/48</td>
<td>300</td>
<td>150/8</td>
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<td>35 (360)</td>
<td>50/24</td>
<td>50/24</td>
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<td>110</td>
<td>400/24</td>
<td>200/24</td>
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<td>150</td>
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<td>25</td>
<td>750/8</td>
<td>500/12</td>
</tr>
<tr>
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<td>200/8</td>
<td>100/8</td>
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<tr>
<td>Didanosin (oral)</td>
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<td>?</td>
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<td>Foscarnet</td>
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<td>4000/8</td>
<td>2000/48</td>
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<td>400/12</td>
<td>400/24</td>
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<tr>
<td>Chloramphenicol</td>
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<td>7</td>
<td>1000/8</td>
<td>1000/12</td>
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<td>Doxycyclin</td>
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<td>23</td>
<td>200/24</td>
<td>200/24</td>
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<td>Fosfomycin</td>
<td>1.5</td>
<td>20</td>
<td>5000/8</td>
<td>5000/24</td>
</tr>
<tr>
<td>Metronidazol</td>
<td>10</td>
<td>11 (34)</td>
<td>500/12</td>
<td>500/12</td>
</tr>
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<td>Pentamidin</td>
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<td>300</td>
<td>300/24</td>
<td>200/24</td>
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<tr>
<td>Sulphamethoxazole</td>
<td>9</td>
<td>50</td>
<td>800/24</td>
<td>800/24</td>
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<td>=Co-trimoxazole (pneumocystis c.p.)</td>
<td>2880/8</td>
<td></td>
<td>1920/12</td>
<td>1920/24</td>
</tr>
</tbody>
</table>

50 percent after 2 \( T_\frac{1}{2} \) 25 percent, after 3 \( T_\frac{1}{2} \) 12.5 percent, after 4 \( T_\frac{1}{2} \) 6.25 percent, and after 5 \( T_\frac{1}{2} \) 3.125 percent. Cholecalciferol has a \( T_\frac{1}{2} \) of 30 days, indicating that it takes 4 months for 95% to be eliminated (4.32 \( \times T_\frac{1}{2} \)).

The decay of drug concentrations (C) in one- or multicompartment kinetics is described by one- or multienzyme temporal terms.

\[ C = \sum C_i \exp(-\text{Lambda}_i \times t) \]

Integration or summation as per the trapezoidal rule yields the area under the curve (AUC).

\[ \text{AUC} = \sum \frac{C_i}{\text{Lambda}_i} \]

The clearance (Cl) is given by the dose (D) and the area (AUC).

\[ \text{Cl} = \frac{D}{\text{AUC}} \]

The volume is the relationship between amount and concentration \( V = M/C \). The amount corresponds to the fraction of the dose \( D \) that is not yet eliminated according to the dominant elimination term \( \text{Lambda}_a \) during time \( t \).

\[ M = D \exp(-0.693 \times \text{Lambda}_a) \]

For simultaneous distribution and elimination, the integrated process must be analyzed.

\[ \text{Vd} = \int M \times dt = \frac{C}{\text{dt}} \]

\[ \text{Vd} = \frac{(D/\text{Lambda}_a)}{\text{AUC}} \]

Since \( (C_1 = \text{AUC}) \) and \( (T_\frac{1}{2} = 0.693/\text{Lambda}_a) \), the most universal pharmacokinetic equation is thus obtained.

\[ \text{Cl} = 0.693 \ \text{Vd}/T_\frac{1}{2} \]

The clearance value is the same for compartment kinetics, physiological models, and system analysis [3]. In building up a pharmacokinetic database, distribution \( \text{Vd} \) and elimination parameters \( (T_\frac{1}{2}) \) must be
documented to characterize the specific kinetics of each drug completely.

Accumulation kinetics

If a drug is repetitively administered accumulation kinetics will apply for each exponential term. After repetitive dosage the accumulation factor of distribution kinetics is much lower and can be neglected as regards elimination kinetics. Following repetitive dosage, a steady state is achieved at the point at which 95% of the first dose has been eliminated, that is after 4.32 times the half-life. Ranitidine has a normal T₁/₂ of 2 h; it is given every 12 h, and no accumulation can occur. For advanced renal impairment, the T₁/₂ is 12 h so that the accumulation maximum, with the risk of toxic side-effects, will occur as late as after 3 days.

The starting dose should be given if the recommended drug levels are to be obtained immediately.

Renal function and the Dettli equation

For drug dosage the most useful estimate of renal function is obtained from the Cockcroft and Gault formula [4]. It yields creatinine clearance (CCR) as a function of age (years), bodyweight (BW), and serum creatinine (Crea µmol/l).

\[
\text{CCR} = \left(140 - \text{Age}\right) \times \frac{\text{BW}}{0.814 \times \text{Crea}}
\]

According to this equation all persons aged 140 years will require dialysis—which sounds not entirely unrealistic. Obviously renal function is a concern not only to nephrologists but also to general practitioners, geriatrists, and gerontologists, since it decreases with age [5]. The age-related decrease in renal function is concealed behind the creatinine-blind range (50 < CCR < 100 ml/min). This is most probably the reason for frequent adverse reactions encountered during drug treatment in the elderly.

Dosage adjustment

There are two different approaches to adjusting drug dosage to impaired renal function: the Dettli rule and the Kunin rule (Figure 1). Dettli’s proportional dose-reduction rule adjusts the maintenance dosage (D/Tau) in proportion to the reduced clearance [6].

\[
\text{D}_{\text{start}} = \text{const.} \times \frac{\text{D}}{\text{Tau}} \times \frac{\text{Cl}}{\text{Cl}_{\text{norm}}}
\]

Alternatively, Kunin’s half-dosage rule is derived from elimination half-life [7]. The normal starting dose is given, and one-half of the starting dose is repeated at an interval (Tau) corresponding to one half-life time.

\[
\text{D}_{\text{start}} = \text{const.} \times \frac{\text{D}}{\text{Tau}} \times \frac{\text{Cl}}{\text{Cl}_{\text{norm}}}
\]

Fig. 1. The Dettli rule and the Kunin rule for dosage adjustment to prolonged T₁/₂ in renal impairment. For ceftazidime the normal T₁/₂ is 2 h, but it increases to 12 h if renal function is impaired by 50%. According to the Dettli rule, the normal dosage (2000 mg/8 h) should be reduced to 1/6 (2000 mg/48 h = 500 mg/12 h). According to the Kunin rule, the maintenance dose is reduced to 1/3 only (1000 mg/12 h). The half-dosage rule as per Kunin yields seven times higher trough concentrations (Cₘₐₓ) than the proportional dose-reduction rule as per Dettli.
Haemodialysis and haemofiltration

The effect of intermittent haemodialysis on simulating drug concentrations is best derived from the clearance term. For dosage adjustments the fraction eliminated ($f_R$) is the more appropriate term. The half-life on dialysis determines the overall effects of natural and extracorporeal elimination during dialysis time ($t$).

$$f_R = 1 - \exp(-0.693 \frac{t}{T})$$

The supplementary dose after haemodialysis ($D_{supp}$) replaces the fraction removed ($f_R$) from the amount in the body that is required to maintain effective drug levels. Theoretically this amount corresponds to the starting dose ($D_{start}$).

$$D_{supp} = f_R D_{start}$$

The dosage after haemodialysis ($D_{HD}$) comprises the supplementary dose plus the dosage adjusted to anuria ($D_{anur}$).

$$D_{HD} = D_{anur} + D_{supp}$$

Foscarnet is administered at 4000 mg every 8 h. The $T$ is 4.5 h and the amount in steady-state is 5500 mg. The $T$ increases to 160 h in anuria and only 500 mol should be given every 48 h. During haemodialysis the $T$ decreases to 4 h, a 0.5 fraction is removed and the supplementary dose should be 2500 mg. The dosage after haemodialysis consists of the anuria-adjusted dose plus the supplementary dose, adding up to 3000 mg to obtain effective levels.

During continuous haemofiltration, the ultrafiltration rate (UF) adds to the renal creatinine clearance ($CCR_{ren}$) to form the total creatinine clearance ($CCR_{tot}$).

$$CCR_{tot} = CCR_{ren} + UF$$

Dosage adjustment for continuous haemofiltration can be based on the linear dependence of drug clearance (or reciprocal $T$) on total creatinine clearance ($CCR_{tot}$) as per the Dettli equation. Vancomycin has a normal $T$ of 6 h, whereas this figure is 120 h for anuria. If an intensive-care patient has a renal creatinine clearance of 5 ml/min and an ultrafiltration rate of 5 ml/min, the total creatinine clearance will be 10 ml/min. By linear interpolation, $T'$ for vancomycin can be estimated as 100 h and the usual dosage of 1000 mg every 12 h should be reduced to 500 mg every 48 h.

Pharmacodynamics

The decision on whether the Kunin rule or the Dettli rule should be used for dosage adjustments depends on the effect that is aimed at. Dosage adjustment is a matter not only of pharmacokinetics but also of pharmacodynamics. It is our aim to maintain the same pharmacodynamic effect in patients in whom pharmacokinetics have changed. The dependence of the effect ($E$) on concentrations ($C$), or the relation between pharmacokinetics and pharmacodynamics (PK/PD), is described by the sigmoid $E_{max}$ model [8].

$$E = \frac{E_{max} C}{EC_{50} + C}$$

From the sigmoid equation it is obvious that there is a concave PK/PD relationship, a linear, and a convex relationship. For example, the effect of anticonvulsive drugs is concave since it is only above a minimum concentration that an effect will be seen. The bactericidal effect of aminoglycosides is linear. The antihypertensive effect of ACE inhibitors is convex, since an increase in concentrations will result not in more antihypertensive action but only in an increased incidence of side-effects. For the most simple case, where ($h = 1$) and ($EC_{50} \gg C$), the effect changes in parallel with concentrations and $T$ of the drug. To calculate more advanced dose adjustments a computer system with PK/PD parameters and PK/PD algorithms will be the task of future work.

References