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Dose adjustment in renal diseases

UOBCOP

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Pharmacokinetic Considerations

- Uremic patients may exhibit pharmacokinetic changes in:
- ***Bioavailability:***
- ***Volume of distribution***
- ***Clearance:***

Bioavailability:

- The oral bioavailability of a drug in severe uremia may be decreased as a result of disease-related changes in gastrointestinal motility and pH caused by nausea, vomiting, and diarrhea.
- Mesenteric blood flow may also be altered.
- E.g: However, the oral bioavailability of a drug such as propranolol (which has a high first-pass effect) may be increased in patients with renal impairment as a result of the decrease in first-pass hepatic metabolism

volume of distribution

- The apparent volume of distribution depends largely on:
  - drug protein binding in plasma or tissues
  - and total body water.
- Renal impairment may alter the distribution of the drug as a result of changes in:

1. fluid balance,
2. drug protein binding,
   - The plasma protein binding of weak acidic drugs in uremic patients is decreased, whereas the protein binding of weak basic drugs is less affected.
   - The decrease in drug protein binding results in a larger fraction of free drug and an increase in the volume of distribution.
   - the net elimination half-life is generally increased as a result of the dominant effect of reduced glomerular filtration.
   - Protein binding of the drug may be further compromised due to the accumulation of metabolites of the drug and accumulation of various biochemical metabolites, such as free fatty acids and urea, which may compete for the protein-binding sites for the active drug.

1.Clearance.

- Total body clearance of drugs in uremic patients is also reduced by either:
  - a decrease in the glomerular filtration rate and possibly active tubular secretion
  - or reduced hepatic clearance resulting from a decrease in intrinsic hepatic clearance.

- In clinical practice, estimation of the appropriate drug dosage regimen in patients with impaired renal function is based on an estimate ***of the remaining renal function of the patient and a prediction of the total body clearance.***

General Approaches for Dose Adjustment in Renal Disease

- Most of these methods assume that the required therapeutic plasma drug concentration in uremic patients is similar to that required in patients with normal renal function.
- Uremic patients are maintained on the same C^{∞}_{av} after multiple oral doses or multiple IV bolus injections.
- For IV infusions, the same C_{SS} is maintained. (C_{SS} is the same as C^{∞}_{av} after the plasma drug concentration reaches steady state.)

1. Dose Adjustment Based on Drug Clearance

- Methods based on drug clearance try to maintain the desired C^{∞}_{av} after multiple oral doses or multiple IV bolus injections as total body clearance, Cl_T, changes. The calculation for C^{∞}_{av} is

$$C^{\infty}_{av} = \frac{FD_0}{Cl_T \tau} \qquad (21.1)$$

For patients with a uremic condition or renal impairment, total body clearance of the uremic patient will change to a new value, Cl^u_T. Therefore, to maintain the same desired C^{∞}_{av}, the dose must be changed to a uremic dose, D^u_0 or the dosage interval must be changed to τ^u, as shown in the following equation:

$$C^{\infty}_{av} = \frac{D^N_0}{Cl^N_T \tau^N} = \frac{D^u_0}{Cl^u_T \tau^u} \qquad (21.2)$$

(normal) (uremic)

Rearranging Equation 21.2 and solving for D^u_0.

$$D^u_0 = \frac{D^N_0 Cl^u_T \tau^u}{Cl^N_T \tau^N} \qquad (21.3)$$

where the superscripts N and u represent normal and uremic conditions, respectively.

- If the dosage interval is kept constant, then the uremic dose D^{u}_{0} is equal to a fraction (Cl^{u}_{T}/Cl^{N}_{T}) of the normal dose, as shown in the equation

$$D_0^{\mathrm{u}} = \frac{D_0^{\mathrm{N}} Cl_{\mathrm{T}}^{\mathrm{u}}}{Cl_{\mathrm{T}}^{\mathrm{N}}} \qquad (21.4)$$

For IV infusions the same desired C_{SS} is maintained both for patients with normal renal function and for patients with renal impairment. Therefore, the rate of infusion, R, must be changed to a new value, R^{u}, for the uremic patient, as described by the equation

$$C_{\mathrm{SS}} = \frac{R}{Cl_{\mathrm{T}}^{\mathrm{N}}} = \frac{R^{\mathrm{u}}}{Cl_{\mathrm{T}}^{\mathrm{u}}} \qquad (21.5)$$

(normal) (uremic)

Dose Adjustment Based on Changes in the Elimination Rate Constant

- The overall elimination rate constant for many drugs is reduced in the uremic patient.
- A dosage regimen may be designed for the uremic patient either by:
  - reducing the normal dose of the drug and keeping the frequency of dosing (dosage interval) constant,
  - or by decreasing the frequency of dosing (prolonging the dosage interval) and keeping the dose constant.
- **Doses of drugs with a narrow therapeutic range should be reduced—particularly if the drug has accumulated in the patient prior to deterioration of kidney function**

- Assuming the V D is the same in both normal and uremic patients and is constant,
- then the uremic dose D_0^u is a fraction (k^u/k^N) of the normal dose:

$$D_0^u = \frac{D_0^N k^u}{k^N} \qquad (21.6)$$

The overall elimination rate constant is the sum total of all the routes of elimination in the body, including the renal rate and the nonrenal rate constants:

$$k^u = k_{nr} + k_R^u \qquad (21.7)$$

where k_{nr} is the nonrenal elimination rate constant and k_R is the renal excretion rate constant.

Renal clearance is the product of the apparent volume of distribution and the rate constant for renal excretion:

$$Cl_R^u = k_R^u V_D^u \qquad (21.8) \qquad k_R^u = Cl_R^u \frac{1}{V_D^u} \qquad (21.9)$$

- Assuming that the apparent volume of distribution and nonrenal routes of elimination do not change in uremia, then $k^u_{nr} = k^N_{nr}$ and $V^u_D = V^N_D$. Substitution of Equation 21.9 into Equation 21.7 gives

$$k_R^u = Cl_R^u \frac{1}{V_D^u} \qquad (21.9) \qquad k^u = k_{nr} + \frac{1}{V_D} Cl_R^u \qquad (21.10)$$

From Equation 21.10, a change in the renal clearance, Cl^u_R, due to renal impairment will be reflected in a change in the overall elimination rate constant k_u.
Because changes in the renal drug clearance cannot be assessed directly in the uremic patient, Cl^u_R is usually related to a measurement of kidney function by the glomerular filtration rate (GFR), which in turn is estimated by changes in the patient's creatinine clearance.

Determination of rate constant for drug when it cannot be determined directly

- When the elimination rate constant for a drug in the uremic patient cannot be determined directly, indirect methods are available to calculate the predicted elimination rate constant based on the renal function of the patient. The assumptions on which these dosage regimens are calculated include the following.
- 1. The renal elimination rate constant (k R) decreases proportionately as renal function decreases. (Note that k R is the same as k e as used before)
- 2. The nonrenal routes of elimination (primarily, the rate constant for metabolism) remain unchanged.
- 3. Changes in the renal clearance of the drug are reflected by changes in the creatinine clearance.

Serum Creatinine Concentration and Creatinine Clearance

- Under normal circumstances, creatinine production is roughly equal to creatinine excretion, so the serum creatinine level remains constant. In a patient with reduced glomerular filtration, serum creatinine will accumulate in accordance with the degree of loss of glomerular filtration in the kidney. The serum creatinine concentration alone is frequently used to determine creatinine clearance, Cl_{Cr}. Creatinine clearance from the serum creatinine concentration is a rapid and convenient way to monitor kidney function.

$$Cl_{Cr} = \frac{\text{rate of urinary excretion of creatinine}}{\text{serum concentration of creatinine}}$$

$$Cl_{Cr} = \frac{C_u V \times 100}{C_{Cr} \times 1440} \qquad (21.11)$$

Calculation of Creatinine Clearance from Serum Creatinine Concentration

- The units for Cl_{Cr} are mL/min.

Adults

$$Cl_{Cr} = \frac{[140 - \text{age (yr)}] \times \text{body weight (kg)}}{72\ (C_{Cr})} \qquad (21.12)$$

For females, use 90% of the Cl_{Cr} value obtained in males.

Children

$$Cl_{Cr} = \frac{0.55 \text{ body length (cm)}}{C_{Cr}} \qquad (21.13)$$

where Cl_{Cr} is given in mL/min/1.73 m^2.

$$\text{LBW (males)} = 50 \text{ kg} + 2.3 \text{ kg for each inch over 5 ft}$$
$$\text{LBW (females)} = 45.5 \text{ kg} + 2.3 \text{ kg for each inch over 5 ft}$$

Table 21.3 Renal Impairment Based on Creatinine Clearance

Group	Description	Estimated Creatinine Clearance (mL/min)
1	Normal renal function	>80 mL/min
2	Mild renal impairment	50–80 mL/min
3	Moderate renal impairment	30–50 mL/min
4	Severe renal impairment	<30 mL/min
5	ESRD[a]	Requires dialysis

[a]ESRD = end-stage renal disease.

Basis for Dose Adjustment in Uremia

- The dose is same:
  - The loading drug dose is based on the apparent volume of distribution of the patient.It is generally assumed that the apparent volume of distribution is not altered significantly, and therefore that the loading dose of the drug is the same in uremic patients as in subjects with normal renal function.
- **The maintenance dose is based on clearance of the drug in the patient.**
  - In the uremic patient, the rate of renal drug excretion has decreased, leading to a decrease in total body clearance. Most methods for dose adjustment assume nonrenal drug clearance to be unchanged. The fraction of normal renal function remaining in the uremic patient is estimated from creatinine clearance.
- Although total body clearance is a more accurate index of drug dosing, the elimination half-life of the drug is more commonly used for dose adjustment because of its convenience.
- Clearance allows for the prediction of steady-state drug concentrations, while elimination half-life yields information on the time it takes to reach steady-state concentration.