**Design of dosage regimen in renally impaired or uremic patients**

**Introduction:**

The kidney is an important organ in regulating body fluids, electrolyte balance, removal of metabolic waste, and drug excretion from the body. Impairment or degeneration of kidney function affects the pharmacokinetics of drugs. Acute diseases, trauma to the kidney or drug intoxication can cause *uremia,* in which glomerular filtration is impaired or reduced, leading to accumulation of excessive fluid and blood nitrogenous products in the body. Uremia generally reduces glomerular filtration and/or active secretion, which leads to a decrease in renal drug excretion resulting in a longer elimination half-life of the administered drug.

In addition to changing renal elimination directly, uremia can affect drug pharmacokinetics in unexpected ways. For example, declining renal function leads to disturbances in electrolyte and fluid balance, resulting in physiologic and metabolic changes that may alter the pharmacokinetics and pharmacodynamics of a drug. Pharmacokinetic processes such as drug distribution (including both the volume of distribution and protein binding) and elimination (including both biotransformation and renal excretion) may also be altered by renal impairment. Both therapeutic and toxic responses may be altered as a result of changes in drug sensitivity at the receptor site. Overall, uremic patients have special dosing considerations to account for such pharmacokinetic and pharmacodynamic alterations.**1**

**Pharmacokinetic Considerations:**

Uremic patients may exhibit pharmacokinetic changes in bioavailability, volume of distribution, and clearance.

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. **2**

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 fluid balance, drug protein binding, or other factors that may cause changes in the apparent volume of distribution. 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. However, 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.

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**2**.

**General Approaches for dosage adjustment in renal disease:**

Several approaches are available for estimating the appropriate dosage regimen for a patient with renal impairment.

The design of dosage regimens for uremic patients is based on the pharmacokinetic changes that have occurred as a result of the uremic condition. Generally, drugs in patients with uremia or kidney impairment have prolonged elimination half-lives and a change in the apparent volume of distribution. In less severe uremic conditions there may be neither edema nor a significant change in the apparent volume of distribution. Consequently, the methods for dose adjustment in uremic patients are based on an accurate estimation of the drug clearance in these patients.**1**

Two general pharmacokinetic approaches for dose adjustment include methods based on drug clearance and methods based on the elimination half-life.

1. **Dose adjustment based on drug clearance:**

For IV infusions the same desired Css (Steady state concentration) should be maintained both for patients with normal renal function and for patients with renal impairment.**3**

Css = R/ Cl **N** T  (N: Normal)  **1** ClT : Total Body clearance

Therefore, rate of infusion, R, must be changed to a new value, RU, for the uremic patient,

Css = RU / Cl **U** T  (U: Uremic)  **2**

1. **Dose adjustment based on changes in the elimination rate constant:**

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.**4**

**ku = knr + 1/VD \* Cl u R 3**

**knr : Non-renal elimination rate constant**

From Equation 3, 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.

A complete pharmacokinetic analysis of the drug in the uremic patient is not possible. Moreover, the patient’s uremic condition may not be stable and may be changing too rapidly for pharmacokinetic analysis.

Each of the above pharmacokinetic approaches for the calculation of a dosage regimen have certain assumptions and limitations that must carefully assessed by clinicians before any approach is taken.

**STEPWISE GUIDE TO ADJUST DRUG DOSAGE FOR PATIENTS WITH RENAL INSUFFICIENCY** (CLINICAL APPROACH)

**Step 1: Take history and perform physical examination**

**Step 2: Determine the degree of renal insufficiency**

* Measure serum creatinine
* Order 24-hour urine collection or calculate creatinine clearance

**Step 3: Review the medication list**

* Ensure that all drugs are still required and that new medications have specific indications
* Evaluate for potential drug interactions
* Check whether dosage adjustment is required for any drug as per the renal function of patient.

**Step 4: Choose less nephrotoxic drugs**

* If the use of nephrotoxic drugs cannot be avoided without patient morbidity or mortality, then therapeutic drug monitoring or monitoring of renal function is mandatory

**Step 5: Select loading doses**

* These are usually the same for patients with both normal and abnormal renal functions

**Step 6: Select a maintenance regimen**

* Either reduce the dose of the drug and maintain the usual dosing interval or maintain the drug dose and extend the interval
* Titrate the dose of the drug to patient effect, if applicable (For example, antihypertensives are dosed based upon blood pressure control, whereas antimicrobials are not adjusted according to response)

Generally, we should consider

* a modest decrease in drug doses when creatinine clearance is <50−60 mL/min
* a moderate decrease in drug doses when creatinine clearance is <25−30 mL/min
* a substantial decrease in drug doses when creatinine clearance is ≤15 mL/min

In order to modify doses for patients with renal impairment, it is possible to decrease the drug dose and retain the usual dosage interval, retain the usual dose and increase the dosage interval, or simultaneously decrease the dosage and prolong the dosage interval

**Step 7: Monitor drug levels**

* Monitor drug levels if monitoring is available to guide further therapy

**Step 8: Reassess**

* Reassess the patient to evaluate drug effectiveness and the need for ongoing therapy
* If nephrotoxic drugs are used, check the patient's serum creatinine and creatinine clearance again

**Measurement of Creatinine Clearance:**

Adults: The method shown in Equation 4 is used to estimate creatinine clearance (ClCr) from serum creatinine concentration (CCr). This method considers both the age and the weight of the patient. **5**

For males,

ClCr = [140 – Age(yr)] X body weight (kg) **/** 72 (CCr)  **4**

For females, use 90% of the *Cl* Cr value obtained in males.

**Children:** Based on length and creatinine concentration,

ClCr = 0.55 X body length (cm)**/** CCr   **5**

where *Cl* Cr is given in mL/min/1.73 m2.

**Dose Adjustment for Uremic Patients**

Dose adjustment for drugs in uremic or renally impaired patients should be made in accordance with changes in pharmacodynamics and pharmacokinetics of the drug in the individual patient. Active metabolites of the drug may also be formed and must be considered for additional pharmacologic effects when adjusting dose. The following methods may be used to estimate an initial and maintenance dose regimen. After initiating the dosage, the pharmacodynamics and pharmacokinetics of the drug should be monitored continuously. Patient's renal function must also be evaluated, which may be changing.**1**

**Basis for Dose Adjustment in Uremia**

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.

After the remaining total body clearance in the uremic patient is estimated, a dosage regimen may be developed by (1) decreasing the maintenance dose, (2) increasing the dosage interval, or (3) changing both maintenance dose and dosage interval.

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.**1**

**Uremic dose: ku/kN \* normal dose**

Overall elimination rate constant in uremic patient: *k* u

Overall elimination rate constant in patients with normal renal function: *k* N

***When dosage interval is kept constant, the uremic dose is always a smaller fraction of the normal dose (eqn 4). Instead of reducing the dose for a uremic patient, the usual dose is kept constant and the dosage interval T is prolonged according to the following eqn5.***

**Dosage interval in uremia, Tu= kN/ku \* TN**

**Tu: Dosage interval**  for the dose in uremic patients.

**TN: Dosage interval for the dose in patients with normal renal function.**

**Conclusion:**

The pharmacokinetics of two-thirds of all drugs depends on renal function. Boiavailability, plasma protein binding, elimination, metabolite clearance or all parameters simultaneously, change in renal failure. Dosage regimen must be designed by taking into account either of following 1) decreasing the maintenance dose, (2) increasing the dosage interval, or (3) changing both maintenance dose and dosage interval. Dosage adjustment in renally impaired patient must be based on elimination half life of drug rather than total body clearance. After initiating the dosage, the pharmacodynamics and pharmacokinetics of the drug should be monitored continuously. Patient's renal function must also be evaluated continuously, which may be changing.

**References:**

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