Pharmacokinetics in Hemodialysis
Vancomycin in Intermittent Hemodialysis

Introduction

Dialysis and transplantation are the two treatments available for the management of patients with end-stage renal disease (ESRD). Dialysis is an artificial process in which the accumulation of drugs or waste metabolites is removed by diffusion from the body into the dialysis fluid.

The two common dialysis treatments are the peritoneal dialysis and hemodialysis. Both processes work on the principle that as the uremic blood or fluid is equilibrated with the dialysis fluid, waste metabolites diffuse through a membrane into the dialysis fluid and are removed. The dialysate contains water, dextrose, electrolytes and other elements similar to normal body fluids without the toxins.

Hemodialysis

Hemodialysis (HD) uses a dialysis machine and filters blood through an artificial membrane and it requires access to the blood vessels to allow the blood to flow to the dialysis machine and back to the body. A variety of HD systems are in use today. The ability of a dialysis system to remove drugs from the body depends on many factors. These factors are:

- Drug characteristics (water solubility, molecular weight, molecular binding, and volume of distribution)
- Mechanical property of dialysis system (surface area, thickness of membrane and porosity)
- Dialysis condition (blood and dialysate flow rate)

The rate of removal of toxin from blood is influenced by blood and dialysate flow, membrane characteristics and properties of the toxin being removed. Solutes from the blood are removed through diffusion and convection. Diffusion is the process whereby the molecule moves down its concentration gradient by passing through pores in the dialysis membrane. Once equilibrium is achieved, the net movement is zero because the rate of movement from the blood to dialysate compartment is equal to the rate from the dialysate to the blood compartment. For most substances, equilibrium is not achieved either because the blood and dialysate flow rates are too rapid or the molecule is too large to easily move through the pores. Urea is a marker of small molecule transport across the dialysis membrane and serves as a measure adequacy. The rate limiting step for the removal of urea is blood flow. A larger molecule, vitamin B₁₂ also has been used as a measure of dialysis which depends on the type of membrane and the duration of the dialysis. Convection is the process that removes toxin during dialysis by ultrafiltration of plasma water from the blood compartment as the result of controlled pressure difference across a semi-permeable membrane which permits water movement through the membrane pores.

Time Required for HD

Dialysis may be required from once every 2 days to 3 times a week with each treatment period lasting 2 to 4 hours.
The time required for dialysis depend upon:

- Amount of residual renal function in the patient.
- Any complicating illness (e.g., DM).
- The size and weight of the patient including muscle mass.
- The efficiency of the dialysis process.

**Drug Administration in HD Patients**

One approach to a dosage adjustment is to replace the amount lost in the dialysate during the treatment period.

This amount can be calculated from the following equation,

\[ \text{Fraction of drug initially in body eliminated by dialysis} = F_D \cdot \left[1 - e^{-k_D \tau}\right] \]

Eq. 1

The amount in the body at the start of dialysis is known from \( V \cdot C_0 \).

A more appealing approach is to restore the amount in the body at the end of dialysis to the value that would have occurred had the patient not been dialyzed. This amount is calculated as follows, the amount remaining in the body at time \( \tau \) had no dialysis been employed is \( V \cdot C_0 e^{-k \tau} \).

The corresponding amount when dialysis is employed is \( V \cdot C_0 k_D \tau \).

The difference between these two terms provides an estimate of the supplemental dose needed to achieve the objective.

\[ \text{Supplementary dose} = V \cdot C_0 \left[ e^{-k \tau} - e^{-k_D \tau}\right] \]

Eq. 2

**Pharmacokinetic Modeling**

The pharmacokinetic model for drugs in patients under going intermittent hemodialysis generally follows one of two patterns:

1. **Maintenance drug dose procedures**
   - Plasma concentrations that are relatively constant between dialysis periods.

This plasma concentration of drug represents the steady-state condition. The rapid decline in the drug concentration corresponds to periods of hemodialysis and the rapid return of the plasma drug concentration to steady-state reflects the administration of a post dialysis replacement dose. This pattern can be represented by the following equations.

\[ C_{\text{PSSAve}} = \frac{(S) (F) \left( \frac{\text{Dose}}{\tau}\right)}{\text{CL}_{\text{pat}}} \]

Eq. 3

This equation is used to predict a steady state plasma concentration produced by a maintenance drug dose if the dosing interval \( (\tau) \) is considerably shorter than patient specific half-life.

Where,

- \( C_{\text{PSSAve}} \) = Steady state plasma concentration.
- \( S = \text{salt form.} \)
- \( F = \text{bioavailability.} \)
- \( \tau = \text{dose interval.} \)
- \( \text{CL}_{\text{pat}} = \text{drug clearance exhibited by the patient during the nondialysis periods.} \)

\[ D_m = \frac{\left( C_{\text{PSSAve}} \left( \frac{\text{CL}_{\text{pat}} (\tau)}{(S)(F)}\right)\right)}{\left( C_{\text{PSSAve}} \left( \frac{\text{CL}_{\text{pat}} (\tau)}{(S)(F)}\right)\right)} \]

Eq. 4

\( D_m = \text{maintenance dose, replaces the amount of drug lost due to the patient ability to eliminate drug.} \)

The patient may also require additional doses following dialysis to replace the drug lost during the dialysis period.
Post Dialysis

Replacement Dose = \( v_d \left( C_{pssAve} \right) \left( 1 - e^{-\left( K_d T_d \right) / T_d} \right) \)

Eq.5

\( K_d = \frac{C_{\text{pat}} + C_{\text{D}}}{V_d} \)

Where

\( \left( V_d \left( C_{pssAve} \right) \right) \) The amount of drug in the body prior to dialysis

\( 1 - e^{-\left( K_d T_d \right)} \) Fraction of drug lost during dialysis

\( k_d = \) elimination rate constant during dialysis

\( C_{\text{pat}} = \) patient's clearance

\( C_{\text{D}} = \) clearance by dialysis

\( V_d = \) volume of distribution

\( T_d = \) duration of dialysis

If the patient's maintenance dose given once daily, then the patient's dose would be calculated using equation 4 on non dialysis days and on dialysis days, the patient's daily dose would be the sum of equations 4 and 5.

2. A single dose is given at the conclusion of each dialysis period

Significant amounts of drug are lost between dialysis periods and additional drug is lost during dialysis. The replacement dose administered at the end of dialysis replaces all of drug lost by the patient's own clearance as well as by dialysis clearance and returns the drug level to a critical concentration. This replacement dose can be calculated by use equation 6.

Post Dialysis

replacement Dose = \( v_d \left( C_{psspeak} \right) \left[ 1 - \left( e^{-\left( K_d T_d \right) / T_d} \right) \right] \)

Eq.6

Where

\( t_1 = \) interdialysis period.

\( T_d = \) dialysis period.

\( K_d_{\text{pat}} \) and \( K_d \) are the elimination rate constants during the inter- and intra-dialysis periods, respectively.

In some cases it may be appropriate to calculate the drug concentrations at the beginning and end of the dialysis period by using the following equations

Pre-dialysis drug conc. = \( C_{\text{PSS peak}} e^{-\left( \frac{C_{\text{pat}} T_d}{V_d} \right)} \)

Eq.7

Post-dialysis drug conc. = \( C_{\text{PSS peak}} e^{-\left( K_d T_d \right)} \)

Eq.8

Estimating Drug Dialyzability

To determine the dialyzability of drug, the apparent volume of distribution, plasma protein binding, the patient's clearance and the drug's half-life should be considered.

1. Apparent Volume of Distribution

To calculate the apparent unbound volume of distribution against which the drug will be dialyzed is by dividing the volume of distribution by alpha (\( \alpha \))

Or the usual free fraction

\( \text{Unbound volume of distribution} = \frac{V_d}{\alpha} \)

Eq.9

2. Estimate the patient's clearance
If the value exceeds 500-700 ml/min, it is unlikely that hemodialysis will add significantly to this clearance value. During the interdialysis period, the patient's total body clearance is very low and the drug concentration declines slowly.

3. Elimination half-life

The elimination half life for the drug in the patient off dialysis is related to the remaining total body clearance (\( CL_T \)) and the volume of distribution (\( V_d \))

\[
t_{1/2} = \frac{0.693 V_d}{CL_T} \quad \text{Eq.10}
\]

Drugs that are easily dialyzed will have a high dialysis clearance (\( CL_D \)) and the elimination half-life will be shorter in the patient on dialysis.

\[
t_{1/2} = \frac{0.693 V_d}{CL_T + CL_D} \quad \text{Eq.11}
\]

\[
K_{ON} = \frac{CL_T + CL_D}{V_d} \quad \text{Eq.12}
\]

Where \( K_{ON} \) is the first-order elimination half-life of the drug in the patient on dialysis.

The fraction of drug lost due to elimination and dialysis may be estimated from equation 13 which based on first-order drug elimination and substitution of \( t \) hours for the dialysis period.

\[
\text{Fraction drug lost} = 1 - e^{-\frac{(CL_T + CL_D)}{V_d} t} \quad \text{Eq.13}
\]

Eq. 13 shows that as the \( V_d \) increases, the fraction of drug lost decreases.

eg. The fraction of drug lost during 4 hours dialysis period for phenobarbital and salicylic acid are more than digoxin and phenytoin because Phenobarbital and salicylic acid have smaller volumes of distribution and smaller molecular weights and aqueous solubility.

**Dialysis clearance**

The most useful concept when dealing with dialysis of drug is clearance. Dialysis clearance is a measure of how effectively a dialyzer can remove a drug from blood. Dialysis clearance \( CL_D \), based on drug concentration in plasma entering the dialyzer \( C_{in} \).

\[
CL_D = \frac{C_{b,in}}{C_{in}} \quad \text{Eq.14}
\]

At steady state, the rate of removal relative to the concentration in the blood entering the dialyzer can be determined in several ways:

A. Extraction from blood
B. Rate of recovery in dialysate
C. Amount recovered in dialysate

**A. Extraction from blood**

This method is by taking the difference between the rates at which the substance enters \( (Q_{b,in} \cdot C_{b,in}) \) and leaves \( (Q_{b,out} \cdot C_{b,out}) \) the dialyzer.

\[
CL_{bd} = \frac{(Q_{b,in} \cdot C_{b,in} - Q_{b,out} \cdot C_{b,out})}{C_{b,in}}
\]

Where,

\( CL_{bd} \) Dialysis blood clearance

\( Q_{b,in} \) and \( Q_{b,out} \) Are the blood flows

\( C_{b,in} \) and \( C_{b,out} \) Are the concentrations in the arterial blood entering and venous blood leaving the dialyzer.

The values of \( Q_{b,in} \) and \( Q_{b,out} \) are not exactly equal, as there is often a 2 to 3 L loss of fluid during a typical 3 to 4 hr dialysis period. The
value of $Q_{b,in}$ is now determined accurately with flow sensors. The value of $Q_{b,out}$ is calculated by multiplying $Q_{b,in}$ by the ratio of hematocrit values across the dialyzer.

**B. Rate of recovery in dialysate**

By using the net rate at which the substance leaves in the dialysate fluid

$$Q_{D,out} \cdot C_{D,out} - Q_{D,in} \cdot C_{D,in}$$

where $Q_{D,out}$ and $Q_{D,in}$ are the dialysate flows leaving and entering the dialyzer.

$C_{D,out}$ and $C_{D,in}$ are the respective concentration.

$$\frac{CL_{bD}}{C_{b,in}} = \frac{(Q_{D,out} \cdot C_{D,out} - Q_{D,in} \cdot C_{D,in})}{C_{b,in}} \quad \text{Eq.15}$$

At the common nonrecirculating (single-pass) dialysis system, $C_{D,in} = 0$

$$CL_{bD} = \frac{Q_{D,out} \cdot C_{D,out}}{C_{b,in}} \quad \text{Eq.16}$$

**C. Amount recovered in dialysate**

Generally the most accurate method of determining dialysis clearance is to calculate the ratio of amount recovered in the dialysate ($V_a \cdot C_a$) to the area under the arterial blood concentration-time curve within the collection period.

$$CL_{bD} = \frac{V_D \cdot C_D}{\int_0^\tau C_{b,in} \cdot dt} \quad \text{Eq.17}$$

Where $V_d$ is the volume of dialysate collected during the interval $\tau$.

$C_D$ is the drug concentration in the dialysate after mixing.

Dialysis clearance depends on the dialysis system, the fraction unbound in blood and the molecular size of the substance. A likely value can be predicted from

$$\text{Blood clearance} = \text{Dialysis clearance} \cdot \frac{113}{\text{M.W.}} \cdot f_{ub}$$

**Eq.18**

$$\text{Plasma clearance} = \text{Dialysis clearance of creatinine} \cdot \frac{113}{\text{M.W.}} \cdot f_u$$

**Eq.19**

where $f_{ub}$ is the fraction unbound in blood, $f_u$ is the fraction unbound in plasma.

Because protein binding is often altered in dialysis patients, a more useful parameter than blood or plasma dialysis clearance is unbound dialysis clearance

$$\text{Unbound clearance} = \text{Dialysis clearance} \cdot \frac{113}{\text{M.W.}}$$

**Eq.19**

The dialysis clearance of creatinine, a readily dialyzable endogenous compound not bound to plasma proteins, is a means of assessing the capability of a given dialysis system to remove drug from the body. With current dialyzer, dialysis clearance values for creatinine are usually between 80 and 200ml/min. the unbound dialysis clearance for drugs and most other substances are usually lower than this because their molecular weights are greater than that of creatinine (113 g/mole) and in the case of dialysis clearance because they are often bound to plasma proteins or blood cells

**Extraction coefficient**

Under steady state condition, rate of removal relative to the rate of presentation is a measure of the efficiency of a dialysis system.
Dialysis clearance and efficiency are measures of the ability of the dialyzer to remove drug from blood, but they don't indicate how readily it is removed from the body.

**Drug elimination**

During dialysis, drug is removed by the dialyzer and by the body's own elimination mechanism therefore

\[
\text{Rate of elimination from body during dialysis} = (CL_u + CL_{u_d}) \cdot Cu \quad \text{Eq. 21}
\]

If the clearance is values are constant with time then on integration, the unbound concentration at any time \( t \) after starting dialysis is

\[
Cu = Cu_o \cdot e^{K_u \cdot t} \quad \text{Eq. 22}
\]

Where \( Cu_o \) is the unbound drug concentration in blood at the start of dialysis

\( K_D \) is the elimination rate constant during dialysis = \( [(CL_u + CL_{u_d})/V_a] \)

\[
e^{-K_D \cdot t} \quad \text{is the fraction of drug remaining at the end of dialysis period } t.
\]

So,

\[
\text{Fraction lost from body during dialysis period} = 1 - e^{-K_D \cdot t} \quad \text{Eq. 23}
\]

The contribution of dialysis to total drug elimination remains to be determined. Of the total drug eliminated during a dialysis period, the fraction removed by dialysis \( f_D \)

\[
f_D = \frac{CL_{u_d}}{(CL_u + CL_{u_d})} \quad \text{Eq. 24}
\]

Fraction of drug initially in body eliminated by dialysis = \( f_D \cdot [1 - e^{-K_D \cdot t}] \) \quad \text{Eq. 25}

**Hemodialysis Adequacy**

To see whether dialysis is removing enough urea, the clinic should periodically—normally once a month—test a patient’s blood to measure dialysis adequacy.

Blood is sampled at the start of dialysis and at the end. The levels of urea in the two blood samples are then compared. Two methods are generally used to assess dialysis adequacy, URR and Kt/V.

**What Is the URR?**

The reduction in urea as a result of dialysis, or the URR, is one measure of how effectively a dialysis treatment removed waste products from the body. URR stands for urea reduction ratio, but it is commonly expressed as a percentage.

\[
URR = \frac{\text{initial level - postdialysis level}}{\text{initial level}} \cdot 100 \quad \text{Eq. 26}
\]

It has been shown that patients generally live longer and have fewer hospitalizations if the URR is at least 60 percent. The URR is usually measured only once every 12 to 14 treatments, which is once a month. But on average the URR should exceed 65 percent.

**What Is the Kt/V?**

The other way to measure dialysis adequacy is the Kt/V. In this measurement \( K \) stands for the dialyzer clearance (mL/min), and \( t \) stands for time. The Kt represents the volume of fluid completely cleared of urea during a single treatment and \( V \) is the volume of water a patient’s body contains.

The Kt/V is mathematically related to the URR but Kt/V takes two additional factors:
(1) Urea generated by the body during dialysis
(2) The extra urea removed during dialysis along with excess fluid.
However, patients who lose more weight during dialysis will have a higher Kt/V for the same level of URR.
The patient information must be provided for the formula for a comprehensive Kt/V to be calculated. The more data supplied and used in the calculation the more accurate it will be.

The primary data that will be requested for each patient for the Kt/V calculation is:
· Patient-specific demographics as height, age, sex
· Estimated dry weight (EDW)
· Pre weight
· Post weight
· Blood Flow Rate (delivered)
· Dialysate (delivered)
· Dialyzer (type and size)
· Treatment Duration
· Hematocrit

How Does the Kt/V Compare with the URR?
On average, a Kt/V of 1.2 is equivalent to a URR of about 63 percent. The standard adopted by the Dialysis Outcomes Quality Initiative (DOQI) group. The average Kt/V should be at least 1.2. In some patients with large fluid losses during dialysis, the Kt/V can be greater than 1.2 with a URR slightly below 65 percent (in the range of 58 percent to 65 percent). In such cases, the DOQI guidelines consider the Kt/V to be the primary measure of adequacy.

Is a Kt/V of 1.2 Good Enough?
The studies generally showed that patients with lower Kt/V and/or URR numbers had more health problems and a greater risk of death.

What Should done if the Kt/V is Below 1.2 or if the URR Is Below 65 Percent?

1. If the Kt/V is always above 1.2 and the URR is close to 65 percent (it may be a few points lower if patient have large fluid losses during dialysis), then the treatment is meeting adequacy guidelines.
2. If your average Kt/V is consistently below 1.2, Since the V value is fixed (it represents the total volume of water in the body), Kt/V can be improved either by increasing K (clearance) or t (session length). To increase t, a longer period dialysis is needed.
The other way to improve the Kt in Kt/V is to increase K, the dialyzer clearance, which depends primarily on the rate of blood flow through the dialyzer.
If the blood flow rate is good, we can get further improvements in clearance.
A few centers are even using two dialyzers at the same time to increase K in large patients. However, the rate of blood flow through the dialyzer is the key, and a good vascular access is very important to make sure we are getting good clearance.

3. If during any given month the Kt/V is very low, the measurement should be repeated, unless there was an obvious reason for the low Kt/V.

Obvious reasons include treatment interruption, problems with blood or solution flow, and some problem in sampling the pre- or postdialysis blood.
If there is no clear-cut reason for the sudden drop, then a problem with needle placement, like accidental needle reversal, or with the vascular access, like recirculation, should be suspected.

Major Component of Dialysis Prescription
- Choose a biocompatible membrane
- Prescribe a Kt/V ≥1.2 or a URR 6.5 %
- Rigorously ensure that the delivered dose equals the amount prescribed
- When the delivered dose is less than that prescribed do the following:
- Increase blood flow rate ≥400 mL/min.
- Increase dialysate flow rate to ≥800 mL/min.
- Use a high-efficiency dialyzer
- Increase treatment time

- Choose dialysate composition: sodium, potassium, bicarbonate, and calcium
- Adjust ultrafiltration rate to achieve patients’ dry weight (assess dry weight regularly)
- Adjust recombinant erythropoietin to maintain hematocrit between 33% and 36%
- Use normal saline, hypertonic saline, or mannitol for treatment of intradialytic hypotension.

All these components are important as contributors to a successful dialysis prescription. The Dialysis Outcomes Quality Initiative (DOQI) recommendations should be followed to achieve an adequate dialysis prescription, and the time on dialysis should be monitored carefully. When the delivered dialysis dose is less that prescribed, the reversible factors should be addressed first.

Factors resulting in a reduction of the prescribed dose of hemodialysis delivered

- Compromised urea clearance
- Access recirculation
- Inadequate blood flow from the vascular access
- Dialyzer clotting during dialysis (reduction of effective surface area)
- Blood pump or dialysate flow calibration error
- Reduction in treatment time
- Premature discontinuation of dialysis for staff or unit convenience
- Premature discontinuation of dialysis per patient request
- Delay in starting treatment owing to patient or staff tardiness
- Time on dialysis calculated incorrectly

- Laboratory or blood sampling errors
- Dilution of predialysis BUN blood sample with saline
- Drawing of predialysis BUN blood sample after start of the procedure
- Drawing postdialysis BUN >5 minutes after the procedure
- Each of the factors listed may play a major role in the reduction of delivered dialysis dose

The frequency of measurement of the delivered dose of hemodialysis should be increased when:

- Patients are noncompliant with their hemodialysis prescriptions (missed treatments, late for treatments, early sign-off from hemodialysis treatments)
- Frequent problems are noted in delivery of the prescribed dose of hemodialysis (such as variably poor blood flows, or treatment interruptions because of hypotension or angina pectoris)
- Wide variability in urea kinetic modeling results is observed in the absence of prescription changes
- The hemodialysis prescription is modified.

Representative drugs for which supplemental doses postdialysis may be required in patients undergoing hemodialysis

- Aminoglycosides
- Other Antimicrobial Agent
  Chloramphenicol, Isoniazid, Flucytosine
- Cephalosporin
  Cefamandol, Cefazolin, Cephalexin
- Immunosuppressive Agent
  Cyclophosphamide, Methotrexate, 5-Fluorouracil
- Penicillin
  Amoxycillin, Ampicillin, Carbenicillin
- Penicillin-G

- **Miscellaneous**
  - Disopyramide, Phenobarbital
  - Theophylline

**Vancomycin in intermittent hemodialysis**

Renal excretion of vancomycin is altered in patients with renal insufficiency. In anephric patients, the average vancomycin elimination half-life is increased to 7.5 days, whereas it is 4–6 hours in normal renal function patients. It has also been reported that total body clearance of vancomycin is correlated with creatinine clearance in patients with altered renal function. Although it is clear that renal clearance of vancomycin is decreased in patients with renal failure, it has also been suggested that nonrenal clearance of vancomycin, which usually accounts for approximately 30% (40 ml/min) of total clearance in patients with normal renal function, is reduced to as low as 5–6 ml/min in patients with terminal renal insufficiency.

The accumulation of unchanged active drug of vancomycin in plasma is likely to occur because both renal and nonrenal clearances are reduced in patients with impaired renal function. For this reason, adjustment of vancomycin dosage in patients with renal impairment should be accompanied by monitoring of plasma vancomycin levels to avoid toxicity. The relationship between vancomycin-induced ototoxicity and plasma concentration of the drug is still undergoing investigation. However, vancomycin-induced nephrotoxicity has been clearly related to drug plasma concentrations. Several studies have been reported. The two major elements that can be concluded from analysis of these studies are as follows: vancomycin is not significantly dialyzable when hemodialysis is performed using a low flux membrane such as cuprophan; and vancomycin is significantly dialyzable when hemodialysis is performed using a high flux membrane such as polysulfone, polyacrylonitrile and polymethylmethacrylate.

Studies of the pharmacokinetics of vancomycin in patients undergoing hemodialysis with high flux membranes demonstrated that there is a rebound in vancomycin plasma concentrations at the end of the session. The plasma profile of vancomycin concentrations versus time indicates that concentrations decrease dramatically during the session and then increase when the session is stopped for 3–6 hours. This rebound may result from drug recirculation from plasma protein binding sites. Recirculation from peripheral compartments is less likely to occur because of the low vancomycin volume of distribution, indicating that the drug remains mainly in plasma. This rebound may be clinically significant, and it must be taken into account when determining vancomycin trough levels. Subsequently, it is recommended that determination of vancomycin trough levels in patients undergoing chronic haemodialysis should be performed before the haemodialysis session.
References


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