Drug Therapy for CKD patients

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Take Home Messages

- CKD results in minimal alterations in the absorption or bioavailability of most drugs.
- The Vd of many drugs is increased in the presence of AKI and CKD as a consequence of volume expansion and/or decreased protein binding.
- The expected decrement in renal clearance, nonrenal clearance (e.g. GI and hepatic drug metabolism and transport) of several drugs is also decreased in CKD patients.
- Individualization of a drug dosage regimen for a patient with impaired kidney function is based on the PD/PK characteristics of the drug, the patient's degree of residual renal function, and their overall clinical condition.

Take Home Messages

- The drug dosing guidelines for CKD patients in many drug information resources are highly variable and may are not optimal for clinical use.
- The effect of HD or PD on drug elimination is dependent on the characteristics of the drug and the dialysis prescription.
- HD clearance data can be used to guide the initial drug dosage regimen recommendation; however, prospective monitoring of serum concentrations is often warranted especially for narrow therapeutic index drugs.

PK Changes: Absorption

- The absorption and bioavailability of some drugs is highly variable in CKD patients.
- The mechanisms are multifactorial and include DI, delayed gastric emptying, and decreased gastric acidity.
- Decreased GI motility 2nd to gastroparesis in patients with DM may delay the t_{max} and may also reduce the C_{max}.
- Urea retention results in a high influx of urea into the gut, results in conversion to ammonia by gastric urease which increase in gastric pH. That may alter the dissolution or ionization properties of weakly basic drugs such as diazepam leading to changes in absorption.

PK Changes: Absorption

- A decrease in gastric acidity (increase in GI pH) associated with the concomitant administration of antacids, H2-receptor antagonists, PPI and phosphate binders has been associated with a lower bioavailability of several ATB and digoxin.
- Since CKD patients are frequently taking many medications, the associated DI will impact the absorption.
- Edema of the GI tract 2nd to cirrhosis or CHF can also decrease the absorption of some medications e.g. oral furosemide.

PK Changes: Absorption

- The bioavailability of only a few drugs (e.g. Felodipine, Sertraline and Cyclosporine) has been increased in CKD patients.
- The mechanism is a decrease in metabolism during the drug's first pass through the GI tract and liver.

PK Changes: Distribution

- The Vd of many drugs is increased in G3a, G3b, G4 and G5 CKD patients and those with preexisting CKD who develop AKI and can lead to a decrease in serum drug concentration.
- The increase in Vd may be the result of pathophysiologic alterations in body composition, fluid overload 2nd to excessive fluid administration or intake, decreased protein binding or increased tissue binding.
- Variability in fluid status is a common issue in patients with severe CKD (G4-5), especially those that are critically ill.
- Many critically ill patients receive large volumes of IV fluids for resuscitation from shock and can subsequently develop edema, pleural effusions or ascites.

Drug	Normal (L/kg)	ESRD (L/kg)	Change from Normal
Increased			
Amikacin	0.20	0.29	45%
Cefazolin	0.13	0.17	31%
Cefoxitin	0.16	0.26	63%
Ceftriaxone	0.28	0.48	71%
Cefuroxime	0.20	0.26	30%
Doripenem	0.25	0.47	88%
Dicloxacillin	0.08	0.18	125%
Erythromycin	0.57	1.09	91%
Furosemide	0.11	0.18	64%
Gentamicin	0.20	0.32	60%
Isoniazid	0.60	0.80	33%
Minoxidil	2.60	4.90	88%
Naproxen	0.12	0.17	42%
Phenytoin	0.64	1.40	119%
Trimethoprim	1.36	1.83	35%
Vancomycin	0.64	0.85	33%

Drug	Normal (L/kg)	ESRD (L/kg)	Change from Normal
Decreased			
Atenolol	1.20	0.90	25%
Chloramphenicol	0.87	0.60	31%
Ciprofloxacin	2.50	1.95	22%
Digoxin	7.30	4.00	45%
Ethambutol	3.70	1.60	57%
Methicillin	0.45	0.30	33%
Metoprolol	5.60	1.00	82%
Pindolol	2.10	1.10	48%
Propranolol	4.40	3.60	18%

PK Changes: Distribution

Effect of Plasma Protein Binding:

- Many drugs have been reported to exhibit altered protein binding in CKD patients.
- Only unbound or "free" drug is able to cross cellular membranes and distribute outside the vascular space.
- The result of a decrease in protein binding is an increase in the apparent Vd.
- Thus, the effect is an alteration in the relationship between total drug concentration and pharmacodynamic effect e.g. phenytoin.

PK Changes: Distribution

Effect of Plasma Protein Binding: Phenytoin

- Protein binding: 90%, primarily to albumin
- Protein binding of phenytoin is significantly decreased 2nd to decreased plasma phenytoin binding affinity for albumin, as well as low serum albumin.
- The resulting increase in unbound fraction (10% in normal kidney to > 20% in CKD-5) results in increased hepatic clearance and decreased total concentrations.
- Thus, in patients with CKD, the therapeutic range based on total phenytoin concentration is shifted down ward from 10-20 mg/L to 4-8 mg/L.

PK Changes: Distribution

Effect of Plasma Protein Binding: Phenytoin

- The total phenytoin concentration that would be observed in CKD-5 patients:

- $C_{total\ normal\ binding} = C_{total\ reported}/[(0.9)(0.48)(albumin/4.4)] + 0.1$

PK Changes: Distribution

Effect of Tissue Binding:

- This is relatively rare and limited to few drugs such as pindolol, ethambutol and most notably digoxin.
- The Vd of digoxin is decreased by up to 50% in patients with CKD-5, leading to elevated serum concentrations.
- Thus in CKD patients (esp. G5), a "normal" total [drug] may be associated with either an adverse reaction 2nd to elevated unbound [drug], or a subtherapeutic response because of an altered plasma-to-tissue [drug] ratio.
- The monitoring of unbound [drug] in CKD patients is warranted for drugs with a narrow therapeutic range, highly protein bound and variability in the unbound fraction.

PK Changes: Distribution

Effect of Vd Calculation Method:

- The 3 most commonly used Vd terms are
  - The central compartment (V_c)
  - Volume of the terminal phase (V_β)
  - Volume of distribution at steady state (V_{ss})
- Vc for many drugs approximates extracellular fluid volume thus may be increased or decreased by acute changes.
- V_β represents the proportionality constant between plasma concentrations in the terminal elimination phase and the amount of drug remaining in the body. It is affected by both distribution characteristics and by the terminal elimination rate constant.

PK Changes: Distribution

Effect of Vd Calculation Method:

- V_{ss} has the advantage of being independent of drug elimination, it is the most appropriate volume term to use when one desires to compare drug distribution volumes between patients with impaired kidney function and those with normal kidney function.
- V_β and V_{ss} will often be similar in magnitude, with V_β being slightly larger.

PK Changes: Elimination

Renal Clearance:

- The term "kidney function" includes the combined processes of glomerular filtration, tubular secretion and reabsorption and endocrine and metabolic functions.
- Reduction in kidney mass, the number of functioning nephrons, renal contribute to the decreased renal excretory capacity observed in those with CKD.
- Renal clearance (CL_R) of a drug is the composite of GFR, tubular secretion and reabsorption.
- $CL_R = [GFR \times fu] + [CL_{secretion} - CL_{reabsorption}]$
  - fu = fraction of the drug unbound to plasma proteins

PK Changes: Elimination

Renal Clearance:

- Drug elimination by filtration occurs by diffusion; while tubular secretion and reabsorption are bidirectional processes that involve carrier-mediated renal transport systems.
- Several drugs are actively secreted by one or more of these transporter:
  - Organic cationic e.g. famotidine, trimethoprim, dopamine
  - Organic anionic e.g. ampicillin, cefazolin, furosemide
  - Nucleoside e.g. zidovudine
  - P-glycoprotein (Pgp) transporter e.g. digoxin, vinca alkaloids, steroids
- For drugs that are primarily filtered, a decrease in GFR will in result in a proportional decrease in renal drug clearance.

PK Changes: Elimination

Non-Renal Clearance:

- CLNR encompasses all routes of drug elimination, excluding renal excretion of unchanged drug, and includes hepatic and extrahepatic metabolism and altered transcellular transport pathways.
- It is mediated largely by kidney disease effects on many cytochrome P450 (CYP) metabolic enzymes e.g. CYP3A, and transporters including Pgp, organic anion-transporting polypeptides (OATPs), and multidrug resistance-associated proteins in the GI tract and hepatobiliary system.

Drug Name	Decreased Change in CL_{NR}
Acyclovir	50%
Aztreonam	33%
Bupropion	↓
Captopril	50%
Carvedilol	↓
Cefotaxime	40%
Ceftriaxone	↓
Cimetidine	46%
Ciprofloxacin	33%
Doripenem	↓
Erythromycin	↓
Imipenem	58%
Isoniazid	↓
Ketorolac	↓
Losartan	↓
Lovastatin	↓
Metoclopramide	66%
Minoxidil	46%
Morphine	40%
Nicardipine	37%

PK Changes: Elimination

Alterations of CYP enzyme activity and transporters:

- CKD may lead to alteration in CL_{NR} due to changes in the activities of uptake and efflux transporters as well as CYP enzymes in the liver an other organs.
- Higher residual CL_{NR} for vancomycin, meropenem and imipenem has been documented in patients with AKI compared to CKD patients who have comparable CLcr.

PK Changes: Elimination

Accumulation of Metabolites:

- G4 and G5 CKD patients who are receiving chronic drug therapy May experience significant accumulation of metabolite(s) as well as the parent compound if their ultimate route of elimination is via glomerular filtration.
- The metabolite may have pharmacologic activity and contribute significantly to clinical response.
- In CKD patients, morphine is metabolized more slowly, and these active metabolites increase, making prolonged narcosis and respiratory depression.
- Normeperidine (metabolite) has CNS stimulatory activity that reportedly produces seizures.

PD

- For concentration-dependent antibiotics such as FQs or AMG, a high ratio of the peak serum concentration to the minimum inhibitory concentration (MIC) has been associated with increased likelihood of clinical success.
- For time-dependent antibiotics such as CEP, the percentage of the dosing interval spent above the MIC is the most important PD parameter to maximize clinical success.

PD

- CKD can affect multiple organ systems and consequently the response to a given drug may change beyond that predicted upon PK changes alone.
- Enoxaparin dosage reduction is required in G4-5 CKD patients due to the accumulation of uremic toxins which results in complex disturbances of the coagulation system leading to and increase in bleeding.
- Successful ATB or antiviral treatment of CKD patients requires not only consideration of PK profiles, but also the drugs' PD, which links measures of drug exposure (e.g. peak trough serum concentrations and AUC).

Estimation of Kidney Function for Drug Dosage Regimen

- The Cockcroft & Gault (CG) equation has been the most commonly used method for over 40 years.
- The Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) have been developed primarily for the identification and classification of CKD patients.
- The automated reporting of eGFR in the clinical setting has led some practitioners to consider substituting in place of eCLcr for renal dose adjustments.

Estimation of Kidney Function for Drug Dosage Regimen

- Average discordance rates for the MDRD and CG equations were between 20-30%.
- The overall discordance rates were 15-25% between CG and CKD-EPI and 7-12% between MDRD and CKD-EPI.
- Serum cystatin C has been an alternative marker to estimate GFR, either alone or in combination with serum creatinine.
- None of these equations for estimating GFR should be use as the sole determinant for drug dosing decision making.
- Drug dosing regimens necessitate careful consideration of the risk: benefit ratio.

Estimation of Kidney Function for Drug Dosage Regimen

- Most drug dosage regimen recommendations are based on eGFR (mL/min)/1.73m² (BSA), thus the BSA must be determined separately. So that the eGFR can be expressed in mL/min.
- Resources:
  - KDIGO classification
  - Aronoff's Drug Prescribing in Renal Failure
  - The Renal Drug Handbook
  - Lexicomp
  - Micromedex
  - American Hospital Formulary Service (AHFS)

Drug	Total Body Clearance[a]
Acyclovir	$CL = 3.37 (CL_{cr}) + 0.41$
Amikacin	$CL = 0.6 (CL_{cr}) + 9.6$
Aztreonam	$CL = 0.8 (CL_{cr}) + 26.6$
Cefazolin	$CL = 0.34 (CL_{cr}) + 6.6$
Ceftazidime	$CL = 1.15 (CL_{cr}) + 10.6$
Ciprofloxacin	$CL = 2.83 (CL_{cr}) + 363$
Digoxin	$CL = 0.88 (CL_{cr}) + 23$
Ganciclovir	$CL = 1.24 (CL_{cr}) + 8.57$
Gentamicin	$CL = 0.983 (CL_{cr})$
Imipenem	$CL = 1.42 (CL_{cr}) + 54$
Lithium	$CL = 0.20 (CL_{cr})$
Ofloxacin	$CL = 1.04 (CL_{cr}) + 38.7$
Piperacillin	$CL = 1.36 (CL_{cr}) + 1.50$
Tobramycin	$CL = 0.801 (CL_{cr})$
Vancomycin	$CL = 0.69 (CL_{cr}) + 3.7$

Estimation of Kidney Function for Drug Dosage Regimen

- If specific recommendation and/or the relationship of kinetic parameters to estimated GFR or CLcr are not available, then we can estimate CL or k of the CKD patient with the method of Rowland and Tozer.

$$Q = 1-[f_e(1-KF)]$$

- Q = kinetic parameter/dosage-adjustment factor
- f_e = the fraction of the drug that is eliminated renally unchanged
- KF = ratio of the patient's eCLcr or eGFR to the assumed normal value of 120 mL/min

Estimation of Kidney Function for Drug Dosage Regimen

- **Example:** If Drug A is 85% eliminated renally unchanged in a patient who has an eCLcr of 10 mL/min, what is the Q factor

$$Q = 1-[f_e(1-KF)]$$

$$Q = 1-[0.85[1-(10/120)]]$$
$$= 1-[0.85\times0.92]$$
$$= 1-0.78$$
$$= 0.22$$

Drug Dosing Regimens for CKD patients

- The initial or "loading" dose for CKD patients should be the same as those with normal kidney function.
- If the drug's Vd is known to be altered in the presence of CKD or a concomitant disease, the dose should be increased proportionally.
- Maintenance dosage regimen guidelines for CKD patients in FDA- or EMA-approved product labeling should be the foundation for ongoing therapy.
- If information is not available or there is marked variance, the stepwise approach can be used.

Stepwise Approach

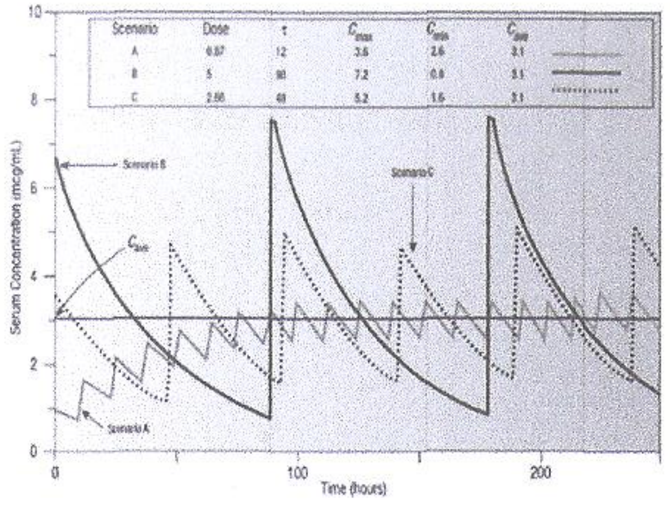
Steps	Actions
Step 1: Obtain history and relevant demographic/clinical information	Ask/obtain patient medical history: prescription medication, OTC medication, tobacco and alcohol use, history of kidney disease, Height and weight
Step 2: Determine kidney function	Measure serum creatine and/or cystatin C Determine eGFR or CLcr for drug dosing Order 24-hour urine collection if necessary
Step 3: Review the medication list	Ensure medications are all indicated Evaluate for potential DI Identify drugs which need to dosage regimen adjusted
Step 4: Individualize treatment regimen	Ascertain best initial dosage regimen For NTIs calculate dosage regimen based on PK and patient's kidney function Titrate the dose of drugs to patient effect

Stepwise Approach

Steps	Actions
Step 5: Avoid nephrotoxic drugs	Discontinue or avoid prescription of nephrotoxic medications if possible
Step 6: Monitor	Monitor drug serum concentrations (if available) to guide further therapy Monitor parameters of drug response and toxicity Monitor kidney function every 3-5 days for acute therapies and monthly or quarterly for chronic medications
Step 7: Reassess	Reassess the patient to evaluate drug efficacy and safety Revise regimen based on drug response or change in patient condition (including kidney function)

Drug Dosing Regimens for CKD patients

- The principle choices to attain the desired average steady-state concentration profile are to decrease the dose or prolong the dosing interval.



Stepwise Approach: calculating Dosage Regimen

Steps	Example: Ciprofloxacin
Step 1: calculate total body clearance of drug with normal kidney function CL_{cr} = 120 mL/min	CL_{norm} = [2.83(CL_{cr})] + 363 = [2.83 (120)] +363 = 702.6 mL/min/1.73m²
Step 2: calculate total body clearance of drug with impaired kidney function CL_{cr} = 15mL/min	CL_{fail} = [2.83(CL_{cr})] + 363 = [2.83 (15)] +363 = 405.5 mL/min/1.73m²
Step 3: calculate Q	Q = CL_{fail}/Cl_{norm} = 405.5/702.6 = 0.58
Step 4: Calculate the maintenance dose (D_f) or adjusted dosing interval (τ_f)	D_n = 500 mg; τ_n= 12 hour D_f = D_n x Q = 500 mg x 0.58 = 290 mg τ_f = τ_n x Q = 12 hour x 0.58 = 20.7 hour

Stepwise Approach: calculating Dosage Regimen

Steps	Example: Ciprofloxacin
Step 5: Choose dosing adjustment: 1. Maintain D_n and use τ_f 2. Maintain τ_n and use D_f	Dosing adjustments: 1. 500 mg every 21 hour 2. 290 mg every 12 hour
Step 6: calculate Df based on practical dosing interval (τ_p)	D_n = 500 mg; τ_f= 21 hour; τ_p = 24 hour D_f = (D_n x Q x τ_p)/ τ_n = (500 mg x 0.58 x 24hour)/12 hour = 580 mg
Step 7: Recommend dosing regimen	500 mg every 24 hour

Dosage Regimen Calculation For a Hemodialysis Patient

A 54-year-old critically ill woman with ESRD was transferred to a medical intensive care unit from the general medical unit, where she was febrile with a temperature of 39°C (102.2°F). Her weight was 64 kg (141 lb) and her height was 65 in. (165 cm). She had a residual CL_{cr} of 5 mL/min (0.083 mL/s), and was receiving high-flux dialysis (F80 polysulfone dialyzer) for 4 hours on Mondays, Wednesdays, and Fridays. She was started on vancomycin for a methicillin-resistant *Staphylococcus aureus* (MRSA) catheter-associated bacteremia and her first dose of 1,000 mg was administered at the end of her HD treatment. The first step is to estimate this patient's pharmacokinetic parameters of vancomycin on the basis of published population data.[96] The V_D in this patient can be estimated to be 54.4 L (0.85 L/kg × 64 kg), and her residual total body clearance (CL_{RES}) estimated from the relationship between CL and CL_{cr} (CL_{RES} = [0.69 × CL_{cr}] +3.7) is 7.15 mL/min (0.12 mL/s) or 0.43 L/hr. The *k* can be approximated as:

$$k = CL_{RES}/V_D$$
$$= 0.43\,L/hr/54.4\,L$$
$$= 0.0079\,hr^{-1}$$

The HD clearance of vancomycin (CL_D) is dependent on the dialyzer and a value of 120 mL/min (2 mL/s; 7.2 L/hr) is a reasonable estimate for this dialyzer.[96,97]

One now can predict what the plasma concentrations of vancomycin will be over the next 24 to 48 hours, assuming the infusion time for the drug (t') was 1 hour. The concentration at the end of the 1-hour infusion (C_{max}) would be:

$$C_{max} = \frac{(Dose/t')}{CL_{RES}}(1 - e^{-kt'})$$
$$= \frac{(1000\ mg/h)}{0.43\ L/h}(1 - e^{-(0.0079)1})$$
$$= (2{,}325.6\ mg/L)(0.0078)$$
$$= 18.1\,mg/L$$

The plasma concentration prior to the next dialysis session (C_{bD}), which is 44 hours away can be calculated as:

$$C_{bD} = C_{max} \times e^{-(CL_{RES}/V_D) \times t}$$
$$= 18.1 \times e^{-0.0079 \times 44}$$
$$= 12.8\,mg/L$$

and the concentration 4 hours later after dialysis (C_{aD}) can be calculated as:

$$C_{aD} = C_{bD} \times e^{-[(CL_{RES}+CL_D)/V_D] \times t}$$
$$= 12.8 \times e^{-[(0.43+7.2)/54.4] \times 4}$$
$$= 12.8 \times e^{-0.14 \times 4}$$
$$= 7.3\,mg/L$$

On the basis of these data, the second dose which should be administered after the second dialysis session should be increased as one generally desires to maintain vancomycin trough concentrations between 15 and 20 mg/L (mcg/mL; 10-14 µmol/L) for a MRSA catheter-associated bacteremia.[98,99] The patient received a vancomycin dose of 1,500 mg 4 hours after the end of the second dialysis session. The increase in serum concentration at the end of this 1-hour infusion (C_{change}) can thus be estimated:

$$C_{change} = \frac{(Dose/t')}{CL_{RES}}(1 - e^{-kt'})$$
$$= \frac{(1500\ mg/h)}{0.43\ L/h}(1 - e^{-(0.0079)1})$$
$$= (3{,}488.4\,mg/L)(0.0078)$$
$$= 27.2\,mg/L$$

Thus, the C_{max} would be approximately 34 mg/L (mcg/mL; 24 µmol/L), the sum of the residual concentration from the first dose of approximately 7 mg/L (mcg/mL; 5 µmol/L) and the C_{change}. The plasma concentration prior to the third dialysis session (C_{bD}), which is 40 hours away can be estimated as:

$$C_{bD} = C_{max} \times e^{-(CL_{RES}/V_D) \times t}$$
$$= 34\,mg/L \times e^{-0.0079 \times 40}$$
$$= 24.8\,mg/L$$

and the concentration 4 hours later after the third dialysis (C_{aD}) can be estimated as:

$$C_{aD} = C_{bD} \times e^{-[(CL_{ns}+CL_s)/V_d] \times t}$$
$$= 24.8 \times e^{-[(0.43+7.2)/54.4] \times 4}$$
$$= 24.8 \times e^{-0.14 \times 4}$$
$$= 14.2\,\text{mg/L}$$

This higher dose would be considered by many to have achieved too high of concentrations since the lowest value during the majority of the dosing interval exceeded 24.8 mg/L (mcg/mL; 17.1 μmol/L).