Chronic Kidney Disease:
Approach to Medication Dosing

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Objectives

- Review physical and chemical changes in CKD that effect drug metabolism and action
- Understand strategies for adjusting medications to ensure safety and efficacy in CKD patients
- Recognize how dialysis modalities effect dosing of medications
- Summarize renal dosing of patients at ANW
Medications and the Kidney

- The kidney is responsible for metabolism and elimination of the vast majority of medications
- Renal excretion of parent compounds and inactive or active metabolites must be considered
- Filtration, tubular secretion, non-hepatic CYP450 metabolism, organic anion/cation transporters
Pharmacokinetics VS. Pharmacodynamics

**Pharmacokinetics**

What the body does to the drug

Example: Atenolol

**Pharmacodynamics**

What the drug does to the body
Pharmacokinetics

Absorption
- Interactions
- Extent
- Transit time

ADME

Elimination
- Drug in Urine
- Metabolites
- Other fluids

Distribution
- Blood
- Tissue
- Fluids

Metabolism
- Active
- Inactive
Pharmacokinetics of Kidney Disease

- Absorption
  - Gastroparesis or slow gut motility in diabetic patients
  - Edema of GI tract
    - Lipophilic drug absorption altered
  - Vomiting or diarrhea (uremic sx?)
  - Phosphate binder therapy
    - D-D interactions
    - Gastric pH
Pharmacokinetics of Kidney Disease

Distribution

- Change in protein binding
  - Hypoalbuminemia and proteinuria
  - Uremic toxins
  - Decreased for acidic drugs such as phenytoin, warfarin, digoxin
  - Increased for basic drugs such as quinidine, lidocaine

- Altered tissue binding

- Alteration in body composition
  - Increased volume of distribution
Pharmacokinetics of Kidney Disease

- **Metabolism**
  - Can see reduced non-renal clearance
  - Alters CYP450 mediated metabolism in liver and other organs
  - Uremic toxins?
  - Downregulation of enzymes due to chronic inflammatory state?

- **Accumulation**
  - Parent compound
  - Active metabolites
    - Meperidine
    - Procainamide
    - Morphine
Pharmacokinetics of Kidney Disease

- Excretion and Elimination
  - Increased half-lives of medications
    - Increased AUC or exposure
    - Antibiotics
    - Opioids
  - Filtration vs. tubular secretion and reabsorption
    - Consider mechanism of excretion and cause of kidney disease! (keflex and ampicillin)
Pharmacokinetic Changes in CKD

- All major pharmacokinetic characteristics are affected by CKD
- Renal replacement therapies may change your approach to dosing of medications
- In combination, these lead to a very high risk patient population for medication complications
Potential Medication Complications

- Increased half-life
- Increased area under the curve (AUC)
- Increased steady-state concentrations

Result = increased risk of potential toxicity and adverse drug reactions!
Drug-Induced Nephrotoxicity

- Intrinsic changes leading to:
  - Obstructive uropathy
    - Acyclovir
    - HIV medications (atazanavir, indinavir)
    - Sulfamethoxazole
  - Acute Tubular Necrosis/Fibrosis
    - Cyclosporine/tacrolimus
    - Aminoglycosides
    - Amphotericin B
    - Contrast media
    - Cisplatin/carboplatin
    - Foscarnet
Drug-Induced Nephrotoxicity

- Hemodynamic mediated renal failure:
  - Cyclosporine, tacrolimus, cocaine
  - ACE Inhibitors or ARBs
  - Diuretics
  - NSAIDs

- Thrombosis
  - methamphetamines

- Interstitial disease
  - Penicillins, NSAIDs, Diuretics
  - Lithium, Cyclosporine, aristolochic acid
Drug-Induced Toxicities

- **Can be avoided** with appropriate monitoring and dosage adjustments!
- Watch closely in patients with one or more nephrotoxic medication
- Very important:
  - CKD patients
  - Requiring Renal Replacement Therapy
  - Factor in dialysis treatments and residual renal function
  - Kidney Transplant Recipients
Drug Prescribing in CKD

- Determine level of kidney function
- Estimate capacity for normal metabolism
- Loading dose
- Maintenance dose
- Interactions
- Drug level monitoring
- Clinical surveillance
Estimating Kidney Function: Utilizing SCr and Equations

- 50+ different equations
- Serum creatinine used to estimate kidney function
- Equations include variables such as age, sex, race, body size in addition to SCr
  - Surrogates for muscle mass
  - Overcome SOME of the limitations of SCr alone
- Focus on Cockcroft-Gault and MDRD4 equations
Cockcroft and Gault: Stable SCr
CrCl (male) = (140 - age) x Wt (kg) x Scr (mg/dL) x 72
CrCl (female) = CrCl (male) x 0.85

Controversy regarding use of lean body weight (LBW) vs total body weight in obese patients
Estimation of Kidney Function

**MDRD**  \[
\text{GFR/1.73m}^2 = \\
170 \times [\text{Pcr}]^{-0.999} \times [\text{Age}]^{-0.176} \times [0.762 \text{ if patient is female}] \times [1.180 \text{ if patient is black}] \times [\text{BUN}]^{-0.170} \times [\text{Alb}]^{0.318}
\]

-or-

**MDRD4 (revised)**  
\[
175 \times [\text{Pcr}]^{-1.154} \times [\text{Age}]^{-0.203} \times [0.742 \text{ if patient is female}] \times [1.212 \text{ if patient is black}]
\]

Automatically reported in Excellian
Estimating Kidney Function

- **Cockcroft-Gault vs. MDRD4**
  - MDRD4 equation intended for staging CKD; underestimates function in patients with GFR > 60 ml/min/1.73 m²
  - MDRD4 result is normalized to 1.73 m²
  - Most published dosing adjustment recommendations for drug therapy are based on Cockcroft-Gault calculations
  - Both likely an overestimation of the patients GFR
    - Tubular secretion of creatinine
    - Changes in laboratory testing methods (i.e. drift)
  - **Cockcroft-Gault still preferred estimation when utilizing results for drug dosing!!**
When should I use MDRD vs C-G?

Use MDRD4 Equation
✓ Staging CKD (eGFR: mL/min/1.73m²)

But it’s not reliable in patients with GFR >60ml/min

Use C-G Equation
✓ Drug dosing (eCrCL: mL/min)

But it’s not reliable in obese patients or GFR>60ml/min
And neither equation is reliable...

- In patients with muscle wasting, amputees, severely obese or malnourished, end-stage liver failure, extremes of age, kidney donors and recipients
- For assessing kidney function when GFR > 60 mL/min/1.73m²
- Dosing toxic medications (foscarnet, cidofovir etc)

For these cases...
- Consider using 24hr urine collection?
  - overestimation by over collection/tubular secretion of creatinine
- Measure inulin, iohexol, DTPA or iothalamate clearance (Gold Standard)

Loading Dose

“Fill up the tank”

- Dependent on volume of distribution
  - Drug properties
  - Physical changes in CKD patient (protein, tissue binding, water balance)

- Increase/Decrease loading dose
  - Decreased: digoxin
    - ~half the normal loading dose is recommended
  - Increased: vancomycin
    - 15-20mg/kg vs. 25mg/kg

- Shortens time to Steady-State
Loading Dose

- **Steady-state is reached in five half-lives**
- **Example: Vancomycin**
  - Usual half life of 6 to 8 hrs- time to ss is 18-24 hrs
  - CKD half life of 18-48+ hrs- time to ss 3-5+ days
  - Under- or overdosing?
Loading Dose
AJ is a 57 y.o. 85 kg ESKD patient who presents to the ED with cough and fever. Chest XR shows left lower lobe infiltrate. Empiric antibiotics including moxifloxacin 400 mg and vancomycin 1 gm IV are given and he is sent to a medicine floor.
Loading Dose Example

- Vancomycin Vd = ~ 0.7 L/kg
- ESRD vancomycin Vd = ~0.92 L/kg

- AJ’s vancomycin peak concentration with 1 gm vancomycin = 12 mg/L
  - Recommended vancomycin trough for pneumonia is 15-20 mg/L!

- If AJ had normal kidney function, peak would be ~ 20 mg/L
Maintenance Dose Modifications in CKD

- No modification required
  - i.e., Clindamycin, azithromycin

- Modification required
  - i.e., Cephalosporins, vancomycin/aminoglycosides

- Avoid!!
  - i.e., Nitrofurantoin, metformin

Consider each and every medication your patient is taking!
Maintenance Dose

- Maintain safe and effective exposure to medication over time
- Many medications need dosing adjustment in CKD
  - Reduced dose, longer dosing interval or both
  - CRRT—may actually need *higher* than standard dosing!
  - Timing of administration in relation to intermittent dialysis
Maintenance Dose Example

- **Vancomycin**
  - Based on patient’s CrCl
  - Vanco Dettli equation
    \[
    T1/2 = 0.00083 \times (\text{CrCl}) + 0.0044
    \]

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Interval (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;65</td>
<td>12</td>
</tr>
<tr>
<td>35-64</td>
<td>24</td>
</tr>
<tr>
<td>21-34</td>
<td>48</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>Single loading dose with kinetics</td>
</tr>
</tbody>
</table>
Vancomycin Summary

- Consider loading dose in patients with GFR less than 30ml/min, or seriously ill
  - Loading dose: 20-25mg/kg (25-35mg/kg ESRD)
  - All others: 15-20mg/kg actual body weight
  - Maintenance dosing based on CrCl

- Monitoring
  - In selected patients
  - 10-15mg/L for most infections
  - 15-20mg/L for meningitis, encephalitis, pneumonia, osteomyelitis, and abscess
  - Pick a dose/interval, then adjust interval based on trough levels
Drug Interactions

- CKD patients are on average of 12-15 maintenance medications
- Need to consider both pharmacokinetic AND pharmacodynamic drug interactions
  - Drug-Drug
  - Drug-Disease State
- High risk for medication complications with number of prescriptions and providers
Drug Level Monitoring

- CKD patients often require more frequent drug level monitoring
- Important to consider timing of drug level
  - Time of last dose and lab draw
  - Relation to dialysis therapy
    - Example vancomycin
  - Free levels vs. total levels – phenytoin/valproic acid
- Utilize pharmacy services
  - Pharmacy to dose antibiotics
  - Ask questions?
Drug Level Monitoring: Example

- Phenytoin (Dilantin)
  - Decreased protein binding in CKD, (uremic toxins, protein wasting, hypoalbuminemia) increased free drug
  - Can have toxicity despite normal Total PHT levels
    - Total Phenytoin = 8mcg/mL, Free 1.8mcg/mL
    - Total Phenytoin= 16mcg/mL, Free 4.5 mcg/mL
    - Also consider free level in liver disease or hypoalbuminemia

- Note: intravenous phenytoin propylene glycol, accumulates in renal failure- arrythmias, hypotension
Clinical Surveillance

- High Risk Patient Population!
  - **Efficacy** - is the medication having the proper effect or producing the desired result?
  - **Safety** - increased vigilance in monitoring for adverse reactions and toxicity

- One dose doesn’t always fit all patients!!
  - Gabapentin, Transdermal Fentanyl
Is a Drug Dialyzable?

- Drug characteristics that affect clearance by hemodialysis
  - Molecular weight (MW)
  - Water solubility
  - Protein binding
  - Volume of distribution
Molecular Weight (MW)

High Flux Dialyzer

MW cutoff > 5,000 - 20,000 Daltons

Blood

Dialysate

Digoxin: 781 Daltons
Vancomycin: 1,486 Daltons
Gentamicin: 149 Daltons
Cefazolin: 477 Daltons
EPO: 30,400 Daltons
Water Solubility

Hydrophobic drugs won’t dialyze off:
- Diazepam
- Carbamazepine
- Trazadone

Hydrophilic drugs may dialyze off:
- Lipid
- Blood
- Dialysate
Protein Binding

High:
- Ceftriaxone (83-96%)
- Phenytoin (90-94%)
- Valproate (80-90%)

Low:
- Fluconazole (11-12%)
- Ceftazidime (5-17%)

Albumin
Blood
Dialysate
Volume of Distribution

Tissue Compartment

Plasma Compartment

Dialysis

Large Vd:
Digoxin (4-7L/kg)

Small Vd:
Gentamicin (0.25-0.5L/kg)
Factors Affecting Clearance on Dialysis

- Dialysate flow rate (stable)
- Blood flow rate (varies greatly)
  - Access dependent
    - AV graft/fistula vs. Permcath/Quinton
- Dialyzer reuse
  - Inpatient vs. outpatient
Clearance as function of Molecule Size and Blood Flow Rate
Timing: Hemodialysis

Before Dialysis:
- Midodrine

With Dialysis:
- EPO/Aranesp
- Iron sucrose
- Calcitriol or paracalcitrol
- Vanco/Cefazolin

After Dialysis:
- Cefazolin, ceftazadime, Aminoglycosides, Amoxicillin/clavulanate, penems, fluconazole
- Ranitidine, gabapentin, dialyvite/nephrocap

Either or...
- Cipro/Levofloxacin, Linezolid, Voriconazole, Metronidazole, Clindamycin, cyclosporine, MMF
- Not significantly removed by dialysis or given with frequent dosing
Peritoneal Dialysis

- Peritoneal membrane acts as dialysis membrane
  - Increased clearance of larger MW drugs
  - Inter-individual differences in clearance

- **Timing:**
  - Continuous (CAPD)
  - CCPD Intermittent/nocturnal +/- daytime dwell (Cycler)

- Less efficient than HD in fluid and solute removal
PD- Factors Affecting Diffusion

- Concentration gradient
  - Both ways, antibiotics IP vs. IV
- Molecular weight (MW)
- Membrane resistance
  - Inflammation
  - Fibrosis or scarring
  - Peritonitis- Drug Bioavailability
    - Vancomycin w/ or w/o (77-91% vs. 52-73%)
    - Gentamicin w/ or w/o (64-100% vs. 49-85%)

Conclusions

- Using knowledge of physical and chemical changes in CKD we can predict or appreciate changes in metabolism and drug action.
- Understanding strategies to improve pharmacologic management of CKD patients enhances safety and efficacy of medications.
- Pharmacists are a great resource for medication-related inquiries i.e. selection, dosing, monitoring!!!
Inpatient Pharmacist Services

- Renal dosing policy
- Pharmacy to dose
  - Vanco/Gent, TPN, Other ABX
- Antibiotic Stewardship Program
  - Anti-infective Advisory Team
- Anticoagulation services
  - Heparin, Fondaparinux, dalteparin,
  - Coumadin, JC NPSG
- IV to PO conversions
- Therapeutic interchanges/Automatic substitutions
- AMI Core Measures
- Outpatient anticoagulation services, H7000, H8000
Renal Dosing Policy

- Pharmacist will NOT automatically adjust dose if any of the following criteria are present:
  - a) Admitting diagnosis of dehydration, recommendations for adjustments should be made after consultation with the physician.
  - b) Unstable serum creatinine concentration (change in SCr > 0.3 mg/dL from two consecutive SCr values).
  - c) Vancomycin and aminoglycoside orders – w/o pharmacist to dose
  - d) DAW, specific communication regarding use of an increased/decreased dose
Renal Dosing Policy

- Antibiotics: Zosyn, fluconazole, ganciclovir, imipenem, Augmentin, Unasyn, cefepime, Cipro, etc.
- Others: famotidine, gabapentin, pregabalin, ketorlac, enoxaparin, etc.
## Pharmacy To Dose

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ROUTE</th>
<th>USUAL PRESCRIBED DOSE</th>
<th>CrCl (mL/min)</th>
<th>DOSAGE REGIMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>piperacillin/tazobactam (Zosyn®)</td>
<td>IV</td>
<td>3.375 GM Q6H</td>
<td>&gt;40</td>
<td>3.375 GM Q6H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20-40</td>
<td>2.25 GM Q6H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;20</td>
<td>2.25 GM Q8H (if on HD, give post HD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.5 GM Q8H</td>
<td>&gt;40</td>
<td>4.5 GM Q8H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20-40</td>
<td>3.375 GM Q8H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;20</td>
<td>2.25 GM Q8H (if on HD, give post HD)</td>
</tr>
<tr>
<td>ciprofloxacin (Cipro®)</td>
<td>IV</td>
<td>200-400 mg Q8-12H</td>
<td>&gt;30</td>
<td>200-400 Q 8-12 H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;30</td>
<td>200-400 Q 18-24 H (HD 400-600mg IV Q24H)</td>
</tr>
<tr>
<td></td>
<td>PO</td>
<td>250-750 mg Q12H</td>
<td>&gt;50</td>
<td>250-750 mg Q12H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30-50</td>
<td>250-500 mg Q12H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;30</td>
<td>250-500 mg 18-24H (HD 500-750 PO Q24H)</td>
</tr>
<tr>
<td>imipenem/cilastatin (Primaxin®)</td>
<td>IV</td>
<td>500 mg Q8H</td>
<td>&gt;40</td>
<td>500 mg Q8H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Higher dosage for life threatening infections)</td>
<td>20-40</td>
<td>500 mg Q12H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;20</td>
<td>250 mg Q12H</td>
</tr>
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</table>
Anti-Infective Advisory Team

- Daily Prospective chart review
  - active anti-infective orders in patients 18 or older
  - excludes Infectious Diseases consulted patients
- Recommendations made based on current guidelines and usage criteria approved by the Pharmacy and Therapeutics (P&T) Committee and the Infectious Diseases physicians
- Recommendations/Interventions
  - Change antibiotic based on lab data
  - Discontinue unnecessary antibiotic(s)
  - Parenteral to oral interchange
  - Change empiric antibiotic therapy
  - Dosage adjustment
  - Change in post-op antibiotic duration
  - Agree with current management
  - Other
Call a Pharmacist!

- Contact the decentral pharmacist

- Anti-Infective Advisory Team
  - Jessica Holt, PharmD x37508
  - Krista Berge, PharmD x37502

- Jay Eidem, PharmD
- Pharmacy Coordinator- Transplant/RMS
  - 612-654-7607 pager
  - 612-863-9134 office
Questions?