Medication Management in the Dialysis Patient

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Disclosures

- Nicole Metzger (including spouse/partner) do not have any financial relationships to disclose.
- Melissa Chesson (including spouse/partner) do not have any financial relationships to disclose.
- M. Salman Singapuri (including spouse/partner) do not have any financial relationships to disclose.

Learning Objectives

1) Describe basic pharmacokinetic and pharmacodynamic principles for the dosing of medications in patients with end stage renal disease (ESRD)
2) Identify common medications that require dose adjustment or should not be used in patients with ESRD
3) Apply basic pharmacokinetic and pharmacodynamic principles to patient scenarios

Introduction

- Diabetes, hypertension and glomerulonephritis are common causes
- ESRD is on the rise - 570,000 patients with 370,000 on hemodialysis (HD)
- 119,000 new cases in 2009 vs. 68,000 in 1994
- By 2025, 712,290 patients with have ESRD
  - 136,166 new cases and 107,760 new deaths annually
- Cost is $17 billion annually in the US

USRDS 2011
General Considerations for Dosing Medications in ESRD

- The impact of dialysis on a patient’s drug therapy is dependent on several factors
- Pharmacokinetic alterations (ADME)
  - Bioavailability
  - Volume of distribution
  - Protein binding
  - Drug metabolism and elimination
- Medication dosing in dialysis
  - Loading and maintenance dosing
- Clearance of medications
  - Dialysis factors
  - Medication-related factors

Pharmacokinetic Alterations

Bioavailability (BA): fraction of the administered dose that reaches the systemic circulation

- Factors to consider:
  - Dissolution and absorption of the chemical form
  - Dosage form
  - Route of administration
  - Stability of the active ingredient in the GI tract
  - First-pass metabolism

Pharmacokinetic Alterations

Volume of Distribution

\[
V_d = \frac{\text{Total amount of drug in the body}}{\text{Plasma concentration of drug}}
\]

Increased \( V_d \)

- Lipophilic
- Decreased plasma protein binding
- Increased tissue binding

Reduced \( V_d \)

- Hydrophilic
- Increased plasma protein binding
- Decreased tissue binding

V\(_d\) of many medications is altered in ESRD

- Extracellular fluid overload may increase the \( V_d \) of hydrophilic medications resulting in decreased serum concentrations

<table>
<thead>
<tr>
<th>Medication</th>
<th>Normal ( V_d ) (L/kg)</th>
<th>ESRD ( V_d ) (L/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>0.28</td>
<td>0.48</td>
</tr>
<tr>
<td>Furosemide</td>
<td>0.11</td>
<td>0.18</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>0.64</td>
<td>1.4</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.64</td>
<td>0.85</td>
</tr>
<tr>
<td>Digoxin</td>
<td>7.3</td>
<td>4</td>
</tr>
</tbody>
</table>
Pharmacokinetic Alterations

Protein Binding

- Plasma protein binding is a key determinant of Vd
- Renal failure may increase or decrease protein binding affecting the amount of free drug available at the site of action
- Drugs that are highly protein bound will stay in the intravascular space resulting in low Vd
- Organic acids that accumulate in ESRD with compete with acidic drugs for protein binding
- Altered concentrations of proteins
  - Decrease in albumin
  - Increase in α1-acid glycoprotein
- Drug metabolites may compete for protein binding

Pharmacokinetic Alterations

Drug Metabolism and Elimination

- Drug metabolism in dialysis patients is unpredictable
- Patients with ESRD may experience accumulation of metabolites and the parent compound
- Renal failure may lead to alterations in non-renal clearance of medications
  - Alterations in transporters
  - Alterations in CYP enzymes

Dialysis Dosing: Loading Dose

- In dialysis patients, loading doses are the same as patients with normal renal function
- Loading doses are adjusted based on Vd and not on renal function
  - If extracellular volume depletion is present, Vd may be reduced and reductions in loading dose should occur

Dialysis Dosing: Maintenance Dosing

- In dialysis patients, maintenance doses are not the same as patients with normal renal function
- Maintenance doses ensure steady-state blood concentrations and lessen the likelihood of sub-therapeutic regimens or overdoses
- There are two options to dose adjustment for ESRD
  1) Reduce the dose
  2) Widen the interval between doses
Dialysis Dosing

- Monitoring drug levels in ESRD is important for certain medications
- Consider the dose administered, timing of administration, and route of elimination of the medication
- Peak concentrations are not commonly utilized
- Trough concentrations are obtained <30 minutes prior to the next dose and reflect clearance and potential toxicity

Clearance of Medications in Dialysis

- Dialysis factors
  - Composition of dialysis filter
  - Filter surface area (i.e. pore size) and dialysis membrane composition
  - Dialysate and ultrafiltration flow rates
  - Blood flow rates
- Medication-related factors
  - Molecular weight medication
  - Degree of protein binding
  - Lipid solubility
  - Volume of distribution

Cases

55 yo M with ESRD due to HTN

HPI: Presents to ED with SOB after missing his last HD session
PMH: ESRD due to hypertensive nephrosclerosis on HD x 4 years
SH: Non-adherence
Meds: Metoprolol 50 mg po BID
VS: BP of 220/140 mmHg, 85 bpm
Neck: JVD up to 10 cm, RU Permacath
Cardiac: S1, S2, and notable for S3 and S4
Lungs: crackles up to the midfield
Extremities: 2+ pitting edema

Images purchased from www.dreamstime.com
55 yo M with ESRD due to HTN

Labs:

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Ca</th>
<th>Phos</th>
<th>PTH</th>
<th>LFTs</th>
<th>EKG</th>
<th>Troponin</th>
<th>Chest X-ray</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>9.2</td>
<td>5.3</td>
<td>322</td>
<td>within normal limits</td>
<td>Tall peaked T waves</td>
<td>0.06</td>
<td>pulmonary edema</td>
<td>Hypertensive emergency due to volume overload</td>
</tr>
</tbody>
</table>

The nephrologist is called for urgent HD, what is the next best step in management?

A. Administer Kayexalate only
B. Administer a bolus of Calcium Gluconate + Insulin + D50 + Albuterol (15mg)
C. Administer a bolus of Calcium Gluconate + Kayexalate
D. Administer a bolus of Calcium Gluconate + Kayexalate + Insulin + D50
E. Administer a bolus of Calcium Gluconate + Insulin + D50 + Albuterol (4mg)

Hyperkalemia in ESRD

- Hyperkalemia is defined as K level ≥ 5.5 mEq/L
- In ESRD – mortality – 3.1 per 1000 patient-year
- Any given month 5 – 10% will have hyperkalemia and 24% at sometime will need emergent HD
- Kayexalate should be avoided in the immediate post-operative period
- May lead to colonic necrosis if used with sorbitol
- Highest risk is the first week post-operatively
- FDA recommendation in 2009
- Avoid on day of HD
Hyperkalemia in ESRD

- Causes of hyperkalemia in ESRD
  - Potassium administration
  - Short HD sessions
  - Medications
  - Fasting
  - Access issues
  - Other causes
- Fasting Hyperkalemia – as a result of suppressed endogenous insulin release

Hyperkalemia and EKG

- Electrocardiographic findings depend upon the level of hyperkalemia
- 46–64% of patients with a serum potassium >6.0 mEq/L exhibit at least one EKG abnormality
- No correlation between the T-wave amplitude or the T wave to R-wave amplitude ratio and serum-potassium concentrations
- Ngugi et al. EKG abnormalities were observed in all (n= 31) patients with a serum potassium ≥6 mEq / L, but also in 23% of those with values between 5.0–5.9 mEq/ L
- As a general rule, greater degrees of hyperkalemia are associated with more severe EKG abnormalities

Calcium in Hyperkalemia

- Calcium should be administered in patients presenting with EKG changes or potassium levels > 6-6.5mEq/ L even in the absence of EKG changes
- Calcium Chloride vs. Calcium Gluconate
- Onset of Action 1-2 minutes lasts up to 60 minutes
- Do inquire about digoxin → digoxin toxicity

Sodium Bicarbonate and Hyperkalemia

- What about the role of sodium bicarbonate?
- Many studies have been done and date back to 1977 by Fraley and Adler
- Administer 100mEq/L Sodium Bicarbonate + D5W
- Blumberg et al (Sodium bicarbonate alone)
- Isotonic vs Hypertonic
  - **Sodium Bicarbonate should not be used**
Albuterol and Hyperkalemia

- How much albuterol should be administered and will it cause tachycardia?
- Montoliu et al first reported use of albuterol (IV route)
  - Tachycardia / general discomfort
- Allon et al
  - 10mg albuterol → decrease K by 0.62
  - 20mg albuterol → decreased K by 0.98
  - HR → 87bpm – 94 bpm (20mg albuterol), Anxiety – 1 subject
- Alternate approach is SQ terbutaline (7μg/kg)
  - speed & simplicity of administration and rapid onset
- Levalbuterol is the R-entantiomer of racemic albuterol
  - 0.63mg → similar efficacy to albuterol 2.5mg with decreased adverse events

Sowinski K et al Am J Kidney Dis 45:1040–1045, 2005

Insulin/D50W and Hyperkalemia

- When to give D50 with insulin?
  - Given to reduce hypoglycemia
  - Do not give if blood glucose ≥ 250 mg/dl

55 yo M with ESRD due to HTN

Plan: After intervention, his potassium is down to 5.5. Plan to admit to the ICU for IV labetalol and HD. After HD, BP is 172/82 mmHg. Over the the next few days his BP averages 160's/90's.

Which oral medication should be started?

A. Lisinopril
B. Losartan
C. Amlodipine
D. Hydralazine
E. Minoxidil

Antihypertensives in ESRD

- ACE inhibitors or angiotensin II receptor blockers (ARBs) should be preferred
  - Regression of left ventricular hypertrophy
  - Reduced sympathetic nerve activity
  - Reduced pulse wave velocity
  - May improve endothelial function
  - May reduce oxidative stress

- For this patient, ACE inhibitors or ARBs would not be the preferred choice due to non-adherence and risk for hyperkalemia

NKF K/DOQI Clinical practice guidelines on Cardiovascular Disease in Dialysis Patients. 2005
**Antihypertensives in ESRD**

- CCB are the most widely prescribed medications
- Advantages include:
  - No removal during HD
  - Inexpensive
  - Do not interfere with electrolytes
- Dihydropyridines are preferred
  - No bradycardia
  - Fewer drug-drug interactions
- Nifedipine XR can lower BP more significantly that amlodipine
  - Gingival hyperplasia

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**Antihypertensives and HD**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Medications</th>
<th>½ life</th>
<th>HD removal</th>
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</thead>
<tbody>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Benazepril</td>
<td>10 hours</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Fosinopril</td>
<td>12 hours</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>12 hours</td>
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<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>11 hours</td>
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<td></td>
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<tr>
<td>Captopril</td>
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<tr>
<td><strong>ARB</strong></td>
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<td></td>
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<tr>
<td>Irbesartan</td>
<td>12 hours</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Losartan</td>
<td>5 hours</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Valsartan</td>
<td>6 hours</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>CCB</strong></td>
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<tr>
<td>Amlodipine</td>
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<tr>
<td>Nifedipine</td>
<td>2 hours</td>
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<tr>
<td>Diltiazem</td>
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</tr>
<tr>
<td>Verapamil</td>
<td>8 hours</td>
<td>No</td>
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</tr>
</tbody>
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**Antihypertensives in ESRD**

- What about vasodilators?
  - Hydralazine is a great antihypertensive; however adherence is a concern
  - On average, HD patients are on at least 12 medications
  - Minoxidil is last line therapy

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<tr>
<td><strong>Vasodilators</strong></td>
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<tr>
<td>Hydralazine</td>
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<td></td>
</tr>
<tr>
<td>Minoxidil</td>
<td>12 hours</td>
<td>No</td>
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</tr>
<tr>
<td><strong>Beta-blockers</strong></td>
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<tr>
<td>Atenolol</td>
<td>6 hours</td>
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</tr>
<tr>
<td>Carvedilol</td>
<td>10 hours</td>
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<tr>
<td>Metoprolol</td>
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<tr>
<td><strong>Alpha, antagonists</strong></td>
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</tr>
<tr>
<td>Labetalol</td>
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</tr>
<tr>
<td>Doxazosin</td>
<td>22 hours</td>
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<td></td>
</tr>
<tr>
<td>Prazosin</td>
<td>5 hours</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
Mechanisms of HTN in ESRD

- 90% of HTN in ESRD is secondary to volume overload
- Effective volume removal via dialysis can remove the need for antihypertensives in ESRD patients

Mechanisms of HTN in ESRD

- Fluid & Volume Overload (80–90%)
- RAAS (5–10%)
- EPO
- Elevated PTH
- Decreased activity of Vasodilators

55 yo M with ESRD due to HTN

The patient agrees to be adherent to his blood pressure medication. He would like to know what time of the day he should take it. What should you tell him?

A. As soon as he gets up in AM
B. With lunch
C. With dinner
D. At bedtime
E. Anytime (as long as he takes it)

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55 yo M with ESRD due to HTN

“Antihypertensive drugs should be given preferentially at night, because it may reduce the nocturnal surge of blood pressure and minimize intradialytic hypotension, which may occur when drugs are taken the morning before a dialysis session” –K/DOQI

Dipping vs. Non Dipping

- Dipping: Blood pressure tends to be the highest in the morning and decreases during throughout the day to reach the lowest levels at night
- 10 – 25% of hypertensive patients fail to manifest this normal nocturnal dipping of blood pressure,
- Defined as a night-time blood pressure fall of >10%.
- These patients are called “nondippers”
- In ESRD, the lack of nocturnal dipping can affect as many as 74%-82% of patients. Nocturnal blood pressure > daytime pressure

74 yo F with ESRD, HTN & DM

HPI: Brought to the ED for AMS. Family reported she had uneventful 4 hr hemodialysis session and did not report CP or SOB.
PMH: ESRD, HTN, Type 2 DM
Meds:
- gabapentin 600mg po TID
- insulin glargine 10 units SQ QHS,
- insulin aspart 4 units with meals
- lisinopril 40mg po QHS
- metoprolol tartrate 25mg po BID

74 yo F with ESRD, HTN & DM

VS: T-36.9C, P-62, BP- 149/89 RR-18
PE: Left lower extremity foot ulcer with erythema
Labs: BMP WNL except for BUN/ SCr at 36/5.8 respectively , potassium of 3.4 mEq/L, and BG of 140 mg/dL
- Troponin: 0.04
Rad: CT head negative, X-ray for osteomyelitis pending
EKG: no ST-elevation or T wave depression
74 yo F with ESRD, HTN & DM

What is the most likely cause of her altered mental status?

A. Hypoglycemia
B. Post HD complication
C. Polypharmacy
D. Gabapentin toxicity
E. Hypokalemia

68 yo F with ESRD, HTN & DM

She is admitted to your service for management of her gabapentin toxicity and a diabetic foot infection. Broad spectrum antibiotics are initiated.

Drug Overdoses in ESRD

- Dose adjustment is of profound importance and all medications should be screened
- Excessive dosing can lead to toxicity
- Many medications can be removed with HD for treatment of toxicity but the poison control center should be contacted for assistance

Antimicrobials and ESRD

- Infections → 2nd leading cause of death (12-36%)
- Primary pathogens are Gram-positive
  - Coagulase negative staphylococci
  - Staphylococcus aureus (MRSA, MSSA)
- Line removal required for S. aureus, Pseudomonas, or Candida.
- Cefazolin, vancomycin, and gentamicin are common
Antimicrobials in ESRD

- Many anti-infectives require dose adjustment in ESRD
  - Reduce the dose
  - Increase the interval
- Beta-lactam accumulation can lead to seizures
- Cefazolin- convenient dosing with HD
  - 2 grams after HD on Monday and Wednesday
  - 3 grams after HD on Friday
- Nafcillin- no renal adjustment required
  - Volume overload
  - Inconvenient dosing regimen for HD patients

Vancomycin
- High molecular weight
- 30-46% protein bound
- Removed with high flux HD
- Loading dose: 20-25 mg/kg x 1
- Maintenance dose: 15-20 mg/kg given after each HD session
- Use total body weight

Gentamicin
- Low molecular weight
- Low volume of distribution
- Low protein binding
- Traditional dosing
- Loading dose: 2 mg/kg/dose
- Maintenance Dose: 1.5 mg/kg/dose
- Use lean body weight

Antimicrobials in ESRD

Common antibiotics that **DO NOT** require dose adjustment
- Azithromycin
- Ceftriaxone
- Clindamycin
- Doxycycline
- Linezolid
- Metronidazole
- Moxifloxacin
- Nafcillin

Antifungals in ESRD

- Fungemia/Candidemia requires catheter removal
- Azole antifungals may require dose adjustment
  - Fluconazole- YES
  - Posaconazole and voriconazole- NO
- Echinocandins DO NOT require renal dose adjustment
Two days after she is initiated on broad spectrum antibiotics, she complains of heart palpitations. VS: BP 122/86 mmHg, HR: 98 bpm EKG: no visible P-waves, consistent with atrial fibrillation
CHADS2 Score: 2
CHA2DS2-VASC Score: 4
HAS-BLED Score: 2

Which of the following would be the BEST choice for anticoagulating this patient?
A. Dabigatran
B. Enoxaparin
C. Warfarin
D. Unfractionated heparin
E. Rivaroxaban

Anticoagulants in ESRD
- Unfractionated heparin infusion **PREFERRED**
  - Minimal renal clearance
  - Reversible with protamine
  - Monitoring available - aPTT, anti-Xa levels
- Low molecular weight heparins (LMWH)
  - Enoxaparin is renally cleared - not recommended with ESRD
  - Dalteparin is renally cleared - no recommended adjustment
- Fondaparinux is renally cleared - **contraindicated** with CrCl < 30 ml/min

Anticoagulation in ESRD
- Preferred oral anticoagulant is warfarin
  - Not renally cleared
  - Reversible with vitamin K, FFP, and clotting factors
  - Monitoring available - PT/INR
- Newer oral anticoagulants
  - Dabigatran - Not studies with CrCl < 30 ml/min
  - Rivaroxaban - Not with CrCl < 30 ml/min
  - Apixaban - dose reduction to 2.5 mg po BID, minimal data
  - No reliable reversal agents
  - No routinely available monitoring

Anticoagulation in ESRD

- What happens when warfarin or unfractionated heparin infusion are not options?
  - Can consider monitored LMWH
  - Can consider treatment-dose subcutaneous unfractionated heparin
  - Apixaban?

Summary

- Check EKG
- Calcium: If potassium > 6.5 with no EKG changes
- Insulin + D50W (avoid if BG ≥ 250mg/dl)
- Albuterol → 10–20mg nebulized; other option is terbutaline
- Sodium bicarbonate not beneficial
- Kayexalate should be avoided in post-op period
- Dialysis is definitive treatment

Summary

- Fluid and volume overload → 90% HTN
- ACEIs and ARBs are preferred for HTN
- CCB are advantageous
- Blood pressure medications should be given at bedtime
- Many anticoagulants are renally cleared and should be avoided in ESRD

Summary

- Most antibiotics require a dose adjustment
- Risk for toxicity is increased with narrow therapeutic window
- Decreased absorption will occur if oral antimicrobials are administered with antacids or phosphorus binders
- Loading doses typically are the same; however, most maintenance doses will have a longer interval
- For PD patients, many antimicrobials can be given intra-peritoneally
Summary

* ESRD is associated with numerous changes in the pharmacokinetic profile of drugs including
  * Chemical structure
  * $V_d$
  * Route of medication elimination
  * Never hesitate to consult a pharmacist

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