ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

ASN Dialysis Advisory Group

ASN DIALYSIS CURRICULUM

Drug Dosing in Dialysis Patients

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Disclosures

- **Genzyme: Investigator-initiated Research Support**
- **Keryx Biopharmaceuticals: Industry-sponsored Research Support**

General Considerations

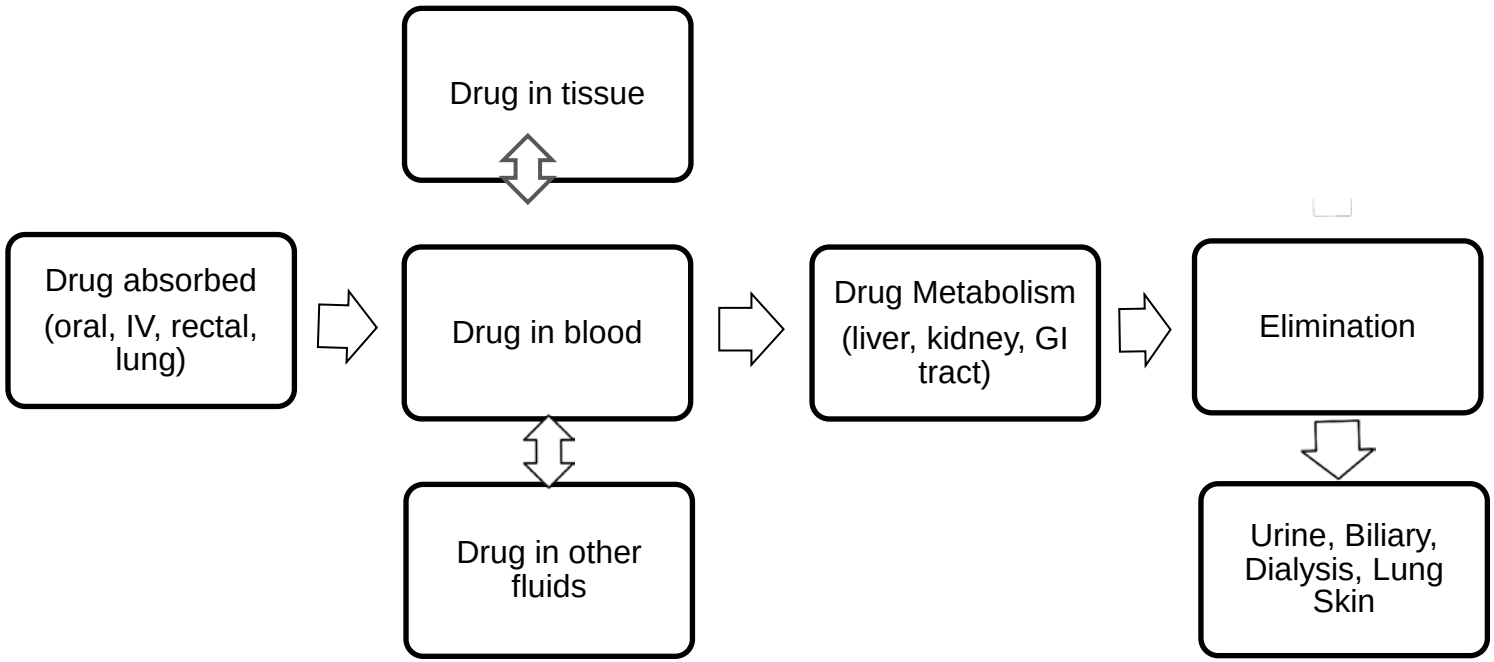
- **Pharmacokinetics**
  - Bioavailability
  - Volume of distribution
  - Protein binding
  - Drug metabolism/renal elimination
- **Dosing in Dialysis**
  - Loading and maintenance dosing
- **Dialysis Clearance of Drugs**
  - Hemodialysis (HD)
  - Hemodiafiltration
  - Continuous renal replacement therapy (CRRT) and peritoneal dialysis (PD)
- **Specific Agent Considerations**

1. Schrier R. *Diseases of the Kidney and Urinary Tract*, *ed. 7,* Philadelphia, PA, Lippincott Williams & Wilkins, 2001.
2. Johnson CA. *Dialysis of Drugs.* Verona, WI, CKD Insights, LLC, 2010.

Pharmacokinetics

- **Pharmacokinetics is the study of the course of a drug in the body and is used to predict serum concentrations and drug activity**
- **Pharmacokinetic studies are frequently not performed in patients with renal failure but physicians should be aware of data when available**

Pharmacokinetic factors to consider in drug distribution:



GI, gastrointestinal. IV, intravenous.

Bioavailability

- **Bioavailability is the fraction of the administered dose that reaches the systemic circulation–bioavailability is 100% for IV injections**
- **Drug bioavailability varies more in renal patients than healthy patients:**
  - Decreased GI Absorption
    - Alkaline environment (from salivary urea converted to ammonia by urease) will minimize absorption of medications that require an acidic environment (such as oral iron)
    - Slowed absorption rates due to reduced peristalsis
    - Slowed absorption due to bowel wall edema
    - Phosphate binders (such as Ca and Al) that form complexes with drugs, making them insoluble for absorption
  - Altered First-Pass Metabolism
    - Decreased biotransformation resulting in increased amounts of active drug in systemic circulation
    - Impaired plasma protein binding resulting in more free drug available for hepatic metabolism

Volume of Drug Distribution

- **Volume of distribution (Vd): the amount of drug in the body divided by the concentration in the blood.**
  - Lipid soluble drugs (such as diazepam) or highly tissue-bound drugs (such as digoxin) have very high volumes of distribution
  - Lipid insoluble drugs, such as neuromuscular blockers, remain in the blood and have a low volume of distribution
- **Extracellular volume overload may increase the apparent volume of distribution of highly water soluble drugs, thus usual doses may result in low plasma levels in volume overloaded patients**
- **Muscle-wasted patients often have decreased apparent volume of distribution, and thus higher plasma levels**

Protein Binding

- **Plasma protein binding is a key determinant of Vd**
- **Drugs that are highly protein bound will stay in the vascular space and have a low Vd**
- **Protein bound drugs are largely inactive**
- **Renal failure may increase or decrease protein binding**
  - Reduced plasma protein binding may result in more free drug available at the site of drug action/toxicity
  - Organic acids that accumulate in renal failure will compete with acidic drugs for protein binding, and a larger fraction of acidic drugs will exist in the unbound active state (salicylate, warfarin, sulfonamides, phenytoin)
    - Total and unbound plasma phenytoin concentrations should be measured when monitoring
  - Basic drugs will bind more readily to non-albumin proteins and there may be increased protein binding
  - Low albumin will result in decreased binding and more active drug

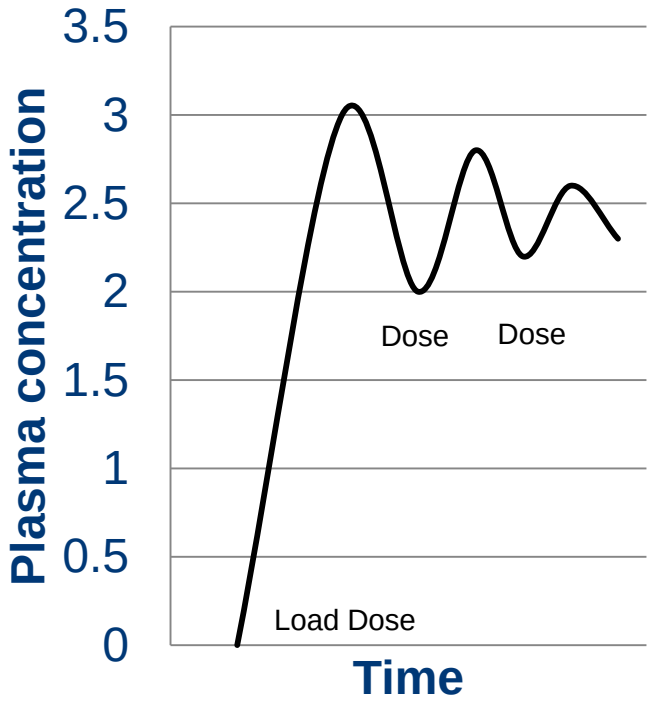
Drug Metabolism/Renal Elimination

- **Clearance of a drug: the volume of plasma from which the drug is completely removed per unit of time**
- **The amount eliminated is proportional to the concentration of the drug in the blood**
- **In dialysis patients, drug metabolism is unpredictable**
- **Non-renal elimination (i.e., hepatic metabolism) may compensatorily increase, remain unchanged, or decrease:**
  - Reduction and hydrolysis are slowed
  - Most drugs undergo hepatic biotransformation to more polar, but less pharmacologically active, compounds that require intact renal function for elimination
  - Accumulation of active or toxic metabolites from parent compounds can occur (examples include procainamide, allopurinol, and meperidine)
- **In end-stage renal disease (ESRD), drugs may accumulate due to impaired glomerular filtration, decreased renal tubular secretion, and impaired renal epithelial cell metabolism**

Drug Dosing–Loading Dose

- **Loading doses are useful for drugs that are eliminated from the body relatively slowly**
  - Such drugs need only a low maintenance dose in order to keep the amount of the drug in the body at the target level
  - Without loading, it would take longer for the amount of the drug to reach target level
  - Loading doses typically are adjusted based on Vd and are not adjusted for renal failure
- **If extracellular volume depletion is present, Vd may be reduced and reductions in loading dose should occur**

Drug Dosing–Loading Dose



Drug Dosing–Loading Dose

- **Three variables are used to calculate the loading dose:**
  - C_p = desired peak concentration of drug
  - V_d = volume of distribution of drug in body
  - F = bioavailability

- **The required loading dose may then be calculated as:**

$$\textbf{Loading dose} = \frac{\textbf{Cp x Vd x Ideal body weight}}{\textbf{F}}$$

- **For an intravenously administered drug, the bioavailability F will equal 1, since the drug is directly introduced to the bloodstream. If the patient requires an oral dose, bioavailability will be less than 1 (depending upon absorption, first-pass metabolism, etc.), requiring a larger loading dose**

Drug Dosing–Maintenance Dose

- **Maintenance doses ensure steady-state blood concentrations and lessen the likelihood of sub-therapeutic regimens or overdoses**
- **In the absence of a loading dose, maintenance doses will achieve 90% of their steady-state level in 3–4½ lives**
- **Two options for ESRD**
  - Reduce the dose
  - Lengthen the interval between doses (more useful for a drug with a wide therapeutic range and long half-life)
- **Maintenance dose can be calculated the same way as loading dose**

Monitoring Drug Levels

- **Monitoring drug levels is important but you must know the dose given, the timing of administration, and route**
- **Peak level is usually obtained 30 minutes following IV dose and 60–120 minutes after oral ingestion**
  - Peak levels reflect the maximum level achieved after rapid distribution and before elimination
- **Trough level is obtained just prior to the next dose, reflects the total body clearance, and may be used as a marker of drug toxicity**

Dialysis Clearance of Drugs

- **Drug factors to consider include**
  - Molecular weight (MW) of drug (major determinant)
    - Small MW molecules will have much larger clearance through diffusion
    - Large MW molecules will be cleared less as clearance depends on convection; drugs with larger MW removed by HD take longer to equilibrate from intra-/extracellular compartments and may result in post-dialysis rebound
  - Protein binding of drug – high protein bound = less clearance
  - Lipid solubility
    - Drugs with large Vd (> 2 L/kg) have lower concentration in plasma, thus less removal and a larger tendency for rebound once HD stops
    - Drugs with small Vd (< 1 L/kg), the greater the dialyzability
  - Drug chemistry
- **Drugs with low MW, limited Vd, and that are water-soluble are most likely to be removed by HD and will require extra dosing**

Dialysis Clearance–HD

- **Dialysis factors to consider**
  - Surface of the dialyzer (i.e., pore size) and dialysis membrane composition
  - Dialysate flow rates
  - Blood flow rates
- **Two major processes by which drugs are cleared during HD**
  - Diffusion–removal of drug by movement down its concentration gradient
    - Diffusion is greater with lower MW drugs (< 1000 Da)
    - Diffusion is enhanced by maximizing concentration gradient between blood and dialysate (Note: hemodiafiltration with large ultrafiltration [UF] will minimize the gradient and lower drug removal)
  - Convection–removal of solute by UF
    - Important for removal of middle and large-MW drugs (> 1000 Da)

Dialysis Clearance–Hemodiafiltration

- **Hemodiafiltration (HDF)**
  - Will remove drug by convection
  - Must be aware of the sieving coefficient of the drug (S), determined by the drug concentration in the ultrafiltrate versus blood after it has passed through the filter
    - $S = \frac{\text{concentration of drug in ultrafiltrate}}{\text{concentration of drug in arterial line}}$
  - Clearance of the drug can be determined by: S x ultrafiltration rate
  - Factors to consider in removal of drug by convection: the degree of protein binding, the electrical permeability across the dialysis membrane, molecular weight of the drug, and the Vd

Dialysis Clearance–CRRT and PD

- **CRRT**
  - Drug removal is dependent on diffusion rather than convection
  - Protein binding plays a central role as unbound drug will diffuse more readily than protein bound drug
  - The MW correlates inversely with diffusion
  - Dose for an average glomerular filtration rate (GFR) of 20–30 ml/minute
- **PD**
  - In general, PD provides minimal drug removal
  - Drugs removed by PD must be small in size and have low Vd
  - Drugs that are highly protein bound may be removed more with PD than HD given the large protein losses which can be observed with PD
- **In general, removal of drugs on HD or CRRT or PD has NOT been tested and is based on theoretical considerations of molecular size and chemical makeup of the drug**

Specific Agents–Analgesics/Sedatives/Psychotropics

- **Most non-narcotic analgesics are hepatically metabolized, thus require little or no dosage adjustment in ESRD**
- **Renal failure may increase the sensitivity to the pharmacologic effects of narcotics**
- **Meperidine (Demerol) accumulates in patients with decreased GFR and may lower the seizure threshold**
- **Morphine also accumulates, avoid repetitive dosing**
- **Neuromuscular blocking agents are renally excreted and may have a prolonged half-life in patients with ESRD**
- **Antidepressants such as tricyclic antidepressants should be used cautiously given the increased risk of adverse side effects**
- **Lithium is water soluble with a small MW and is easily removed with HD**
  - However, it equilibrates slowly from the intra- to extracellular space; prolonged HD may be required for adequate removal

Specific Agents–Antimicrobials

- **Most antibiotics require a dose adjustment in patients with ESRD**
- **Many drugs have a narrow therapeutic window**
- **Pharmacokinetic parameters already discussed may alter the way antimicrobials are handled or excreted**
- **For orally administered agents, decreased absorption or co-binding will occur if 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 intraperitoneally**

Specific Agents–Cardiovascular

- **Antihypertensive Agents**
  - Most agents can be safely prescribed in patients with ESRD
  - Postdialysis dosing or extra doses after HD may be necessary for certain antihypertensive agents:
    - Angiotensin converting enzyme inhibitors (ACE-I): all are dialyzable except fosinopril
    - Angiotensin receptor blockers (ARB): none are dialyzed
    - B-blockers: atenolol and metoprolol are dialyzable but labetolol and carvedilol are not
    - Calcium channel blocker: amlodipine is not dialyzable
- **Anticoagulants**
  - Low-MW heparin
    - Will accumulate in patients with ESRD so prefer to avoid
    - If used, follow anti–factor Xa levels and reduce the dosing interval

Specific Agents–Endocrine/Rheumatologic

- **Endocrine**
  - Hypoglycemic agents that are renally excreted should be avoided (such as certain sulfonylureas)
  - PD patients can be administered insulin intraperitoneally
- **Rheumatologic**
  - Increased risk of adverse effects with allopurinol due to accumulation of its metabolite
  - Colchicine has an increased risk of myopathy and polyneuropathy

Specific Agents–Neurologic

- **Phenytoin is frequently used in ESRD patients**
  - In ESRD, the Vd of phenytoin is increased while the degree of protein binding is decreased
  - Thus, low total plasma phenytoin levels may not reflect subtherapuetic drug levels as the free level may be adequate
  - Must monitor free and total phenytoin levels in ESRD patients

Summary

- **ESRD is associated with numerous changes in the pharmacokinetic handling of drugs including:**
  - Bioavailability
    - Decreased bioavailability of orally administered drugs
    - Impaired first-pass metabolism may increase bioavailability
  - Volume of distribution
    - Increased apparent Vd for volume overloaded patients
    - Decreased apparent Vd for muscle-wasted patients
  - Protein binding
    - Acidic drugs will exist more in the unbound active state
    - Basic drugs will bind more readily
    - Low albumin will result in decreased binding
  - Impaired drug metabolism and renal elimination
  - When prescribing agents in ESRD, be aware of the chemical structure, the Vd, and the route of elimination of medications