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**

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:

- Drug absorbed (oral, IV, rectal, lung)
- Drug in blood
- Drug Metabolism (liver, kidney, GI tract)
- Drug in tissue
- Drug in other fluids
- Elimination
- Urine, Biliary, Dialysis, Lung, Skin

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
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

![Diagram showing plasma concentration over time with load dose and doses marked.]
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:
  \[
  \text{Loading dose} = \frac{C_p \times V_d \times \text{Ideal body weight}}{F}
  \]

• 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)
• **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: $S \times \text{ultrafiltration rate}$
  • 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
• **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 subtherapeutic 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