Drug Dosing in AKI

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Drug Dosing Considerations

- Multiple variables influencing responses to drug regimen:
  - Patient's residual drug clearance
  - Fluid accumulation
  - Delivery of RRT
  - Patient's current kidney function
  - Corresponding drug elimination influenced by the decline, stabilization or recovery of AKI
- Renally eliminated drugs esp agents with a narrow therapeutic range, serum drug concentration measurements and assessment of PD responses are necessary

Drug Dosing Considerations

- PK studies in patients with AKI (and CKD) are fairly limited
- The use of dosing guidelines based on data derived from patients with stable CKD may not reflect the clearance and volume of distribution in critically ill AKI patients
- Pharmacotherapy regimen decisions should further take into consideration 4 distinct phases of AKI
  - Earlier, spc. Initiation
  - Extension
  - Maintenance
  - Recovery phase

Drug Dosing Considerations

- Scr measurements lag behind kidney function, while urine output maybe a more current surrogate marker of function
- Edema can significantly increase the Vd of many drugs
- Increased fluid distribution into the tissues (e.g. sepsis and anasarca in heart failure) can also contribute to a larger Vd and thereby reduce the proportion of drug in the plasma that is available to be removed by RRT
- Volume overload, reductions in cardiac output or liver function can significantly alter the PK profile of most drugs

Drug Dosing Considerations

- If rapid onset of activity is desired, a loading dose may be necessary to promptly achieve desired serum concentrations
- Maintenance dosing regimens should be reassessed frequently and be based on the patient's most current kidney function
- Several physiochemical and PK characteristics can alter drug clearance during RRT
  - Molecular weight
  - Protein binding
  - Vd
  - Degree of renal clearance or fraction eliminated by the kidneys

Drug Dosing Considerations

- RRT-mediated drug clearance is inversely related to molecular weight
- IHD efficiently clears drugs with a small molecular weight (e.g. < 500 Da)
- CRRT can efficiently clear much larger solutes (e.g. < 15,000 Da)
- Protein binding can also affect clearance in both IHD and CRRT as the drug-protein complexed increase molecular weight (e.g. > 50,000 Da) thus making it difficult to pass through the pores in the hemofilter

Drug Dosing Considerations

- Patients with hypoalbuminemia will have a higher fraction of unbound drug, thus a larger amount of the agent may be removed during RRT
- Drugs with a large Vd are extensively distributed to extravascular tissues, leaving only a small fraction of the drug in the vascular compartment and limiting drug removal
- During CRRT, drugs with a large VD (>1 L/kg) will exhibit higher clearance due to the extended length of therapy

Drug Dosing Considerations

- There are marked differences in drug removal between the different RRT modalities.
- CVVH
  - Drug removal primarily occurs via convection/ultrafiltration
  - Convection is the passive transport of drug molecules at the concentration at which they exist in plasma water into the ultrafiltrate
  - Convective removal is most efficient for smaller molecules, typically < 15,000 Da (15kDa) in size

Drug Dosing Considerations

- Clearance of a drug by RRT is a function of the membrane permeability for the drug, which is sieving coefficient (SC) and the ultrafiltration rate (UFR)
  - Sieving Coefficient (SC)
    - SC is the ratio of a solute or drug the ultrafiltrate to that in plasma water
    - A SC of 1 = free transport across the membrane
    - A SC of 0 = no transport across the membrane
    - Estimated by measuring the concentration of solute pre-filter or in plasma (Cp) and the concentration of solute in the ultrafiltrate (Cuf)

$$SC = Cuf/Cp$$

Drug Dosing Considerations

- Sieving Coefficient (SC)
  - SC is often approximated by the fraction unbound (fu), or the fraction of drug unbound to protein in the plasma
- **Clearance of a drug by CVVH**
  - Drug is largely driven by convection

$$Cl_{CVVH} = UFR \times SC$$

$$Cl_{CVVH} = UFR \times fu$$

Drug Dosing Considerations

- **Clearance of a drug by CVVHD**
  - Is a combination of both convection and diffusion, but diffusion is the main mechanism for solute removal
  - During diffusion, solutes move down a concentration gradient from an area of higher concentration (plasma) to an area of lower concentration (dialysate)

$$Cl_{CVVHD} = DFR^{*} \times fu$$

- DFR = dialysate flow rate

Drug Dosing Considerations

- **Clearance of a drug by CVVHD**
  - Is a combination of both convection and diffusion, but diffusion is the main mechanism for solute removal
  - During diffusion, solutes move down a concentration gradient from an area of higher concentration (plasma) to an area of lower concentration (dialysate)

$$Cl_{CVVHD} = DFR^{*} \times fu$$

- DFR = dialysate flow rate

Drug Dosing Considerations

- **Clearance of a drug by CVVHDF**
  - Is a combination of both diffusion and convection

$$Cl_{CVVHDF} = Cl_{CVVH} + Cl_{CVVHD}$$

$$Cl_{CVVHDF} = (UFR + DFR) \times fu$$

Drug Dosing Considerations

- Individualization of pharmacotherapy for a patient receiving CRRT is dependent on
  - Patient's residual kidney function
  - Clearance of drug by CRRT
  - Properties of drug: molecular weight, Vd, Protein binding, SC
- Differences in the rate of drug removal:
  - Modes of CRRT
  - Within each mode: filter membrane composition, variable degrees of drug binding to the membrane, permeability characteristics of the membrane

Drug Dosing Considerations

- Factors influencing drug clearance during CRRT:
  - UFR
  - Blood flow rate
  - DFR
- CRRT can rapidly remove excess fluid from edematous patients, thereby changing the Vd of drugs with limited distribution
- Drug clearances attained by IHD, CRRT, and PIRRT all differ from each other and must be added to any endogenous drug clearance that the patient generates

Drug Dosing Considerations

- The approach to hemodialysis may also change on a daily basis, especially in hemodynamically unstable individuals with AKI:
  - Type of dialyzer/filter used
  - Duration and degree of hemofiltration compared with convection
  - Blood flow rate
- Individualization of a dosing regimen may require daily assessment of the clinical status of the patient and any planned or recently administered hemodialysis