Extracorporeal Removal of Drugs and Toxins

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KEYWORDS

• Drug • Toxin • Dialysis • CRRT • Dosing

This article reviews the principles of drug and toxin removal by extracorporeal circuits and the appropriate management of patients on renal replacement therapy. The principles of drug removal and therapeutic dosing in intermittent and continuous therapies as well as the use of intermittent hemodialysis for the removal of toxic substances are discussed. The considerations involved in the calculation of drug dosages and toxin removal are reviewed; however, there is a paucity of information related to veterinary patients. Therefore, much of this information is extrapolated from human data.

The type of extracorporeal therapy used can greatly affect the extent of drug and toxin removal. The available modalities include intermittent hemodialysis and three types of continuous renal replacement therapies (CRRTs). Intermittent hemodialysis is primarily a diffusive process, whereas CRRT uses a combination of diffusion, convection, and adsorption. The continuous modalities include continuous venovenous hemofiltration (CVVH), a purely convective modality; continuous venovenous hemodialysis (CVVHD), a diffusive modality; and continuous venovenous hemodiafiltration (CVVHDF), which combines the aspects of both convection and diffusion. Convection uses hydrostatic pressure to force fluids and dissolved solutes out of the blood and across the semipermeable membrane of the dialyzer, whereas diffusion uses the tendency of solutes to move from an area of high concentration to that of low concentration to remove substances from the blood. Convective modalities allow for the removal of small- and medium-sized molecules, whereas diffusive modalities are limited to smaller molecules.[1] This difference has significant implications regarding drug removal. The final mechanism of solute clearance is adsorption, which refers to the adherence of solutes to filter membranes, leading to increased removal from plasma. Adsorption is saturable and therefore plays only a minor role in clearance unless the filter is changed more frequently than every 18 to 24 hours.[2]

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In addition to the type of extracorporeal therapy chosen, there are numerous other variables that play a role in determining the extent of drug removal or clearance during treatment, including the various membrane and solute characteristics.

MEMBRANE AND PRESCRIPTION CHARACTERISTICS

Membrane characteristics affecting drug clearance include the filter material, filter pore size, and filter surface area. In addition, the dialysis prescription, namely the ultrafiltration rate (Q_{uf}), dialysate rate (Q_d), blood flow rate (Q_b), and for convective modalities, the selection of pre- versus post-dialyzer replacement fluids have a considerable effect on the clearance.[3] Higher permeability filters can result in significantly higher drug clearance rates than less permeable membranes, especially for intermediate–molecular weight drugs such as vancomycin.[4] The age of the filter can also affect the clearance because its performance changes over time, particularly in continuous treatment modalities.[5]

DRUG AND TOXIN (SOLUTE) CHARACTERISTICS

The solubility, volume of distribution (V_d), molecular weight, protein binding, charge, and degree of renal and nonrenal eliminations contribute to the clearance of a drug during extracorporeal renal replacement therapies.[3] Antibiotics are arguably the most important group of drugs to consider because they are commonly administered to patients with acute kidney injury undergoing dialysis and their blood levels can be significantly influenced by extracorporeal therapy. This is a critical point because underdosing of antibiotics may result in treatment failure, whereas overdosing may result in unacceptable toxic side effects for the patient.

Several antimicrobial properties influence dialytic clearance. Solubility describes whether a drug is hydrophilic or lipophilic. Hydrophilic drugs, such as β-lactams, glycopeptides, and aminoglycosides, are unable to passively cross the plasma membrane of the cells, and so their distribution is limited to the extracellular fluid. The hydrophilic drugs are usually excreted unchanged by the kidney. Lipophilic drugs, such as macrolides, fluoroquinolones, tetracyclines, and chloramphenicol, may freely cross the plasma membrane of the cells, so they are widely distributed into the intracellular compartment. Lipophilic drugs usually require metabolism through various pathways before elimination.[3]

V_d is another crucial consideration. This term describes the volume in which a drug would need to be dissolved to obtain the observed blood concentration, assuming homogenous mixing in the body. V_d is the primary pharmacokinetic consideration used to determine the initial (loading) dose of an antimicrobial.[6] V_d determines the dose needed to achieve a desired plasma concentration (C_p) for intravenous medications using the following calculation[1]:

$$\text{Dose} = C_p \times V_d \times \text{body weight in kilograms}$$

A large V_d indicates that a drug is highly tissue bound and that only a small proportion of the drug is within the intravascular compartment, available for clearance by extracorporeal therapy.[1] V_d can be increased during critical illness and renal dysfunction but should not be affected by the selected extracorporeal therapy.[6] A large V_d (>1 L/kg) decreases the likelihood of a drug being substantially removed by hemodialysis or CRRT, assuming there is enough time for the drug to distribute. Drugs with a small V_d ($\leq$1 L/kg) are more likely to be cleared by extracorporeal therapies.[5] A drug with a large V_d but high clearance during intermittent hemodialysis is removed