Drug Dosing in Critically Ill Patients with Acute Kidney Injury and on Renal Replacement Therapy

Sai Saran¹, Namrata S Rao², Afzal Azim³

ABSTRACT

Acute kidney injury (AKI) complicates in around 40–50% of patients in intensive care units (ICUs), and this can account for up to 80% mortality, especially in those patients requiring renal replacement therapy (RRT). Appropriate drug dosing in such patients is a challenge to the intensivists due to various factors such as patient related (appropriate body weight, organ clearance, serum protein concentration), drug related (molecular weight (MW), protein binding, volume of distribution (Vd), hydrophilicity, or hydrophobicity), and RRT related (type, modality of solute removal, filter characteristics, dose, and duration). Therapeutic drug monitoring (TDM) of drugs can be a promising solution to this complex scenario to titrate a drug to its clinical response, but it is available only for a few drugs. In this review, we discussed drug dosing aspects of antimicrobials, sedatives, and antiepileptics in critically ill patients with AKI on RRT.

Keywords: Acute kidney injury, Critically ill, Drug dosing.

Indian Journal of Critical Care Medicine (2020): 10.5005/jp-journals-10071-23392

Introduction

Acute kidney injury (AKI) occurs in around 40–50% of patients admitted in ICUs and around 4% of patients who develop AKI require renal replacement therapy (RRT).¹ ² The mortality of patients with severe AKI progressing to RRT requirement in intensive care units (ICU) is as high as 80%, ranging from 20 to 90%, with 8 of 100 such patients per year developing chronic kidney disease (CKD) and becoming dependent on RRT.³ Besides the complications of AKI such as fluid overload, refractory metabolic acidosis, sepsis, cardiac dysfunction, and dyselektrolytemia, coexisting conditions such as multiorgan failure syndrome also contribute to high mortality in these settings.⁴

Inappropriate drug dosing probably contributes to excessive mortality, as it cannot be easily estimated from the varying pharmacokinetic and pharmacodynamic conditions in critically ill patients.⁵–⁷ The major factors that influence drug dosing in critically ill patients are altered volume of distribution (Vd), altered protein binding (PB), and altered clearance from various organs (predominantly liver and kidney) due to coexisting organ failures.⁵ In addition to RRTs, the use of extracorporeal membrane oxygenation (ECMO) can influence drug concentrations, adding to the complexity of drug dosing.⁶ ⁷ Appropriately drug dosing in such patients is a challenge to the intensivists due to various factors such as patient related (appropriate body weight, organ clearance, serum protein concentration), drug related (molecular weight (MW), protein binding, Vd, hydrophilicity, or hydrophobicity), and RRT related (type, modality of solute removal, filter characteristics, dose and duration) represented in Table 1.⁵ ⁷ ⁹

The implications of these factors with regard to various drugs such as antimicrobials (Tables 2 and 3), sedatives (Table 4), and antiepileptics (Table 5) are highlighted in this article, as they are the drugs most commonly used in ICUs for which the clinicians require a thorough understanding. The ICU charts can have polypharmacy, and the dosing aspects of various other drugs in such scenarios are beyond this review.

Importance of Appropriate Dose

While underdosing can result in lack of therapeutic effect and development of resistance (in the case of antimicrobials) and

© The Author(s). 2020 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted use, distribution, and non-commercial reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
How to Prescribe Drugs for Critically Ill Patients with AKI on RRT

Table 1: Factors to be considered for drug dosing for critically ill acute kidney injury patients on RRT

| Patient related | Drug related | RRT related |
|----------------|--------------|-------------|
| Body weight: IBW, ABW, LBW, TBW | Molecular weight | Type of modality: IHD, PIRRT, CRRT |
| Residual renal function | Protein binding | Mechanism of solute removal (diffusion, convection, adsorption) |
| Other organ failures (change in nonrenal clearance) | $V_d$ | Membrane characteristics ($K_{tu}$, $K_{tu}$, SC, SA) |
| Serum protein concentration | $\log P$ | Pre- or post-dilution in CRRT |
| Blood pH | Competition with other drugs | Dose of dialysis |
| Serum electrolytes | Variations in $V_d$ | Treatment duration |
| Variations in $V_d$ | | Recirculation in vascular access |

Table 2: Hydrophilic and lipophilic properties of drugs

| Type | Hydrophilic ($-\log P$) | Hydrophobic ($+\log P$) |
|------|-------------------------|------------------------|
| Properties | Tissue distribution limited to extracellular space | Tissue distribution with intracellular accumulation |
| $V_d$: 0.1–0.3 L/kg | $V_d$: >0.6 L/kg | Hepatic clearance |
| Renal clearance | | |
| In sepsis | Loading dose | No need |
| Changes in maintenance dose | No need | |
| In renal failure (AKI) | Dose replacement after RRT | Extra dose during/ post RRT |
| Examples | Aminoglycosides | Fluoroquinolones |
| Beta-lactams | Glycylcycline | Ketolides |
| Glycopeptides | Lincomamides | |
| Lipopeptides | Linezolid | |
| Polymyxins | Macrolides | |
| Fluconazole | Flucytosine | Metronidazole |
| Acyclovir | Streptogamins | |
| Azoles | Tetracycline | Tigecycline |
| Protease inhibitors | TMP-SMZ | Amphotericin B |
| | | Echinocandins |

AKI, acute kidney injury; IBW, ideal body weight; ABW, actual body weight; LBW, low body weight; TBW, total body weight; $V_d$, volume of distribution; RRT, renal replacement therapy; $\log P$, octanol-partition coefficient; IHD, intermittent hemodialysis; PIRRT, prolonged intermittent renal replacement therapy; CRRT, continuous renal replacement therapy; $K_{tu}$, ultrafiltration coefficient; $K_{A}$, mass transfer coefficient; SC, sieving coefficient; SA, saturation area.

Debate of Body Weight in the Critically Ill Patient

The calculation of creatinine clearance and dose of RRT is based on the total body weight (TBW) which may be erroneous, if the patient has received large fluid volume earlier, and consideration may be given to “normal TBW,” arrived after discussion with the patient’s family. Lean body weight is an estimate of the mass of nonfatty cells and connective tissue and is calculated from TBW and body mass index. Adjusted body weight (IBW + 0.4 (TBW – IBW)) (IBW being ideal body weight derived from the patient’s height) is preferred for obese patients. Drug dosing for hydrophilic medications should usually be based on TBW and for hydrophobic medications on LBW. Apart from this, other patient characteristics such as residual organ functions, serum protein status, blood pH, and serum electrolytes also play a role in deciding the drug prescription.

Augmented Renal Clearance Affecting Drug Dosing

Clearance is defined as the volume of plasma from which solute is completely removed per unit time. It is a proportionality factor expressed as a ratio of elimination (by all routes) to the plasma drug concentration (clearance = rate of elimination/plasma concentration). Total body clearance is a reflection of clearance of a drug through various organs such as liver, kidney, lungs, mucosa, and skin. In addition, extracorporeal clearance through RRT or ECMO needs to be added. The organ clearances keep changing in critically ill, falling in liver and renal failure and hypothermia, and increasing in conditions with hyperdynamic circulation—a situation known as augmented renal clearance (ARC). Augmented renal clearance is defined as estimated GFR >130 mL/minute/1.73 m² that can happen in the initial phase of sepsis, burns, or trauma, where the presence of hyperdynamic circulation leads to increased renal blood flow and glomerular hyperfiltration. This phenomenon results in underdosing of the drug (especially hydrophilic medications) due to enhanced renal elimination.

Importance of the Current $V_d$

This is the ratio of the amount of drug in the body at a given time and plasma concentration at that time. The $V_d$ in critically ill patients can increase by more than 100% when compared to healthy volunteers. Usually drugs with $V_d \leq 1$ L/kg stay in the intravascular time of approximately 48–72 hours. In addition, critically ill patients with AKI experience rapid changes in $V_d$ and renal hemodynamics, which can undermine the use of creatinine clearance equations for drug dosing based on package inserts which are suggested for stable CKD patients in outpatient departments.
compartment, and such drugs are associated with significant removal during RRT, when compared with drugs with $V_d \geq 1$ L/kg. When a drug is administered intravenously, it first gets distributed to the highly vascular organs (heart, brain) followed by less vascular organs (muscle) and lastly to the lipophilic compartment (fat), thus achieving steady state concentration ($V_{dss}$) nearly after 4 to 5 half-lives. Drugs like sedatives in ICU get sequestered in less vascular compartments after prolonged continuous infusions, causing high-elimination $t_{1/2}$ after discontinuation, a phenomenon labeled as "context-sensitive half-time (CSHT)". Sedative drugs with lower CSHT are preferable in the ICU setting.

### Drug Characteristics

**MW**

Table 2 provides the drug characteristics governing dosing strategies in the ICU and Table 3 for antimicrobials, Table 4 for sedatives, and
How to Prescribe Drugs for Critically Ill Patients with AKI on RRT

Table 4: Pharmacological properties of sedatives which can influence dosing in acute kidney injury and renal replacement therapy

| Property | Propofol | Midazolam | Lorazepam | Dexmedetomidine | Fentanyl | Morphine | Remifentanil |
|----------|-----------|-----------|-----------|-----------------|----------|----------|-------------|
| MW (Da)  | 178       | 325       | 321       | 200             | 336      | 285      | 376         |
| \(V_{ss}\) (L/kg) | 2–10       | 1.1–1.7   | 0.8–1.3   | 2–3             | 3–5      | 3–5      | 0.2–0.3     |
| Clearance (mL/kg/minute) | 20–30      | 6.4–11    | 0.8–1.8   | 10–30           | 10–20    | 15–30    | 30–40       |
| Protein binding% | 90–92      | 94–98     | 88–92     | 93              | 84       | 20–40    | 80          |
| Hydrophilic (H) or lipophilic (L) | L (+++) | L (+++) | L (+) | L (+++) | H | L (+++) |
| Elimination \(t_{1/2}\) | 4–7 hours  | 1.7–2.6 hours | 11–22 hours | 2–3 hours | 2–4 hours | 2–4 hours | 0.7–1.2 hours |
| Renal elimination | No | Yes | No | No | Yes | No | No |

Table 5: Pharmacological properties of antiepileptics which can influence dosing in acute kidney injury and renal replacement therapy

| Property | Phenytoin | Carbamazepine | Levetiracetam | Valproic acid |
|----------|-----------|---------------|---------------|--------------|
| MW (Da)  | 252       | 236           | 170           | 144          |
| \(V_{ss}\) (L/kg) | 0.5–0.6 | 0.8–1.2 | 0.5–0.7 | 0.1–0.4 |
| Protein binding% | 90–95 | 75–95 | <10 | 80–90 |
| Hydrophilic (H) or lipophilic (L) | L | L | H | L |
| Elimination \(t_{1/2}\) | 7–42 hours | 30–60 hours | 6–8 hours | 9–16 hours |
| Renal elimination (%) | <5 | 70 | 66 | 70–80 |
| Therapeutic concentration range (μg/mL) | 10–20 | 4–12 | NA | 50–100 |
| Therapeutic free drug levels (μg/mL) | 1–2 | NA | NA | 2.5–10 |
| Additional replacement during/post RRT | Not required\(^a\) | Not required\(^a\) | Yes | Not required\(^a\) |

\(^a\)Correlates with TDM; MW, molecular weight; \(V_{ss}\), steady state volume of distribution

Table 5 for antiepileptics. The MW of the drug expressed in dalton (Da) plays a key role in drug dosing in patients on RRT as the drugs with MW<500 labeled as “small molecules” (urea, potassium, phosphorus, sodium) are removed by diffusion modalities (IHD: intermittent hemodialysis, SLEDD: sustained low-efficiency extended daily dialysis, CVVHD: continuous venovenous hemodialysis). Drugs with MW between 500 and 5,000 Da are labeled as “middle molecules” (albumin), these can be removed from circulation by convection-based modalities [CVVHF, CVVHDF, sustained low-efficiency extended daily dialysis with filtration (SLED-F)] depends upon the sieving coefficient (SC) ratio of ultrafiltrate to plasma solute concentration. Substances with MW of more than 5000 Da are labeled as “large molecules” (albumin), which can be better removed by convective RRT modalities (CVVHDF: continuous venovenous hemofiltration).6 A drug with a negative log \(P\) value in positive range are labeled hydrophilic with an approximate \(V_{ss}\) of 0.1–0.3 L/kg. These drugs are limited to extracellular space, predominantly cleared by kidneys, require a loading dose before administration, and require a change in maintenance dose during the treatment based on the existing renal clearance. These drugs are easily removed by RRT and need an extra replacement dose during or after the RRT, in order to maintain their level in therapeutic concentration range. Drugs with log \(P\) value in positive range are labeled hydrophobic, with their \(V_{ss}\) ranging more than 0.6 L/kg and having good intracellular penetration. These drugs labeled as “lipophilic” are usually eliminated through hepatic pathway; and they usually do not require a loading dose, alteration in the maintenance dose in renal failure, nor an alteration during or after RRT.

**Hydrophilicity**

Octanol–water partition coefficient expressed as log \(P\) measures the lipophilicity or hydrophilicity of a drug.5 A drug with a negative log \(P\) is deemed hydrophilic with an approximate \(V_{ss}\) of 0.1–0.3 L/kg. These drugs are limited to extracellular space, predominantly cleared by kidneys, require a loading dose before administration, and require a change in maintenance dose during the treatment based on the existing renal clearance. These drugs are easily removed by RRT and need an extra replacement dose during or after the RRT, in order to maintain adequate plasma drug concentrations. Drugs with log \(P\) value in positive range are labeled hydrophobic, with their \(V_{ss}\) ranging more than 0.6 L/kg and having good intracellular penetration. These drugs labeled as “lipophilic” are usually eliminated through hepatic pathway; and they usually do not require a loading dose, alteration in the maintenance dose in renal failure, nor an alteration during or after RRT.

**Effect of RRT Modality Selection**

The modality of RRT also influences drug dosing, with filtration methods leading to more drug clearance when compared to diffusion methods.27 Removal of drugs in convection-based modalities [CVVHDF, SLEDD] depends upon the sieving coefficient (SC) ratio of ultrafiltrate to plasma solute concentration.
of the filter membrane. In diffusion-based modalities (IHD, SLED, CVVHD), the concentration gradient between the dialysate and the plasma compartments (saturation coefficient (SA), the ratio of dialysate to plasma solute concentration) and dialyzer efficiency determine drug and solute removal. Efficiency of a dialyzer (KdA is the mass transfer coefficient) is the maximum theoretical clearance of the dialyzer in milliliter per minute for a given solute at infinite blood and dialysis solution flow rates. It is the ability to remove small MW substances such as urea, which is related to its surface area. Dialyzers with KdA < 500 are labeled as “low efficiency” which can be used for small patients or in patients at high risk of dialysis disequilibrium syndrome in whom lower solute clearance is targeted. Dialyzers with a KdA between 500 and 800 are labeled as moderate efficiency dialyzers and dialyzers with a KdA > 800 are known as high efficiency, many of the modern dialyzers have a KdA of between 1200 and 1600 mL/minute in vitro. Another dialyzer-related factor with implications on drug dosing is the dialyzer flux. While originally, ultrafiltration coefficient (Ku) is a measure of water permeability upon applying pressure gradient was used to define the dialyzer flux and β2 microglobulin clearance is used more commonly in the last decade. Dialyzer membranes are classified as low flux (<10 mL/minute), medium flux (10 to 20 mL/minute), and high flux (>20 mL/minute). Flux of a dialyzer is directly proportional to water permeability. In most settings, high-flux dialyzers are used commonly. With low-flux dialyzers, the clearance of molecules with MW > 1000 Da is almost negligible. High-flux dialyzers are characterized by high porosity with significant removal of drugs having MW > 1000 Da, even in diffusion-based modality of RRT. So it should be kept in mind that when a high-flux dialyzer is being used, the convective clearance may not be negligible and certain drugs might need postdialytic replacement.

Pharmacokinetic and Pharmacodynamic Targets of the Drug

Apart from the knowledge of these properties, in order to maximize the efficacy of antimicrobials, the drug dose adjustments should meet its most appropriate pharmacokinetic and pharmacodynamic parameters (PK/PD target), like the percentage of time above the minimum inhibitory concentration (%T > MIC) in time-dependent antimicrobials, peak concentration to MIC ratio (Cmax/MIC) in concentration-dependent drugs, and the ratio of 24-hour area under the curve to MIC (AUC24h/MIC). Optimal modification of drugs with time-dependent killing property is to reduce the dose and maintain the same frequency of administration; whereas for concentration-dependent drugs, it is to alter the frequency, rather than the dose in AKI.

Role of TDM

For drugs with a narrow therapeutic window and in a backdrop of constantly changing Vd, the TDM can guide the clinician to the nearest approximate dose. The TDM is at present available only for a few antimicrobials (vancomycin, amikacin), antiepileptics (phenytoin, valproate), antiarrhythmics (digoxin), and antipsychotics (lithium). The TDM is done after the establishment of steady state concentration (after 4 to 5 half-lives), and it is not available for majority of the drugs in use in ICUs. Further research evaluating the practicality of daily TDM, as well as the clinical benefits and cost-effectiveness of TDM compared to routine practice, is awaited.

Conclusion

The presence of AKI and subsequent initiation of RRT requires vigilant timely reassessment of drug doses in the critically ill patients, by meticulously following PK and PD principles of the drugs. In settings where drug dosing remains uncertain, it is reasonable to err on the lower doses for sedatives to avoid prolonged ICU stays and on higher doses for antimicrobials to ensure effective therapy and prevent emergence of drug resistance.

Authors Statement

The manuscript has been read and approved by all the authors, and each author believes that the manuscript represents honest work.

References

1. Negi S, Koreeda D, Kobayashi S, Iwashita Y, Shigematu T. Renal replacement therapy for acute kidney injury. Ren Replace Ther 2016;2(1):31. DOI: 10.1186/s41100-016-0043-1.
2. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005;294(7):813. DOI: 10.1001/jama.294.7.813.
3. Murugan R, Kellum JA. Acute kidney injury: What’s the diagnosis? Nat Rev Nephrol 2011;7(4):209–217. DOI: 10.1038/nrneph.2011.13.
4. Libório AB, Leite TT, De Oliveira Neves FM, Teles F, De Melo Bezerra CT. AKI complications in critically ill patients: association with mortality rates and RRT. Clin J Am Soc Nephrol 2015;10(1):21–28. DOI: 10.2215/CJN.04750514.
5. Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient: concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev 2014;77:3–11. DOI: 10.1016/j.addr.2014.07.006.
6. Scoville BA, Mueller BA. Medication dosing in critically ill patients with acute kidney injury treated with renal replacement therapy. Am J Kidney Dis 2013;61(3):490–500. DOI: 10.1053/j.ajkd.2012.08.042.
7. Pistolesi V, Morabito S, Di MF, Regolisti G, Cantarelli C, Faccadori E. A guide to understanding antimicrobial drug dosing in critically ill patients on renal replacement therapy. Antimicrob Agents Chemother 2019;63(8):e00583-19. DOI: 10.1128/AAC.00583-19.
8. Cheng V, Abdul-Aziz M-H, Roberts JA, Shekar K. Optimising drug dosing in patients receiving extracorporeal membrane oxygenation. J Thorac Dis 2018;10(55):S629–S641. DOI: 10.21037/jtd.2017.09.154.
9. Varghese JM, Roberts JA, Lipman J. Antimicrobial pharmacokinetic and pharmacodynamic issues in the critically ill with severe sepsis and septic shock. Crit Care Clin 2011;27(1):19–34. DOI: 10.1016/j.ccc.2010.09.006.
10. Zamoner W, de Freitas FM, Garms DSS, de Oliveira MG, Balbi AL, Ponce D. Pharmacokinetics and pharmacodynamics of antibiotics in critically ill acute kidney injury patients. Pharmacol Res Perspect 2016;4(6):e00280. DOI: 10.1016/j.prp2.280.
11. Li J, Xie S, Ahmed S, Wang F, Gu Y, Zhang C, et al. Antimicrobial activity and resistance: influencing factors. Front Pharmacol 2017;8:364. DOI: 10.3389/fphar.2017.00364.
12. Prestinaci F, Pezzotti P, Pantasti O. Antimicrobial resistance: a global multifaceted phenomenon. Pathog Glob Health 2015;109(7):309–318. DOI: 10.11179/2047773215Y.000000030.
13. Seller-Pérez G, Herrera-Gutiérrez ME, Maynar-Moliner J, Sánchez-Izquierdo-Riera JA, Marino A, Do Pico JL. Estimating kidney function in the critically ill patients. Crit Care Res Pract 2013. 1–6. DOI: 10.1155/2013/529524.
14. Waiker SS, Bonventre JV. Creatinine kinetics and the definition of acute kidney injury. J Am Soc Nephrol 2009;20(3):672–679. DOI: 10.1681/ASN.2008070669.
15. Sunder S, Jayaraman R, Mahapatra H, Sathi S, Ramanan V, Kanchi P, et al. Estimation of renal function in the intensive care unit: the
How to Prescribe Drugs for Critically Ill Patients with AKI on RRT

14. Covert concepts brought to light. J Intensive Care 2014;2(1):1–7. DOI: 10.1186/2052-0492-2-14.

16. MacDonald J, Moore J, Davey V, Pickering S, Dunne T. The weight debate. J Intensive Care Soc 2015;16(3):234–238. DOI: 10.1177/175143714565059.

17. Ferrari F, Sartori M, Milla P. Antibiotic adjustment in continuous renal replacement therapy. In: Ronco C, Bellomo R, Kellum JA, Ricci Z. Critical Care Nephrology. 3rd ed., Canada: Elsevier; 2019. pp. 1051–1067.e1. DOI: 10.1016/B978-0-323-44942-7.00175-8.

18. Bilbao-Meseguer I, Rodríguez-Gascón A, Barrasa H, Isla A, Solinís MA. Augmented renal clearance in critically ill patients: A systematic review. Clin Pharmacokinet 2018;57(9):1107–1121. DOI: 10.1007/s40262-018-0636-7.

19. Gonçalves-Pereira J, Póvoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of β-lactams. Crit Care 2011;15(5):R206. DOI: 10.1186/cc10441.

20. Villa G, Neri M, Bellomo R, Cerda J, De Gaudio AR, De Rosa S, et al. Nomenclature for renal replacement therapy and blood purification techniques in critically ill patients: practical applications. Crit Care 2016;20(1):283. DOI: 10.1186/s13054-016-1456-5.

21. Zhao W, Jacqz-Aigrain E. Principles of therapeutic drug monitoring. Handb Exp Pharmacol 2011;205:77–90. DOI: 10.1007/978-3-642-20195-0_3.

22. Zeitlinger MA, Derendorf H, Mouton JW, Cars O, Craig WA, Andes D, et al. Protein binding: Do we ever learn? Antimicrob Agents and Chemother 2011;55(7):3067–3074. DOI: 10.1128/AAC.01433-10.

23. Kuang D, Verbine A, Ronco C. Pharmacokinetics and antimicrobial dosing adjustment in critically ill patients during continuous renal replacement therapy. Clin Nephrol 2007;67(5):267–284. DOI: 10.5414/cnp67267.

24. Farrokh S, Tahsili-Fahadan P, Ritzl EK, Lewin JJ, Mirski MA. Antiepileptic drugs in critically ill patients. Crit Care 2018;22(1):153. DOI: 10.1186/s13054-018-2066-1.

25. Mahmoud SH. Antiepileptic drug removal by continuous renal replacement therapy: a review of the literature. Clin Drug Investig 2017;37(1):1–13. DOI: 10.1007/s40261-016-0457-0.

26. Leo A, Hansch C, Elkins D. Partition coefficients and their uses. Chem Rev 1971;71(6):525–616. DOI: 10.1021/cr60274a001.

27. Ward RA, Ronco C. Dialyzer and machine technologies: application of recent advances to clinical practice. Blood Purif 2006;24(1):6–10. DOI: 10.1159/000089429.