INVITED ARTICLE

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

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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 (V_d), 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.

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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 dyselectrolytemia, 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 (V_d), altered protein binding (P_B), 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.[5,8] 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, V_d, 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 seizures (antiepileptics); overdosing can lead to adverse effects such as excess sedation, prolonged organ support requirements and length of ICU stay (in the case of sedatives), cardiac arrhythmias, and hepatic and nephrotoxicity in antiepileptics and antimicrobials.[10] In case of antimicrobials, if the drug concentration is not above the mutant prevention concentration, the resistant strains in the mutant selection window can increase, leading to the development of selection pressure and therapeutic failure of the antimicrobials.[11] This can increase the multi-drug resistant, extensively drug resistant, and pan-drug resistant microorganisms, which have already been labeled as high-priority organisms by the World Health Organization.[12]

Validity of Estimated Glomerular Filtration Rate for Drug Dosing

The problem of drug dosing starts with identifying AKI, as even now the estimation of glomerular function rate relies on creatinine, a molecule, which at baseline, is influenced by many factors in ICU such as muscle mass, diet, volume status, etc.[13] Also, dynamic changes in GFR precede changes in serum creatinine values by a lag

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Table 1: Factors to be considered for dug 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_{UF}, K_0A, SC, SA)
Serum protein concentration	log *P* value	Pre- or post-dilution in CRRT
Blood pH	Competition with other drugs	Dose of dialysis
Serum electrolytes		Treatment duration
Variations in V_d		Recirculation in vascular access

IBW, ideal body weight; LBW, low body weight; ABW, actual 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_{UF}, ultrafiltration coefficient; K_0A, mass transfer coefficient; SC, sieving coefficient; SA, saturation area

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
	Renal clearance	Hepatic clearance
In sepsis	Loading dose	No need
	Changes in maintenance dose	No need
In renal failure (AKI)	↓ maintenance dose	No change
Dose replacement after RRT	Extra dose during/ post RRT	Usually not required
Examples	Aminoglycosides	Fluoroquinolones
	Beta-lactams	Glycylcycline
	Glycopeptides	Ketolides
	Lipopeptides	Lincosamides
	Polymyxins	Linezolid
	Fluconazole	Macrolides
	Flucytosine	Metronidazole
	Acyclovir	Streptogramins
	Azoles	Tetracycline
		Tigecycline
		TMP-SMZ
		Amphotericin B
		Echinocandins
		Protease inhibitors

AKI, acute kidney injury; TMP-SMZ, trimethoprim-sulfamethoxazole; ↓: decrease

time of approximately 48–72 hours.[14] 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.[7] Although various formulas are available to estimate glomerular filtration rate (GFR) for drug dosing, taking into consideration the V_d, ongoing creatinine production, blood urea nitrogen, serum albumin, fluid balance, they are yet to be validated in ICU population.[15] Jelliffe's equation corrects for fluctuations of serum creatinine over time, and its modified version adjusts for cumulative fluid balance.[15] It has been suggested that serum cystatin C-based estimation might be better correlated with GFR than serum creatinine-based equations in critically ill patients. Aminoglycoside clearance performs well in the estimation of renal function but may not be preferred universally, as it unnecessarily uses an antimicrobial agent for a diagnostic test as well as the risk of nephrotoxicity. A promising experimental technique, the optic ratiometric fluorescent analyzer can rapidly determine renal function, was standardized again iohexol clearance, but no human studies have been reported yet.[15]

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.[16] 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 a play 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.[7] In addition, extracorporeal clearance through RRT or ECMO needs to be added.[8,17] 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).[5] Augmented renal clearance is defined as estimated GFR >130 mL/minute/1.73 m^2 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.[18] In few studies, creatinine clearance of even 190 mL/minute/1.73 m^2 was also reported in postoperative patients, further adding to the challenge of drug dosing. This can be seen in around 20–65% of critically ill patients.[18] This concept of ARC needs to be considered in the initial phase of drug dosing where hyperdynamic circulation is suspected as it can lead to subtherapeutic drug levels.

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.[19] Usually drugs with $V_d \leq 1$ L/kg stay in the intravascular

Table 3: Properties of antimicrobials which can influence dosing in acute kidney injury and renal replacement therapy

Antimicrobial	*MW (Da)*	*Protein binding %*	*V_d (L/kg)*	*L/H*
Colistin	1,634	50	0.34	L and H
Imipenem/cilastatin	317–380	20	0.14–0.23	H
Meropenem	437	2	0.35	H
Doripenem	438	8	16.8	H
Ertapenem	490	85	0.2	H
Aztreonam	435	56	0.2	H
Piperacillin–tazobactam	517–300	30/30	0.18	H
Ampicillin–sulbactam	255–232	25/38	0.2	H
Cefoperazone–sulbactam	645–232	85	0.14–0.20	H
Ceftazidime–avibactam	547–265	8–10	0.28–0.31	H
Vancomycin	1,485	50	0.7	H
Teicoplanin	1,887	90	0.8–1.6	H
Linezolid	337	31	40–50 L	H
Daptomycin	1,620	92	0.09–0.1	L
Tigecycline	585	71–89	7–9	L
Minocycline	457	70–75	80–115 L	L
Doxycycline	444	90	0.9–1.8	L
Fosfomycin	138	<3	20–22 L	L
Amikacin	585	3–11	0.3	H
Metronidazole	171	<20	0.6–1.1	L
Azithromycin	785	7–15	33	L
Clarithromycin	748	80	250 L	L
Ciprofloxacin	331	20–40	2.1–2.7	L
Levofloxacin	361	20	1.25	L
Ceftriaxone	600	85–95	6–14 L	L
Cefepime	480	16–20	0.33–0.40	H
Cefazolin	454	86	0.14	H
Ceftazidime	546	5–17	0.28–0.36	H
Clindamycin	450	94	2	L
Trimethoprim–sulfamethoxazole	253	65	12–18 L	H
Chloramphenicol	323	60		L
Crystalline amphotericin B	921	>95	4	L
Liposomal amphotericin B	924	90	131	L
Fluconazole	306	<10	0.6–0.8	H
Voriconazole	349	58	4.5	L
Isavuconazole	437	99	6.4	L
Caspofungin	1,213	97	0.15	H
Anidulafungin	1,140	99	0.6	H
Micafungin	1,292	99	0.4	H and L
Acyclovir	225	<20	0.8	H
Ganciclovir	255	1–2	1.17	H
Oseltamivir	312	3	25–45 L	H

MW, molecular weight in dalton; V_d, volume of distribution (L/kg); L, lipophilic; H, hydrophilic; L, liter

compartment, and such drugs are associated with significant removal during RRT, when compared with drugs with $V_d \geq 1$ L/kg.[5]

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 (Vdss) 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

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_{dss} (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	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	Yes	No	No	Yes	No

MW, molecular weight; Da, Dalton; NA, not available

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_{dss} (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_{dss}, 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" (vitamin B_{12}, inulin) which can be better removed by convective RRT modalities (CVVHF: continuous venovenous hemofiltration).[17] Substances with MW of more than 5000 Da are labeled as "large molecules" (albumin), these can be removed from circulation by adsorption or plasmapheresis.[20] When combined modalities are being used, the prediction of drug removal becomes very difficult, unless therapeutic drug monitoring (TDM) is available.[21]

Protein Binding

During critical illness, the concentration of acute phase reactants such as α-1 acid glycoprotein rises, while the plasma albumin concentration falls.[10] This can lead to increase in adverse effects of drugs with high affinity of binding to α-1 acid glycoprotein such as clindamycin, lidocaine, trimethoprim, and haloperidol and rapid clearance of the free drug (leading to lack of clinical benefit or development of resistance), especially drugs with high affinity to albumin. The difference in protein binding of drugs in controlled laboratory settings (where drugs are tested) and in critically ill patients is attributable to variations in blood pH, calcium ion concentration, other drugs coadministered, and coexisting conditions such as hyperbilirubinemia.[22] Only the free fraction of a drug is susceptible to removal by RRT.[5] Highly protein-bound drugs (teicoplanin, tigecycline, echinocandins) are difficult to be removed from any form of RRT.[23] The commonly usedantiepileptics are comprised of small molecules (<500 Da) and are highly protein bound, with significant alteration in unbound free fraction of the drug due to variation in serum protein concentration in critically ill, thereby requiring monitoring of free fraction of the drug apart from the protein-bound fraction in order to maintain their level in therapeutic concentration range.[24] Drugs with low protein binding like levetiracetam require additional doses during or post RRT, as significant portion of the drug can be removed by RRT.[25]

Hydrophilicity

Octanol–water partition coefficient expressed as log *P* measures the lipophilicity or hydrophilicity of a drug.[26] A drug with a negative log *P* is deemed hydrophilic with an approximate V_d 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 as hydrophobic, with their V_d ranging more than 0.6 L/kg and having good intracellular penetration. These drugs labeled as "lipophilic"[5] 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 [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]

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.[7] Efficiency of a dialyzer (K_0A 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.[20] It is the ability to remove small MW substances such as urea, which is related to its surface area. Dialyzers with K_0A <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 K_0A between 500 and 800 are labeled as moderate efficiency dialyzers and dialyzers with a $K_0A > 800$ are known as high efficiency, many of the modern dialyzers have a K_0A of between 1200 and 1600 mL/minute *in vitro*.[20] Another dialyzer-related factor with implications on drug dosing is the dialyzer flux. While originally, ultrafiltration coefficient (K_{UF} is a measure of water permeability upon applying pressure gradient) was used to define the dialyzer flux and β_2 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).[27] 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.[27] 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 (C_{max}/MIC) in concentration-dependent drugs, and the ratio of 24-hour area under the curve to MIC (AUC_{24}/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.[10]

Role of TDM

For drugs with a narrow therapeutic window and in a backdrop of constantly changing V_d, 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).[21] 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.

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