Review

Clinical review: Drug metabolism and nonrenal clearance in acute kidney injury

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Abstract

Decreased renal drug clearance is an obvious consequence of acute kidney injury (AKI). However, there is growing evidence to suggest that nonrenal drug clearance is also affected. Data derived from human and animal studies suggest that hepatic drug metabolism and transporter function are components of nonrenal clearance affected by AKI. Acute kidney injury may also impair the clearance of formed metabolites. The fact that AKI does not solely influence kidney function may have important implications for drug dosing, not only of renally eliminated drugs but also of those that are hepatically cleared. A review of the literature addressing the topic of drug metabolism and clearance alterations in AKI reveals that changes in nonrenal clearance are highly complicated and poorly studied, but they may be quite common. At present, our understanding of how AKI affects drug metabolism and nonrenal clearance is limited. However, based on the available evidence, clinicians should be cognizant that even hepatically eliminated drugs and formed drug metabolites may accumulate during AKI, and renal replacement therapy may affect nonrenal clearance as well as drug metabolite clearance.

Introduction

The incidence of acute kidney injury (AKI) among hospitalized patients is increasing [1,2]. Although this increased incidence may in part be due to critically ill patients representing a larger proportion of patients that are admitted into hospitals and the increased recognition of AKI, this finding is of great concern because AKI has been associated with high rates of in-hospital mortality [3-5]. Many developments have occurred over the past several decades that have improved the care provided to patients with AKI, in particular developments relating to renal replacement therapy (RRT). However, our understanding of AKI is continuously evolving, including an appreciation of the changes in drug pharmacokinetics and pharmacodynamics that occur with AKI.

Glomerular filtration, tubular secretion, and renal drug metabolism are the processes by which many drugs are removed by the kidneys. It is clear that AKI will affect all of these processes and thus the renal clearance of drugs and toxins. However, what is not well understood is the effect that AKI has on the clearance of these substances by other organ systems (nonrenal clearance). This nonrenal drug clearance typically is dominated by hepatic clearance, but drug metabolism can occur in a variety of organs. Although rarely studied directly, some have observed that nonrenal clearance may change with the onset of AKI (Table 1).

Of the drugs summarized in Table 1, particularly vancomycin, none would be considered by clinicians to be drugs with important nonrenal clearances, but nonrenal clearances in AKI have been found to be quite different from those observed in patients with normal renal function or with end-stage renal disease. These alterations in nonrenal clearance could be considered 'hidden' drug clearance changes because they usually would go unrecognized. Although it is probable that these changes in nonrenal clearance exist for other drugs, we are not aware of other published reports.

Why has the phenomenon of nonrenal clearance differences between patients with normal renal function and those with AKI not been identified with other drugs? One reason why this 'hidden clearance' change may be missed is that therapeutic drug assays are not readily available in the clinical setting of the intensive care unit for many drugs. Furthermore, there is a paucity of pharmacokinetic studies conducted in AKI patients. The US Food and Drug Administration does not mandate pharmacokinetic studies in patients with AKI as part of the approval process [6], and consequently there is little

AKI = acute kidney injury; CKD = chronic kidney disease; CYP = cytochrome P450; Fr_{EC} = fractional extracorporeal clearance; MMAAP = monomethylaminoantipyrine; OAT = organic anion transporter; PAH = p-aminohippurate; P-gp = P-glycoprotein; RRT = renal replacement therapy.

Table 1

Drugs recognized to exhibit altered nonrenal clearance in acute kidney injury in clinical studies

Drug	Normal renal function	Acute kidney injury	End-stage renal disease
Imipenem	130 ml/minute [55-58]	90 to 95 ml/minute [8,59]	50 ml/minute [8,60,61]
Meropenem	45 to 60 ml/minute [62-64]	40 to 60 ml/minute [65,66]	30 to 35 ml/minute [63,64]
Vancomycin	40 ml/minute [67]	15 ml/minute [7]	5 ml/minute [68,69]

incentive for these studies to be funded by the pharmaceutical industry.

The changes in nonrenal clearances of imipenem and vancomycin were a serendipitous discovery [7,8]. In the case of vancomycin, it appeared that vancomycin nonrenal clearance declined as the duration of continuous RRT increased [7]. We observed that, as AKI persisted, vancomycin nonrenal clearance slowed until it approached values associated with end-stage renal disease. Our serendipitous findings suggested that further study is warranted in this area, because the mechanism(s) underlying these nonrenal clearance changes have not been elucidated. Currently, most investigations into these nonrenal clearance alterations are being conducted in animal models, especially with respect to the effects of inflammation, like that seen in AKI [9]. It is likely that the nonrenal clearances of many more drugs are altered in AKI. A more complete understanding of these mechanisms will hopefully lead to better methods of monitoring for nonrenal drug clearance changes and development of more precise dosing adjustment strategies.

Boucher and coworkers [10] thoroughly reviewed the pharmacokinetic changes that may occur with critical illness overall, but not in AKI specifically, and these changes are not reviewed here. In order to understand how AKI influences nonrenal clearance, it is important to identify the component(s) of nonrenal clearance that are affected. Nonrenal clearance is the aggregate of all drug removal pathways excluding those related to the kidneys; consequently, nonrenal clearance would include such pathways as hepatic, pulmonary, intestinal, and so on. For the most part, hepatic metabolism comprises the largest component of nonrenal clearance, typically converting medications to less toxic and more water soluble compounds to facilitate elimination from the body.

Hepatic metabolism

It is likely that there are many mechanisms by which AKI changes hepatic drug metabolism. Altered tissue blood flow and protein binding represent some of these factors. However, retained azotemic or uremic molecules may also have a direct impact on metabolic enzymes and drug transporters. Abundant clinical evidence exists describing changes in hepatic drug metabolism during chronic kidney disease (CKD) [11-17]. The number of studies addressing changes in hepatic metabolism in AKI is far more limited. Much of what has been learned to date on this topic has been derived from animal models of kidney disease, cell cultures, and microsomal homogenates.

Animal data

Table 2 highlights the results of animal studies investigating the effect of AKI on hepatic metabolism. From Table 2 it is apparent that, depending on the drug that is studied, AKI may increase, decrease, or have no effect on hepatic drug metabolism. These varying results are consistent with the findings of studies investigating the effects of CKD on drug metabolism [11-13,15]. When interpreting the findings presented in Table 2, one must recognize that although AKI may not demonstrate a change in hepatic drug metabolism, it is still possible to observe changes in serum drug concentration because other pharmacokinetic changes may be occurring. For example, AKI may change intestinal absorption or metabolism, or it may alter plasma protein binding [18-23].

To consider AKI as a single homogenous entity is an oversimplification because there are many etiologies of AKI and each of their clinical presentations are distinct. AKI induced by nephrotoxins often manifests with a different clinical picture than AKI induced by hypoxia, sepsis, or autoimmune diseases. For example, nephrotoxicity related to both gentamicin and cyclosporine are generally considered dose related. However, cyclosporine is associated with altered renal hemodynamics and vasoconstriction, whereas gentamicin toxicity is associated with drug accumulation in the renal cortex (with concentrations several fold greater than in plasma) and acute tubular necrosis. Consequently, it is plausible that various etiologies of AKI may also affect hepatic metabolism differently, as illustrated for diltiazem in Table 2. Furthermore, as shown in Table 3, not all hepatic cytochrome P450 (CYP) enzymes are affected by AKI, and the extent of the effect on hepatic clearance via CYP may depend on the mechanism of experimental kidney injury.

Another important consideration regarding the effect of AKI on drug metabolism is that an observed change in CYP activity in a particular organ cannot be extrapolated to other organs. Okabe and coworkers [24] demonstrated that the

Table 2

Animal studies investigating the effect of AKI on hepatic drug metabolism

Drug	Animal	AKI model	Authors' conclusion on effect of AKI on hepatic metabolism
Ajmaline [18]	Rat	Uranyl nitrate	↔
Clarithromycin [26]	Rat	Uranyl nitrate	↔
Cyclosporine [21]	Rat	Gentamicin	↔
Diltiazem [70]	Rat	Uranyl nitrate	↑
Diltiazem [71]	Rabbit	Folate	↓
Etoposide [72]	Rat	Uranyl nitrate	↔
Losartan [19]	Rat	Uranyl nitrate and bilateral ureter ligation	↔
Metoprolol [22]	Rat	Bilateral ureteral ligation	↔
Metoprolol [23]	Rat	Glycerol	↔
Propranolol [20]	Rat	Cisplatin	↔
Propranolol [22]	Rat	Bilateral ureteral ligation	↔
Tacrolimus [73]	Rat	Cisplatin	↓
Telithromycin [27]	Rat	Uranyl nitrate	↔
Theophylline [74]	Rat	Uranyl nitrate	↑

↑, increase, ↓, decrease, ↔, no change; AKI, acute kidney injury.

Table 3

The effect of AKI on the activity of selected rat model CYP enzymes

Rat CYP	Effect	AKI model
2A1	↔	Uranyl nitrate induced kidney injury
2B1/2	↔	Uranyl nitrate induced kidney injury
2C6	↔	Nephrectomy
	↔	Bilateral ureteral ligation
	↔	Glycerol-induced kidney injury
	↓	Cisplatin-induced kidney injury
2C11	↓	Uranyl nitrate induced kidney injury
2D2	↔	Nephrectomy
	↔	Bilateral ureteral ligation
	↔	Glycerol-induced kidney injury
	↔	Cisplatin-induced kidney injury
2E1	↑	Uranyl nitrate induced kidney injury
3A1 (3A23)	↑	Uranyl nitrate induced kidney injury
3A2	↓	Nephrectomy
	↔	Bilateral ureteral ligation
	↓	Glycerol-induced kidney injury
	↔	Cisplatin-induced kidney injury

Data from [24,25,75]. ↑, increase; ↓, decrease; ↔, no change; AKI, acute kidney injury; CYP, cytochrome P450.

change in CYP activity in the intestine and liver may not necessarily be the same. Specifically, during glycerol-induced AKI in rats, there was a significant increase in CYP3A4 activity in the intestine despite a significant decrease in CYP3A4 activity in the liver.

Observations made at the CYP level may not translate to clinically meaningful systemic changes in drug pharmacokinetics. The data presented in Table 3 suggest that in the rat model of uranyl-nitrate induced AKI there is an induction of CYP3A1 [25]; therefore, it would be expected that serum concentrations of drugs metabolized by this pathway, such as clarithromycin and telithromycin, would be decreased. However, the hepatic metabolism of clarithromycin [26] and telithromycin [27] was not significantly different between rats with AKI and control animals (Table 2). There are a number of potential reasons for these seemingly contradictory observations. For instance, perhaps other pharmacokinetic changes occurred when AKI was induced, such as changes in plasma protein binding or altered transporter expression/function that offset increased CYP3A1 activity. As mentioned above, cytochrome expression in other organs may not necessary mimic the changes that occur in the liver. Thus, even though there is induction of hepatic CYP3A1 in the liver, enzymes in the intestine and/or kidneys may not be affected or may be inhibited.

Extrapolating the findings presented in Table 3 to humans is complicated by the fact that rat CYP is not necessarily equivalent to human CYP because of isoenzyme differences. Evidence of the effect of AKI on drug metabolism in humans is much more difficult to obtain, and the number of studies available is small.

Human data

We were able to locate a single human study that investigated the influence of AKI on a drug that is highly hepatically metabolized [28]. That study characterized the pharmacokinetics of monomethylaminoantipyrine (MMAAP), which is the pharmacologically active form of dipyrine (metamizol), and its metabolites in critically ill patients with AKI. Heinemeyer and colleagues [28] noted that the clearance of MMAAP was significantly reduced in patients with AKI compared with those with normal renal function. MMAAP is usually cleared by hepatic metabolism to N-formylaminoantipyrine and N-acetylaminoantipyrine. However, the rates of appearance of N-formylaminoantipyrine and N-acetylaminoantipyrine were also significantly reduced. Based on these observations, the authors suggested that the decreased rate of MMAAP clearance in AKI patients may be due to reduced hepatic metabolism. They acknowledged, however, that there are other potential explanations for reduced MMAAP clearance, such as hypoxia and reduced protein synthesis during critical illness as well as competitive metabolism with concomitantly administered drugs. Decreased MMAAP clearance could also be due to decreased cardiac output, altering hepatic blood flow.

Transporters

Drug metabolism and clearance are also affected by transporter activity. Transporters may facilitate drug uptake or removal in various organs throughout the body. To date, few transporter studies have been conducted in the setting of AKI, and all that have been conducted have been in animal models or cell cultures. This review focuses on organic anion transporters (OATs) and P-glycoprotein (P-gp), because they are important in the transfer of drugs across cell membranes and have been studied in animal models of AKI. Like CYP, there are interspecies differences with respect to transporter subtypes and tissue distribution, and these differences must be considered when attempting to extrapolate data derived from animals to humans.

P-glycoprotein

P-gp is an ATP-dependent efflux pump that is widely expressed in normal tissues, including the intestines, liver, and kidneys. P-gp plays an important role in the transport of lipophilic compounds from inside cells to the intestinal lumen, bile, and urine. The removal of compounds from the intracellular milieu prevents accumulation of drug or toxin within tissues and facilitates the clearance of these substances from the body.

In rats with induced kidney injury, there was increased expression of P-gp in the kidney [29-31] but not in the liver [30,31] or intestines [32]. What is interesting is that despite increased renal P-gp expression, the clearance of P-gp substrates was decreased in the kidney. Decreased P-gp activity was also noted in the liver and intestines. These observations indicate that AKI may result in a systemic suppression of P-gp function. Considering the role played by P-gp, the implications of reduced P-gp function in the intestines, liver, and kidneys are decreased gastrointestinal secretion, hepatic biliary excretion, and renal tubular secretion of P-gp substrates such as vinblastine, vincristine, methotrexate, digoxin, and grepafloxacin [32,33].

Organic anion transporters

OATs are predominantly found in the basolateral membrane of the renal tubules and facilitate the uptake of small organic anions from the peritubular plasma into renal tubular cells, where they are then effluxed across the apical membrane by other transporters into the tubular lumen. Induction of AKI in ischemia-reperfusion rat models demonstrates decreased OAT1 and OAT3 mRNA as well as protein expression [34-36]. The reduced quantity of OATs translated into decreased renal uptake of p-aminohippurate (PAH; an organic anion), significantly decreased PAH renal excretion, and thus significantly lower PAH clearance.

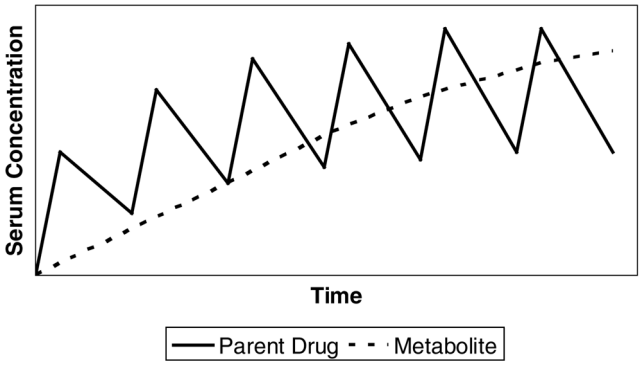
Although the role played by OATs in nonrenal drug clearance has not been characterized, decreased OAT1 and OAT3 activity as a result of AKI could decrease the renal secretion of drugs such as methotrexate, nonsteroidal anti-inflammatory drugs, and acetylsalicylic acid [16]. Thus, in addition to AKI having an effect on drug metabolism, AKI also affects transporter function. The decreased activity of P-gp and OATs in AKI would contribute to decreased drug clearance and may potentially result in increased drug exposure.

Disposition of formed metabolites in AKI

Once formed, drug metabolites, like the parent compound, must be cleared from the body. The clearance of drug metabolites is of particular importance if the formed metabolites are pharmacologically active. In AKI, metabolites that are normally renally eliminated may be retained [37-42], and accumulation is more likely to be problematic with repeated dosing (Figure 1). Table 4 lists drugs with known active or toxic metabolites that accumulate in renal disease. Many of these drugs are commonly administered in the intensive care setting.

As with the parent drug, accumulation of pharmacologically active metabolites results in a more pronounced expression of drug response, whether that response is 'toxic' or 'therapeutic'. In the case of morphine, accumulation in renal failure of the pharmacologically active metabolite morphine-6-glucuronide [43] yields an analgesic effect that necessitates lengthening the dosing interval after the first 2 days of morphine therapy. Use of patient-controlled analgesia may allow patients with kidney injury to titrate their own dose. Because morphine-6-glucuronide has pharmacologic activity, patient-controlled analgesia should account for the contribution of morphine-6-glucuronide to pain control. Similarly, lengthening the dosing interval should be considered when codeine products are used because of retention of pharmacologically active metabolites, particularly after a few days of therapy have elapsed and metabolite serum concentrations increase.

Figure 1



Serum concentration profile of parent drug and metabolite in impaired metabolite clearance. Presented is a schematic of the serum concentration profile of parent drug and metabolite that may occur with impaired metabolite clearance with repeated drug doses, particularly if the metabolite has a long half-life.

Effect of renal replacement therapy on nonrenal drug clearance

Because evidence suggests that uremic toxins may be responsible for changes in metabolism that occur during AKI, it is plausible that removal of these toxins with RRT may reverse the nonrenal clearance changes that are observed in AKI. In a pharmacokinetic study of telithromycin in patients with renal impairment, Shi and coworkers [44] noted that, as the degree of renal function worsened, telithromycin exposure increased (as indicated by area under the curve). However, in patients with severe renal impairment requiring dialysis, telithromycin administration 2 hours after dialysis resulted in drug exposure that was comparable to that in healthy individuals. This led the investigators to consider whether clearance of uremic toxins by dialysis had an effect on drug metabolism.

The observation reported by Shi and coworkers [44] was corroborated by a more recent study by Nolin and colleagues [45] in which they specifically examined this issue. The ^{14}C-erythromycin breath test was used as a marker of CYP3A4 activity, and patients had a 27% increase in CYP3A4 activity 2 hours after dialysis compared with before dialysis. CYP3A4 activity was inversely related to plasma blood urea nitrogen concentrations. Nolin and colleagues concluded that conventional hemodialysis used during the uremic state acutely improved CYP3A4 function. Both of these studies, conducted in CKD patients receiving intermittent hemodialysis, suggested that similar effects of RRT in AKI patients might also occur.

RRT removal of metabolites must also be considered. Indeed, pharmacokinetic studies of metabolite removal by any type of

Table 4

Drugs with renally eliminated active or toxic metabolites that may accumulate in AKI

Drug	Drug class	Accumulated substance	Clinical consequence of metabolite accumulation
Allopurinol	Xanthine oxidase inhibitor	Active metabolite oxypurinol	Increased risk for immune-mediated hypersensitivity reaction
Codeine	Opioid analgesic	Active metabolites norcodeine and morphine	CNS depression, respiratory depression
Dolasetron	Anti-emetic	Active metabolite hydrodolasetron	Q-T prolongation/ECG changes
Meperidine	Opioid analgesic	Toxic metabolite normeperidine	Anxiety, agitation, tremors, twitches, myoclonus, seizure
Midazolam	Benzodiazepine	Active metabolites 1-hydroxymidazolam and 1-hydroxymidazolamglucuronide	Apnea, sedation, drowsiness
Morphine	Opioid analgesic	Active metabolite morphine-6-glucuronide	CNS depression, respiratory depression
Mycophenolate mofetil/ mycophenolic acid	Immunosuppressant	Inactive glucuronide metabolite displacing mycophenolic acid from albumin and resulting in increased free mycophenolic acid concentration	Leukopenia
Procainamide	Anti-arrhythmic	Active metabolite N-acetyl procainamide (NAPA)	Sinus bradycardia, sinus node arrest, Q-T interval prolongation
Propoxyphene	Opioid analgesic	Active metabolite norpropoxyphene	Cardiotoxicity resulting in dysrhythmias
Quinidine	Anti-arrhythmic, antimalarial	Active metabolite 3-hydroxy quinidine	Additive Q-T interval prolongation
Voriconazole - intravenous formulation	Antifungal	Vehicle sulfobutyl ether β-cyclodextran sodium (SBECD)	Demonstrated proximal tubule toxicity in rats

Data from [37,39,40,43,76-82]. AKI, acute kidney injury.

RRT are rare [42,46-48]. However, because active metabolites may be removed during RRT, it is important to be cognizant that drug doses may need to be adjusted with the initiation and cessation of RRT.

It is generally accepted that supplemental drug doses are required during RRT only when the extracorporeal clearance of a drug exceeds 20% to 30% of total body clearance [49-51], also known as fractional extracorporeal clearance (Fr_{EC}). Fr_{EC} is mathematically expressed as follows:

$$Fr_{EC} = \frac{Cl_{EC}}{Cl_{EC} + Cl_{NR} + Cl_{R}}$$

Where Cl_{EC} is the extracorporeal clearance, Cl_{NR} is the nonrenal clearance, and Cl_{R} is the renal clearance. Because AKI changes renal clearance and potentially nonrenal clearance, AKI could alter the Fr_{EC} of drugs during RRT.

Practical applications

Although current drug dosing strategies during AKI are problematic, including an inability to quantify glomerular filtration rate accurately, clinicians diligently attempt to adjust renally eliminated drugs. Recognizing that there are limitations to drug dosing guidelines for renal disease and RRT, such as extrapolation of CKD data to AKI and constant changes in how RRT is provided, references are available to clinicians [52]. Less prominent in the clinician's mind are dose adjustments for changes in hepatic clearance during AKI. Even with drugs that are predominantly hepatically cleared, clinicians often do a poor job of adjusting doses to account for hepatic disease.

As stated above, for drugs such as those listed in Table 1, where renal clearance overshadows the 'lesser' hepatic clearance, dosages are almost never adjusted to account for changes in nonrenal clearance. There are no known clinically useful biomarkers or systems that are analogous to creatinine clearance for adjusting drug doses in hepatic injury. To assist clinicians in adjusting drug doses for fulminate liver disease, drug dosing tables exist [53,54]. However, these charts are typically not applicable to milder forms of liver disease and have not been validated in patient populations with critical illness or renal disease.

As outlined above, alterations in drug metabolism in AKI are highly complicated and poorly studied, but they are possibly quite common. At present, our understanding of how AKI affects drug metabolism and clearance is limited. AKI studies are generally small in number and typically have not been conducted in humans. Extrapolation of results derived from animal studies is problematic because of interspecies variations in metabolizing enzymes and transporters. Moreover, investigation of an isolated component of drug clearance in a single organ may not be representative of what occurs on a systemic level, taking into consideration all of the variables that may affect drug metabolism and clearance. Even if all of the pharmacokinetic effects of AKI have been accounted for, pharmacodynamic response to a given serum drug concentration may be modified by cytokines, chemokines, and inflammatory mediators that are present during critical illness.

The presence of multiple disease states in critically ill patients with AKI adds another layer of complexity when attempting to predict how AKI changes drug metabolism and nonrenal clearance. There is growing evidence that specific disease states such as sepsis, burns, and trauma also influence CYP and transporter activity, independent of whether AKI is also present. Because of the lack of human studies, the complexity of acute illness, and the multiple pathways that are involved in drug metabolism and clearance, it is difficult to provide clear-cut rules on how drug dosing should be approached.

Considering the evidence we have to date, how can the clinician apply some of the presented information to the care of patients with AKI? We would offer the following three suggestions.

First, recognize that AKI not only changes the renal clearance of drugs but also the nonrenal clearance. Even drugs that are primarily hepatically eliminated may accumulate during AKI. Periodically, monitor serum drug concentrations or pharmacodynamic response when feasible, even for drugs that are considered to be predominantly hepatically cleared. Because AKI is a dynamic process, continual monitoring of serum drug concentration is necessary, particularly with changes in drug dose and clinical status.

Second, metabolites may accumulate with AKI. Be aware of potential pharmacologically active metabolite accumulation with AKI. Also, consider dose adjustment when enough time has elapsed such that metabolite accumulation is likely to have occurred. Use clinical monitoring tools, such as sedation and pain scales, along with clinical judgment to guide your decision.

Third, RRT affects drug removal directly, but these therapies may also have an impact on the nonrenal clearance of drugs. Initiation of RRT may hasten hepatic clearance of drugs that are cleared by CYP3A4, such as amiodarone, cyclosporine, erythromycin, midazolam, nifedipine, quinidine, and tacrolimus. RRT may further modify the pharmacokinetic and dynamic changes of parent compounds/metabolites; drug dose and response should be evaluated when RRT is started and stopped.

Conclusion

The apparently simple question 'What is the right drug dose for this patient with AKI?' is a troubling one for clinicians.

This article is part of a review series on
Renal replacement therapy,
edited by John Kellum and Lui Forni.

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Unfortunately, the answer is not as simple as the question. The answer to this question is continually changing. Factors such as changes in renal function, the contributions of RRT, changes in the patient's volume status, and alterations in organ function are all influential. These factors change from minute to minute in the dynamic AKI patient. Regular therapeutic drug monitoring should be a standard of care when treating patients with AKI. However, the paucity of clinically available drug assays limits the usefulness of monitoring drug concentrations. Until drug assays are readily available to clinicians, the factors discussed in this review should be considered when addressing the question, 'What is the right drug dose in AKI?'

Competing interests

The authors declare that they have no competing interests.

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