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Drug use and nephrotoxicity in the intensive care unit

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Patients cared for in the intensive care unit (ICU) undergo multiple interventions to treat serious medical conditions. In addition to the acute illness being treated, underlying chronic conditions require ongoing drug therapy. As a result, these patients are exposed to numerous pharmaceutical agents, many of which have narrow therapeutic windows and toxic potential. Comorbid conditions, altered drug pharmacokinetics, and drug–drug interactions further enhance the risk for both drug overdosing and underdosing and adverse medication effects. Underdosing is complicated by reduced efficacy, whereas overdosing results in various end-organ toxicities. One such complication is acute kidney injury (AKI), a relatively common problem in the ICU, which results from multiple insults. Importantly, potentially nephrotoxic medications contribute significantly to the development of AKI. In view of these issues, it is crucial that clinicians caring for these patients use appropriate drug dosing based on the knowledge of altered pharmacokinetics, vigilant monitoring of drug efficacy and toxicity, recognition of drugs with nephrotoxic potential, and early identification of drug-induced AKI when it develops.

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Numerous medications are prescribed to seriously ill patients in the intensive care unit (ICU). Although they provide significant benefits, adverse events may develop from these agents, including acute kidney injury (AKI), hepatotoxicity, neurological dysfunction, cardiopulmonary toxicity, and other end-organ disturbances. It is therefore incumbent on all clinicians who provide ICU care to identify these relatively common complications in patients, with an eye toward prevention. In addition, practitioners must recognize the high-risk profile of critical care patients who suffer from several chronic disease states—this is crucial to understanding why end-organ toxicity occurs after exposure to certain drugs. In this regard, pharmacokinetic changes accompanying ICU diseases must be factored into drug dosing to maximize efficacy and minimize toxicity. This approach can reduce or eliminate potentially preventable adverse end-organ effects. An example that will be discussed below in greater detail is AKI.

Several studies have documented that AKI occurs frequently in the ICU, affecting as many as two-thirds of patients.[1–5] It is often the result of multiple insults and may be severe enough to require renal replacement therapy (RRT) in ~6% of patients.[4,5] As with other acute organ injury syndromes, AKI has significant consequences, which include prolonged hospital length of stay, increased hospital-related morbid events, development of chronic kidney disease (CKD), and requirement for acute and/or chronic RRT.[6] Increased hospital and overall mortality also complicate this untoward event.[6]

The major culprits that cause AKI include processes, such as infections complicated by sepsis, systemic inflammatory response syndrome, and septic shock, cardiac, hepatic, and multiorgan dysfunction/failure, as well as volume depletion. Many of these events prime the kidney for injury by causing renal hypoperfusion and promoting oxidative stress.[7] Importantly, nephrotoxic drugs contribute to AKI in 19–25% of cases in the ICU.[4,8] In fact, 22.2% of the top 100 drugs used in an adult ICU at a tertiary care center were considered potentially nephrotoxic.[9] Thus, ICU patients are at a considerable risk of developing AKI, and the critical care clinician must be familiar with the drugs that commonly cause nephrotoxicity. This will facilitate appropriate preventive maneuvers, early identification, and directed disease management.

COMMON ICU DISEASE STATES AND COMORBID CONDITIONS

Not surprisingly, patients with significant underlying chronic disease states are admitted to the ICU with acute, life-threatening illnesses. The processes noted in Table 1 enhance the risk for development of one or more of a number of complications that require admission to and care in the ICU. The same comorbid conditions that associate with critical illness also increase the risk for development of both ischemic and nephrotoxic AKI.

The comorbidities that most notably increase the risk for drug-induced nephrotoxicity are underlying acute kidney disease or CKD, sepsis, advanced cirrhosis and liver failure, acute or chronic left heart failure, pulmonary hypertension with/without right heart failure, and various types of malignancies. In addition, a number of major surgical procedures, such as cardiac surgery, aortic surgery, and major intra-abdominal surgery enhance nephrotoxic AKI risk. All of these (Table 2) increase renal injury by one or more of the following: (1) disturbing renal hemodynamics, (2) altering drug pharmacokinetics, and/or (3) directly injuring the renal parenchyma (primarily ischemia). The common clinical ICU syndromes that increase the risk for drug-induced AKI are reviewed.

Table 1 | Common preexisting comorbidities in ICU patients

Older age (>65 years)
Diabetes mellitus
Chronic kidney disease
Cirrhosis and other forms of liver disease
COPD, pulmonary hypertension, and other forms of lung disease
Cardiovascular disease (CAD, CMP, arrhythmias)
Malignancy and its treatment (drugs, HSCT)
Hypertension
Morbid obesity

Abbreviations: CAD, coronary artery disease; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit.

Table 2 | Risk factors for drug-induced nephrotoxicity in the ICU

Chronic risk factors
Older age (>65 years)
Chronic kidney disease
Diabetes mellitus
Malignancy
Cardiovascular disease
Liver disease
Chronic pulmonary disease
Hypertension
Peripheral vascular disease
Acute risk factors
Sepsis/infection
Volume depletion (true and effective)
Acute decompensated heart failure
Hypotension
Complex (major) surgery
Trauma
Mechanical ventilation

Abbreviation: ICU, intensive care unit.

ICU SYNDROMES ASSOCIATED WITH INCREASED AKI RISK

Sepsis

Sepsis, systemic inflammatory response syndrome, and septic shock are commonly encountered in the ICU. In addition, sepsis-associated AKI is a frequent complication in patients; in fact, sepsis is the most common cause of AKI in the ICU, accounting for up to 50% of cases.[5,7,10–12] Renal hemodynamics are profoundly affected by sepsis, whereby the systemic vasculature is dilated but vasoconstriction predominates in the kidney. In addition, patients may develop intravascular volume depletion from the combination of anorexia, extrarenal fluid losses, and third spacing of fluids from leaky capillaries. These changes expose the kidney to reduced perfusion and parenchymal ischemia, even in the absence of frank hypotension. When shock develops, renal ischemia is more severe and tubular injury/necrosis occurs. Finally, intrarenal disseminated intravascular coagulation may occur with sepsis and further injure the parenchyma.

Therefore, it is not surprising that sepsis is associated with AKI in the ICU. Importantly, the underlying patient comorbid conditions (Table 1) magnify the aberrant renal physiology of sepsis. In addition, these same insults enhance the risk for certain drugs to cause nephrotoxic AKI, either alone or in addition to ischemic acute tubular injury. As will be reviewed later in the discussion of pharmacokinetic changes in critical care patients, unrecognized renal insufficiency compounds the problem by the use of excessive drug dosing for true glomerular filtration rate (GFR).

Heart failure

Advanced cardiac failure commonly requires ICU level of care, in particular when acute decompensated heart failure supervenes. Renal function often deteriorates in this setting because of systemic neurohormonal response, reduced cardiac output, elevated renal venous pressure, and systemic hypotension.[13–15] In some cases, intra-abdominal compartment syndrome can develop. Reduced renal perfusion is the end result of these physiological changes, allowing prerenal AKI or what has recently been coined 'acute cardiorenal syndrome' to develop.[14,15] At the other end of the spectrum, acute tubular injury and frank necrosis may supervene as this process becomes more severe and prolonged. Drugs with nephrotoxic potential are more likely to cause AKI in this milieu, especially medications that further worsen renal perfusion (such as nonsteroidal anti-inflammatory drugs (NSAIDs), vasopressors), directly injure renal tubules, or precipitate within tubular lumens during sluggish urine flow due to low GFR and obstructing tubular casts. Drug overdosing associated with impaired drug metabolism and unrecognized renal impairment further exacerbates AKI risk.

Liver disease

Patients with acute hepatic failure and decompensated cirrhosis are often admitted to the ICU for evaluation and therapy. The physiology of liver failure is similar to that of sepsis with a vasodilated systemic circulation, prominent

blood pooling in the splanchnic circulation, and renal arteriolar vasoconstriction.[16–19] The presence of tense ascites can increase renal venous pressure in a manner similar to the intra-abdominal compartment syndrome. The resulting reduced renal perfusion pressure and elevated renal venous pressure increases the risk for AKI, whether due primarily to hepatorenal syndrome or a superimposed insult, such as nephrotoxic medications. In this case, NSAIDs, hydroxyethyl starch, intravenous radiocontrast, and direct tubular toxins are likely to induce AKI. Disturbed pharmacokinetics, such as impaired hepatic drug metabolism, have a contributory role in this group.

Chronic kidney disease

Chronic kidney disease is a common comorbidity in ICU patients. It is intuitive that disease in the major drug excretory organ, as manifested by either decreased GFR or proteinuria, will be associated with increased risk for nephrotoxic AKI. The reduced volume of functional parenchyma and smaller number of nephrons increases nephrotoxic risk. Treatment with excessive doses of potentially nephrotoxic drugs, due to incorrect GFR estimates, often occurs in the elderly, catabolic states, and with muscle wasting, which further increases AKI risk. It is not well appreciated that, in addition to reduced drug excretion, other pharmacokinetics are also aberrant in CKD. Drug metabolism by the liver (and kidney) is also impaired. For example, the activity of several cytochrome-P-450 enzymes and drug transporters (namely P-glycoprotein, organic anion transporter) is reduced in CKD.[20–22] As a result, hepatically metabolized drugs will accumulate and increase tissue exposure, which may lead to systemic toxicity and AKI, if the drug has nephrotoxic potential.[21]

Malignancy

Not uncommonly, patients with various types of cancer are admitted to the ICU. They frequently have developed neutropenic sepsis, pulmonary embolism, cardiac or liver failure, kidney disease, or a complication of bone marrow/hematopoietic stem cell transplantation.[23,24] Although very often related to the chemotherapeutic regimen, the acute illness may also be a consequence of the underlying malignancy. As with the diseases previously discussed, reduced renal perfusion, ischemic tubular injury, and direct parenchymal injury from tumor invasion or tumor lysis increase the risk for development of AKI from various medications. Radiocontrast, NSAIDs, and numerous chemotherapeutic agents are also included.

PHARMACOKINETIC CHANGES IN ICU PATIENTS

Outside innate drug toxicity and the disease states discussed above, one of the major factors leading to drug-induced systemic toxicity is disturbed medication pharmacokinetics in critically ill patients (Table 3). All phases of drug pharmacokinetics are disturbed in ICU patients, including absorption, distribution, metabolism, and clearance.[25] These changes are often the result of organ dysfunction, particularly in the kidneys and liver, the acute-phase response of the underlying critical illness, multiple drug interactions, and therapeutic interventions, including intravenous fluids, diagnostic procedures, and various medications.[25–27] Individual differences in the pharmacogenetics of drug transport systems and metabolizing enzymes may be exacerbated in this setting, further increasing the risk of toxicity.

Table 3 | Pharmacokinetic differences in ICU patients

Altered oral drug bioavailability (decreased > increased)
Intestinal atrophy, dysmotility, and reduced transport function
Reduced intestinal and hepatic metabolism
Altered volume of distribution (increased or decreased)
Increased or decreased extracellular fluid space
Decreased protein concentration or binding
Altered tissue permeability
Microenvironment pH disturbances
Altered drug metabolism/biotransformation (decreased > increased)
Altered CYP-450 drug metabolism
Altered drug cellular transport
Altered renal drug clearance (decreased > increased)
Reduced GFR
Reduced proximal tubular drug secretion (drug competition, endogenous organic anions/cations, tubular injury)

Abbreviations: CYP, cytochrome P; GFR, glomerular filtration rate; ICU, intensive care unit.

Bioavailability

Although drug bioavailability is less of an issue with intravenously administered medications, oral, subcutaneous, and intramuscular drugs often have altered bioavailability in ICU patients. Reduced absorption of enteral drugs occurs because of a number of factors, including increased gastric pH (alters the drug-ionized state), bowel dysmotility, formation of insoluble drug complexes in the intestines, nutrient–drug interactions, and bowel edema.[25] Acute decompensated heart failure and cirrhosis will reduce oral bioavailability due to bowel edema and impaired intestinal perfusion. A less-appreciated cause of reduced absorption is intestinal atrophy with associated decreased surface area and cellular enzyme activity, which can occur as a result of as little as 3 days of reduced enteral feeding.[25,28] On the basis of these data, it is prudent to dose medications intravenously and to initiate enteral feeds early to avoid gut atrophy. Less commonly, reduced intestinal/hepatic metabolism of enteral drugs actually increases their bioavailability.[28]

Distribution

Drug distribution is significantly altered in ICU patients for various reasons. This is due primarily to changes in the factors that determine distribution: blood delivery, tissue permeability, microenvironment pH, and drug characteristics, such as lipid solubility, pKa, and protein binding.[25] The initial concentration of a drug after intravenous administration is determined by dose and volume of distribution (V_d),

a hypothetical space representing total body drug concentration divided by plasma blood concentration. In critical illness, V_d may be increased or decreased depending on the level of total body water, level of renal function, and changes in protein concentration and binding affinity.[25–27] Increased drug V_d often develops from early goal-directed therapy for sepsis, edematous states, such as cirrhosis and acute hepatic failure, nephrotic syndrome, right and left heart failure, and many illnesses associated with shock requiring aggressive volume repletion to maximize end-organ perfusion. Efficacy can suffer if drug dosing is not adjusted to these changes. Reduced V_d may be seen with older age and volume depletion from vomiting, diarrhea, blood loss, and diuretics. AKI and CKD may also reduce the V_d of certain drugs by altering tissue binding.[20,25] Drug therapy that does not account for this will lead to excessive dosing and end-organ toxicity.

Metabolism

Drug metabolism is disturbed by many of the critical illness states.[25–27] The two major metabolic pathways for drugs are categorized as phase I and II. Although the liver is the major organ involved in these pathways, the intestines, kidneys, and other organs also participate to a lesser degree. Phase I entails oxidation, reduction, and hydrolysis of certain drugs. Hepatic metabolism is influenced by the level of blood flow, hepatocyte enzyme activity, and protein binding. Vigorous hepatic blood flow allows drugs with high extraction ratios to be rapidly cleared; these drugs accumulate when perfusion is reduced by hypotension/shock, vasoconstrictor drugs, ventilation with positive end expiratory pressure, and impaired cardiac output.[25–27] For drugs with low extraction ratios, the enzyme function is most important and is performed primarily by the cytochrome P-450 system. An essential component of enzyme function is tissue transporter activity, which participates in uptake and removal of drugs from the liver and other metabolizing organs.[25–28] Drug transporters such as p-glycoprotein and organic anion transporter may be affected by critical illness states, such as inflammation, sepsis, CKD/AKI, acute or chronic liver disease, hypotension, burns, and trauma.[25–28] In general, these processes have variable effects on transporter activity, while predominantly reducing cytochrome P-450 enzyme activity. Thus, the metabolism of drugs in ICU patients is clearly altered and likely contributes to efficacy and toxicity issues. AKI may result when potentially nephrotoxic drugs and/or their active metabolites accumulate.[29]

Excretion

Drugs are eliminated from the body by both renal and nonrenal pathways. Hepatic clearance is considerable for lipophilic drugs, whereas hydrophilic drug excretion is largely a function of renal clearance. Currently used markers of kidney function, such as serum creatinine concentration, are suboptimal, especially in the ICU setting. Resuscitation with large volumes of crystalloid will dilute serum creatinine concentration masking the presence of AKI or misinforming about the stage of CKD. Creatinine production is also reduced in sepsis, further limiting its potential as a marker of kidney injury.[30] Thus, abrupt decreases in GFR initially may be accompanied by little or no change in the serum creatinine. As a result, parent drugs and active metabolites from liver metabolism that are excreted by the kidneys, accumulate and can cause toxicity. In addition, drug clearance is affected by the etiology of critical illness. As compared with normal subjects, burn patients more often have increased clearance because of younger age, aggressive fluid resuscitation, and hypermetabolic state.[25] In contrast, studies on patients in medical and surgical ICUs demonstrate no change or reduced drug clearance as compared with normal subjects.[25] However, these are only generalizations, and patients with any of the noted illnesses can have increased, unchanged, or decreased drug clearance, emphasizing the need for individualized dosing. Thus, ICU patients are at risk for underdosing with loss of efficacy and adverse toxic events from drug overdosing, especially when GFR is overestimated by an inaccurate parameter, such as serum creatinine.

With severe AKI in the ICU, some form of RRT is often required. Acute intermittent hemodialysis and various forms of continuous RRT are used to provide clearance, metabolic control, and fluid balance. Drug clearances and changes in pharmacokinetics must be considered with addition of this therapy.[31] Not only must drug dosing take into account RRT-associated clearances but also dialysis-induced changes in V_d and drug distribution, as well as the associated improvement in hepatic and other organ drug metabolism. The latter point is important and not commonly appreciated with dialytic therapy of the uremic patient. In addition, one must recognize that extracorporeal drug clearances are different with chronic RRT (CRRT) and intermittent hemodialysis. As will be discussed later, continuous convective clearance requires dosing regimens that are distinct from intermittent diffusion-based hemodialysis.

Finally, pharmacokinetic changes that occur with critical illness are by no means static but rather represent a dynamic process. Many change as the clinical status of the patient changes. For example, eradication of infection, recovery of end-organ dysfunction, improvement in intravascular volume status, and enhanced nutritional status are but a few of the changes that occur in this unique subset of patients. Alternatively, patients may deteriorate and develop worsening anasarca, hypotension, new end-organ failure, and a progressive decline in clinical status. As such, these changes must be kept in mind when prescribing medications, with vigilant monitoring as integral to appropriate therapy.

DRUG DOSE ADJUSTMENT IN ICU PATIENTS

On the basis of the altered drug pharmacology of ICU patients, prescription of drugs to these patients should be carefully contemplated. Understanding the general pharmacological principles in ICU patients combined with knowledge of individual patient pharmacokinetic differences will

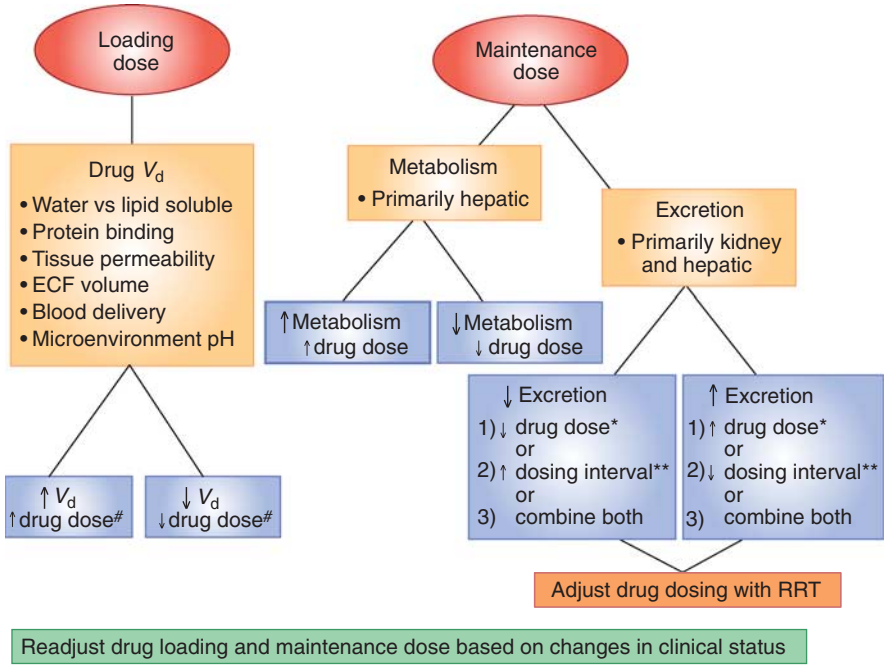

Figure 1 | A simplified approach to loading and maintenance drug dosing in the ICU. For loading dose, estimate the drug V_d (taking in account drug and patient characteristics) and dose accordingly using the simple formula. For maintenance dose, estimate the renal clearance (CrCl) for the drug and adjust the dose and/or dosing interval accordingly. #Loading dose = standard dose × (patient's V_d/normal V_d). *Maintenance dose = standard dose × (patient's CrCl/normal CrCl). **Maintenance dosing interval = standard interval × (normal CrCl/patient's CrCl). CrCl, creatinine clearance; ECF, extracellular fluid; ICU, intensive care unit; RRT, renal replacement therapy; V_d, volume of distribution.

allow more informed dosing strategies. This therapeutic approach will facilitate maximal efficacy and minimal toxicity by limiting underdosing and overdosing. To best achieve this, it is critical to work collaboratively with the clinical pharmacist in the ICU. A simple approach is to guide drug dosing by applying the pharmacokinetic principles that affect drug loading dose and maintenance dose (Figure 1). Loading dose takes into account primarily the V_d, drug solubility (lipid vs water), protein binding, and tissue permeability.[32,33] A formula that can be used to modify drug dose based on V_d is loading dose = standard loading dose × (patient's V_d/normal V_d). In contrast, maintenance dose primarily takes into account the status of hepatic metabolism and more importantly, renal excretion.[32,33] To guide maintenance dosing, formulas based primarily on kidney function can modify the dose or dosing interval: maintenance dose = standard dose × (patient's CrCl/normal CrCl), or maintenance dosing interval = standard dosing interval × (normal CrCl/patient's CrCl), or a combination of the two approaches (reduced dose and increased interval). The presence of RRT will require an adjustment in dosing to account for drugs that are efficiently removed by this modality and the improvement in hepatic metabolism that accompanies correction of uremia.[31] Knowledge of the underlying drug characteristics and the effect of both acute illness and chronic comorbid conditions on pharmacokinetic principles, along with vigilant monitoring will allow a reasonably safe dosing regimen in most ICU patients. The influence of critical illness on drug pharmacokinetics and dosing is evident in the following scenario. A patient with septic shock receives early goal-directed therapy with 6 l of saline for hypotension. The patient is edematous and oliguric with increasing serum creatinine. Intravenous antibiotics must be administered to treat infection. An informed approach to drug dosing is as follows: the loading dose of a water-soluble drug must be increased because of the larger V_d, whereas the maintenance dose must be reduced to account for reduced renal drug excretion, with some contribution from impaired hepatic metabolism.

As extracorporeal drug clearances vary based on the modality used in ICU patients, dosing regimens must be appropriately adjusted to the dialytic therapy. With CRRT, the convective mode of clearance and the continuous nature of the procedure make the impact of drug size, V_d, and drug–membrane interactions less important as compared with intermittent hemodialysis.[31] Maintenance drug dosing in patients on CRRT is best estimated using total creatinine clearance (patient + therapy). With high-volume CRRT (> 25 ml/kg per h), most drugs should be dosed based on a creatinine clearance between 25 and 50 ml/min.[31] In contrast, maintenance drug dosing with intermittent hemodialysis should be guided by published dosing recommendations based on creatinine clearance < 10 ml/min with postdialysis administration. Thus, as a patient transitions from CRRT to intermittent hemodialysis (or *vice versa*), drug dosing must be adjusted accordingly.

Table 4 | Common forms of drug-induced AKI in the ICU

Hemodynamic AKI
Nonsteroidal anti-inflammatory drugs (NSAIDs)
RAAS inhibitors
Calcineurin inhibitors (cyclosporine, tacrolimus)
Vasopressors
Acute tubular necrosis
Radiocontrast
Nephrotoxic antimicrobials
Osmotic nephropathy
Hydroxyethyl starch (HES)
Intravenous immunoglobulin (IVIG containing sucrose)
Crystal nephropathy
Highly active anti-retroviral therapy (HAART)
Acyclovir
Ciprofloxacin
Sodium phosphate purgatives
Acute interstitial nephritis
Antibiotics (β-lactams, sulfa-based, quinolones)
Proton pump inhibitors, H_2 antagonists
Anti-convulsants

Abbreviations: AKI, acute kidney injury; H_2, histamine-2; ICU, intensive care unit; NSAIDs, nonsteroidal anti-inflammatory drugs; RAAS, rennin–angiotensin–aldosterone system.

NEPHROTOXIC COMPLICATIONS OF ICU DRUG THERAPY

Many drugs are associated with nephrotoxicity in the ICU and they have been reviewed in detail in previous reviews.[34–36] Innate drug toxicity, aberrant renal hemodynamics, underlying kidney disease, and altered drug pharmacokinetics all have a role in their enhanced nephrotoxicity. Broad categories of drug nephrotoxicity in the ICU will be briefly touched on; Table 4 lists some common examples.

Hemodynamic AKI

Hemodynamic or prerenal AKI is common in the ICU. Patients have disturbed systemic and renal hemodynamics, capillary leak syndrome, and extensive fluid losses. In addition, underlying CKD and hypertensive arteriosclerosis are common. These factors predispose patients to hemodynamic AKI when therapy with NSAIDs, renin–angiotensin–aldosterone system blockers, high-dose systemic vasoconstrictors, or calcineurin inhibitors is undertaken.[37] Each acts by different mechanisms to reduce GFR. NSAIDs reduce vasodilatory prostaglandins, renin–angiotensin–aldosterone system blockers inhibit angiotensin-II effects on the efferent arteriole, and vasoconstrictors and calcineurin inhibitors increase afferent arteriolar tone.[38] In general, the reduction in GFR is rapidly reversible.

Acute tubular injury

Acute kidney injury from acute tubular injury/necrosis occurs frequently in ICU patients. The same risk factors that predispose to prerenal AKI also increase the risk for tubular injury. Direct tubular toxicity is well known with drugs frequently used in the ICU—aminoglycosides, anti-fungal agents, and radiocontrast are examples. Crystal-induced tubular injury and luminal obstruction is more likely to occur in these patients when intravenous drugs such as acyclovir, sulfa-based medications, ciprofloxacin, and methotrexate are administered.[39] An interesting and under-recognized cause of acute tubular injury is the entity known as 'osmotic nephropathy.' Intravenous immunoglobulin using a sucrose stabilizer causes AKI, with the renal lesion characterized by swollen proximal tubular cells filled with abundant lysosomal vacuoles.[39] It has recently been recognized that certain forms of hydroxyethyl starch increase AKI in sepsis and cardiac surgery when compared with other volume expanders.[40] The kidney lesion observed is identical to the one noted with sucrose.[39]

Acute interstitial nephritis

Acute interstitial nephritis (AIN) is without doubt the most difficult cause of AKI to firmly establish in the ICU. The absence of clinical or laboratory findings to suggest an allergic drug reaction is a major reason, while exposure to numerous drugs makes it nearly impossible to identify the likely causative agent. As AIN is an idiosyncratic drug reaction, risk is based primarily on the sheer number of drugs this group is exposed to in the ICU setting. Nonetheless, as drug-induced AIN has been described to cause AKI in 3–10% (as high as 27% in selected patients), one must remain vigilant to the possibility.[41] Although any medication can cause AIN, certain drugs (Table 4) are more likely and they are broadly classified as antimicrobials, anti-ulcer agents, anti-convulsants, diuretics, and a host for other medications.[41] To make the diagnosis, a high index of suspicion for drug-induced AIN as the cause of AKI and a confirmatory kidney biopsy are required.

CONCLUSIONS

Drug use is extensive in the ICU, and although life saving, is fraught with complications and various forms of toxicity. One notable complication is drug nephrotoxicity, which develops more readily in ICU patients because of the underlying comorbid conditions that enhance risk. Furthermore, acute ICU illnesses are associated with hemodynamic changes that reduce renal perfusion, complications that directly injure the renal parenchyma, and altered drug pharmacokinetics—all of these increase the risk for drug-induced AKI and other drug-related complications. Nephrologists and intensivists working in the ICU can potentially reduce drug toxicity by recognizing the high-risk profile of these patients. Pharmacokinetic changes accompanying ICU diseases, individualized to each patient, must be factored into drug dosing to maximize efficacy and minimize toxicity. Close collaboration with a clinical pharmacist and applying fundamental pharmacokinetic principles to drug administration is required. This approach can go a long way in eliminating or reducing drug nephrotoxicity and other adverse end-organ drug effects.

DISCLOSURE

The author declared no competing interests.

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