CHAPTER 219

Calcineurin Inhibitors and Other Immunosuppressive Drugs and the Kidney

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OBJECTIVES

This chapter will:

1. Define potential mechanisms underlying the nephrotoxicity of immunosuppressive drugs in the intensive care unit (ICU).
2. Analyze pharmacologic interactions among immunosuppressive agents and other drugs used in ICU patients.
3. Evaluate clinical outcomes after adjustments or reductions in the immunosuppressive regimen.

Drug-induced nephrotoxicity can cause acute kidney injury (AKI) in patients in the intensive care unit (ICU). Drug toxicity may cause tubular damage (tubular cell apoptosis and necrosis), interstitial inflammation (interstitial nephritis), vascular injury (thrombotic microangiopathy), and alteration of tubular cell functions (i.e., decreased membrane transport, defective mitochondrial function, and increased levels of oxidative stress species).[1] However, the progression from functional impairment to renal failure usually involves additional factors, such as metabolic disorders associated with diabetes, sepsis, hypovolemia, or infusion of contrast media.[2]

Several drugs may be responsible for renal damage in ICU patients. These include antibiotics (aminoglycosides), antimycotic agents, and immunosuppressive drugs (Box 219.1).

Glucocorticoids

Glucocorticoids are used frequently to treat ICU patients because of their potent antiinflammatory effects. Despite their efficacy in combating inflammation, they are characterized by a broad range of toxic effects, such as hypertension, glucose intolerance, and cardiovascular disease, which contribute to an increased risk of premature death, particularly among renal transplant recipients, from atherosclerotic heart disease.

BOX 219.1

Classification of Immunosuppressive Drugs

- Glucocorticoids
- Antimetabolites
  - Azathioprine
  - Mycophenolic acid
  - Methotrexate
- Calcineurin inhibitors
  - Cyclophilin-binding drugs (e.g., cyclosporine)
  - FKBP12-binding drugs (e.g., tacrolimus)
- mTOR inhibitors
  - Sirolimus
  - Everolimus
- Monoclonal antibodies
  - Bevacizumab
  - Cetuximab
  - Panitumumab
  - Rituximab
- Fusion proteins
  - Belatacept
- Intravenous immune globulins

mTOR, Mammalian target of rapamycin.

Other reported toxic effects include lymphoproliferative disorders, dyslipidemia, weight gain with central obesity, peptic ulcer formation, pancreatitis, cataract formation, diabetes, osteoporosis with avascular necrosis of bone, growth retardation, and personality disorders. The role of corticosteroid therapy in increasing a patient's risk of life-threatening infections and metabolic abnormalities has been well established.

To avoid the development of the aforementioned complications, the drug dose should be tapered during the course of the disease. Tapering must be done carefully to avoid recurrence of the disease and presence of cortisol deficiency resulting from suppression of the hypothalamic-pituitary-adrenal axis during the period of steroid therapy. Because of the availability of combinations with other immunosuppressants, corticosteroids can be avoided in most patients or administered for only a short period at low dosage.

Azathioprine

Azathioprine is an antimetabolite, an imidazole derivate of 6-mercaptopurine. It has been used in clinical transplantation for more than 30 years. The most important side effects of this drug are thrombocytopenia and leukopenia. Azathioprine is converted to inactive 6-thiouric acid by xanthine oxidase. Because this enzyme is inhibited by allopurinol, this drug combination is contraindicated. In the presence of renal impairment, the azathioprine dose must be reduced by 75% when the creatinine clearance rate is between 10 and 50 mL/min and by 50% when it is less than 10 mL/min.

Mycophenolic Acid

Mycophenolate mofetil (MMF) is a prodrug of the mycophenolic acid (MPA). MMF is hydrolyzed to form MPA, which is the active metabolite of the drug. MPA is not metabolized by CPY3A (cytochrome P450, family 3, subfamily A) enzymes. Thus MMF can be administered in combination with other drugs metabolized by this enzymatic complex. The immunosuppressive mechanism is based principally on the inhibition of inosine monophosphate dehydrogenase, a key enzyme in de novo synthesis of purine nucleotides. Based on its pharmacokinetics and pharmacodynamics, this drug may be used safely in patients with renal disorders, because it is associated with a decreased relative risk of renal failure[3] and provides significant protection against long-term deterioration of renal function.[4] The most common adverse events are related to the gastrointestinal tract. Neurotoxicity and hepatotoxicity have not been observed with MMF. MMF is absorbed primarily by intestinal cells and should not be administered simultaneously with antacids, cholestyramine, or oral ferrous sulphate. In addition, MMF can modify the tubular secretion of several drugs used in the ICU (acyclovir, valacyclovir, ganciclovir, and valganciclovir) and thus increase blood levels of these agents.

No large-scale studies have examined the incidence of adverse effects of MMF in ICU patients treated with this drug. The studies that do exist are too small to allow generalizations.[5] However, a large number of patients with solid organ transplants have been treated with MMF. Regarding viral infections, in one study of heart transplant recipients, a higher incidence of herpes zoster was associated with MMF.[6] The risk of cytomegalovirus infection is of even greater concern in patients treated with MMF.

Methotrexate

Methotrexate is administered at high doses for the treatment of various immunologic diseases, such as rheumatoid arthritis and psoriasis, and neoplasias (e.g., osteosarcoma and Burkitt's lymphoma). In patients with reduced diuresis and acid urine, methotrexate or its metabolites precipitate in tubules with sequential obstruction and nephrotoxicity. The phenomenon is reversible by hyperhydration and urine alkalinization before methotrexate administration. In the presence of persistent oliguria, leucovorin can be administered to reduce nephrotoxicity. Carboxypeptidase-G2, which hydrolyzes methotrexate and inactivates its metabolites, also can be used. Persistent oliguria points to the need for renal replacement therapy, with charcoal hemoperfusion and sequential hemodialysis.[7,8]

Calcineurin Inhibitors

Patients treated with calcineurin inhibitors (CNIs) have a higher risk of developing acute and chronic renal injury than other immunosuppressors.[9] Acute nephrotoxicity is dose dependent and reversible after adjusting or reducing the dosage. On the other hand, the development of chronic renal damage is usually irreversible.[10]

The recent application of "omics" (transcriptomics, proteomics, and metabolomics) to the study of acute kidney damage induced by CNIs has shown that these drugs result in mitochondrial disturbances, in addition to activation of Nrf2-induced oxidative damage and the unfolded protein response pathway, which includes three branches (ATF6, PERK, and ATF4).[11] Nrf2 and ATF4 appear to be particularly important in these processes.

The aforementioned molecular mechanisms of CNIs cause endothelial damage by reducing the release of L-arginine nitric oxide (NO) and prostaglandin E (PGE) and increasing the production of transforming growth factor beta-1 (TGF-β1) and vasoconstrictors, such as thromboxane and endothelin-1. CNIs also may increase the sympathetic tone.[12] However, the renal vasoconstriction occurs even

in denervated kidneys. The reduced glomerular filtration rate (GFR) and renal plasma flow secondary to vasoconstriction seem to be correlated with the dosage and time of administration.[13] The decrease in renal plasma flow and GFR can be antagonized by calcium channel blockers via the inhibition of endothelin-mediated calcium entry into vascular smooth muscle cells.[14] Thus calcium channel blockers may be an important antihypertensive strategy in ICU patients treated with cyclosporine A (CsA). The activation of the intrarenal renin-angiotensin system plays an essential role in the pathogenesis of chronic CsA-related nephrotoxicity because of increased release of renin from afferent and efferent arterioles and glomerular capillaries. Potential biomarkers for the diagnosis of acute CNI-induced nephrotoxicity are cyclophilin B, aminoacyl-tRNA synthetase, and basigin,[15] but validation studies are required to demonstrate reproducibility and sensitivity.

The chronic administration of CNIs is responsible for several serum electrolyte impairments, such as hypercalcemia, hypomagnesemia, and hyperkalemia. These conditions must be controlled to avoid major clinical complications in critically ill patients. The concomitant administration of drugs commonly used in ICU patients may increase these secondary effects of CNIs. Hyperkalemia secondary to CsA administration may be life threatening. It can be potentiated by concomitant administration of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta blockers.[16] Hypercalcemia and, especially, hypomagnesemia may predispose individuals to seizures, with secondary effects on the clinical outcomes of ICU patients.

Acute vascular damage is an uncommon clinical complication associated with CNI treatment. Such damage easily may be misdiagnosed as hemolytic uremic syndrome and thrombotic thrombocytopenic purpura, which often are observed in the ICU. An accurate diagnosis is needed to discriminate acute vascular damage from these conditions.

CNI-induced nephrotoxicity may lead to the development of chronic renal damage. In such cases, interstitial fibrosis, exacerbating preexisting renal alterations, may result in a rapid decline in renal function, leading to end-stage renal disease (ESRD). Several studies have identified the common mechanism responsible for chronic CNI-induced nephrotoxicity,[13] although a number of issues remain to be elucidated. According to current evidence, the development of interstitial fibrosis is associated with increased expression of osteopontin (a potent macrophage chemoattractant secreted by tubular epithelial cells),[17] chemokines (a class of cytokines that are strong chemoattractants for a variety of hematopoietic cells),[18] and TGF-β (a powerful stimulator of extracellular matrix production).[19] Increased TGF-β gene and protein expression is the result of decreased secretion of NO, as well as increased local concentrations of angiotensin II. The beneficial effect of ACE inhibitors and ARBs in attenuating the evolution of chronic renal injury consists of reducing the angiotensin II concentration. Indeed, several studies have demonstrated that concomitant administration of ACE inhibitors and ARBs significantly reduced arteriolopathy, interstitial fibrosis, tubular atrophy, and improved blood pressure levels.[20]

CNIs are metabolized by hepatic cytochrome P-450 (CYP) enzymes, including CYP3A4 and CYP3A5, and are transported out of cells via P-glycoproteins (ABCB1). Staatz et al. demonstrated that after the administration of CsA in 24 healthy volunteers selected on the basis of their CYP3A5 genotype, CsA clearance was similar, irrespective of the CYP3A5 genotype (i.e., positive or negative CYP3A5).[21] However, the mean blood levels of two CsA metabolites (AM19 and AM1c9) were higher in those with a positive CYP3A5 genotype.[21] They concluded that the accumulation of CsA in tissues was genotype dependent and recommended that single determination of CYP3A5 genotype was necessary.

TABLE 219.1

Drugs That Interfere with Cyclosporine

DRUGS THAT INCREASE CsA BLOOD CONCENTRATIONS	DRUGS THAT LOWER CsA BLOOD CONCENTRATIONS
Allopurinol	Carbamazepine
Amiodarone	Nafcillin
Bromocriptine	Octreotide
Cimetidine	Orlistat
Clarithromycin	Phenobarbital
Colchicine	Phenytoin
Danazol	Rifabutin
Diltiazem	Rifampin
Erythromycin	Ticlopidine
Fluconazole	
Itraconazole	
Ketoconazole	
Lansoprazole	
Methylprednisolone	
Metoclopramide	
Nicardipine	
Rabeprazole	
Verapamil	

CsA, Cyclosporine.

Several drugs used in the ICU may interfere with CNI metabolism and therefore influence efficacy and toxicity. All the drugs listed in Table 219.1 should be used with caution in patients receiving CNIs.

An increase in the CsA plasma concentration after the administration of various antibiotics (i.e., azithromycin, clarithromycin, erythromycin, norfloxacin, imipenem, and quinupristin/dalfopristin) has been observed. Such increases may lead to major clinical complications, such as the progression of renal dysfunction (in cases of concomitant administration with ciprofloxacin, gentamicin, tobramycin, vancomycin, and trimethoprim-sulfamethoxazole), reduction of immunosuppressive effects (in the presence of ciprofloxacin) and secondary toxic effects, such as central nervous system disturbances and seizures (in the presence of imipenem). Although these secondary effects may be well known in clinical practice, the question of whether there is a "safe" chronic dose of CsA that is effective immunologically but does not cause progressive renal dysfunction is difficult to answer because of a lack of controlled clinical trials. Short-term (1-year) studies of patients receiving CsA for nonrenal autoimmune diseases (e.g., early insulin-dependent diabetes mellitus and uveitis) suggest that a maintenance dose of less than 5 mg/kg/day may not lead to progressive chronic nephrotoxicity.[22] However, a longer (2-year) trial in which 5 mg/kg/day was given for uveitis reported a mean elevation in plasma creatinine concentration of 0.4 mg/dL (35 μmol/L) and a fall in the mean GFR from 116 to 75 mL/min. Another CNI such as tacrolimus (FK506) also is metabolized by the CYP3A5 enzyme; it should be susceptible to many of the drug interactions noted for CsA.[23] Therefore even in patients with normal renal function, initial signs of nephrotoxicity should be investigated carefully through laboratory testing, and it is highly recommended that the plasma concentrations of CNIs be monitored frequently in patients receiving CNI therapy.

Renal vasoconstriction induced by CNIs causes local hypoxia or ischemia, leading to the formation of free radicals

and reactive oxygen species.[24] Therefore once early renal insufficiency occurs, the first step is the reduction of the CNI dosage and the administration of dopamine and misoprostol to increase renal perfusion. In clinical trials, the CNI dosage was minimized or withdrawn with the aim of decreasing chronic CNI nephrotoxicity in organ transplants. The same protocols can be used for ICU patients who are receiving immunosuppressive therapy. However, most of the evidence available to date is not in favor of complete CNI avoidance, whereas the minimization protocol appears to be a more viable strategy.[25]

As shown by a recent systematic review and meta-analysis of immunosuppression therapy in cases of solid organ transplantation treated, the rates of rejection were similar using the generic immunosuppressives cyclosporine, tacrolimus, and mycophenolate mofetil. However, the clinical outcomes were not stated, because many of the studies had a short follow-up. Therefore in the absence of high-quality data showing bioequivalence, a patient receiving generic immunosuppressive drugs in the ICU must be controlled carefully for through blood levels.[26]

Mammalian target of rapamycin (mTOR) inhibitors, sirolimus and everolimus, are used in organ transplant patients, but they also are promising therapeutic options in immunosuppression and oncology. Temsirolimus and ridaforolimus have antitumor activity in various cancers. The mTOR is a key regulator kinase in the process of cell division. The mTOR inhibitors sirolimus and everolimus are similar immunosuppressants, whose mechanism of action is linked closely to inhibition of mTOR kinase. Sirolimus, also known as rapamycin, is a macrolide antibiotic compound, which is related structurally to tacrolimus. Everolimus is a similar compound, with a shorter half-life. Sirolimus was developed originally as an antifungal agent. It was later found to have immunosuppressive and antiproliferative properties that may be useful in the treatment or prevention of proliferative diseases, such as tuberous sclerosis, psoriasis, and malignancy. mTOR inhibitors can be tubulotoxic and produce hypokalemia and hypomagnesemia as a result of kaliuresis and magnesuria. In the presence of renal impairment, dosage adjustment of sirolimus is not required, considering the low level of nephrotoxicity of this drug. However, in the presence of hepatic impairment, dosage reductions of approximately one third the normal maintenance dose should be used. The use of these drugs in critically ill patients requires monitoring of hemoglobin and other blood cell counts because anemia, thrombocytopenia, and leukopenia can be caused by mTOR inhibitors. In addition, frequent measurements of the drug concentration in the blood are recommended. Stomatitis, caused by the direct effect of mTOR inhibitors on oral and nasal mucosa, is more frequent when these inhibitors are used in combination with MMF.[27] Strategies aimed at preventing stomatitis are based on oral hygiene and avoiding spicy, acid, or hot foods. In the presence of pain, topical corticosteroids and anesthetics can be used.

In the presence of pneumocystis pneumonia, pentamidine should be contraindicated because of its interaction with sirolimus. Instead, treatment with trimethoprim/sulfamethoxazole or clindamycin/primaquine is recommended. In patients with anemia and iron deficiency, a combination of oral supplementation of iron and erythropoietins should be considered, with careful monitoring of erythropoietin. When proteinuria (>1 g/day) is present, mTOR inhibitors must be discontinued because of the risk of worsening renal function. Strategies for managing proteinuria include the use of ACE inhibitors or ARBs, dietary sodium, and protein restriction.[28] mTOR inhibitors can be used to minimize CNI exposure in the presence of chronic nephrotoxic damage. However, blood levels of mTOR inhibitors must be monitored at regular intervals to detect intraindividual differences in the dose requirements of patients.

The combined administration of CNIs, mainly tacrolimus, and mTOR inhibitors may increase the risk for the development of insulin resistance and diabetes, with this risk appearing to be dose dependent. To combat this risk, dose minimization of CNIs and mTOR inhibitors is suggested. Diet and oral antihyperglycemic agents or insulin also are recommended. Metformin usually is used as first-line treatment in the presence of hyperglycemia but not when there is a reduced eGFR (<60 mL/mm/L, 73 m^2). Because hypoglycemia may occur during metformin therapy, glycemia and HbA1c levels must be monitored in patients receiving mTOR inhibitors.

Monoclonal Antibodies

Human monoclonal antibodies (mAb) that neutralize VEGF are used for the treatment of many solid tumors, including renal cell carcinoma, colorectal, lung, and breast cancer. Bevacizumab is a VEGF-targeted mAb. Bevacizumab therapy can lead to the development of hypertension and proteinuria because VEGF blockade induces endothelial dysfunction, with reduced production of nitric oxide and prostacyclin and overproduction of endothelin-1. VEGFR3 blockade at the endothelial level also leads to hypertension. In patients treated with mAb, accurate monitoring of blood pressure is necessary during the course of the therapy, particularly in hypertensive patients. In these cases, calcium channel blockers or ACE inhibitors/ARBs are the first-line treatment.[29] Before bevacizumab treatment, patients should be screened for the presence of proteinuria. Their renal function also should be assessed.

Other mAbs, such as cetuximab and panitumumab, both of which are antiepidermal growth factor receptors, are used to treat patients with malignancies. These can cause urinary magnesium wasting. Because their receptors are located in the epithelium of the distal convoluted tubule and promote magnesium ion reabsorption, blockade of these receptors causes magnesium reabsorption, thus inducing severe hypomagnesemia. Therefore the measurement of magnesium in blood and urine is necessary.

Rituximab is an anti-CD20 monoclonal antibody used primarily in the treatment of lymphoid malignancies. Its use may result in severe renal toxicity, including AKI, in patients with high levels of circulating tumor cells (>25,000/mm^3) or a high tumor burden, such as those with tumor lysis syndrome.[30] Although there are no established published guidelines for the dosage, rituximab may be discontinued in patients whose serum creatinine values rise or who develop oliguria during treatment.

Belatacept

Belatacept is a recently introduced immunosuppressor for use in organ transplantation. The drug acts as a competitive antagonist of CD28-CD80/CD86 by inducing binding between T cells, antigen-presenting cells, or dendritic cells.[31] It was introduced in kidney transplant therapy in the last few years as a substitute for CNIs or in association with MMF or alemtuzumab. Among patients, tolerance of belatacept has been good, with reduced side effects and a good health-related quality of life. Belatacept is contraindicated in

individuals with EBV-negative serology at baseline because of the occurrence of PTLD in some belatacept-treated patients.

Intravenous Immune Globulin

The administration of intravenous immune globulin (IVIG) can result in drug-induced nephrotoxicity. As shown in previous research, there is a risk of AKI in ICU patients treated with IVIG[32] and in patients with hepatitis B virus–related liver disease who undergo orthotopic liver transplantation and receive intravenous anti-HBV immunoglobulin to combat HBV recurrence.[33] Most of the reported cases of AKI involve IVIG infusions that contain sucrose as a stabilizing agent. Older patients and patients with preexisting renal impairment or diabetes mellitus are predisposed to IVIG-induced nephrotoxicity.[34] The clinical picture consists of oliguric renal failure, with renal replacement therapy required in up to 33% of patients. In more than 80% of these cases, AKI appears to be reversible. Renal damage in these patients is the result of tubular uptake of sucrose as a consequence of the infusion of sucrose-containing IVIG, leading to osmotic cellular swelling and damage. IVIG-associated nephropathy is similar to osmotic nephrosis induced by mannitol or dextran therapy. Similar nephropathy was observed in ICU patients with severe sepsis after the administration of hydroxyethyl starch used for volume restoration in patients with septic shock.[35] In older patients and those with renal impairment or diabetes, prevention consists of limiting the dose applied, lengthening the dosing interval, or avoiding sucrose-containing IVIG preparations.

CONCLUSION

Drug-induced nephrotoxicity is a relatively common cause of ICU-acquired AKI and can be induced by a variety of drugs via different mechanisms. Prevention leads to decreased morbidity and reduction in the lengths and costs of hospital stays. Keys to prevention include minimization of the use of potential nephrotoxins, especially in high-risk patients, and early detection of AKI, with subsequent rapid cessation of the causative agent.

CNIs are associated with adverse events, particularly nephrotoxicity, which may modify the long-term renal survival. To obtain significant improvements in renal outcomes, CNIs must be replaced with new immunosuppressive regimens. The use of MMF in CsA- and tacrolimus-sparing regimens is associated with improved renal function while maintaining adequate immunosuppression. Finally, it is important to adjust the dosage of immunosuppressant agents according to their plasma concentration, which should be monitored at regular intervals.

Key Points

1. It is increasingly common for intensive care physicians to be involved in the care of patients with various pathologies who are treated with immunosuppressive therapy for various reasons (e.g., allografts).
2. It is important that intensive care physicians are familiar with immunosuppressive drugs and their potential nephrotoxicity.
3. Common immunosuppressants include antimetabolites (mycophenolate mofetil, mycophenolate sodium, and azathioprine), CNIs (cyclosporine and tacrolimus), and mTOR inhibitors (sirolimus and everolimus).
4. Protocols for avoidance, minimization, and/or withdrawal of immunosuppressive drugs should be used in the ICU and include frequent monitoring of the plasma concentrations of these drugs.

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A complete reference list can be found online at ExpertConsult.com.

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