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Summary: Opioid use and misuse in the United States has been at epidemic proportions and is predicted to increase further in the setting of the Coronavirus disease 19 pandemic. Acute kidney injury is a condition associated with significant morbidity and increased mortality. We review the literature on the effect of opioids on kidney function and critically examine the association between opioid use and acute kidney injury and identify at-risk populations in whom opioids should be used with caution. We also discuss the role of biomarkers in elucidating this condition and propose preventive measures, novel therapeutic options, and research directions.

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Opioids are a class of drug that bind to specific receptors in the central and peripheral nervous systems and interrupt the transmission of pain signals via second messenger G-protein pathways. Opioids can be classified as endogenous and exogenous (natural, semisynthetic, and synthetic).¹ Binding at the receptor may result in agonistic, partial agonistic, or antagonistic outcomes. (Table 1). The three central nervous system opioid receptors are μ , κ , δ ; in addition, opioid receptors are found in the peripheral nervous system as well as various organs.² The opioid receptors can affect complex outcomes, based on the ligand, location of the receptor, and the end-organ or system it influences. For example, opioids can enhance the parasympathetic effect of the vagus nerve, which in the myocardium can result in bradycardia and a decrease in cardiac inotropy.^{3,4} When central opioid receptors are activated leading to increased renal sympathetic nerve effect, it leads to vasoconstriction and renal ischemia. This renal ischemia promotes further sympathetic activity, and if not resolved can lead to ischemic acute kidney injury (AKI). Renal ischemia can occur with morphine, owing to

such increased renal sympathetic activation, and can be decreased with naloxone (a central opioid antagonist).⁵

TRENDS IN OPIOID USE AND ABUSE

In 2008, Manchikanti and Singh⁶ noted that although Americans comprise 4.6% of the world's population, they consume 80% of the world's opioid supply, most notably 99% of the hydrocodone supply. Outside of the prescribed use of opioids, their euphoric effect leads to abuse of the drug with unfortunate consequences.^{7,6} From 2000 to 2014, the Centers for Disease Control reported that nearly half a million people in the United States died from opioid overdose.⁷ Reports also have suggested increases in local, national, and worldwide abuse of opioids over the past 2 to 3 decades.^{8,9} Opioid abuse was reported to be increasing nationally, and across several age groups including pediatric and young adults.^{10–12} In the United States, opioid overdose, intensive care unit admission, and deaths between 2001 and 2015 have increased significantly.¹³ Intensive care unit admissions for opioid overdose have a high in-hospital mortality rate.¹⁴ In 2018, the Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act, also known as the SUPPORT for Patients and Communities Act, was passed¹⁵ to help end the opioid crises via continuing medical education for best pain management practices, prescribing limits, prescription drug monitoring programs, and systematic support for recovery from addiction. Systematic support is comprised of medication-assisted recovery, monitoring outlier prescribers of opioids to Medicare part D based on geography, and supporting communities of recovery, which also helps with housing. Since then, data have shown a decrease in opioid use,¹⁶ however, the Coronavirus disease 19 pandemic is predicted to diminish or reverse system-based gains.¹⁷ Opioid use has increased in ventilated patients and those in hospice, leading to temporary fentanyl shortages of titratable agents during the Coronavirus disease 19 pandemic.^{18,19}

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Table 1. Classification, Potency, and Characteristics of Opioids and Opioid Antagonists

Opioid	Type	Morphine 10 mg SC Equivalence	Comments	
Naturally derived				
Codeine	Agonist	60 orally	Prodrug of morphine	
Morphine	Agonist	10 SC or IM		
Semisynthetic				
Hydrocodone	Agonist	1 IM, 2 orally	Short-acting antagonist (0.5 h) Very-long-acting antagonist (24 h) Medication-assisted therapy requires 6-16 mg/d (contains naloxone)	
Hydromorphone	Agonist	1.3 SC		
Oxycodone	Agonist	5 orally		
Oxymorphone	Agonist	1 SC		
Naloxone	Antagonist	Nonanalgesic		
Naltrexone	Antagonist	Nonanalgesic		
Buprenorphine	Partial agonist	0.3 IM		
Synthetic				
Fentanyl	Agonist	0.75 IM		Very short acting (<1 h)
Loperamide	Agonist	Nonanalgesic		Antidiarrheal, abuse, P-glycoprotein substrate
Meperidine	Agonist	75 SC or IM	Seizures caused by metabolite accumulation	
Methadone	Agonist	10 IM	Very long acting (24 h)	
Tramadol	Agonist	50-100 orally	Seizures possible with therapeutic dosing	
Methylnaltrexone	Antagonist	Nonanalgesic	Peripherally acting antagonist; reverses opioid-induced constipation	

IM, intramuscularly; SC, subcutaneously.

Goldfrank's Toxicologic Emergencies 11e, Nelson et al 2019.

EPIDEMIOLOGY OF AKI

AKI is defined as any of the following: an increase in serum creatinine level by 0.3 mg/dL within 48 hours; or an increase in serum creatinine level 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume less than 0.5 mL/kg per hour for 6 hours.²⁰ A large US population ($n = 3,787,410$) study estimated that the community-based incidence of non-renal replacement therapy (RRT)-requiring AKI and RRT-requiring AKI were 384.1 and 24.4 per 100,000 persons-years, respectively.²¹ AKI increasingly is recognized as an important contributor to morbidity, mortality, and economic loss worldwide²²; the estimated unadjusted mortality associated with an episode of AKI recently was estimated at 23.9% in adults and 13.8% in children.²³

EPIDEMIOLOGY AND ASSOCIATION OF AKI WITH OPIOID USE

Adverse effects of opioids include nausea, constipation, and urinary retention, which can contribute to the development of AKI. In addition, the pitfalls of inappropriate opioid dosage in the setting of impaired renal function is well documented.^{24,25} Despite these adverse effects, the incidence of AKI stemming from opioids is unclear.

The true incidence of AKI from opioid use likely is under-reported because only hospitalized events are known. Most reports that draw a clear association between opioids and AKI are related to heroin, which is a Schedule I illicit drug in the United States.²⁶ In patients with illicit drug use leading to rhabdomyolysis, 46% developed AKI with a 3.4% mortality rate.²⁷ The

association between AKI and prescription opioids is less clear. Intriguingly, in a large prospective cohort study, the lifetime opioid use in people with chronic kidney disease (CKD) was associated with reduced estimated glomerular filtration rate (GFR) and albuminuria, but not with the rapid kidney function decline of AKI.²⁸ On the other hand, another study involving 55,747 elderly individuals (mean age, 82.14 y) from New Zealand identified opioids as a risk factor for AKI.²⁹

Fassio et al¹⁶ noted that after the implementation of the opioid safety initiative, opioid use decreased; however, patients continued to be at greater risk of adverse events with opioids, including for AKI, even when compared with nonsteroidal anti-inflammatory (NSAID) use. During the study, the investigators noted a decrease in opioid use incidence rates, whereas NSAID use stayed the same. Despite this, AKI, cardiovascular events, and all-cause mortality were higher with opioid use than with NSAID use.

The incidence of AKI from urinary retention is not well defined and observational reports have suggested 10% of urinary retention cases may be owing to medications such as opioids.³⁰ In the elderly and in patients with renal dysfunction, most opioids, except buprenorphine, have a longer half-life of the active drug and metabolites.³¹ Elderly patients additionally can be at greater risk for AKI because of comorbid conditions such as benign prostatic hypertrophy.

EFFECTS OF OPIOIDS AND MECHANISM OF AKI

Although opioids may be used safely for pain control and anesthesia, inappropriate use with higher doses, the presence of toxins, drug interactions, and other conditions such

as dehydration, chronic liver or kidney dysfunction, or benign prostatic hypertrophy may increase the risk of AKI. Opioid use may result in AKI owing to systemic effects such as dehydration and hypotension, with resultant ischemic-reperfusion injury and free radical generation. Other possible mechanisms include rhabdomyolysis and urinary retention. Administration methods such as intravenous drug use also may result in the spread of hepatitis B and C and human immunodeficiency virus (HIV). These chronic viral infections can result in kidney injury over varying periods of time with AKI or CKD. Opioids can exert direct cellular effects such as renal lipidosis³² as noted on kidney biopsy specimens of patients on methadone. However, many of these cases include confounding factors, such as hepatitis B and C infections.³³ Opioids also can induce AKI in susceptible individuals via indirect mechanisms such as modulation of the parasympathetic and sympathetic nervous systems, renin-angiotensin-aldosterone system (RAAS), and the antidiuretic hormone (ADH) axis as discussed later.

PRERENAL ISCHEMIA AND REPERFUSION INJURY

Dehydration, changes in parasympathetic and sympathetic activation, and polypharmacy can result in ischemic AKI and subsequent reperfusion injury. (Fig. 1). Recurrent ischemia can result in AKI that may be irreversible and progress to CKD.

Dehydration

Dehydration resulting from opioid-induced changes in mentation or nausea can result in dehydration and ischemic AKI. Another less well-known contributor to opioid-related dehydration is opioid effects on human chemosensory function, especially olfactory perception. Limited data have shown that use of opioids reduced olfactory perception by affecting the trigeminal ganglia nuclei.³⁴

Olfactory input contributes largely to taste perception, and opioid users report alterations in taste.³⁵ This in turn leads to dehydration from reduced dietary intake.

Enhanced Parasympathetic Effect and Reduced Sympathetic Effect

Activation of opioid peptide receptors can inhibit myocardial excitation-contraction coupling. In an animal study, stimulation of peripheral opioid peptide receptors with a synthetic μ opioid agonist in normotensive animals resulted in a prolonged decrease in arterial pressure.³⁶ Although the findings of cardiac endorphin effects in decreasing myocardial contractility and attenuating the sympathetic response are relatively new, earlier work has shown similar effects with opioid anesthetics; it was noted that renal blood flow was lower with the opioid fentanyl when compared with other anesthetics such as ketamine.³⁷ Usually, in the range of renal autoregulation with intact renal innervation, renal blood flow is a reflection of cardiac output. The decrease in sympathetic input from fentanyl resulted in a decrease in cardiac output and renal blood flow with a compensatory increase in plasma renin.

Combining opioids with benzodiazepines can decrease cardiac function with bradycardia and vasodilation, further leading to orthostatic hypotension, hypotension, and syncope.³⁸ Overall, opioids increase parasympathetic nervous system effects, resulting in a decrease in heart rate and mean arterial pressure (MAP). Systemic hypotension impairs renal hemodynamics when renal arterial pressure decreases to less than 70 mm Hg, and glomerular filtration ceases when the renal arterial blood pressure decreases to less than 50 mm Hg.³⁹

The kidney is sensitive to ischemia-reperfusion injury, albeit to a lesser degree than the brain or heart.⁴⁰ Oxygen levels decrease across a gradient starting at the renal cortex and going deeper toward the medulla. Correspondingly, renal cortical cells are more affected by

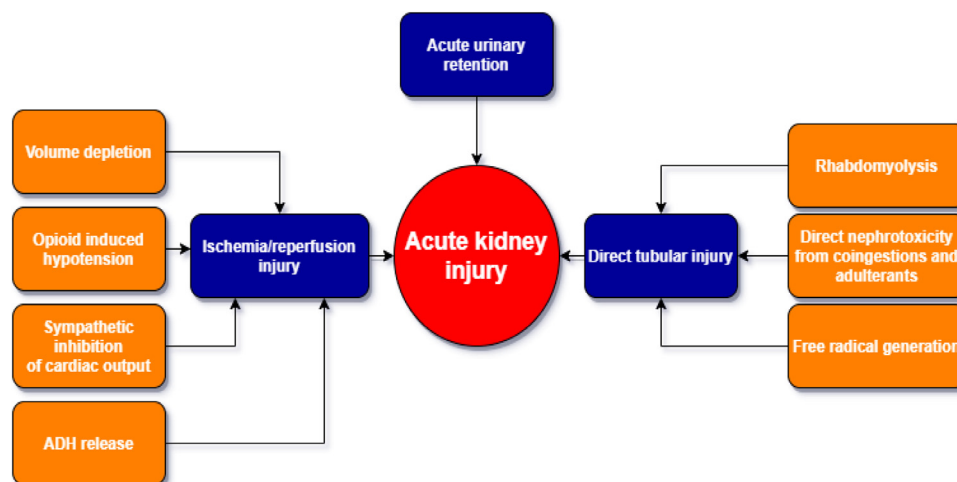


Figure 1. How opioids cause acute kidney injury.

ischemia than renal medulla cells. The outer medullary cells have the capacity to switch to anaerobic metabolism in the setting of hypoxia, and the inner medulla uses anaerobic glycolysis.⁴¹ In the native kidney, ischemia-reperfusion injury presents as AKI, and in the transplanted kidney as early graft failure.⁴²

Renal ischemia, commonly called *prerenal*, traditionally has been considered to be a reversible cause of AKI, and rehydration leads to improvement in GFR. However, recurrent dehydration can cause AKI to progress to CKD, as noted in the kidney injury model seen in Meso-American nephropathy, an entity reported among farm workers in the setting of repeated dehydration and AKI that led to CKD. Further contributing to the pathology are chronically activated vasopressin, RAAS, and polyol-fructokinase pathways in the kidney, along with subclinical rhabdomyolysis and nephrotoxin exposure.⁴³ Kidney biopsy specimens in patients with Meso-American nephropathy have glomerular ischemia, glomerulosclerosis, tubular atrophy, interstitial fibrosis, and progressive renal failure.⁴⁴ Although the exact mechanism is yet to be determined, urinary tubular markers neutrophil gelatinase-associated lipocalin and interleukin 18 are increased.⁴⁵

Free Radical Generation

Oxidative stress results in the formation of free radicals, which can damage cells. Antioxidant enzymes and substances such as superoxide dismutase, glutathione peroxidase, catalase, and glutathione help with redox processes that combat the damage caused by oxidative stress. Opioids can contribute to oxidative stress either by increasing the production of free radicals or decreasing antioxidant function. Morphine demonstrably can cause oxidative stress with the production of free radicals and a decrease in the levels of anti-oxidants.^{46–48} In an in vivo model, mice dosed with morphine had increased albuminuria after 72 hours with effacement of podocyte foot processes; in vitro examination of human podocytes showed that morphine decreased the slit diaphragm constituting molecules such as nephrin, podocin, and cluster of differentiation-2-associated protein; this suggested podocyte injury as a possible mechanism for morphine to alter the glomerular filtration barrier.⁴⁹

Rhabdomyolysis

Rhabdomyolysis is a well-delineated cause of AKI and its pathophysiologic mechanisms are renal vasoconstriction from dehydration, intraluminal cast formation from myoglobin precipitation, and direct heme-protein-induced cytotoxicity. In rhabdomyolysis, AKI with acute urate nephropathy is related to the high rates of generation and urinary excretion of uric acid and direct nephrotoxicity of free iron released from myoglobin.⁵⁰ Opioids have been

reported to cause rhabdomyolysis in excessive doses,⁵¹ but the exact causative mechanism is unclear.

Urinary Retention

Urinary retention can lead to renal injury by way of backward flow pressure resulting in hydronephrosis and irreversible renal scarring. Rawal et al⁵² performed urodynamic studies on 30 male volunteers aged 20 to 28 years after administration of epidural, intramuscular, and intravenous morphine and found that irrespective of dose, all subjects receiving epidural morphine showed marked relaxation of the detrusor muscle and a corresponding increase in the maximal bladder capacity leading to urinary retention, whereas intramuscular and intravenous morphine had minimal effect. The presence of opiate receptors in the micturition center in the pons and the urinary bladder may contribute to this effect. Relief of bladder pressure also may contribute to sequelae such as postobstructive diuresis and electrolyte derangements.⁵³

Effect on RAAS and ADH Systems

RAAS responds primarily to changes in mean arterial pressure, which may explain the complexity of the overall effects of opioids on the RAAS. Opioids increase thirst after being administered for pain control and with reduced urine flow.⁵⁴ Animal research has indicated that opioids partly function in the hypothalamic thirst center, which can result in alterations in thirst sensation.⁵⁵ Limited data suggest that morphine results in nonosmotic ADH release.^{56,57} Rats nephrectomized before administration of morphine no longer show morphine-induced water intake, pointing to involvement of the kidneys in the dipsogenic effect of morphine. Rats who are renin-depleted via clipping of one renal artery and then removal of the clipped kidney a month later showed an opioid-induced water intake linearly related to the basal plasma renin level, an effect not seen in rats with normal renin levels. Interestingly, captopril, an inhibitor of the angiotensin-converting enzyme that increases circulating renin and angiotensin I levels, increased morphine-induced water intake, whereas the competitive antagonist of angiotensin II, saralasin, had no such effect. These results suggest a permissive interaction between morphine and the RAAS at the circulating angiotensin I or renin level, with the dipsogenic effect of morphine dependent on an intact RAAS.⁵⁸

PREVENTION AND TREATMENT OF AKI IN THE SETTING OF OPIOID USE

Hydration

Early hydration is essential to limit vasoconstriction, which is a physiologic response to maintain adequate

Table 2. Methods to Prevent AKI When Using Opioids

Intervention	Mechanism
Hydration	Improve renal perfusion
Naloxone	Sympathetic inhibition
HIF prolyl-hydroxylase inhibitors	Promote HIF-related mechanisms to protect against ischemia
TLR2 blockade	Inhibition of inflammatory response to ischemia
Thymoquinone	Reduce free radical generation
κ -opioid receptor agonist	Reduce free radical generation

AKI, acute kidney injury; HIF, hypoxia-inducible factor; TLR2, Toll like receptor 2.

MAP, usually at the expense of a decrease in GFR. (Table 2). Timely rehydration therapy increases MAP and reverses vasoconstriction, allowing GFR and renal tubular flow to return to normal, followed by an appropriate increase in urine output. Physicians should monitor both fluid intake and urine output. Patients on chronic opioids should be educated to maintain an adequate amount of urine by staying well hydrated. Patients with altered mentation or nausea require intravenous fluids. No clear evidence suggests optimal intravenous fluid doses, but prescribers should balance adequate MAP requirements while avoiding adverse events such as pulmonary edema. In rhabdomyolysis-induced AKI, animal studies suggest a prophylactic benefit to intravenous fluid with bicarbonate, but this benefit is less clear in human studies. A large study of patients with trauma and rhabdomyolysis comparing 0.9% sodium chloride intravenous solution with intravenous bicarbonate with mannitol found no significant differences between the groups.⁵⁹

Monitoring and Preventing Urinary Retention in the Setting of Opioid Use

Time-limited perioperative use of opioids may cause transient renal function changes, and are managed by keeping patients well hydrated and closely monitoring urine output, frequently with a bladder catheter.

Meperidine, a long-acting opioid, has been shown to be an independent risk factor for urinary difficulties after elective cholecystectomy.⁶⁰ Perioperative use of morphine and fentanyl reportedly decrease GFR and urine output, suggesting value to monitoring urine output in this setting.⁶¹

Medication Combinations That Could Increase the Risk of AKI

In the management of chronic pain, anti-inflammatory medications such as NSAIDs often are used before, or combined with, opioids. The combination of the two may increase the risk for AKI in a vulnerable population.

NSAIDs decrease the effects of renal prostaglandin and could lead to AKI by causing renal tubular damage, interstitial nephritis, or nephrotic syndrome, while opioids may decrease MAP and cause urinary retention.⁶² Although the combination of these medications may be used safely, patients should be advised to be well hydrated and monitor adequate urine output, and have their renal function monitored regularly.

Drug Choice and Dosing

Opioid pharmacokinetics can be affected by renal function. A select few opioids are metabolized by the kidney, such as meperidine. Although many opioids are metabolized in the liver, clearance of the metabolites may be via the kidney, as in the case of morphine and codeine. When a prodrug such as codeine is metabolized, the drug and the intermediary metabolites can build up in the various compartments, resulting in unwanted side effects.

Rational dose adjustments of opioids is crucial to prevent adverse effects including AKI in high-risk populations. Few opioids are metabolized by the kidney, an example being meperidine. Although many opioids are metabolized in the liver, clearance of the metabolites may be via the kidney, as in the case of morphine and codeine. Certain opioids such as buprenorphine appear to be less dependent on kidney clearance, and have a lower risk of accumulation. These opioids would be the drug of choice for the elderly.

Future Therapeutics

Known blockers of harmful side effects could help reduce the kidney injury caused by opioids. Morphine triggers apoptosis of mesangial cells in both HIV transgenic mice and controls via the production of superoxide, and in the HIV mice the pro-apoptotic effect of morphine could be blocked by the protease inhibitor saquinavir via reduction of superoxide.⁶³

In the mouse model, Liu et al⁶⁴ found pretreatment with κ opioid-receptor agonist u50448h, used to prevent renal ischemia-reperfusion injury in cardiac myocytes and neuronal cells, significantly decreased apoptosis, as well as the serum levels of creatinine and blood urea nitrogen. A possible mechanism included the significantly increased superoxide dismutase activity and nitric oxide levels by activating the phosphatidylinositol 3-kinase and protein kinase B pathways, which may offer protection against renal ischemia-reperfusion injury.

Morphine, in addition to its analgesic function, has antiangiogenic effects.⁶⁵ Hill et al⁶⁶ noted in a mouse model that l-mimosine and dimethylxalylglycine, molecules that activate hypoxia inducible factor (HIF) by the inhibition of HIF hydroxylases, helped protect the

Table 3. Biomarkers in AKI

Name (Abbreviation)	Known Inciting Factors	Proposed Functional Role in AKI
Neutrophil gelatinase–associated lipocalin (NGAL) Kidney injury molecule 1 (KIM-1)	Ischemia, toxin Ischemia-reperfusion	Protective: apoptosis inhibition Protective: promotes removal of apoptotic and necrotic products
Interleukin 18 Liver-type fatty acid–binding protein (L-FABP) Angiotensinogen (Atg)	Ischemia-reperfusion, toxin Ischemia, cardiac surgery Cardiac surgery, others	Proinjury: inflammatory cytokine Protective: antioxidant Proinjury: RAAS activation
Tissue inhibitor of metalloproteinase-2 (TIMP-2) Insulin like growth factor binding protein 7 (IGFBP-7)	Cardiac surgery, critical illness Critical illness	Protective: unclear mechanisms Protective: cell-cycle arrest

AKI, acute kidney injury; RAAS, renin-angiotensin-aldosterone system. Alge and Arthur.⁷⁸

kidneys from ischemia-reperfusion injury. Possible pharmacologic activation of HIF may be an option to protect the kidney from ischemia. Ongoing clinical trials of HIF stabilizers for the treatment of anemia in CKD hopefully will shed light on this.

Toll-like receptors are receptors that help with recognizing pathogens and host substances released during injury. In the kidney, Toll-like receptor 2 messenger RNA from renal tubular cells increased with renal ischemia-reperfusion injury, and in the mouse model Toll-like receptor 2 blockade is a possible mechanism for prevention of ischemic kidney injury.⁶⁷

Limited data have suggested that morphine could increase the generation of free radicals, with possible renal free radical injury, which may be prevented with thymoquinone; but no clinical evidence yet supports this.⁶⁸

AKI Requiring RRT

Myoglobin is a large molecule that ideally should be filtered well with continuous RRT (CRRT) membranes. However, studies using CRRT for rhabdomyolysis are inconclusive about any benefit over conventional dialysis therapy for those with AKI resulting from rhabdomyolysis.⁴⁷ Uncontrollable events such as filter clotting may result in variations in dialysis dose, which prevents finding any clear advantage of CRRT in this setting.⁶⁹

DO BIOMARKERS OF AKI CHANGE WITH OPIOID USE?

The timely and accurate diagnosis of AKI with the use of serum creatinine has many pitfalls. The delay between the increase in serum creatinine and changes in GFR can impair accurate estimates of onset of injury.⁷⁰ In addition, there is considerable variability among patients in the correlation between serum creatinine and baseline GFR, owing to differences in functional renal reserve and in creatinine synthesis rates.^{70,71} Creatinine kinetics also cannot pinpoint the etiology of AKI or site of injury (ie, glomeruli, interstitium, or tubules).

Identification of a specific biomarker of injury will be challenging given the multifaceted mechanisms of opioid-associated AKI. Few established biomarkers of kidney injury have been identified⁷² in the context of opioid-associated AKI (Table 3).

In an analysis of the National Health and Nutrition Examination Survey 2009 to 2010 involving 3,980 participants, prescription opioid use ($\beta = 0.19$; $P = .002$) was associated with higher urinary albumin-creatinine ratio values in comparison with NSAIDs ($\beta = 0.17$; $P = .105$).⁷³

Are certain opioid medications better at preventing AKI? The evidence is unclear. Although retrospective human data in 130 patients during cardiopulmonary bypass showed remifentanyl use did not increase the incidence of postoperative AKI after cardiac surgery, in the mouse model, a study showed lower levels of the AKI biomarker neutrophil gelatinase–associated lipocalin in the renal ischemia-reperfusion injury model with dexmedetomidine as compared with the group treated with remifentanyl.⁷⁴

Sakai et al⁷⁵ conducted a retrospective study on 80 patients to clarify the effect of the use of remifentanyl during cardiopulmonary bypass on the incidence of postoperative AKI and reported that the incidence of AKI was not significantly different in the remifentanyl group and controls (51% versus 36%; $P = .10$).

Opioid-induced increases in central sympathetic tone may worsen AKI owing to renal ischemia. In a mouse model, naloxone blockade of central opioid receptors attenuated ischemic AKI through the inhibition of renal sympatho-excitation.⁵

Methadone is a long-acting weak opioid agonist with limited euphoric effects. Methadone was first used to treat opioid dependence in the mid-1960s, and was officially approved for this in 1972 by the US Food and Drug Administration. Methadone generally is considered safe in renal disease owing to a lack of renally cleared metabolites. Because a methadone prescription has significant restrictions, office-based treatment of opioid dependence uses the partial agonist buprenorphine, which has fewer regulatory controls.⁷⁷

CONCLUSIONS

Opioid use and AKI are two rapidly emerging health issues. Opioids have direct and indirect interactions with the kidney that may impair renal function. However, the incidence of opioid-associated AKI remains under-reported and its mechanisms remain to be clearly elucidated. Injury-specific biomarker studies involving opioids will be illuminating. Novel therapeutic options for opioid-associated AKI are intriguing but glaringly lack randomized clinical data at this time. More research in this area is needed to address the knowledge gap in this critical unmet medical need.

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