Analgesic Therapy in Patients with Chronic Kidney Disease: A Case-Based Approach

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Physicians must consider a variety of factors when prescribing analgesic therapy to patients with chronic kidney disease (CKD). Altered pharmacokinetics and drug metabolism in this group of patients increases risk of drug toxicity. Also, certain analgesics can worsen kidney function and they should be avoided in CKD patients. This review uses a case-based approach to illustrate principles of managing analgesic therapy in CKD patients. These cases will demonstrate the nephrotoxic potential of these agents, review adverse effects of inappropriate medication dosing, outline medications that are considered safe or contraindicated in the CKD population, and review proper drug dosing.

OVERVIEW OF PAIN SYNDROMES

Pain is considered a major health problem, with more than 50 million Americans suffering from uncontrolled symptoms.[1] Unrecognized pain syndromes remain widespread and negatively impact a patient's perceived quality of life. Pain has been designated as the fifth vital sign and can be generally defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage."[1] The amount of suffering experienced by an individual varies based on multiple factors including physical, psychological, social, and spiritual stressors and beliefs. Therefore, management of pain is highly individualized.

A number of obstacles prevent a physician from fully addressing a patient's pain. One important barrier is the patient's view of analgesic medications. Many patients do not seek pain relief for fear of narcotic addiction or loss of mental capacity. Similarly, physicians have concerns that prevent them from prescribing adequate analgesic medication, such as fear of persecution as well as inadequate training in appropriate assessment and treatment of various pain syndromes. Once both physician and patient have agreed to institute pain management, a number of factors must be considered prior to initiating therapy. Most available evidence for pain management is obtained from data generated in the treatment of pain in cancer patients; however, many of principles can also be applied to nonmalignant pain.

As an initial step in pain therapy, nonpharmacologic methods should be attempted prior to initiation of drug therapy. Nonpharmacologic options (eg, surgery for bone stabilization and tumor debulking, nerve plexus ablation, radiotherapy, transcutaneous electrical nerve stimulation, acupuncture, aromatherapy), cognitive and behavioral techniques (biofeedback, imagery, distraction), and local therapies (eg, massage, exercise, mechanical vibration, heat or ice) are available to manage pain. The World Health Organization (WHO) has devised a "ladder" system to help structure initial and adjuvant analgesic medication choices (**Table 1**).

PAIN IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Pain is highly prevalent in patients with multiple comorbidities, including those with CKD. These patients are difficult to treat because they possess altered pharmacokinetics and drug metabolism, both of which disturb therapeutic windows and increase drug-associated toxicity.[2] The gastrointestinal and renal systems figure prominently in the absorption, metabolism, and excretion of analgesics. Altered end-organ function predisposes individuals to adverse events because of disturbances in local and systemic protective homeostatic mechanisms. It is essential that physicians recognize those patients with altered drug handling prior to prescribing analgesic medications. In particular, patients with CKD are at risk to develop toxicity. Accordingly, the presence of renal dysfunction should influence the physician's choice of analgesic regimens. The CKD staging system helps identify patients with various levels of renal dysfunction (**Table 2**).[3] In fact,

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Table 1. World Health Organization 3-Step Pain Relief Ladder

Step 1: mild pain (rating of 1–4 on 0–10 scale)
Non-narcotic analgesics (eg, acetylsalicylic acid, acetaminophen, nonsteroidal anti-inflammatory drugs)
± Adjuvant therapy*
Step 2: mild to moderate pain (rating of 5–6 on 0–10 scale)
Opioids (eg, codeine, oxycodone, hydrocodone, tramadol)
± Nonopioid
± Adjuvant therapy*
Step 3: moderate to severe pain (rating 7–10 on 0–10 scale)
Opioids (eg, morphine, hydromorphone, methadone, fentanyl, oxycodone)
± Nonopioid
± Adjuvant therapy*

Adapted from WHO's pain relief ladder. Available at www.who.int/cancer/palliative/painladder/en. Accessed 21 Mar 2005.

*Medications to counteract opioid side effects or provide additional analgesia (eg, anticonvulsants, antiepileptics, corticosteroids, and/or step 1 medications).

several strategies are available to aid physicians in implementing analgesia in CKD patients (**Table 3**).

The number of people with CKD is on the rise; an estimated 6.2 million patients have early renal dysfunction and approximately 800,000 have more advanced CKD approaching end-stage renal disease. It is difficult to estimate the prevalence of pain in this population because renal failure is often silent until the disease is very advanced. In a study of dialysis patients, more than 80% reported some pain, and 55% of those patients rated their pain as severe.[4] In the same study, patients reported osteoarthritis, musculoskeletal pain, and neuropathies as the most common causes of pain.

One potential confounding issue surrounding analgesic therapy in patients with CKD is their huge pill burden. On average, CKD patients ingest 7 different medications daily; these include drugs required to manage their underlying comorbid diseases as well as those used to treat CKD and its associated complications (eg, renal osteodystrophy, cardiovascular disease, metabolic acidosis, anemia).[5] The addition of 1 or 2 more medications to this already substantial regimen significantly increases the risk for adverse drug interactions. As well, CKD patients represent a special challenge because of the complex relationships that exist between the clearance of many medications and the prevailing level of renal function, making the determination of optimum drug dosing difficult. Inadequate dosing may result in undertreatment of pain in some patients. More dangerous is the overtreatment of pain, which can increase the risk of life-threatening side effects due to excessive or unadjusted drug dosing in the setting of a reduced glomerular filtration rate (GFR). For all patients, decisions regarding analgesic regimens should consider previous exposures, pharmacokinetics, and level of pain experienced; this is particularly important for CKD patients. Finally, patients with CKD are at high risk to develop acute or chronic decreases in GFR from certain medications. These deleterious effects can reduce residual renal function and accelerate the need for renal replacement therapy.

CASE 1: A MAN WITH KNEE PAIN

A 64-year-old African American man with longstanding diabetes, hypertension, and a stable creatinine concentration of 2.5 mg/dL is seen by his primary care physician for worsening pain in his knees. The patient is subsequently diagnosed with bilateral osteoarthritis. A nonsteroidal anti-inflammatory drug (NSAID) is recommended by his primary care physician; however, the patient is concerned about taking any drug that may worsen his renal failure.

Case Discussion

In a patient with osteoarthritis without CKD, appropriate initial therapy includes NSAIDs, acetaminophen, selective cyclooxygenase-2 (COX-2) inhibitors or possibly tramadol. In contrast, certain medications are potentially harmful and nephrotoxic to CKD patients. The risk and benefit of each agent needs to be reviewed prior to their administration to this group of patients. If deemed appropriate and initiated as therapy, CKD patients should be closely monitored while receiving these analgesics. Medications commonly employed for osteoarthritis and other types of acute or chronic pain are reviewed below.

NONSELECTIVE NSAIDS

NSAIDs are nonselective COX-1 and COX-2 inhibitors that relieve pain through peripheral and central effects. The therapeutic action of NSAIDs occurs primarily through the inhibition of COX-2, which decreases prostaglandin synthesis believed to be important in the inflammatory and pain response. COX-1 inhibition, on the other hand, is thought to account for side effects, including gastric mucosal damage and platelet inhibition. NSAIDs are used as primary or adjuvant therapy at all steps of the WHO analgesic ladder (Table 1). There is no evidence that they are more effective for certain types of pain rather than others; however, they are most often prescribed for musculoskeletal injuries. A meta-analysis of conventional

Table 2. Staging System and Action Plan for CKD

Stage	Description	GFR (mL/min per 1.73 m²)	Action*
—	At increased risk for CKD	≥ 90 with risk factors†	Screening CKD risk reduction
1	Kidney damage‡ with normal or increased GFR	≥ 90	Diagnosis and treatment Slow progression of CKD Treat comorbidities Cardiovascular disease risk reduction
2	Mild decrease in GFR	60–89	Estimate progression
3	Moderate decrease in GFR	30–59	Evaluate and treat complications
4	Severe decrease in GFR	15–29	Prepare for renal replacement therapy
5	Kidney failure	< 15 or dialysis	Replacement if uremic

Adapted from National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) Advisory Board. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Dis 2002;39(2 Suppl 2):S65, with permission from Elsevier Science.

CKD = chronic kidney disease; GFR = glomerular filtration rate.

*Includes actions from preceding stages.

†Risk factors: hypertension, dyslipidemia, diabetes mellitus, anemia, systemic lupus erythematosus, chronic analgesic ingestion.

‡Kidney damage as manifested by abnormalities noted on renal pathology, blood, urine, or imaging tests.

NSAIDs found no evidence for analgesic superiority of one NSAID over others, but side effect profiles can differ significantly.[6]

The incidence of renal toxicity in healthy individuals on therapeutic doses of NSAIDs is very low (< 1%).[7] However, patients with CKD or with predisposing factors are at higher risk and must be managed accordingly. NSAIDs should be avoided or employed cautiously in patients with stage 4 or higher CKD (GFR < 30 mL/min). When NSAIDs are given to CKD patients for pain management, precise indications and a limited time course of therapy is key.[8] NSAIDs should be started at the lowest effective dose, doses should be adjusted for those drugs that are excreted primarily by the kidney, and blood pressure, weight (a marker for edema formation), renal function, and electrolytes should be closely monitored.

NSAID-Induced Acute Renal Failure

There are detailed accounts of NSAID-related acute renal toxicity, particularly in predisposed patients (**Table 4**); however, the actual incidence and prevalence of NSAID-induced acute renal failure (ARF) is not well documented. ARF is most frequently related to reversible afferent arteriolar vasoconstriction and hemodynamic changes in GFR. This effect is mediated by inhibition of vasodilatory renal prostaglandins (PGE_2 and PGI_2), leading to a decrease in renal blood flow and GFR. Although considered unimportant in healthy subjects, prostaglandin-mediated hemodynamic influences are significant in patients with true or effective hypovolemia and those with CKD. It is important to note that elderly patients without these abnormalities may also be at risk for NSAID-induced ARF owing to a decline in renal function and changes in renal prostaglandin excretion that occurs with normal aging.[9]

All NSAIDs are not equivalent in their modification of prostaglandin production. Ketorolac, an intravenous (IV) NSAID indicated for severe pain, is an extremely potent COX inhibitor and has a high potential for inducing renal impairment if used for more than 5 days. The IV route of administration accounts for much of its nephrotoxicity. Of the oral NSAIDs, indomethacin has the greatest effect on renal function, whereas aspirin carries the lowest risk for decreasing GFR and causing ARF.[10] Decreased excretion of ketorolac and indomethacin in the setting of renal insufficiency contributes to their nephrotoxicity. In general, ARF due to hemodynamic factors reverses rapidly, typically within 3 to 5 days.

Another form of NSAID-induced ARF is idiosyncratic acute interstitial nephritis (AIN). Although all NSAIDs have been shown to induce AIN, it occurs more commonly with proprionic acid derivatives (ie, ibuprofen, fenoprofen, naproxen).[11] In contrast to other hypersensitivity reactions, clinical findings such as eosinophilia,

Table 3. Pain Medication Guidelines for Patients with CKD

Determine the type, origin, and intensity of pain.
Determine level of kidney function by 24-hour urine or GFR estimate equations:
Cockcroft-Gault: [140 – age in years] × weight in kg/[72 × serum creatinine] (The result is multiplied by 0.85 for females.)
Abbreviated MDRD: 186 × [serum creatinine (mg/dL)]$^{-1.154}$ × [age (years)]$^{-0.203}$ × [0.742 if female] × [1.21 if African-American]
Review medication list for potential drug-drug interactions.
Attempt to choose the least nephrotoxic medication; consider shorter-acting drugs with limited toxic metabolites and low interaction potential.
Generally begin therapy with a lower drug dose; adjust dose and interval based on level or stage of CKD.
Increase compliance by informing patient of expected efficacy and toxicity.
Consider prophylaxis for known adverse effects.
Monitor medication levels if appropriate.
Reassess kidney function and requirement for pain medication on a regular basis.

CKD = chronic kidney disease; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.

Table 4. Predisposing Factors for NSAID-Induced Acute Renal Failure

Decreased effective blood volume (eg, from congestive heart failure, cirrhosis, nephrotic syndrome, anesthesia, shock)
Decreased absolute volume (eg, from hemorrhage, sodium and water depletion)
Acute renal failure
Chronic kidney disease
Medications (eg, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, aldosterone receptor antagonist, diuretics, cyclosporine)
Renal transplantation
Advanced age

Adapted from Buckalew V, Appel R. Analgesics and the kidney. In: Greenberg A, Cheung AK, editors. Primer on kidney disease. 3rd ed. San Diego: Academic Press; 2001:284, with permission from Elsevier.

NSAID = nonsteroidal anti-inflammatory drug.

eosinophiluria, rash, and fever are rare. Patients with NSAID-induced AIN typically have proteinuria and nephrotic syndrome. Additionally, nephrotic syndrome secondary to minimal change disease or membranous nephropathy (and rarely papillary necrosis) may be induced by acute NSAID therapy.

Finally, classic analgesic nephropathy may develop from habitual consumption of these analgesics over several years. It is characterized histopathologically by renal papillary necrosis and chronic interstitial nephritis. Analgesic nephropathy often leads to the insidious development of renal failure.

Other Renal Effects

In addition to ARF, NSAIDs have been associated with a number of other renal effects that may directly impact the CKD patient. NSAIDs have been linked to worsening hypertension by increasing sodium and water reabsorption in the nephron. By antagonizing the effects of prostaglandins that enhance renal sodium chloride and water excretion, NSAIDs promote volume overload. In one meta-analysis, the average increase in blood pressure was 5 mm Hg, but the effect was most profound in those patients with preexisting hypertension.[12] Not unexpectedly, NSAIDs are also associated with increased edema formation and decreased diuretic effectiveness. Prostaglandins, especially PGE_2, promote sodium chloride excretion in part by decreasing sodium chloride reabsorption in the loop of Henle. NSAID inhibition can reduce response to loop diuretics (eg, furosemide, torsemide, ethacrynic acid) and contribute to intractable pulmonary and peripheral edema in patients with limited renal reserve. Electrolyte disturbances may also develop during NSAID therapy. As noted above, impaired renal water excretion can precipitate mild to moderate hyponatremia in CKD patients. Also, severe and potentially life-threatening hyperkalemia can occur with NSAID use in susceptible patients, including patients with renal insufficiency, severe hyperglycemia, or patients taking medications that interfere with the renin-angiotensin-aldosterone pathway (ie, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists).

Because prostaglandins mediate renin release from juxtaglomerular cells, inhibition of their formation by these drugs can induce hyporeninemic hypoaldosteronism. Insufficient production of aldosterone is associated with a defect in renal potassium excretion by principal cells in the cortical collecting duct, increasing the risk for hyperkalemia.

Aspirin and NSAIDs

In therapeutic doses, acetylsalicylic acid (aspirin), which primarily inhibits COX-1 enzyme function, does not impair renal function in patients with normal renal function. Similar to other NSAIDs, patients with CKD may experience a transient decrement in renal function with aspirin dosages above 325 mg/d. Aspirin and

NSAIDs should not be combined because they may reduce GFR in at-risk patients in an additive fashion. In addition, NSAIDs may be deleterious to the cardioprotective effects of aspirin. Regular aspirin use does not influence hypertension or increase risk for CKD when given in doses recommended for the prevention of cardiovascular events.[13,14] However, aspirin should be avoided in patients with acute glomerulonephritis, cirrhosis with ascites, and children with congestive heart failure to avoid potential nephrotoxicity. In all others with CKD, risk versus benefit should be assessed. If routine aspirin therapy is undertaken, careful monitoring of renal function should be performed at regular intervals.

SELECTIVE COX-2 INHIBITORS

The selective COX-2 inhibitors are a unique and relatively new class of NSAID, commonly prescribed for pain relief in patients with a history of gastritis or peptic ulcer disease. Patients with CKD are at higher risk for adverse gastrointestinal events and bleeding; therefore, this group of drugs is particularly appealing in this population. Unfortunately, patients with CKD were specifically excluded from many trials comparing selective COX-2 inhibitors with traditional NSAIDs, and as a result, the gastrointestinal protective effects of COX-2 inhibitors have not been proven conclusively in patients with advanced CKD. Furthermore, patients at risk for adverse renal events, especially those with CKD, were not examined in the early drug trials. Thus, their nephrotoxic potential was not studied.

Another potential benefit in CKD patients, albeit theoretical and untested, is platelet sparing by selective COX-2 inhibitors.[15] However, there are concerns that these drugs may increase the risk for cardiovascular and nephrotoxic events as compared with conventional NSAIDs. This concern was raised after an analysis of large drug trials in which the selective COX-2 inhibitors were associated with worse cardiovascular outcomes compared with traditional NSAIDs.[16] Selective COX-2 inhibitors decrease vasodilatory and platelet anti-aggregatory prostacyclin (PGI_2) and favor the production of prothrombotic eicosanoids (thromboxane A_2). This platelet effect has been hypothesized to underlie the increased cardiovascular thrombotic events noted in patients treated with selective COX-2 inhibitors. However, not all patients are at risk for this complication, only those with underlying cardiac and cerebrovascular disease.

In addition to the potential for increased cardiovascular events, selective COX-2 inhibitors may be more potent inducers of hypertension than traditional NSAIDs. In a trial evaluating gastrointestinal protective effects of these drugs, more patients developed hypertension in the COX-2 inhibitor (rofecoxib) group than the NSAID (naproxen) group (mean increase in systolic blood pressure, 4.6 mm Hg).[17]

Selective COX-2 inhibitors appear to have a similar risk for reducing GFR and promoting adverse renal effects as compared with NSAIDs.[18,19] As with NSAIDs, CKD patients are at increased risk for reductions in GFR when prescribed selective COX-2 inhibitors.[20] Dependence on renal prostaglandins to maintain renal blood flow and GFR in CKD patients underlies ARF risk. Furthermore, in predisposed persons, there appears to be no difference in vasoconstriction-mediated GFR reduction between selective COX-2 inhibitors and nonselective NSAIDs. Other adverse renal effects, such as hypertension, edema formation, hyponatremia, hyperkalemia, and metabolic acidosis are similar for selective COX-2 inhibitors and nonselective NSAIDs. Thus, there appears to be no significant benefit for the use of COX-2 inhibitors over NSAIDs in CKD patients, and they should be prescribed with the same precautions utilized for administration of all NSAIDs.

ACETAMINOPHEN

The National Kidney Foundation recommends acetaminophen as the non-narcotic analgesic of choice for patients with CKD.[13] Acetaminophen has potent analgesic and antipyretic effects but mild anti-inflammatory properties. It is a weak inhibitor of both COX-1 and COX-2, although the true mechanism of analgesia remains unknown. Acetaminophen is metabolized by the liver and does not require dose adjustment when used in CKD patients. There is no evidence that occasional use causes renal injury, but it has been suggested that very large doses for prolonged periods can cause papillary necrosis.[15] Additionally, case-control studies have shown a weak association between acetaminophen use and CKD. These data are inconclusive because patients with underlying CKD were previously advised not to take NSAIDs prior to initiation of the study, introducing bias favoring worse outcomes in patients given acetaminophen. When recommending acetaminophen to CKD patients, it is important to note that many over-the-counter preparations contain combinations of acetaminophen with aspirin, NSAIDs, and other potentially harmful ingredients. Patients should be advised to examine labels closely. If acetaminophen is ineffective for pain control, nonacetylated salicylates (eg, salsalate) may be a reasonable option and should be considered for CKD patients.

TRAMADOL

Tramadol, a centrally acting non-narcotic agent, is a potential alternative analgesic to NSAIDs, COX-2

inhibitors, and acetaminophen for CKD patients. Tramadol acts on mu opioid receptors, giving it a similar therapeutic and side effect profile as opioids but presumably without the same abuse potential. This analgesic also inhibits the reuptake of monoamines (norepinephrine and serotonin) by nerve cells, which is thought to reduce central nervous system pain sensing. However, the serotonin syndrome (characterized by nausea, tremor, seizures, confusion, disseminated intravascular coagulation, respiratory failure, hyperthermia, and occasionally death) may be triggered by the concurrent use of tramadol and selective serotonin reuptake inhibitors (SSRIs).[20]

Tramadol is metabolized in the liver and eliminated by the kidneys. The elimination half-life of 5 hours is unpredictably increased in patients with CKD and may be twice as long.[21] Seizures and respiratory depression have been rarely described in CKD patients. To avoid drug toxicity, it is reasonable to prescribe dosages that do not exceed 200 mg/d for CKD patients with a GFR less than 30 mL/min (CKD stage 4 and 5).

CASE 1 THERAPY

To avoid nephrotoxicity in this patient with stage 4 CKD, both an NSAID and selective COX-2 inhibitor were not prescribed. Instead, the patient is advised to begin acetaminophen 1000 mg every 6 hours, not to exceed 4 g/d, for his osteoarthritis. The patient returns after 1 month and reports that the pain has improved to 4 out of 10. The patient is then given tramadol 50 mg every 6 hours as needed in addition to acetaminophen. The patient reports complete relief of pain on most days with minimal pain (2 out of 10) once a month.

CASE 2: A WOMAN WITH NEUROPATHIC LEG PAIN

A 68-year-old woman with a 25-year history of type 2 diabetes, a proteinuria level of 1.1 g on a recent 24-hour urinalysis, and a calculated creatinine clearance of 40 mL/min/1.73 m^2 (CKD stage 3) presents with complaints of a burning sensation in both of her legs. The burning pain has progressively worsened over the past several weeks and is now impairing her ability to sleep at night. She has been taking acetaminophen without any improvement and is requesting something stronger. Her current medications include losartan, regular insulin, atenolol, furosemide, and amlodipine.

Case Discussion

Neuropathic pain is a common complication in patients with longstanding, poorly controlled diabetes mellitus. This same group of patients tends to develop other end-organ involvement, including retinopathy and nephropathy. The presence of advanced CKD often adds a uremic component to the neuropathic process, which is likely present in the case patient. Proper therapy frequently involves off-label use of anticonvulsant and/or antidepressant agents. Anticonvulsants are believed to work at the level of the spinal cord, whereas antidepressants reduce pain sensation by enhancing inhibitory thalamospinal pathway signals. In clinical practice, the physician's choice of analgesic agent is often guided by the drug's side effect profile and the patient's ability to comply with the regimen.[22] Patients who continue to have pain despite these therapies may benefit from low-dose opioid drugs. However, opioids should not be employed as first-line therapy for neuropathic pain. Opioids are discussed in more detail below.

ANTICONVULSANTS

Gabapentin is an anticonvulsant agent that is structurally similar to the neurotransmitter γ-aminobutyric acid. Gabapentin has been used to treat peripheral neuropathy, postherpetic neuralgia, and restless leg syndrome.[11] Not surprisingly, the main adverse effects often involve the central nervous system. Somnolence, dizziness, ataxia, fatigue, and nystagmus are some of the notable adverse effects. One major advantage of using gabapentin is the limited number of interactions it has with other medications. This drug is excreted unchanged in the urine, and its elimination is directly linked to the level of GFR. As a result, gabapentin should be used with caution in patients with CKD, and the dose should be adjusted accordingly. In patients with severe CKD (GFR < 15 mL/min), the recommended dose is 300 mg every other day.[20]

Carbamazepine is structurally related to the tricyclic antidepressants (TCAs). It has only slight analgesic properties but is able to modify pain by reducing synaptic transmissions along nerve fibers. Carbamazepine is metabolized in the liver, and it is not necessary to adjust the drug dose for patients with CKD. Neurologic side effects reported with carbamazepine are similar to those described with gabapentin. However, potentially serious adverse effects, such as agranulocytosis, cardiac arrhythmia, hepatitis, and renal failure, have also been reported. Routine drug levels should be obtained and monitoring of erythrocyte count and liver and renal function is recommended for the duration of therapy. Abrupt drug withdrawal may precipitate seizures; therefore, a medication taper is recommended.

Newer anticonvulsant drugs that show potential for

use in treating neuropathic pain include tiagabine, lamotrigine, valproate, topiramate, and oxcarbazepine. These agents have not been specifically studied in CKD patients and are currently being evaluated for their efficacy in controlling neuropathic pain.

ANTIDEPRESSANTS

Tricyclic Antidepressants

TCAs block (in varying degrees) the reuptake of various neurotransmitters at the neural membrane. Although patients may experience some relief of acute pain, TCAs are typically recommended for treatment of chronic pain. The maximum analgesic benefit may not be achieved for several weeks. TCAs undergo glucuronidation in the liver and form pharmacologically active metabolites. Lipophilic metabolites can then cross the blood-brain barrier; this effect contributes to the development of lethargy, seizures, weakness, and respiratory failure at higher drug levels. The primary route of elimination of TCAs and their metabolites is by the kidneys, although rates vary among the different TCA drug types. These metabolites may accumulate in patients with CKD, leading to increased drug sensitivity and more adverse reactions.

TCAs indirectly affect the heart via anticholinergic activity. They also possess direct quinidine-like cardiotoxicity that, along with indirect effects, can precipitate electrocardiographic changes (eg, tachycardia) and clinical effects (eg, hypotension).[20] Conversely, increased blood pressure (by unidentified mechanisms) may be observed in patients on TCAs taking clonidine for hypertension. Finally, anticholinergic effects of TCAs can lead to urinary retention and bladder obstructive symptoms. In patients with CKD, TCAs should be started at the lowest dose and titrated up slowly as tolerated.

Selective Serotonin Reuptake Inhibitors

Other antidepressants, such as SSRIs, have been evaluated for pain management. Their favorable side effect and medication interaction profiles make them attractive for use in CKD patients. Chronic pain syndromes and depression often coexist. Furthermore, pain complaints, including those related to factors other than the depressive features of chronic pain, improve with the use of various classes of antidepressants. Currently, little evidence exists for the use of the newer SSRI antidepressants in patients with pain without depressive symptoms.

As a class, SSRIs are better tolerated than TCAs and are highly effective in various mood disorders (eg, major depressive disorder, generalized anxiety disorder). However, their efficacy in the treatment of neuropathic pain is not well established.[23] Although SSRIs have little or no analgesic effect on their own, they may add to the efficacy of some TCAs. For example, duloxetine, an investigational antidepressant, possesses characteristics of both TCAs and SSRIs. This agent is a balanced selective serotonin and norepinephrine reuptake inhibitor. In animal pain models, duloxetine is an effective analgesic. It decreases pain behavior in animals that are subjected to formalin-induced pain states.[24]

CASE 2 THERAPY

The patient begins gabapentin 300 mg daily for her diabetic neuropathic pain. The patient does not tolerate the medication (dizziness, fatigue), and she is switched to nortriptyline 25 mg at bedtime. The patient is also started on sertraline 50 mg daily and continued on acetaminophen as needed. The patient returns in 6 weeks and reports that she has been sleeping better and has more energy.

CASE 3: A MAN WITH MULTIPLE MYELOMA AND SPINAL PAIN

A 70-year-old man with back pain is diagnosed with multiple myeloma. Several lytic lesions in his thoracic spine account for the patient's back pain. A monoclonal spike is noted on the urine protein electrophoresis. Results of renal function testing is abnormal, with the patient's serum creatinine concentration fluctuating between 3.2 to 3.7 mg/dL. The physician prepares to order an analgesic medication regimen to relieve the patient's nagging back pain.

Case Discussion

Severe, debilitating pain with spinal involvement in multiple myeloma often requires a multidrug regimen. In general, cautious opioid administration, corticosteroid therapy, and at times, bisphosphonate adjuvant therapy may be warranted in these patients. Pain management must be undertaken carefully in elderly patients with CKD. Altered metabolism of various medications occurs in the elderly, especially in those patients with underlying CKD.

OPIOIDS

Opioids are the cornerstone of treatment for patients with acute or chronic moderate to severe pain. Numerous routes of delivery are available, including subcutaneous, IV, transdermal, aerosol, and oral dosing. In general, oral administration is preferred if the patient is able to swallow pills. Opioids as a class

Table 5. Common Opioid Adverse Effects

Adverse Effect	Prevalence (%)	Comments
Constipation	80	Requires treatment for duration of therapy
Nausea/vomiting	15–30	Transient (2–3 days)
Sedation	20–60	At initiation or increased dose
Myoclonus	60	May herald toxicity in CKD patients
Pruritis	2–10	Transient
Respiratory depression	Rare with chronic therapy	Stop opioid and restart at 30%–50% of dose in few hours; use naloxone if severe

CKD = chronic kidney disease.

include all drugs that act at opioid receptors (mu, kappa, delta, etc). These receptors are found throughout the central nervous system, in the dermis, and within joints.[25] Different opioid agents often have different affinities for receptors, partly explaining the clinical variations in side effect profiles and patient tolerability of these drugs (**Table 5**). Recent evidence suggests that endogenous opioids participate in the control of various kidney-specific functions.[26] For example, in patients placed on a sodium-restricted diet, central opioid pathways are activated that stimulate sodium reabsorption independent of renal nerve activity. Endogenous opioids are also involved in the homeostatic circulatory and renal excretory responses to plasma expansion. They act through alterations in the production and effect of atrial natriuretic peptide and antidiuretic hormone to reduce salt and water excretion.[27] Finally, it has been hypothesized that endogenous opioids play an important role in the pathogenesis of uremia. High plasma β-endorphin levels develop in patients with severe renal impairment. It is possible that excessive concentrations of this endogenous opioid may contribute to uremic symptoms, such as pruritis, nausea, myoclonus, and altered mental status. It is also believed that opioids can exacerbate the effects of uremia based on the similarity of symptoms observed following acute opioid administration.

Adverse Effects of Opioids

Although some opioids are well tolerated, others are problematic for patients with CKD. Morphine, propoxyphene, and meperidine rely heavily on intact kidney function to efficiently excrete their metabolite. This is an important point because these metabolites are the primary source of toxicity. For instance, metabolites of propoxyphene (ie, norproproxyphene) cannot be dialyzed or reversed with naloxone and carry the additional risk of hypoglycemia and cardiotoxicity. Long-term morphine use is associated with the accumulation of morphine-3-glucuronide and morphine-6-glucuronide, both of which readily cross the blood-brain barrier and accumulate in the cerebrospinal fluid. Furthermore, morphine may interact with other pain medications. For example, the bioavailability and half-life of morphine is increased by some TCA medications.[28] Morphine is safe as short-term therapy in patients with CKD, but it is recommended that the dosing interval be increased to 6 to 8 hours and the initial dose decreased by 30% to 50%.[29]

Other opioids with prolonged half-lives in CKD include codeine, oxycodone, and hydromorphone. Seizures, myoclonus, orofacial dyskinesias, and central nervous system depression have been reported with greater frequency in CKD patients.[29] Opiate administration can promote other rare but potentially serious complications such as further renal impairment (by inducing rhabdomyolysis) and fibrillary glomerulonephritis. Production and elimination of opiate metabolites can vary by patient, and each case should be given individual consideration. Patients should also be counseled that tablets, particularly sustained release forms, should not be altered prior to ingestion—chewing, dissolving, or crushing these medications may lead to rapid release and potentially lethal drug concentrations. The best strategy for use of these medications in CKD patients is to use opioids metabolized by the liver, including fentanyl and methadone, which are not highly dependent on GFR.

CORTICOSTEROIDS

Corticosteroids are used primarily for their anti-inflammatory and anti-tumor effects. They may also be useful to relieve nerve compression pain, headaches associated with increased intracranial pressure, pain from distention of the liver capsule, and bone pain. The optimal drug, dose, and route are not entirely clear, but dexamethasone is the most commonly prescribed corticosteroid for the aforementioned forms of pain. It is important to monitor therapeutic response

within the first week of treatment. If the patient does not experience significant relief of symptoms in 4 to 7 days, the drug should be discontinued. No dosage adjustment is required for CKD; however, high doses of corticosteroids may contribute to worsening hypertension, renal salt and water retention, and bone disease in patients with underlying predisposition to these conditions.

BISPHOSPHONATES

Bisphosphonates are a class of drugs that inhibit bone resorption by binding to calcium phosphate crystals within the bone matrix, thereby disrupting osteoclast activity. Established indications for these drugs are hypercalcemia, Paget's disease, and osteolytic metastases. Large amounts of data support the use of bisphosphonates in the treatment of bone pain caused by multiple myeloma or breast cancer.[30] The optimal dose and duration of therapy is still under debate. Patients should be informed that immediate relief is unusual, and several monthly infusions may be needed before noticeable effects are seen.

The efficacy and safety of bisphosphonates in patients with CKD has not been established.[31] A potential concern of bisphosphonate use in CKD patients is the exacerbation of underlying renal failure. Both pamidronate and zoledronate have been noted to cause kidney injury when prescribed in either high doses or with chronic therapy. Pamidronate is associated with the development of focal and segmental glomerulosclerosis, minimal change disease, and chronic tubular injury.[32,33] Zoledronate, a new bisphosphonate, has been associated with renal injury limited to the tubules and interstitium.[34] There is also the theoretical possibility that adynamic bone disease and increased fracture risk may be precipitated in CKD patients with evidence of underlying renal osteodystrophy. At this time, long-term therapy with bisphosphonates remains controversial in the CKD population and should be undertaken with caution.

CASE 3 THERAPY

The patient's multiple myeloma with spine involvement is initially treated with fentanyl 50 µg IV every 2 hours as needed. In addition, the patient is given methylprednisolone 250 mg and pamidronate 60 mg IV. The patient has relief from his back pain with this combination of medications. Unfortunately, he develops pneumonia requiring intubation during the hospitalization. The patient is placed on comfort care and a morphine drip is initiated.

CONCLUSION

Managing pain in patients with CKD can be extremely challenging for physicians attempting to maximize analgesia and quality of life while also minimizing adverse events. Nonpharmacologic therapies are readily available to treat localized mild to moderate pain and are attractive because they do not depend on intact renal function and have little effect on underlying CKD. The stepwise approach to pain management advocated by the WHO (Table 1) can be used as a guide for the initiation of medication analgesia, with some important modifications.

For mild to moderate pain, acetaminophen remains the analgesic of choice. NSAIDs and selective COX-2 inhibitors can be used cautiously for short-term pain relief, with close attention to increases in blood pressure, edema formation, and renal and electrolyte abnormalities. Anticonvulsants are potent adjuvant medications, but they have serious neurologic side effects that are heightened in the presence of CKD. Antidepressants are beneficial in reducing pain by altering depressive symptoms that often accompany pain syndromes. Altered pharmacokinetics and pharmacodynamics of these drugs mandate cautious dosage and scheduling practices in CKD patients. Narcotic analgesic medications that are excreted via the kidneys (eg, meperidine, propoxyphene) should be avoided and are considered contraindicated in patients with CKD owing to the risk of severe toxicity. Opioids can be employed safely in CKD patients with proper drug dosing and monitoring. **Table 6** lists some categories of pharmacologic agents and their precautions in CKD patients.

Patients with complex pain problems may benefit from referral to a pain center where both medical and psychological therapies are integrated. It must be remembered that pain is unnecessary and should be treated aggressively like any other chronic condition. The presence of underlying CKD should provoke caution but not induce reticence in the employment of medications to assist in pain management. **HP**

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Table 6. Pharamacologic Agents and their Precautions in CKD Patients

Drug	Precaution
NSAIDs and COX-2 inhibitors	Limit use in ARF, CKD, elderly, volume overload, hypertension, and hyperkalemia
Acetaminophen	Use with caution in patients with liver disease
Tramadol	Risk for serotonin syndrome when used with SSRIs; decrease dose in CKD
Anticonvulsants	
Gabapentin	Decrease dose in CKD
Carbamazepine	Monitor drug levels, cell counts, and liver function tests
Antidepressants	
Tricyclic antidepressants	Start at low dose and monitor for anticholinergic effects
SSRIs	Risk for serotonin syndrome when used with tramadol
Opioids	
Morphine	Decrease dose, limit duration, increase dosing interval
Propoxyphene	Risk of arrhythmia and hypoglycemia; avoid in CKD
Meperidine	Avoid because of increased risk of CNS symptoms
Corticosteroids	Risk for increased blood pressure and fluid retention
Bisphosphonates	Associated with ARF; efficacy and safety not established; dosage should be reduced in CKD

ARF = acute renal failure; CKD = chronic kidney disease; CNS = central nervous system; COX-2 = cyclooxygenase-2; NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor.

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