In-Depth Clinical Review

Pain management in patients with chronic kidney disease

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Abstract

Pain has been reported to be a common problem in the general population and end-stage renal disease (ESRD) patients. Although similar data for pre-ESRD patients are lacking, we recently reported that the prevalence of pain is also very high (>70%) among pre-ESRD patients at a Los Angeles County tertiary referral centre. The high prevalence of pain in the CKD population is particularly concerning because pain has been shown to be associated with poor quality of life. Of greater concern, poor quality of life, at least in dialysis patients, has been shown to be associated with poor survival. We herein discuss the pathophysiology of common pain conditions, review a commonly accepted approach to the management of pain in the general population, and discuss analgesic-induced renal complications and therapeutic issues specific for patients with reduced renal function.

Keywords: analgesics; chronic kidney disease; NSAIDS; opioids; pain

Introduction

Pain is one of the most common complaints in clinical practice because it is a symptom for a myriad of physical and mental problems. Indeed, chronic non-malignant pain has been reported to affect 11–24% of the general population [1–3]. Among dialysis patients, Murtagh et al. had documented a mean pain prevalence of 47%, with a range of 8–82% [4]. Similar data for pre-end-stage renal disease (pre-ESRD) or chronic kidney disease (CKD) stage 1–4 patients, however, are lacking. Nonetheless, in a recent small study involving 130 CKD patients at a tertiary referral medical centre in Los Angeles, California, the prevalence of pain, whether acute or chronic, was reported to be over 70% [5]. The sources of pain were musculoskeletal (62%) followed by other organ systems including gastrointestinal (13%), genitourinary (10%), haematological/oncological (10%), central and peripheral nervous system (9%), cardiovascular (7%) and others (10%) [5].

The high prevalence of pain in the CKD population is particularly concerning because pain has been shown to adversely affect quality of life [6]. In a cross-sectional analysis in the Renal Research Institute-CKD study, the presence of physical pain in patients with CKD stages 3–5 was found to be associated with lower quality of life scores (QOL) (as measured by the Medical Outcomes Study Short Form-36 (SF-36)) compared to that of the general population. Where a higher numerical value for QOL indicates better quality of life, the mean QOL scores were 67.4 ± 27.1, 59.0 ± 29.2 and 75.2 ± 23.7, for CKD, dialysis and general population, respectively, \( P < 0.0001 \) for both dialysis and general population when compared with CKD patients [6]. In dialysis patients, poor QOL scores were associated with hospitalization and death [7,8]. Whether CKD patients suffer the same fate is unknown.

Because pain is a common problem that has been shown to have a negative impact on quality of life, and both pain and its treatment can lead to various morbidities, more notably in the CKD population, prompt recognition and proper management of pain in this population are critical.

We herein review the pathophysiology, clinical manifestations and general management guidelines for pain with special considerations for pre-ESRD patients to optimize pain control while minimizing both renal and non-renal complications.

The significance of pain

The spectrum of acute-to-chronic pain is believed to encompass important biological roles. The evolutionary development of the sensation for acute pain is thought to be protective and well adaptive for organisms against potential injurious events or actions. The evolutionary preservation of mechanisms to allow for the persistence of pain beyond...
the healing phase or various chronic pain syndromes, however, is presumed to be a maladaptive diseased state [9].

**Acute pain**

Acute pain sensation results from the direct stimulation of sensory neurons found throughout the body, known as nociceptors. Nociceptors receiving input from outer body tissues are responsible for somatic pain, while those receiving input from internal organs are responsible for visceral pain. Nociceptors can be stimulated by mechanical, thermal, chemical and inflammatory stimuli. Substances released from tissue injury including vasoactive peptides (i.e. calcitonin gene-related protein, substance P, neurokinin A) and mediators such as prostaglandin E2, serotonin, bradykinin and epinephrine can sensitize peripheral nociceptors [10,11]. Action potentials generated from the stimulation of nociceptors are conducted in the peripheral nervous system along the sensory neuron axon via peripheral nerves to the dorsal root ganglion and spinal cord dorsal root, where central terminals of the neurons can synapse with dorsal horn neurons and allow for transmission to the brain. Nociceptors have two different types of axons, the rapidly conducting thinly myelinated Aδ fibre and the more slowly conducting unmyelinated C fibre axons. The clinical relevance of these two different axon types is reflected in the two phases of acute pain. The pain sensed in the first phase, i.e. an initial extremely sharp pain, is associated with the fast-conducting Aδ fibres while the pain sensed in the second phase, typically a more prolonged and less intense feeling of pain following the injury, is mediated by the slowly conducting C fibre axons. The pain signal may be modulated at various points in both segmental and descending pathways by neurochemical mediators including endogenous opioids and monoamines including serotonin and epinephrine. The mechanisms whereby CNS-active drugs such as opioids, antidepressants and anticonvulsants alleviate pain rely on their interaction with specific pain modulating receptors (i.e. μ, κ, δ opioid receptors) and neurochemicals (reviewed in 9, 11–13).

**Chronic pain**

Pain lasting longer than 3 months or beyond the duration required for complete tissue healing is typically classified as chronic pain. Chronic pain may arise from prolonged tissue injury with persistent activation of nociceptors, a lesion or disease affecting the somatosensory system known as neuropathic pain, or other indistinct mechanisms [14]. In the event where tissue damage has occurred, acute infiltration of inflammatory cells and associated surrounding inflammatory reactions become the noxious stimuli to stimulate nociceptors, an effect that gives rise to inflammatory pain. It is believed that inflammatory pain serves to minimize movement or further stress to the damaged area until complete healing has occurred [9,12,13,15].

Neuropathic pain has been defined by the International Association for the Study of Pain as pain that arises as a direct consequence of a lesion or disease affecting the somatosensory system [14]. Neuropathic pain is thought to involve peripheral or central sensitization, or both. Peripheral sensitization is a process where regenerated C-fibres of damaged axons develop pathological spontaneous activity and amplified excitability and sensitivity to various mechanical, chemical and thermal stimuli. Central sensitization refers to the increase in general excitability of spinal cord dorsal horn neurons as a result of peripheral nerve injury. The hyperexcitability of spinal cord neurons has been attributed to increased neuronal background activity, enhanced activity in response to noxious stimuli and expanded neuronal receptive fields. Other mechanisms of neuropathic pain include the spontaneous firing of higher order neurons in the presence of injured or disrupted peripheral sensory pathways, a process known as deafferentation (e.g. phantom limb pain, diabetic neuropathy, post-herpetic neuralgia); loss of inhibitory interneuronal activity; development of abnormal electrical communications across adjacent demyelinated axons, a process known as ‘ephaptic cross-talk’; or release of neuroexcitatory substances by non-neural glial cells [9,12,13,16]. In sympathetic pain associated with the complex regional pain syndrome (also known as reflex sympathetic dystrophy), where a painful stimulus can trigger autonomic activity at the same dermatomal level of the spinal cord, ephaptic cross-talk between sensory and sympathetic fibres is thought to play a role [9,12,13,17].

While the pathophysiology of various neuropathic pain conditions can be explained, the mechanisms of many other pain syndromes remain to be elucidated. Many pain conditions have neuropathic features but lack any known injury or dysfunction of the nervous system to be considered as neuropathic pain. These conditions have been classified as non-neuropathic pain syndromes and include myofascial headaches, fibromyalgia, chronic back and neck pain among others [9,12,13].

**Clinical manifestations of pain**

Most often, acute pain is described as sharp, aching or throbbing. While acute somatic pain may be easily described and localized, the same may not necessarily apply to acute visceral pain. Acute pain typically resolves within days to weeks. In contrast, chronic pain is usually not manifested with an easily identifiable aetiology or duration. In general, the overall pattern of pain quality and spatial characteristics under chronic pain conditions differs considerably between neuropathic and non-neuropathic pain. In a recent study, Dworkin et al. documented that patients with peripheral neuropathic pain reported significantly more intense hot, cold, sensitive, itchy and surface pain and significantly less intense dull and deep pain than patients with non-neuropathic pain [18]. Common symptoms for neuropathic and non-neuropathic pain syndromes are summarized in Table 1 [12,13,18,19].

**Rating the intensity of pain**

In addition to characterizing the chronicity and quality of pain, it is also important to assess the intensity of pain
for proper pharmacologic selection. Pain intensity may be measured using one of three major pain rating scales including verbal, numerical and visual analogue scales. The McGill Pain Questionnaire developed by Ronald Melzack is the most widely used verbal pain scale since its introduction in 1975 [20]. The questionnaire lists 20 groups of words that are used to describe and rate the intensity of pain. The 20 groups of words chosen are divided into four major groups to describe sensory qualities (e.g. flickering, pinching, itchy, dull), affects (e.g. tiring, frightful, vicious, blinding), overall evaluation (e.g. annoying, intense, unbearable) and other miscellaneous characteristics (e.g. radiating, tight, cool, nauseating). The higher the score obtained out of 78 maximum points, the greater the pain. The Wong-Baker faces pain rating scale is another widely used system to rate pain intensity. It involves pictures of a smiling face indicating the absence of pain (0 out of 5 score) to severe facial grimacing and tearing for the worst pain (5 out of 5 score) [21]. The Wong-Baker pain rating scale is especially useful for paediatric patients and those with poor verbal communications. Finally, a numerical rating scale consisting of a range of numbers, typically from 0 to 10, is probably one of the most widely used systems. A numerical rating scale is generally based on a subjective 10-point scoring system, where 0 denotes the absence of pain and 10 the worst pain imaginable.

**Pain management**

Optimal pain management requires a multidisciplinary approach that may include both pharmacologic and non-pharmacologic interventions. The selection of specific therapeutic modalities relies on the duration, aetiology, pathophysiology and intensity of pain.

### Non-pharmacologic interventions

In acute pain, topical thermal therapy may be applied to the affected area in addition to pharmacologic therapies. While superficial heat is thought to be helpful in decreasing local muscle spasm and pain in the acute phase of injury, cryotherapy (i.e. ice packs) has been suggested to reduce local metabolism, acute inflammation, and hence pain [22–24]. Physiological studies, however, have suggested that compared to heat therapy, cryotherapy offers greater restorative and therapeutic effect, while topical heat limits its benefit to palliative effects [22].

Under many chronic pain conditions, rehabilitative options including exercise programs in conjunction with the use of physical modalities including transcutaneous electrical stimulation (TENS), topical thermal therapy or ultrasound may be considered. Studies involving animal models of inflammation have revealed that the use of TENS can modulate pain perception via alterations in the peripheral nervous system as well as the spinal cord and descending inhibitory pathways [24,25]. While TENS has been proposed to be beneficial for both acute and chronic pain, it is probably most effective for postoperative pain, osteoarthritis and chronic musculoskeletal pain [26]. The effectiveness of ultrasound therapy for musculoskeletal pain remains questionable [27].

The National Center for Complementary and Alternative Medicine (NCCAM) has also recognized six general categories of therapies for pain including mind-body interventions, diet and lifestyle modification, herbal remedies, manual healing, bioelectromagnetics and pharmacologic-biologic treatments [28]. Complementary and alternative medical options should be considered in cases where benefit-versus-risk ratios are unequivocally favourable [29]. Under pain conditions caused by a direct mass effect, evaluation for possible surgical corrective measures is appropriate. Finally, any modifiable social issues and

### Table 1. Pain symptoms of common non-neuropathic and neuropathic pain syndromes

| Non-neuropathic pain syndromes | Neuropathic pain syndromes |
|--------------------------------|---------------------------|
| **Symptoms**                  |                           |
| Chronic tension headache      | Post-stroke pain           |
| Transformed migraine          | Throbbing, shooting, or burning pain ipsilateral to weak side; loss of temperature differentiation |
| **Symptoms**                  | Trigeminal neuralgia       |
| Chronic neck or back pain     | Occasional twinges of mild to severe shooting pain that may be triggered by manipulation of areas supplied by the affected trigeminal nerve |
| Fibromyalgia                   | Sciatica                   |
| Chronic dull or sharp pain that may be associated with muscle stiffness | Mild to sharp, burning, electric-shock-like pain that radiates from lumbar spine to buttock and down the back of leg; may be associated with muscle weakness or numbness in affected areas |
| Myofascial pain syndrome      | Complex regional pain      |
| Constant deep pain associated with and caused by ‘trigger points’ | Intense burning or aching pain in association with oedema, skin discoloration, change in temperature, abnormal sweating and hypersensitivity in affected areas |
| Phantom limb pain             | Diabetic neuropathy        |
| May include feelings of cold, warmth, itchiness, tingling or tearing | Symmetrical numbness and/or burning pain in distal extremities |
|                               |                           |

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Table 2. Pharmacologic management of common non-neuropathic and neuropathic pain syndromes

| Non-neuropathic pain syndromes | Preferred initial agents |
|-------------------------------|-------------------------|
| Chronic tension headache      | NSAIDS, acetaminophen; consider adding TCA |
| Transformed migraine          | TCA                     |
| Chronic neck or back pain     | TCA                     |
| Fibromyalgia                  | Cyclobenzapine, tramadol; consider adding TCA, pregabalin |
| Myofascial pain syndrome      | NSAIDS; consider TCA   |

| Neuropathic pain syndromes    |                          |
|-------------------------------|--------------------------|
| Post-stroke pain              | TCA; consider gabapentin |
| Trigeminal neuralgia          | Anticonvulsants (i.e. carbamazepine); consider adding baclofen |
| Sciatica                      | Prednisolone, diclofenac; consider adding TCA |
| Complex regional pain         | Acute: prednisone; chronic: calcitonin if pain is associated with immobilization or disuse |
| Diabetic neuropathy           | TCA, gabapentin; consider pregabalin, tramadol, duloxetine |
| Phantom limb pain             | Gabapentin; consider tramadol |

NSAIDS: non-steroidal anti-inflammatory drugs; TCA: tricyclic antidepressants.

Table 3. Common opioids used in the management of pain

| Route | Relative potency to oral morphine* | Renal adjustment |
|-------|-----------------------------------|------------------|
|       |                                   |                  |
| Weak opioid analgesics          |                                   |                  |
| Propoxyphene Oral                | 0.1                               | Consider dose adjustment below; no clear data |
| Codeine Oral                     | 0.1                               | Suggested dose adjustment below |
| Dihydrocodeine Oral              | 0.1                               | Suggested dose adjustment below |
| Meperidine Oral                  | 0.1                               | Use with great caution if at all; not for chronic pain |
| Tramadol Oral                    | 0.2                               | GFR <30 ml/min: dose q 12 h; maximum dose 100 mg/day in advanced CKD |
| Strong opioid analgesics         |                                   |                  |
| Morphine Oral                    | 1                                 | Suggested dose adjustment below |
| Hydrocodone Oral                 | 2                                 | Suggested dose adjustment below |
| Oxycodone Oral                   | 2                                 | Suggested dose adjustment below |
| Hydromorphone Oral               | 3.75–7.5                          | Suggested dose adjustment below |
| Levorphanol Oral                 | 4–8; longer half-life than MS     | Insufficient information; use with caution |
| Fentanyl Patch                   | 150                               | Insufficient information; use with caution |

*Relative potency of common opioids in oral formulation (with the exception of fentanyl, which is in patch formulation) compared to oral morphine. All dose conversions must be confirmed with the pharmacists and clinically correlated. It is generally recommended to use a lower dose when switching between opioids.

Suggested dose adjustment: for GFR >50 ml/min, give 100% dose used in normal patients; GFR 10–50 ml/min, give 75% dose; GFR <10 ml/min, give 50% (35–38).

MS: morphine sulfate.

In 1986, the World Health Organization established an evidence-based ‘3-step ladder’ pharmacologic management guide for mild (~1–3 out of 10 pain score), moderate (4–6 out of 10 pain score) to severe (7 or greater out of 10 pain score) levels of malignant pain that has been since adapted and widely accepted for other populations including CKD and ESRD patients with persistent nonmalignant or malignant pain [32,35].

Unless otherwise indicated (as listed in Table 2), the ‘first step’ pharmacologic intervention for mild pain typically involves the use of non-opioid analgesics including acetaminophen or non-steroidal anti-inflammatory drugs. If pain persists and/or the pain is moderate, the ‘second step’ involves the addition of low-potency opioids such as codeine, oxycodone, dihydrocodeine or hydrocodone. In addition, tramadol, a centrally acting agent that inhibits norepinephrine and serotonin reuptake by nerve cells and acts on micro-opioid receptors, may be also be used. In cases where pain persists despite the addition of low-potency opioids or the pain is severe, the ‘third step’ may require the addition of morphine, hydromorphone, psychological or physical factors that may contribute to pain perception must be identified and promptly managed [30,31].

Pharmacologic management of pain for non-CKD patients

An appropriate selection of pharmacologic agents for the treatment of pain relies on an accurate understanding of its aetiology, duration, intensity, and if possible, underlying pathophysiology. Generally, in mild acute pain, non-steroidal anti-inflammatory drugs (NSAIDS) or acetaminophen may be chosen as the first-line agent [32]. The initial pharmacologic agent of choice for mild chronic pain, however, typically depends on its underlying aetiology and/or pathophysiology. Evidence-based first-line therapeutic options for specific pain syndromes are summarized in Table 2 [12,13]. Modifications to the initial therapy may be subsequently made as dictated by the degree of pain control achieved and desired.
methadone or fentanyl [32–35]. Table 3 lists common opioids used in the management of pain, their relative potencies compared to oral morphine and suggested dose adjustment in patients with CKD [35–38].

At any step in the ladder of pain management, adjuvant analgesics may be added based on the underlying aetiology of pain and/or its associated symptoms. These agents include antidepressants for chronic pain conditions, corticosteroids for inflammatory conditions, antiepileptics for neuropathic pain, muscle relaxants for musculoskeletal pain and bisphosphonates for malignancy-associated bone pain [12,30,32] (Table 2).

**Important considerations for the treatment of pain in CKD patients**

While the algorithm for the management of pain applies to both non-CKD and CKD patients, modifications in the prescription of some analgesics are required due to problems associated with reduced drug or metabolite elimination (Table 4).

**Aspirin and nonsteroidal anti-inflammatory drugs**

As a class, the non-steroidal anti-inflammatory drugs are well known to have direct nephrotoxic effects including renal vasoconstriction and clinically significant reduction in GFR via renal prostaglandin inhibition, interstitial nephritis with or without the nephrotic syndrome associated with the development of minimal change disease, membranous glomerulonephropathy or other less common lesions; fluid and electrolyte abnormalities including hypotension, hyperkalaemia, type 4 renal tubular acidosis and other complications including oedema, hypertension and acute or chronic renal papillary necrosis [39–41]. In a meta-analysis involving 54 clinical trials, the hypertensive effect of NSAIDS was observed to be significant for patients with existing hypertension compared to those without hypertension [42]. Depending on dietary salt intake adjustment, the mean systolic blood pressure increase was observed to be 3.6–6 mmHg for indomethacin and naproxen, but minimal or none for sulindac, aspirin and ibuprofen [42]. In another meta-analysis, Johnson et al. reported that the NSAIDS hypertensive effect was greater for patients receiving antihypertensive medications compared to those receiving placebo, 4.7 versus 1.8 mmHg, respectively, and greatest for those receiving β-blockers. In addition, among all commonly used NSAIDS included in the study, the greatest hypertensive effect was observed with piroxicam [43]. If NSAIDS must be used, aspirin, the agent with the lowest adverse effect on glomerular filtration, may be considered [44–47]. Nevertheless, it is still advisable to extend the dosing frequency from every 4 h to 4–6 h. Although the actual clinical advantages have been questioned, NSAIDS with reportedly lower renal haemodynamic compromise such as sulindac and salsalate may be considered [48–50]. Long-acting NSAIDS or those having a half-life >12 h should be avoided to prevent persistent and clinically significant depression in GFR induced by NSAIDS inhibition of renal vasodilatory prostaglandins [51]. An adequate fluid intake and avoidance of concurrent use of contrast dyes, potentially nephrotoxic or haemodynamically compromising drugs must be addressed. If clinically safe, temporary discontinuation of diuretics or inhibitors of the renin–angiotensin–aldosterone system, or both, may be considered. Selective COX-2 inhibitors induce similar adverse effects as NSAIDS including oedema formation, exacerbation of pre-existing hypertension and acute kidney injury, and should be similarly avoided (reviewed in 52). A close follow-up to monitor volume overload, especially in patients with known congestive heart failure, renal function deterioration and other adverse effects, is warranted with the use of either NSAIDS or COX-2 inhibitors.
Acetaminophen alone or in combination with a low-potency opioid does have mild anti-inflammatory properties and has been shown to be effective in both acute and chronic inflammatory conditions [53,54]. While acetaminophen has been considered to be the safest non-narcotic analgesic in CKD patients, it must be cautioned, however, that it may be nephrotoxic with chronic high dose use. In a study involving lifetime nonnarcotic analgesic use and decline in renal function in women, those who consumed >3000 g of acetaminophen had a multivariate-adjusted odds ratio for a decline in GFR of at least 30 ml/min/1.73 m² over 11 years of 2.04 (1.28–3.24, 95% confidence interval) compared to those who consumed <100 g over the same time period [55]. Minimizing the dose and frequency of acetaminophen intake should be considered, particularly for patients with a GFR <10 ml/min/1.73 m² (i.e. increase the dose interval from every 6 to 8 h) [56].

**Tramadol**

Tramadol is generally preferred for moderate pain in CKD patients because it is not known to be directly nephrotoxic. Nonetheless, it must be noted that its systemic elimination is reduced with advanced CKD (GFR <30 ml/min/1.73 m²). The active metabolite of tramadol, O-demethyl tramadol, is produced in the liver and excreted by the kidneys. The average 5-h half-life of O-demethyl tramadol may be doubled in patients with advanced CKD [57,58]. Higher blood levels of the compound may induce respiratory depression and reduce the seizure threshold in uraemic patients [59]. In addition, it must be cautioned that tramadol may precipitate the serotonin syndrome in patients taking selective serotonin reuptake inhibitors (e.g. fluoxetine, sertraline, paroxetine) [60]. The maximum dose of tramadol prescribed to advanced CKD patients has been suggested to not exceed 50 mg orally twice a day [61].

**Other opioids**

With the exception of methadone, the majority of opioids recommended for both moderate and severe pain undergo hepatic biotransformation and renal excretion as the primary route of elimination. The significant renal retention of active or toxic metabolites of commonly used opioids including, but not limited to, morphine, oxycodone and propoxyphene can occur among advanced CKD patients and lead to profound central nervous system and respiratory depression and hypotension [35,47]. In addition, myoclonus and seizures are well-recognized serious neurological complications with the use of high doses of morphine, hydromorphone, meperidine, fentanyl and diamorphine [35,47,62]. Dose reduction for most opioids in patients with reduced renal function must therefore be considered to avoid drug accumulation and associated complications. In general, dose reduction to 75% of normal dose for glomerular filtration rates between 10 and 50 ml/min, and dose reduction to 50% for glomerular filtration rates <10 ml/min, may be considered (Table 3) [37]. Further dose adjustments may be required based on patients’ overall pro- toplasmin and prognosis and should be done at the clinician’s discretion.

The use of methadone and fentanyl may be recommended for severe pain in CKD patients. While methadone is also metabolized by the liver as other opioids, its main metabolite is excreted via both gastrointestinal and renal routes. Moreover, there is evidence to suggest that compensatory faecal excretion of methadone metabolites occurs in patients with renal impairment [63]. Methadone and its metabolites thus do not generally accumulate significantly in patients with renal insufficiency. Although fentanyl is a potent synthetic opioid and follows the same pattern of drug elimination as other opioids, its metabolites are inactive and non-toxic [64,65]. The use of the fentanyl transdermal system, however, is reserved for opioid-tolerant patients with persistent moderate-to-severe chronic pain that requires continuous and prolonged opioid administration and who have failed other pharmacologic interventions due to its high potential for serious and life-threatening complications with hypoventilation [66].

**Conclusions**

In summary, pain is a common problem in the general population, ESRD patients and most likely pre-ESRD CKD patients (stages 1–4). In the management of pain, the clinician must assess the duration, aetiology, pathophysiology and intensity of pain and address all potentially beneficial non-pharmacologic and pharmacologic therapeutic options. The World Health Organization guidelines for the step-wise selection of analgesics based on pain severity in patients with malignancy have been shown to be effective and adaptable for CKD patients. However, special considerations must be given to the CKD population to minimize direct analgesic-induced renal-related complications and other drug-accumulation-related complications due to reduced renal clearance.

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