Seminars in Dialysis

DRUG THERAPY: SPECIAL CONSIDERATIONS IN DIALYSIS PATIENTS

An Approach to Pain Management in End Stage Renal Disease: Considerations for General Management and Intradialytic Symptoms

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ABSTRACT

The prevalence and severity of symptoms in patients with advanced chronic kidney disease is higher than those of the general population and comparable to those with other chronic and serious medical conditions. Despite the prevalence and severity in this population, symptoms continue to be under-recognized and inadequately managed. The recognition of specific intradialytic pain syndromes such as pain related to arteriovenous access, headaches, muscle cramps or generalized pain by providers may aid in improving patient compliance and quality of life. The approach to pain management in end stage renal disease patients follows that of the general population with specific considerations regarding clearance and potential side effects guiding selection of agents. Overall, evidence is limited regarding the pharmacology of many medications in this population.

Epidemiology

The prevalence and severity of symptoms in patients with advanced chronic kidney disease (CKD) is higher than those of the general population and comparable to those with other chronic and serious medical conditions. Studies of patients with CKD, end stage renal disease (ESRD) on haemodialysis (HD) and those on HD with high comorbidity scores have reported an average number of symptoms ranging from 9 to 10.5 (1–3). This is similar to those reported by ambulatory and inpatient cancer patients, 9.7–11.5 symptoms, respectively (2). The burden may be higher in the ESRD population, as general tools such as the McGill Pain Questionnaire or the Memorial Symptom Assessment Scale Short Form, are not specific to patients with ESRD who may experience additional symptoms such as restless legs and muscle cramps (1,2).

Pain is one of the most commonly reported symptoms, estimated to affect over 58% of CKD patients, of which 49% is moderate to severe in intensity (1,2,4,5). Though data in Stage 5 CKD, peritoneal dialysis (PD), and conservatively cared for patients is limited, available evidence suggests similar prevalence and severity (5). This is in contrast with the general population, of which 2–45% experience chronic pain (2).

Despite this burden, symptoms continue to be under recognized and inadequately managed (6,7). Providers underreport 60–97% of symptoms and underestimate severity in 63% of cases (1,7). While it is true that there are evidence-based non-pharmacological management strategies for pain, especially of musculoskeletal origin, analgesic medications remain a crucial component to pain management. In one study, 74%, of ESRD patients with moderate to severe pain, or pain that "moderately to extremely" interfered with work were not prescribed medications (8). Recently it has been described that between July 2006 and December 2008, 38–50% of US HD patients were prescribed at least one opioid, compared to previous estimates of 14.9% (8,9). Though this suggests an increase in prescribing, there were no data regarding the appropriateness, duration or dosing of opioids during this period.

Uncontrolled pain leads to increased utilization of health care through increased readmission rates, and longer hospital stays in other conditions, and is likely to have similar effects in the ESRD population. Pain has been consistently shown to negatively

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Seminars in Dialysis—2015
DOI: 10.1111/sdi.12372

impact health-related quality of life (HRQL) in this patient population. Dialysis and CKD patients with moderate or severe pain have a higher prevalence of depression, insomnia, irritability, inability to cope with stress, increased perception of burden of illness, decreased perception of social support and decreased life satisfaction (10–12). As compared to those without pain, dialysis patients with pain are three times more likely to consider withdrawing from dialysis, which may be reflective of a decrease in quality of life (10). Interference with dialysis treatments also occurs: one study has shown 11.3% of patients with pain shortened at least one dialysis session, and 5.6% shortened sessions at least once a month (13). Evidence suggests that adequate treatment of pain will result in improved HRQL (14).

Barriers

Barriers to adequate recognition and treatment of pain include time constraints, lack of standardization of pain assessment and management tools, misconceptions that chronic pain is more difficult to assess and treat, and that pain is an unavoidable outcome of ageing and of dialysis (15,16). Education and experience of health care providers is also important. For each year of practice, providers are more likely to identify the presence of symptoms (7). Some providers do not assume the responsibility to treat symptoms that are "unrelated" to dialysis and therefore are reluctant to prescribe analgesics (16). In these instances, communication with other health care providers is essential in establishing who will manage symptoms. Primary care physicians are more likely than nephrologists to prescribe medications for most symptoms, including pain (6). For patients and families, barriers may include ethnic or cultural factors relating to the experience of pain, stoicism, fear of opioids, fear of addiction or of being labelled "an addict," poor compliance due to unexpected adverse effects and not wanting to increase an already large pill burden.

Intradialytic Pain

This is a unique subset of pain syndromes that requires specific attention and includes pain related to arteriovenous (AV) access, dialysis related headaches (DH) and muscle cramps.

AV Access Pain

Etiology of AV access pain includes cannulation discomfort, steal syndrome and central vein stenosis (13,17–19). Pain is more common in patients who have had AV fistulas (AVF) for less than one year (13). Brachiobasilic AVFs are associated with the highest incidence of severe pain, suggested to be a result of scarring from superficialization and transposition, as well as deep tissue injury with cannulation (13). Chronic pain has been associated with a structural lesion in 46.7% of cases, the majority of which (85%) improved with intervention (13). For example, distal revascularization interval ligation procedures for chronic ischaemic pain has been shown to be effective at relieving pain in up to 90% of patients (20).

Topical analgesics may be of benefit for cannulation pain. Several small studies have shown efficacy of topical anaesthetics such as lidocaine prilocaine cream (EMLA: Eutectice mixture of 2.5% lidocaine and 2.5% prilocaine in an oil/water emulsion; APP Pharmaceuticals, Schaumburg, IL) and ethyl chloride vapocoolant spray (18,21–23). Vapocoolant sprays work through evaporation that decreases skin temperature and causes desensitization of receptors or through inactivation of channels that are involved with pain transmission (18). Unlike the spray that can be applied seconds before puncture, application of the cream must be 45–60 minutes prior for maximal absorption into the cutaneous tissue. A comparative study of the cream and spray show similar efficacy in preventing cannulation pain (18). Both are well-tolerated with mild side effects including local skin reactions (18,21,23).

Headaches

It is estimated that up to 48% of dialysis patients experience this pain syndrome (24–27). In an attempt to differentiate DH from other types of secondary headache disorders, the International Headache Society defined DH in 2004 as (25)

- At least three attacks of acute headaches fulfilling the last 2 criteria.
- Patient is on HD.
- Headaches develop during at least half of HD sessions.
- Headaches resolve within 72 hours of HD session and/or ceases altogether after successful transplantation.

The aetiology of DH is unclear, though likely related to physiological changes that occur during dialysis (25). Associations with elevated calcium and phosphate, and low magnesium have been described and may cause cerebral vessel vasoconstriction and inability of auto regulation (27,28). A greater reduction in urea has also been associated, postulated to result in brain oedema, which has been demonstrated post dialysis in a small imaging study (24,29). Observations also note a correlation with elevated pre-dialysis blood pressure, suggesting avoidance of large fluid shifts may be of benefit (24).

Due to uncertain causative factors and a lack of evidence based medicine, there are no guidelines regarding treatment of DH. Medications such as ergotamine used as treatment for other secondary headaches should be avoided due to the risks of vasoconstrictive effects on the AVF (26,30). Small studies of altering dialysis prescriptions including

shortening treatments from 4 to 2 hours, and use of sodium ramping or individualized dialysate sodium concentrations have been of benefit (31–35). Case reports describe benefit of using midodrine, or angiotensin converting enzyme inhibitors, though not with angiotensin receptor blockers (36,37).

Muscle Cramps

Muscle cramps are sudden, recurrent, tonic or clonic painful, involuntary muscle contractions, likely neurological in origin, that usually involves the lower extremities, but may also involve the abdomen, arms and hands (38,39). Many factors have been associated with cramps, including volume contraction in the setting of increased ultra filtration, hypotension, changes in plasma osmolality, hyponatremia, tissue hypoxia and carnitine deficiency (39). Cramps affect 33–85% of dialysis patients, a quarter of whom report occurrence at least weekly (38). In addition, they contribute to 18% of early terminations of treatment (40).

A non-pharmacological approach to intradialytic relief of cramps includes local massage, including sequential compression devices, correction of hypotension by decreasing ultrafiltration and correction of hypo-osmolality by giving hypertonic saline or mannitol (39,41). A small study using sodium ramping showed a decrease in hypotensive episodes and intradialytic symptoms, including cramps (31).

As reviewed by Kobrin, a meta-analysis and several controlled trials have shown benefit of quinine in reducing the frequency of both interdialytic and intradialytic cramps by reducing excitability of nerve stimulation (39). Although it had been used off-label for dialysis-related cramps, numerous adverse events, including death, has lead the FDA to recommend against its use (39).

The use of various vitamins and supplements for cramp prevention has been investigated. Creatine monohydrate may enhance muscle metabolism and energy stores (42). A small study of 10 patients with intradialytic cramps were randomized to receive either 12 g of oral creatine or placebo prior to dialysis over a 4 week period (42). A 60% decrease in cramps was observed in the creatine group (2.6 ± 1.8 versus 6.4 ± 0.9, $p < 0.05$), as well as fewer hypotensive episodes, although not statistically significant. Symptoms recurred during a subsequent 4 week wash out period (42).

Vitamin E, an antioxidant, has been shown to be of benefit (43). Nineteen HD patients were given 400 IU of vitamin E over a 12 week period with a 68.3% decrease in cramps from baseline (43). Another study evaluated the effect of vitamin C, which is depleted in uraemia and is a cofactor in carnitine synthesis, alone and in conjunction with vitamin E on muscle cramps (38). For the treatment groups of vitamin E, vitamin C, combination or placebo, the cramp reduction was 54%, 61%, 97% and 7%, respectively. Short-term use of vitamin E and C was well-tolerated without any adverse effects (38,43). Biotin 1 mg/day has also been of benefit (44).

A meta-analysis of six studies of L-carnitine suggests no benefit (45). Although, there was borderline statistical significance that favoured its use (OR 0.3, 95% confidence interval 0.09–1.0, $p = 0.05$) this was largely influenced by one study, which when excluded lead to the loss of statistical significance (45).

Pharmacological Approach to Pain Management

Despite at least 13 reviews of approaches to pain management in this population, validation studies are limited (5). Evidence-based guidelines for chronic, non-cancer pain in the general population advocates for use of the World Health Organization three-step analgesic ladder. This approach has preliminary evidence for validity in ESRD patients, with 96% achieving pain control after a 4 week treatment period (4), This step-wise approach requires specific consideration of the clearance and potential adverse effects of analgesics. A thorough pain history should be undertaken in an effort to identify the underlying aetiology and subsequently target therapy though in many instances, including CKD, causes are often multifactorial and not reversible.

Step 1 of the ladder is for treatment of mild pain, rated 1–3 on a 10 point scale, with analgesics including acetaminophen, and non-steroidal anti-inflammatory drugs (NSAIDS) (46). *Step 2* is the next step in escalation, or is for treatment of moderate pain, rated 4–6 and includes weak opioids. Severe pain, rated 7–10, is treated with *step 3* agents, or stronger opioids (4,46). A fourth step has been recommended for management of pain crises and include interventional procedures or patient controlled analgesics (47). Use of adjuvant therapy such as steroids, anxiolytics, anticonvulsants, nerve membrane stabilizers, NMDA receptor antagonists, antidepressants and cannabinoids is recommended to control side effects of opioids, uncontrolled pain or as opioid sparing medications, and are particularly beneficial in the effective treatment of neuropathic pain (46,47). In addition, if adverse effects are experienced, medications on the same "step" can be interchanged, as well as incorporating use of non-pharmacologic treatments (48).

The National Kidney Foundation recommends acetaminophen as the non-narcotic analgesic for mild to moderate pain in patients with CKD (49). NSAIDs are generally not preferred due to concern for worsening of hypertension, oedema, hyperkalaemia, and reduction in glomerular filtration rate (GFR), but can be used cautiously, for time limited trials in ESRD patients under close physician supervision (49–53).

Hydromorphone is a preferred short acting opiod in ESRD patients. It undergoes hepatic metabolism into byproducts including hydromorphone-3-glucor-

onide which has neuroexcitatory effects but does not provide analgesia (54). A small study has shown an increasing area under the curve (AUC) with decreasing renal function at a ratio of 1:2:4 for patients with normal (CrCl >80 ml/minute), moderate (CrCl 40–60 ml/minute) and severe (<30 ml/minute) renal dysfunction (55). A prolonged half life of 39.4 ± 16 hours was seen in severe renal impairment as compared to 14.8 ± 11.3 hours in normal renal function (55). Therefore, patients with advanced renal dysfunction who are not maintained on dialysis may be at risk for accumulation or toxicity if not carefully monitored. Side effects including tremor, myoclonus, agitation and cognitive dysfunction have been described in advanced CKD (GFR < 60 ml/minute/1.73 m^2) and those managed conservatively without dialysis (54,56). However, dialysis patients have good tolerance and mild side effects as dialysis limits this accumulation. Hydromorphone has low protein binding (19%), low molecular weight and a low volume of distribution (1.22 l/kg). Dialysis removes 40–55% of pre-dialysis levels (55,57). Some have expressed concern that given the relatively high clearance, patients maintained on hydromorphone may be at increased risk of pain or withdrawal during dialysis (57). Given the changes in pharmacokinetics in ESRD, titration should start at low doses, with an increased dosing interval and with close monitoring for side effects (55).

Oxycodone has a larger volume of distribution (2.6 l/kg) and higher protein binding (46%) than that of hydromorphone, also suggesting that it may be able to be dialysed (58). A case report of controlled-release oxycodone showed reduction in plasma levels of the parent drug and byproducts by 32–52% after 2 hours of dialysis. Although predominately metabolized by the liver, up to 19% of the parent drug is excreted in the urine (59). In patients with renal dysfunction (CrCl <60 ml/minute), the half life, AUC and peak levels (*C*max) of the parent drug and metabolites are increased (59). Extended half life has also been noted in dialysis patients (5). This suggests that patients with renal failure may be at risk of drug accumulation if dosed on a regular schedule. CNS toxicity and respiratory depression in dialysis patients has been reported (60,61). Due to limited available evidence regarding use of oxycodone in ESRD patients, potential adverse effects and high abuse potential, cautious use is recommended (5,62).

Tramadol undergoes hepatic metabolism into active metabolites which are predominately (95%) renally excreted (63). Half life is doubled in renal insufficiency and dialysis minimally clears (7%) the medication (50,64). As reviewed by Kurella et al., tramadol may be epilipetogenic in low seizure threshold states, such as uraemia. It is also known to cause respiratory depression (50). Cautious use in dialysis patients should include a reduction in dose and increase in dosing interval, for example starting at 50 mg every 12 hours and a maximum daily dose of 200 mg (50,62,64). The extended release formulation of tramadol has not been studied in renal impairment and is contraindicated in CrCl <30 ml/minute (63).

Methadone undergoes hepatic metabolism and is a preferred agent in ESRD patients. Increased elimination in stool has been described in anuric patients compared to patients with higher levels of renal function (65). In case reports, serum levels of methadone have been noted to be in the normal range in HD and PD patients (65). Due to the high protein binding (60–90%) and high volume of distribution (4.1–6.7 l/kg), methadone is not well-dialysed with one study showing a decrease in plasma concentrations by only 15% after dialysis (57). When used in ESRD patients, close monitoring during titration is recommended with starting doses 50–75% of normal and without supplementation post dialysis (58,65). As methadone will prolong the QT interval monitoring is essential in this population as electrolyte abnormalities are common.

Buprenorphine may be a useful strong opioid in ESRD, though larger studies in this patient population are needed before it can be strongly recommended. With increased affinity compared to morphine, it is a partial μ receptor agonist and κ receptor antagonist. It is hepatically metabolized into inactive buprenoprhine-3-glucoride and norbuprenorphineactive. Norbuprenorphine has less affinity for the aforementioned receptors than the parent compound, and does not cross the blood brain barrier (66,67). Buprenorphine is excreted mostly in the faeces, whereas the metabolites undergo renal excretion. These metabolites have been described to accumulate in CKD (67). Properties including a large volume of distribution and high protein binding (96%), do not favor removal during dialysis. A study of 10 HD patients using transdermal buprenorphine up to 70 μg/h confirmed this. Blood concentrations of parent compound and metabolites were stable before and after dialysis, and pain relief maintained (66,68).

Fentanyl is preferred for patients on a stable pain regimen and should be avoided in patients who are opioid naïve. Like buprenorphine, it can be administered through a transdermal route for chronic use or intravenously for acute titration. It undergoes hepatic metabolism into inactive products and is well-tolerated in ESRD patients (69). It is likely not cleared well by dialysis given its high protein binding (80%), low water solubility and high volume of distribution (4 l/kg) (58).

Medications to avoid in ESRD patients include codeine, hydrocodone, meperidine, morphine and tapentadol (Table 1).

Neuropathic pain

There are a wide variety of causes of neuropathic pain in ESRD patients. Given the growing

TABLE 1. Recommended to avoid in ESRD

Medication	Pharmacokinetics in ESRD	Observed toxicities
Morphine (58,90–94)	• Active metabolite, morphine-6-glucoronide (M6G) is renally cleared • M6G accumulates in renal insufficiency • M6G concentration is 15 times higher in the CSF of HD patients compared to those with normal renal function • There can be equilibration of lipophillic molecules post dialysis and continued CNS effects	• Respiratory and CNS depression • Myoclonus • Lethal intoxication
Codeine (50,90,95–97)	• Hepatic metabolism into active metabolites. Reduced clearance of parent drug and metabolites in renal insufficiency • Single dose study shows increased half-life from 4.04 ± 0.6 to 18.60 ± 9.03 hours in HD patients. Therefore, there is a risk for drug accumulation	• Nausea and vomiting • Hypotension • Respiratory arrest • CNS depression
Hydrocodone (50,90,98)	• Limited data in renal failure • 85% of the oral dose is excreted as parent drug or metabolite in the urine within 24 hours • Risks of adverse effects increased with renal insufficiency and accumulation of drug	
Tapentadol (99–101)	• Not recommended due to limited information regarding use in severe renal insufficiency • Undergoes first pass metabolism into inactive metabolites, 99% of which are excreted in the urine • No change in AUC or Cmax of parent compound in severe renal insufficiency • AUC of metabolite tapentadol-O-glucorinde increased 5.5 times in severe renal impairment • Large volume of distribution 540 ± 98 l after intravenous administration with low protein binding (20%)	
Meperidine (96,102–104)	• Hepatic metabolism into active metabolite normeperidine, which is renally excreted • Half life of normeperidine is increased in renal insufficiency • Normeperidine increases risk of seizure. • Normeperidine/meperidine ratio increased in renal insufficiency as compared to normal renal function • Case report of HD used in overdose, suggesting drug can be dialysed	• Case reports of seizure, myoclonus and altered mental status in renal insufficiency
Tramadol – Extended release (63)	• Has not been studied in renal insufficiency	
Duloxetine (89)	• Elevated *C*max and AUC in ESRD patients	

proportion of patients with ESRD secondary to diabetes mellitus, a significant cause of pain is diabetic peripheral neuropathy. In one Italian study, neuropathy was diagnosed in 61.3% of dialysis patients. The majority of which, 44.9%, was secondary to a systemic disease and a minority, 16%, attributed to uraemic neuropathy (70). Carpal tunnel syndrome (CTS) has been estimated to affect approximately one quarter (28.5%) of dialysis patients, and is positively correlated with time on dialysis (71,72). There is conflicting data as to the incidence of CTS in HD versus PD patients with some reports of significantly lower rates (<1%) in PD (73,74). Compression of the median nerve by increased hand volume and venous pressure in the arm with vascular access may be a contributing factor (75). Ulnar neuropathy has been described in 41–60% of HD patients (76). Symptoms include pain, numbness or tingling in the elbow, distal arm, medial hand or fifth digit which can lead to functional impairment if untreated (76). It may be caused by repeatedly placing pressure on the cubital tunnel of the arm with vascular access during dialysis (76).

The International Association for the Study of Pain (IASP) developed evidence based guidelines for management of neuropathic pain. Treatment in the ESRD population follows these general guidelines as limited studies have specifically included this subset of patients (77). Recommended first line treatments include antidepressants, such as tricyclic antidepressants (TCAs), serotonin and norepinephrine reuptake inhibitors (SNRIs), calcium channel $\alpha 2$-δ ligands such as gabapentin and pregabalin, and topical lidocaine (78). Opioids are used as

adjuvant therapy for pain relief during titration of first line medications, or in acute pain settings (4,78)

Gabapentin and pregabalin have been specifically evaluated in ESRD patients and are the preferred medications for neuropathic pain. In a prospective cross over study, HD patients with painful peripheral neuropathy received 6 weeks of treatment with either gabapentin, 300 mg, after dialysis or pregabalin, 75 mg, daily. After a 2 week washout period, the alternative agent was used for an additional 6 weeks (79). Both agents were successful at improving pain, symptoms of depression, subjective descriptions of sleep and health related quality of life scores (79,80). There were similar rates of adverse events, most commonly dizziness, somnolence and dry mouth (80).

Gabapentin is excreted unchanged by the kidneys. Serum levels increase linearly and toxicity correlates with declining renal function (81). On non-HD days, the half life was increased to 132 hours, which was reduced to 4 hours with HD. This is compared to its half life of 6–8 hours in patients with normal renal function (82,83). Gabapentin has low protein binding favouring its ability to be dialysed, with approximately 35% cleared with HD (50,81,82). Plasma levels have been noted to increase by 30% after 2 hours of dialysis, likely due to redistribution of the drug (83). Gabapentin dosing in ESRD patients has been recommended up to 300 mg daily, with a supplemental dose of 200–300 mg after each dialysis treatment (50,62). For pregabalin, dosing for CrCl <15 ml/minute has been recommended to be 25–75 mg/day with supplemental doses given after dialysis based on daily dose (84). However, despite these generalized recommendations, it may be reasonable to approach the dosing more conservatively, especially in elderly or frail patients (5). An example of this approach for gabapentin is 100 mg post dialysis in HD patients and 100 mg every other night in stage 5 CKD patients managed conservatively (5). Similarly, pregabalin may provide relief with doses as low as 25 mg after each dialysis or 25 mg every other night in stage 5 CKD patients managed conservatively (5). It is imperative that patients are closely monitored for efficacy or adverse effects, and doses titrated appropriately and in a timely manner.

The anticholinergic effects of TCAs such as sedation, orthostatic hypotension and dry mouth may be poorly tolerated in ESRD patients and limit their use (50,77). Desipramine and nortriptyline have less anticholinergic effects than amitriptyline and should be considered if a TCA is going to be prescribed (50,77). TCAs undergo hepatic metabolism with elevated conjugated metabolites in dialysis patients, which may contribute to the limiting side effects (50,85). A single dose study in continuous ambulatory PD patients found wide variation in half life, but no significant difference as compared to controls with normal renal function (86). As QT prolongation is described, caution is recommended in patients with conduction abnormalities, and electrolyte abnormalities (50). Dosing should start low and in the evening to avoid effects of sedation. There should be slow titration over a course of weeks with monitoring for adverse effects (50,77).

Serotonin norepinephrine reuptake inhibitors like venlafaxine and duloxetine may be better tolerated than TCAs due to less anticholinergic symptoms, but are less effective (77). In ESRD patients, the half life of venlafaxine is increased by 180% with poor removal of parent drug and metabolite by dialysis (87,88). It should be used cautiously, with a 50% dose reduction post-dialysis (88). Duloxetine undergoes hepatic metabolism and renal excretion. The parent drug is highly protein bound (95.7%) with a large volume of distribution, and is not well-dialysed (89). The *C*max and AUC of duloxetine and its inactive metabolites were elevated at least twofold in ESRD patients. There is a lack of consensus regarding use in ESRD. Some sources recommend avoiding use in a CrCl <30, while others suggest starting at a very low dose and titrating based on response with a maximum dose of 30 mg daily (5).

Conclusion

Patients with ESRD carry a high symptom and pain burden, which is identified and managed inadequately. The recognition of specific intradialytic or interdialytic pain syndromes by providers may aid in improving patient compliance and HRQL. Although evidence is limited regarding the pharmacology of many medications in ESRD, the step-wise approach to pain management should follow that of the general population. This includes the conservative dosing of opioids with small increases in doses titrated to analgesia and adverse effects for patients with moderate to severe pain that results in detriments to physical function and HRQL and that does not respond to non-opioid analgesics. Specifically considering clearance and potential adverse effects is required when selecting analgesics for patients with ESRD.

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