Abstract
Chronic kidney disease (CKD) is one of the most frequently seen comorbidities in patients suffering from musculoskeletal conditions; it is defined by a glomerular filtration rate (GFR) under 60 ml/min/1.73 m2. The following paper focuses on providing a dosage adjustment guideline depending on how advanced renal impairment is. A literature search was carried out using the following items: pharmacokinetics, side effects, drug interactions and dosage, pain medication and antirheumatic drugs in renal failure.

The use of non-steroidal anti-inflammatory drugs is inadvisable for a GFR < 30 ml/min as they all pose the risk of inducing acute renal damage, as well as worsening of the underlying chronic renal disease. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided due to the possibility of kidney disease progression. Paracetamol is an analgesic often chosen in this category of patients. As far as opioid analgesics are concerned, methadone is the only one that can be used without dosage adjustment. Physiotherapy remains a good and safe option for treatment in patients with musculoskeletal complaints.

The use of analgesics in patients with CKD continues to be a challenge, as more research is needed.

Key words: chronic kidney disease, pain, medication, antirheumatic drug.

1. Introduction
Patients with chronic kidney disease (CKD) have a large number of comorbidities that modulate the response to pain. Chronic pain is common in CKD and affects 50% of hemodialysis patients. From this category, 82% show moderate to severe pain.

One study reported up to 47% chronic pain in CKD stage 5 patients (1).

The etiology of pain can be iatrogenic in some procedures, but is more often due to comorbidities such as arterial disease or diabetes. The most frequent cause of pain is represented by musculoskeletal disorders (63%), of which osteoarthritis is the most common, followed by peripheral vascular disease, bone diseases (renal osteodystrophy, osteoporosis with vertebral fractures), arthritis, and peripheral neuropathy (2).

CKD affects the renal excretion mechanism of drugs and the pharmacokinetic processes involved in their distribution (e.g., absorption, clearance, extrarenal distribution, metabolism). Improper dosage adjustment of medications is common in patients with renal impairment and may cause frequent adverse effects or poor therapeutic outcomes.

The general principles of assessment, pain management and analgesia should be prescribed taking into account the WHO recommendations for pain management in these patients, with careful and frequent monitoring of possible side effects of the drug itself or its metabolite accumulation data. Clinical management should be performed by a multidisciplinary team that includes a clinical nephrologist and a pharmacist (3).

The K/DOQI Advisory Board has divided the progression of CKD into five stages (see Table 1).

Table 1. Stages of CKD

<table>
<thead>
<tr>
<th>Stages</th>
<th>CKD Stage</th>
<th>Glomerular filtration rate ml/min/1.73m²</th>
<th>Creatinine clearance (CrCl) ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal kidney function</td>
<td>1</td>
<td>&gt;90</td>
<td>120</td>
</tr>
<tr>
<td>Mild decreased function</td>
<td>2</td>
<td>60-89</td>
<td>20-50</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>30-59</td>
<td>10-20</td>
</tr>
<tr>
<td>Severe</td>
<td>4</td>
<td>15-29</td>
<td>&lt;10</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>5</td>
<td>&lt;15</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>
Knowing the adverse drug reactions in patients with CKD is particularly important because only in this way can further damage of residual kidney function be prevented (4,5,6).

For patients with significant glomerular filtration rate (GFR) reductions, dose adjustment and avoidance of certain analgesics is necessary because of a change in the pharmacokinetics and pharmacodynamics of several analgesics or their metabolites. Patients with CKD have an increased risk of adverse effects due to several aspects such as: comorbidities, increased susceptibility to medication, reduction of muscle/body mass, reduced therapeutic and toxic dose, and accumulation of medication due to low excretion. These pharmacokinetic characteristics and pharmacodynamic changes depend on the pharmacological agent itself, the stage of renal insufficiency and whether the patient undergoes dialysis (7,8).

An increased number of patients with CKD are elderly, and this may further enhance the sensitivity of these patients to analgesics.

The quality of life of patients with CKD is impaired both by the underlying disease and the presence of pain (9,10).

Monitoring of renal function is required in all situations where the drug that needs to be administered has renal toxic effects or is renally excreted.

In most cases of acute and chronic pain in CKD patients, physiotherapy should be performed as a non-pharmacological alternative.

In what follows, the authors aim to review most of the drugs used in pain management and their restrictions in patients with CKD, using their own experience.

**ANALGESICS**

**STAGE I ANALGESICS**

**Acetaminophen**

It is considered the first option in the treatment of pain. It should be kept in mind that long-term use itself may cause nephrotoxicity. Many authors do not consider dose adjustment with a GFR = 50 ml/min (maximum dose 4 g/day), but frequent comorbidities in CKD patients require caution. A GFR below 50 ml/min requires dose reduction (11,12).

**Non-steroidal anti-inflammatory drugs (NSAIDs)**

They should be avoided even in minor/mild renal insufficiency, but in certain situations they are accepted in stage 1 CKD. Prostaglandins mediate the compensatory vasodilation of related arterioles that vascularize the glomerulus to maintain GFR states of hypovolemia and hypotension (13).

NSAIDs lead to the renal exhaustion of prostaglandins with vasodilatory effects and allow for uncontrolled vasoconstriction. From a clinical point of view, these mechanisms can have catastrophic and unpredictable effects by diminishing blood flow. Generally, the triad NSAIDs, diuretics and angiotensin-converting enzyme (ACE) inhibitors can severely affect GFR and renal function. However, in most cases, the effect may be transient, without clear evidence of long-term impaired renal function. The risk of using NSAIDs in this patient group should be considered in relation to benefit. If NSAIDs are to be used, they should be limited to the shortest possible duration and renal function should be monitored closely. NSAIDs should be avoided in patients with additional risk factors that may affect kidney function, such as older age, diabetes mellitus, and the use of ACE inhibitors. One of the limited indications of NSAID administration is gout attack (14,15,11,4).

Topical use of NSAIDs is recommended as an alternative to general administration.

**STAGE II ANALGESICS**

**Codeine.** Half-life is significantly prolonged in CKD. Accumulation of active metabolites may lead to severe adverse reactions (e.g., respiratory arrest, narcolepsy and severe hypotension).

In mild CKD, the normal daily dose is permitted with function monitoring. In moderate CKD, a 75% reduction of the normal dose is required, and in severe CKD, 50% of the normal dose is needed (16).

**Tramadol.** The active metabolite is renally excreted.
In mild CKD - 50-100 mg in a single dose can be administered, moderate impairment increases the dose interval - 50-100 mg divided into 2 doses, and in severe damage it should be avoided.

In end-stage renal disease, at CrCl <30 ml/min, 50-100 mg dose s every 12 hours (maximum: 200 mg/day). Retard forms of tramadol will not be prescribed in patients with CrCl <30 ml/minute (16).

STAGE III ANALGESICS

Morphine
Morphine is metabolized by the liver; 5-10% is excreted unchanged by the kidney. The hepatic metabolites of morphine, such as morphine-6-glucuronide (M6G) and morphine-3-glucuronide, are associated with hyperalgesia and neurotoxicity when accumulated in patients with severe renal impairment. At a GFR of 50 ml/min, the dose is reduced to less than 50%, and morphine is avoided in patients with a GFR below 50 ml/min. Morphine is removed by dialysis (4,2).

Oxycodone. It is metabolized in the liver and less than 10% is renally excreted. It should be used with great caution in moderate renal impairment; a second-line agent should be considered in CKD. Dosage adjustment is recommended (data is poor) according to the following schedule:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Total oxycodone daily dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>150-300</td>
</tr>
<tr>
<td>50-60</td>
<td>75-150</td>
</tr>
<tr>
<td>30-49</td>
<td>25-75</td>
</tr>
<tr>
<td>&lt;15</td>
<td>25-50</td>
</tr>
</tbody>
</table>

Fentanyl
It has a safe pharmacological profile in patients with CKD. Hepatic metabolism is reduced, less than 10% is renally excreted. Dosage adjustment is recommended according to the following schedule:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Total fentanyl daily dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>150-300</td>
</tr>
<tr>
<td>50-60</td>
<td>75-150</td>
</tr>
<tr>
<td>30-49</td>
<td>25-75</td>
</tr>
<tr>
<td>&lt;15</td>
<td>25-50</td>
</tr>
</tbody>
</table>

Methadone
Methadone is fecally excreted, with no active metabolites. It is not removed by dialysis. No dose reduction is needed up to a GFR of 10 ml/min (17).

ADJUVANT ANALGESICS

This category consists of drugs that can be administered in association with other medications, or in certain situations they can be administered individually.

1. Gabapentin
Gabapentin is excreted unchanged in the urine. In our practice we used the following dose adjustment (see Table 2):

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Total gabapentin daily dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>900-3600</td>
</tr>
<tr>
<td>50-79</td>
<td>600-1800</td>
</tr>
<tr>
<td>30-49</td>
<td>300-900</td>
</tr>
<tr>
<td>15-29</td>
<td>150-600</td>
</tr>
<tr>
<td>&lt;15</td>
<td>150-300</td>
</tr>
</tbody>
</table>

2. Pregabalin
Dose adjustment is recommended according to the following schedule (see Table 3):

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Total pregabalin daily dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>300-600</td>
</tr>
<tr>
<td>50-60</td>
<td>150-300</td>
</tr>
<tr>
<td>30-49</td>
<td>75-150</td>
</tr>
<tr>
<td>15-29</td>
<td>25-75</td>
</tr>
<tr>
<td>&lt;15</td>
<td>25-50</td>
</tr>
</tbody>
</table>

3. Dexamethasone. It does not require dose adjustment, but attention should be paid to urea retention.

4. Amitriptyline. A tricyclic antidepressant with no renal excretion, it can be used in renal impairment at doses of 10-25 mg/day up to 75 mg/day, depending on the patient’s response (19,20).

OTHER MEDICATIONS

1. Colchicine
In mild (CrCl: 50-80 ml/min) and moderate CKD (CrCl: 30-50 ml/min), dose adjustment is not required, but patients should be carefully monitored for possible side effects.

In severe CKD (CrCl < 30 ml/min): no dose adjustment is required, but a treatment course should not be repeated more than once every two weeks. For patients requiring repeated treatment, alternative therapy should be considered. Colchicine is not eliminated by hemodialysis, so there is a risk of myo/neurotoxicity (21).

2. Allopurinol
Dosage adjustment in renal impairment is required depending on creatinine clearance (CrCl):

Parenteral doses:
- CrCl less than 3 ml/min: 100 mg/day with prolonged dosing interval;
- CrCl: 3-10 ml/min: 100 mg/day;
- CrCl: 10-20 ml/min: 200 mg/day.

Oral doses:
- CrCl less than 10 ml/min: 100 mg, 3 times/week;
- CrCl: 10 ml/min: 100 mg on alternate days;
- CrCl: 20 ml/min: 100 mg once/day;
- CrCl: 40 ml/min: 150 mg once/day;
- CrCl: 60 ml/min: 200 mg once/day.

In hemodialysis patients, administration of allopurinol is unnecessary because uric acid is eliminated by hemodialysis. Switching to febuxostat is recommended in every case of CKD with hyperuricemia. In special cases where allopurinol is recommended, the dose administered at the end of the hemodialysis session should not exceed 200 mg/session (21).

3. Febuxostat
No dose adjustment is necessary in patients with mild or moderate CKD. There are no consistent data for GFR below 30 ml/min. The effects of delaying renal impairment in patients with CKD have been demonstrated in several studies, and not only in those with hyperuricemia or gout. In clinical trials, it has been demonstrated to reduce uremia faster than allopurinol (22,23,24).

Conclusions
Pain management in patients with CKD is challenging because of the difficulty in choosing between different drugs due to direct renal toxicity or comorbidity. Choosing a medicine should be done with caution using clinical judgment to avoid further deterioration in renal function. Knowing the pharmacokinetics of analgesic drugs helps the clinician predict renal tolerance and response to treatment.

Conflicts of interest
The authors of this paper state that there are no conflicts of interest regarding the study methodology, results and conclusions drawn.

References


