

Analgesics use for kidney failure*

Uso de analgésicos em pacientes com insuficiência renal

Rioko Kimiko Sakata¹, Marcelo Henrique Gomes Nunes¹

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ABSTRACT

BACKGROUND AND OBJECTIVES: The use of drugs to treat renal failure has particularities due to pharmacokinetic changes present in such population. This study aimed at supplying subsidies for a rational choice of analgesics to be used in patients with renal failure.

CONTENTS: Information is provided about pain prevalence and etiology in renal failure patients. In addition, the use of anti-inflammatory drugs, opioid analgesics and adjuvant drugs for pain management is addressed.

CONCLUSION: Adjusting pharmacological therapy to renal function impairment may provide effective treatment with less adverse effects.

Keywords: Analgesics, Pain management, Renal failure.

RESUMO

JUSTIFICATIVA E OBJETIVOS: O uso de fármacos para o tratamento da dor em pacientes com insuficiência renal apresenta particularidades devido às alterações farmacocinéticas presentes nessa população. O objetivo deste estudo foi fornecer subsídios para uma escolha racional dos analgésicos a serem utilizados em pacientes com função renal deficiente.

CONTEÚDO: São fornecidas informações sobre prevalência e etiologia da dor em pacientes com insuficiência renal. Além disso, aborda-se a utilização de anti-inflamatórios, analgésicos opioides e fármacos adjuvantes para o tratamento da dor.

CONCLUSÃO: O ajuste da terapêutica farmacológica ao comprometimento da função renal é capaz de prover um tratamento eficaz e com menos efeitos adversos.

Descritores: Analgésicos, Insuficiência renal, Manuseio da dor.

INTRODUCTION

Chronic renal failure (CRF) is a common clinical condition followed by several associated diseases¹. Due to increased survival with the advent of renal replacement therapy and renal transplantations, CRF patients are increasingly submitted to surgical procedures, with the need for effective analgesic therapy in the postoperative period. They are also submitted to several procedures inducing acute pain, such as frequent punctures for dialysis.

Moreover, CRF patients are subject to chronic painful syndromes of different etiologies². In addition to musculoskeletal and degenerative disorders, consequence or not of the kidney disease, this is a population with increased incidence of peripheral vascular ischemic disease and peripheral neuropathies.

This study aimed at reviewing pain prevalence in patients with renal failure stressing etiologies, and at discussing aspects about drugs to its management.

RENAL FAILURE AND PAIN

In a study, authors have observed the prevalence of manifestations in patients chronically submitted to hemodialysis. Authors have emphasized that musculoskeletal pain complaints were reported by 54% of patients of that study, something which so far had never been documented³. Cramps were observed in 43%, headache in 19% and chest pain in 10%.

Pain epidemiological characteristics in chronic renal failure patients are poorly known. Most data are from studies on the quality of life or associated symptoms in patients chronically submitted to hemodialysis⁴⁻⁷.

In a population of chronic renal patients submitted to hemodialysis, there were pain complaints of different etiologies². Musculoskeletal pain was the most common cause. A small percentage has complained of pain induced by chronic dialytic treatment, such as those triggered by cramps, headache and caused by fistula puncture. Musculoskeletal pain was observed in 63.1% of patients, being osteoarthritis in 19.4%, undiagnosed pain in 18.4%, inflammatory arthritis in 6.8%, fracture in 9.7%, renal osteodystrophy in 4.9% and discitis/osteomyelitis in 1.9%. Dialysis-induced pain was present in 13.6% of patients, peripheral polyneuropathy in 12.6%, associated to peripheral vascular disease in 9.7% and carpal tunnel syndrome in 1.9%. Other causes of pain, corresponding to 18.4% of patients were: trauma, polycystic renal dis-

1. Federal University of São Paulo, São Paulo, SP, Brazil.

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Correspondence to:

Rioko Kimiko Sakata
Rua Três de Maio 61/51 – Vila Clementino
04044-020 São Paulo, SP, Brasil.
E-mail: riokoks.dcir@epm.br

ease, cancer and calciphylaxis.

In a different study, authors have evaluated pain complaints of chronic renal patients admitted to nephrological units. Fifty three percent of patients have reported more than one cause for their pain⁸. Reasons were: surgical trauma (43.3%), peripheral vascular disease (32.1%), dialysis-related pain (26.4%), peripheral neuropathy (18.9%), osteoarthritis (9.4%), inflammatory arthritis (9.4%), cancer (9.4%), renal osteodystrophy (7.5%), gout (5.7%), calciphylaxis (3.8%), osteomyelitis (1.9%), osteoporotic fracture (1.9%) and polycystic renal disease (1.9%).

Pain management is inadequate for a significant number of renal failure patients. Several factors may be pointed as responsible for such. Pain is not recognized as a major problem for chronic renal patients. In addition, pharmacokinetic changes and pharmacological interactions are very frequent in this population, making difficult or inhibiting management.

THERAPIES

Anti-inflammatory drugs, dipyron and paracetamol

Anti-inflammatory drugs

Non-steroid anti-inflammatory drugs (NSAIDs) are used in the general population to treat mild to moderate pain. These agents block prostaglandins synthesis through the inhibition of cyclooxygenase enzymes (COX). COX type 1 (COX-1) is called constitutive, being expressed in most tissues; COX type 2 (COX-2) is primarily induced, being mostly present in inflamed tissues^{9,10}.

NSAIDs may increase the risk of bleeding in patients with uremia, for their synergistic effects on platelet aggregation inhibition¹¹.

Renal prostaglandins synthesis inhibition is responsible for fluid retention, systemic hypertension and electrolytic disorders observed with the use of NSAIDs. There is edema in 3-5% of chronic anti-inflammatory users¹². In hypertensive patients, it was observed increase of approximately 5mmHg in blood pressure¹³. Rennin release inhibition by renal prostaglandins, with less sodium supply to distal tubules is responsible for hypercalcemia and other electrolytic disorders observed with the use of NSAIDs. Hypercalcemia is pronounced especially in patients with uncompensated diabetes, heart failure, multiple myeloma, and users of angiotensin-converting enzyme, betablockers and potassium-sparing diuretics¹¹. NSAIDs also induce reversible decrease in glomerular filtration rate (GFR). Residual renal function in patients under renal replacement therapy is critical for the well-being of such patients. It is associated to longer survival, less weight gain between sessions and better solute clearance¹¹.

Indomethacin is the NSAID decreasing GFR the most¹⁴. Naproxen, diclofenac, piroxicam and ibuprofen have intermediate effect. Aspirin is the NSAID interfering the least with GFR¹⁵. Notwithstanding COX-2 induction being more often observed in inflammation sites, it is constitutively expressed in the kidney and has important function in the maintenance of renal hemodynamics. There is benefit with the use of se-

lective COX-2 inhibitors in patients with increased risk of hemorrhages. However, such drugs have renal effects similar to non-selective inhibitors, being contraindicated for renal failure patients¹¹.

Dipyron and paracetamol

These are drugs with analgesic and antipyretic action and little or no anti-inflammatory activity. They have weak inhibitory activity on COX-1 and COX-2^{16,17}.

Dipyron action mechanism is still controversial. Experimental trials have shown inhibition of adenylate cyclase activation by hyperalgesic substances and direct blockade of calcium entrance in nociceptors¹⁸. Other authors have reported analgesic properties from the action of dipyron metabolites on prostaglandins synthesis in the central nervous system (bulbus and periaqueductal gray matter)¹⁹.

Dipyron has high clinical efficacy, low cost, broad availability and safety margin, especially for renal patients⁹.

Antipyretic action mechanism proposed for paracetamol associates the drug to the inhibition of prostaglandins synthesis in the hypothalamus⁹. As analgesic, the drug has to be able to activate inhibitory serotonergic antinociceptive pathways²⁰. Paracetamol is effective in doses up to 90mg.kg⁻¹ or 4g.day⁻¹. There is hepatotoxic activity when administered in high doses (150mg.kg⁻¹, or 5-30g). Liver injury occurs by depletion of glutathione stocks, leading to the building up of toxic metabolites in the hepatocyte, and to histopathological findings of centrilobular necrosis²¹. There are reports of kidney toxicity after administration of glutathione to treat liver toxicity. Glutathione may provide the formation of nephrotoxic compounds which culminate with the activation of caspases and liposomal enzymes, starting apoptosis and renal dysfunction²².

Paracetamol is the analgesic of choice for elderly patients or those with impaired renal function²³. In therapeutic doses, renal toxicity is rare¹⁰. There is no need for dose adjustment in renal failure, but some authors recommend increasing dose intervals from 6 to 8 hours when GFR is below 10 mL.min⁻¹²⁴.

Opioid analgesics

Tramadol

This is a drug with agonist activity on opioid receptors (μ), and inhibitory action on serotonin and norepinephrine reuptake, increasing such inhibitory neurotransmitters in the medullary synapse. It is metabolized in the liver, being 30% of the drug and 60% as active metabolites, excreted by the urine²⁵. Although forming active metabolites, the risk of toxicity is low²⁶.

Due to its action mechanisms, it is an effective drug to treat nociceptive and neuropathic pain, with the advantage of promoting less sedation and ventilatory depression as compared to agonist opioids. Nausea is a common adverse effect. In patients under drugs decreasing convulsive threshold, such as selective serotonin reuptake inhibitor antidepressants, it may trigger epileptic crises, in addition to serotonergic syndrome²⁷.

In advanced CRF, elimination half-life may double, being necessary to decrease the dose - 200mg.day⁻¹ if GFR is below

30mL.min⁻¹, and 100mg.day⁻¹ if GFR is below 10mL.min⁻¹ 25. It is dialyzable and safe for patients with dialytic CRF²⁶. Since it is easily removed by hemodialysis, it should be administered after the sessions²⁸.

Codeine

This is a morphine derivative with moderate analgesic activity. Its liver metabolizing gives origin to codein-6-glucoronide (80%), and 5% is demethylated to morphine, which forms active metabolites which depend on renal excretion^{29,30}.

Analgesic activity of this drug comes from the action of its metabolites on μ opioid receptors^{30,31}.

In patients with CRF, renal clearance of codeine and its metabolites is significantly decreased, with higher risk of severe adverse effects, such as sedation, ventilatory depression and hypotension³². This way, care is needed when prescribing codeine to patients with renal failure³¹. Due to its high distribution volume and molecular weight, it is not easily removed by hemodialysis and should be avoided in patients needing renal replacement therapy³¹⁻³³. Risk of toxicity is uncertain. It is dialyzable, but should be avoided, if possible, for patients with dialytic CRF²⁶.

Oxycodone

This is a semi-synthetic opioid with twice the analgesic potency of morphine. Its onset of action is one hour after oral administration and duration is 12h for the scheduled release formulation³⁴.

It is metabolized in the liver and the drug depends on the kidney for the excretion of active metabolites and part of the original compound³⁵. In the presence of renal failure there may be drugs build up and adverse effects as a consequence of the action of metabolites on the central nervous system³¹. Oxycodone should be avoided if GFL is below 60mL.min⁻¹ 34. For being hydrosoluble, it is dialyzable. There are, however reports of lethargy and ventilatory depression in dialytic patients under multiple oxycodone doses per day³⁶.

Toxicity risk is uncertain. It is not known whether it is dialyzable and whether it is safe for dialytic CRF patients²⁶.

Morphine

This is the most widely studied opioid for renal failure. It is metabolized in the liver into morphine-3-glucoronide (M3G) and morphine-6-glucoronide (M6G), in addition to the formation of diamorphine and normorphine. M6G is approximately 10 times more potent than its original compound. All metabolites and 10% of the original drug depend on renal excretion³⁷.

There is M6G build up in renal failure, causing ventilatory and CNS depression. Since its blood-brain barrier crossing is slow, adverse effects of M6G may be long-lasting, persisting even after drug withdrawal or dialytic treatment, in spite of good drug and its metabolites clearance by dialysis³⁸.

Analgesic and adverse effects of this drug are correlated to morphine and M6G plasma concentrations. This way, there is the need for decreasing the dose in 25%, 50% and 75% when

there is CRF in stages 3, 4 and 5, respectively³⁷. When safer opioids are available, morphine should be avoided in patients with renal failure³⁹.

Recommended dose for patients with GFR above 50mL/min is 100%; for GFR 10-50mL/min it is 75% and for GFR below 10mL/min it is 50%⁴⁰.

Toxicity risk is uncertain. It is dialyzable, but should be avoided, if possible, for patients with dialytic CRF²⁶.

Meperidine

This is a synthetic opioid with shorter duration analgesia as compared to remaining commonly used drugs. It has approximately 1/10 of morphine potency. Its active metabolite, normeperidine, has long elimination half-life (15-40h) and depends on renal excretion. There may be build up of this metabolite in renal failure patients with adverse effects such as shivering, myoclonus, seizure and delirium. So, it should not be used in patients with renal failure⁴¹. Remember that this opioid should not be used not only in patients with renal failure, but also in those with normal renal function and acute or chronic pain. In addition to having no advantage over other opioids, it easily induces addiction. Toxicity risk is high. Meperidine is dialyzable, but it is unsafe for dialytic CRF patients²⁶.

Fentanyl

This is a synthetic liposoluble opioid, approximately 80 times more potent than morphine. In addition to solution for intravenous or neuraxial use, it became popular due to its transdermal presentation, which reaches balance with plasma in approximately 12h after its application, with continuous release of the drug for 72h. It is adequate to treat pain in patients with stable opioid doses³⁴.

Some countries have the oral transmucosal solution which provides fast absorption and is useful to treat incidental pain³⁴.

Fentanyl is metabolized in the liver, with formation of inactive metabolites³¹. It does not form active metabolites²⁶. Since a minor percentage of the drug is excreted unaltered by the urine, this is a safe drug for renal failure patients⁴². Due to its high molecular weight, high protein binding, low hydro-solubility and high distribution volume, the drug is not easily dialyzable⁴³. It is not dialyzable but is safe for dialytic CRF patients²⁶.

Recommended dose for patients with GFR above 50mL/min is 100%; for GFR between 10 and 50mL/min is 75% and for GFR below 10mL/min it is 50%⁴⁰.

Methadone

This is a synthetic opioid 5-10 times more potent than morphine. In addition to action on opioid receptors, it has antagonist effects on N-methyl-D-aspartate (NMDA) receptors³⁴.

It is sold as racemic mixture where the isomer L-methadone acts on μ opioid receptors, while D-methadone acts on NMDA receptors. Due to its pharmacodynamics, it is useful to treat nociceptive and neuropathic pains⁴⁴.

In spite of its liposolubility, it has high bioavailability after oral administration. It is extensively bound to acid alpha-1-glycoprotein, with broad tissue distribution, responsible for build up and long elimination half-life during chronic treatment with this opioid³⁴.

It is metabolized in the liver and intestines, resulting in inactive metabolites, being most part eliminated by the bile. It does not form active metabolites²⁶. So, even not being cleared by hemodialysis, it is safe for renal failure patients⁴⁵. However, there is the need for frequent evaluation with dose and interval adjustments because it is a long-lasting drug.

Recommended dose for patients with GFR above 50mL/min is 100%; for GFR between 10 and 50mL/min it is 100% and for GFR below 10mL/min it is 50-75%⁴⁰. It is not dialyzable but is safe for dialytic CRF patients²⁶.

ANTICONVULSANTS

Gabapentine

This is an anticonvulsant primarily used to treat neuropathic pain, with well tolerated adverse effects. It was synthesized as analog of gamma-aminobutyric acid (GABA), but does not significantly interact with this or other neurotransmitters. Its action mechanism is through the binding to alpha-2-delta subunits of voltage-dependent calcium channels, decreasing calcium entrance in nervous terminations and the release of excitatory neurotransmitters⁴⁶.

It is excreted unaltered by the urine being the elimination dependent on GFR. Approximately 35% of the drug are cleared during hemodialysis. This drug needs dose adjustment according to GFR estimates when administered to patients with renal failure⁴⁷.

If GFR is equal to or above 80mL/min⁻¹ maximum daily dose may be 900 to 3600mg; if GFR 50 to 79, from 600 to 1800mg; if GFR between 30 and 49, 300-900mg; if GFR between 15 and 29, 150 to 600mg and if GFR below 15, 150 to 300mg⁴⁸.

Pregabalin

As gabapentin, pregabalin is a structural GABA analog without GABAergic activity and acts on calcium channels alpha-2-delta receptors. It is rapidly absorbed after oral administration, with bioavailability above 90%, and maximum plasma concentration reached one hour after its ingestion⁴⁹.

It suffers little metabolism in humans (less than 2%), being excreted unaltered by the urine. So, it does not interact with liver enzymatic system, having little pharmacological interaction. However, there is the need for dose adjustment for patients with GFR below 60mL/min⁻¹ ⁵⁰.

If GFR is equal to or above 60mL.min⁻¹ maximum daily dose may be 600 mg; if GFR between 30 and 59, of 300mg; if GFR between 15 and 29, 150mg; and if GFR below 15, 75mg⁵¹.

Carbamazepine

This is an anticonvulsant with anticholinergic, antidepressant, antiarrhythmic actions, in addition to inhibiting neuromuscular transmission. It induces increase of antidiuretic

hormone release. Its action mechanism is through the inhibition of sodium channels, suppressing spontaneous activity of A-delta and C fibers and decreasing glutamate release in nervous terminations⁴⁶.

Used since the 1960s, it is still considered a first line drug to treat trigeminal neuralgia⁵². However, its clinical use requires attention, due to pharmacological interactions and adverse effects on the central nervous system⁵³. It has high bioavailability after oral administration. There is 72% renal excretion, being 3% unaltered. Since a small portion of the original compound is excreted by the urine, there will be no pharmacokinetic alteration in patients with impaired renal function⁴⁶.

Oxcarbazepine

In spite of structural similarities with carbamazepine and of same clinical indications, oxcarbazepine has major pharmacokinetic differences⁴⁶. As opposed to carbamazepine, it does not induce cytochrome P450, which significantly decreases its interaction with other substances⁵⁴.

Its clinical effect is due to voltage-dependent sodium channels block, in addition to modulating calcium channels types N and P⁴⁶.

There is 95% absorption of the dose by the gastrointestinal tract. Less than 1% of the dose is eliminated unaltered by the urine⁹. However, in patients with renal failure, dose should be cut in half, due to significant plasma level increase of its derivative mono-hydroxi, its primary metabolite⁵⁴.

Similarly to carbamazepine, there is possibility, higher with oxcarbazepine, of dermatological reactions and hyponatremia during treatment with this anticonvulsant⁴⁶.

ANTIDEPRESSANTS

Tricyclic antidepressants

Tricyclics are considered first line drugs to treat neuropathic pain⁵⁵. Tertiary amines, such as amitriptyline, are potent norepinephrine and serotonin reuptake inhibitors, whereas secondary amines, such as nortriptyline, act predominantly on norepinephrine reuptake⁵⁶.

Amitriptyline bioavailability is low after oral administration. Its elimination is primarily renal, during several days, and the drug is not dialyzable due to its strong binding to plasma proteins⁵⁵. However, there is no need for dose adjustment in renal failure⁵⁷. Common amitriptyline adverse effects are poorly tolerated by renal failure patients. Among them, there are dry mouth, cardiac conduction abnormalities, weight gain, sedation and orthostatic hypotension.

Nortriptyline is an active amitriptyline metabolite. It suffers extensive first liver passage effect, with formation of active metabolites. It causes less anticholinergic and cardiovascular effects than its original compound, being better tolerated⁵⁵. There is no need for dose adjustment in renal failure⁵⁷.

Venlafaxine forms an active metabolite (O-demethylvenlafaxine)^{58,59} and approximately 87% of the administered dose are excreted by the urine in the first 48h, being 5% as venlafaxine, 26% as O-demethylvenlafaxine and 27% as inactive

metabolites. Its elimination half-life is similar to fluoxetine (3 to 5 days), but in renal failure there is 50-180% increase^{60,61}. Duloxetine forms active metabolites which are mostly excreted unaltered by the urine and in less quantity by feces^{62,63}. Duloxetine should be avoided in patients with creatinine clearance below 30mL/min⁶².

CONCLUSION

The use of analgesics in patients with renal failure is a challenge. Adequate treatment should take into consideration pain intensity and duration and pharmacokinetic changes caused by renal disease. Matching drugs to patients' clinical conditions may provide satisfactory analgesia with minor adverse effects and without deterioration of underlying clinical conditions.

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