Review

Anna Sołtysik[1, 2], Michał Graczyk[3], Jarosław Woroń[4, 5]

[1]Regional Specialised Hospital No. 4 in Bytom, Poland
[2]"San-Med" Palliative Medicine Outpatient Clinic and Home Hospice, Poland
[3]Department of Palliative Care, Nicolaus Copernicus University in Toruń, *Collegium Medicum* in Bydgoszcz, Poland
[4]Institute of Clinical Pharmacology, Department of Pharmacology, Faculty of Medicine, Jagiellonian University, *Collegium Medicum*, Krakow, Poland
[5]Anaesthesiology and Intensive Care Clinical Department, University Hospital in Krakow, Poland

Use of opioid analgesics in chronic kidney disease

Abstract

Opioid analgesics differ in terms of their potency and the way they impact opioid receptors. The choice of a drug should also depend on its non-opioid effects, which give them their special properties. However, it is the patient that is the most important factor of variability; the type of pain and the patient's clinical situation are the aspects that should be taken into account when starting the treatment.

Patients with impaired renal function require special attention. Opioid analgesics in chronic kidney disease should be adjusted to the degree of renal impairment, which will determine choices at the initial stage of the treatment and during its continuation. In the case of hydrophilic drugs or drugs with active metabolites, their dose should be adjusted to the degree of renal failure, the course of treatment should be monitored, and drug doses — both in background and breakthrough pain — should be modified, if necessary. In this group of patients, lipophilic opioid analgesics such as buprenorphine, fentanyl and methadone may be the right choice. In the case of insufficient analgesia, the same rules of titration apply to determine the optimal dose as in patients with normal renal function.

Palliat Med Pract 2022; 16, 3: 156–166

Key words: pain management, chronic kidney disease, opioid analgesics

Introduction

Analgesics comprise compounds characterised by different structures, mechanisms of action, pharmacokinetic profiles, and analgesic potency. They are divided into non-opioid drugs and opioids. Opioid analgesics are one of the compounds that are most commonly used in anaesthesia and in the postoperative period to relieve acute pain and treat chronic pain both in cancer and non-cancer patients [1–3]. Medications are selected based on the mechanism of pain, but the limitations resulting from the patient's comorbidities must also be taken into consideration. One of such comorbidities is chronic kidney disease (CKD). Opioid drugs do not have a direct nephrotoxic effect, but they may accumulate and lead to renal

Address for correspondence:
Anna Sołtysik
Regional Specialised Hospital No. 4 in Bytom, Poland
e-mail: soltysik.a.k@gmail.com

Palliative Medicine in Practice 2022; 16, 3, 156–166

DOI: 10.5603/PMPI.2022.0010

failure. For this reason, in patients taking analgesics for long periods of time, it is important to periodically monitor renal function and analyse symptoms reported by patients [4, 5]. Before initiating opioid therapy, factors affecting their pharmacokinetics and pharmacodynamics should be assessed, i.e.:

- age — differences in pharmacokinetic and pharmacodynamic (PK/PD) properties play a major role in accordance with the assumption that the glomerular filtration rate (GFR) declines at an average rate of approx. 0.75 mL/min/year in people aged 35–40 years; in people aged 55–60 years the rate of decline in GFR may increase up to 1 mL/ /min/year (faster in men) [6, 7]. It is worth noting that the change in PK/PD parameters is not only age-dependent, it is a complex function: age — multimorbidity — dietary habits — other drugs;
- body weight — pharmacokinetic parameters of opioids (apart from distribution) are related to lean body mass, and dosing should be based on ideal body weight, e.g. in elderly patients, there is an increase in body fat compared to lean body mass, which increases the total volume of distribution and may result in prolonged effects [6]. It is also important to reduce the body water content in the elderly, which affects the distribution of hydrophilic drugs. However, a reduction in the amount of water is relative and, in each case, requires taking the specific clinical situation into account. The problem will be even more complex when the patient takes diuretics at the same time;
- renal function;
- changes in the acid-base balance that affect the degree of binding to proteins [8].

Chronic kidney disease is a set of clinical symptoms and abnormalities observed in additional tests, resulting from a chronic progressive and irreversible reduction in the number of active nephrons. In CKD, both excretory and endocrine functions of the kidneys are impaired [9]. In developed countries, the number of patients dying from diagnosed end-stage renal failure, especially those not eligible for dialysis or consciously opting out of such treatment, is increasing [10].

The average prevalence of CKD in the general population is estimated at approx. 10%. This number is increasing due to the increasing prevalence of hypertension and diabetes, which are very often accompanied by pain [9]. According to literature data, nearly 75% of haemodialysis patients suffering from moderate to severe pain did not receive adequate analgesic treatment [11, 12]. Murtagh et al. assessed the prevalence of symptoms in patients with stage 5 advanced CKD not receiving dialysis — pain was present in an average of 53% (42–63%) of the patients included in the study [13].

The degree of elimination of many drugs (there are also non-filtration renal mechanisms of drug elimination) is proportional to GFR. However, it should be remembered that opioid analgesics are weak organic bases, and changes in urine pH may affect the relation between glomerular filtration and renal excretion [14]. The acidification of the urine caused by the intravenous administration of vitamin C or high doses of cranberry extracts leads to an enhanced elimination of the drug by the kidneys, which shortens the half-life and increases the risk of pain in patients who receive morphine and oxycodone parenterally [15, 16].

GFR may be measured using the Cockroft-Gault equation or the MDRD (modification of diet in renal disease) equation [15]. The Cockcroft-Gault formula is used to determine the glomerular filtration rate in patients with a stable creatinine level based on the measurement of serum creatinine level after taking body weight, age and gender into account. To obtain the correct value for women, the result should be multiplied by 0.85 [17].

$$\text{eGFR} = \frac{(140 - \text{age}) \times \text{body weight [kg]}}{\text{serum creatinine [mg/dL]} \times 72}$$

Due to the fact that the Cockroft-Gault formula takes body weight into account, GFR values may be overestimated in obese patients and/or those with oedema and underestimated in cachectic ones. It should also be borne in mind that an increase in serum creatinine level may only be observed when about 60% of nephrons are damaged and even later in patients with cachexia. This increase is delayed in relation to changes in GFR in early stages of the disease [18]. Apart from the creatinine level, the MDRD formula also takes age, sex, race and urea and albumin levels into account. The result should be multiplied by 0.762 for women and by 1.18 for African-Americans [17].

$$\text{eGFR} = 170 \times \text{creatinine level [mg/dL]}^{-0.999} \times \times \text{age}^{-0.176} \times \text{urea level}^{-0.170} \times \text{albumin level [g/dL]}^{0.318}$$

There is also a short (simplified) MDRD formula where, in order to obtain the correct result, the value obtained should be multiplied by a coefficient of 0.742 and, in the case of African-Americans, by an additional coefficient of 1.21 [17, 19].

$$\text{eGFR} = 186.3 \times \text{creatinine level [mg/dL]}^{-1.14} \times \text{age}^{-0.203}$$

The glomerular filtration rate gradually decreases by an average of 0.75–0.9 mL/min/year in people over the age of 30–35 (Table 1) [19].

Table 1. Classification of chronic kidney disease (CKD) [9, 17, 20]

CKD stage	eGFR [mL/min]	Description	
1	≥ 90	Kidney disease with normal eGFR, proteinuria, microhaematuria, leukocyturia, urinary casts	Normal renal function but there are changes in the urine, structural abnormalities or genetic features that indicate kidney disease
2	60–89	Latent chronic renal failure	Slightly impaired renal function but other features indicate kidney disease
3a	45–59	Compensated chronic renal failure	Moderately impaired renal function
3b	30–44	Compensated chronic renal failure	
4	15–29	Uncompensated chronic renal failure	Severely impaired renal function
5	< 15	End-stage chronic renal failure or renal replacement therapy	

In patients with impaired renal function, there are significant changes in the pharmacokinetics of the opioid drugs used, which depends, e.g., on the presence of active metabolites, the volume of distribution, and the hydrophilicity/lipophilicity of opioids. The elimination of parent drugs and their metabolites (through glomerular filtration or excretion by renal tubules) may be impaired. The bioavailability of drugs is also altered, e.g., due to changes in gastric juice pH or changes in gastrointestinal motility, which may be caused by opioids and drugs that have spasmolytic effects. Changes in the distribution, metabolism and binding of drugs to proteins, as well as escape distribution, such as ascites, may also occur in this group of patients. They often have comorbidities, e.g. cachexia and hypoproteinaemia causing changes in the volume of drug distribution [15, 21]. In people with renal failure, opioids differ in terms of efficacy and tolerance [22]. Their use may lead to a higher incidence of adverse effects due to changes in drug pharmacokinetics in this group of patients, and this effect varies depending on the opioid used [14].

Opioids affect the genitourinary system; urinary retention and urge to urinate are common, especially in older people. On the one hand, this is due to an increase in the tone of the bladder sphincter; on the other hand, the tone of the bladder detrusor muscle and the amplitude of ureteral contractions also increase [1]. Opioids reduce diuresis as a result of a decreased renal flow and GFR and decreased vasopressin secretion in response to osmotic stimuli [6]. The risk of complications resulting from the accumulation of substances is the greatest for drugs that are excreted from the body by the kidneys in active form or as active metabolites [23].

Codeine

It is a μ-opioid receptor agonist that is 10 weaker than morphine [24, 25]. The major metabolic pathways of codeine are glucuronidation to codeine-6-glucuronide (80% of metabolites), N-demethylation to norcodeine by CYP3A4 (approx. 10% of the drug), and O-demethylation to morphine by CYP2D6 (≤ 10% of the drug). Then, codeine and its metabolites are eliminated from the body almost exclusively by the kidneys, mainly in the form conjugated with glucuronic acid [9]. A small amount is excreted in an unmetabolised form in the urine (less than 17%) [6]. The biotransformation of codeine to morphine is considered to be the main mechanism of analgesia [6]. The activity of the CYP2D6 isoenzyme varies widely. As many as 5–10% of Caucasians do not have this isoenzyme, which makes them insensitive to codeine (poor metabolisers). However, its overexpression is observed in a few per cent of the population (ultrarapid metabolisers); such an overexpression leads to a rapid conversion of codeine into morphine [26].

Both codeine and its metabolites are excreted by the kidneys and accumulate in patients with renal disease, which may cause toxic symptoms [9, 27]. Some sources suggest reducing the dose of codeine (e.g. by 50%) and carrying out careful titration [9]. However, given the transformation of codeine into morphine, which is not advisable in this group of patients, codeine should not be used in people with renal failure [14].

Dihydrocodeine

Dihydrocodeine (DHC) is an analogue of codeine. Its metabolism is similar to that of codeine, but unlike

this substance, DHC is an active drug [24, 28]. Due to the fact that the polymorphism of CYP2D6 does not affect the analgesic effect of DHC, the drug produces the same analgesia in poor metabolisers [9, 25, 26]. DHC is mainly eliminated by the kidneys in the form of metabolites. It is not recommended in patients with severe renal failure [9].

Tramadol

It is a synthetic analgesic and a pure non-selective weak agonist of μ-, κ- and δ-opioid receptors, which have a particular affinity for the μ-receptor in the CNS; however, this effect is produced by the metabolite O-desmethyltramadol [26]. Additionally, tramadol blocks the reuptake of serotonin and norepinephrine to a small extent and enhances the secretion of serotonin [6, 24]. For this reason, the administration of naloxone only partially reverses the analgesic effect of tramadol [6]. Secondarily to noradrenergic effects, it also affects alpha-2-adrenergic, NMDA, and benzodiazepine (GABA-A) receptors [6]. Tramadol is a racemic mixture of two enantiomers. Both enantiomers exert an effect on the monoamine system, but only the (+) enantiomer, O-desmethyltramadol, has an effect on opioid receptors [24]. O-desmethyltramadol is the major metabolite of tramadol, synthesised by CYP2D6. The other metabolite is inactive N-desmethyltramadol, synthesised by CYP3A4. However, there is an increased risk that it will cause convulsions in patients with renal failure. The parent drug mainly affects the serotonergic system, whereas the active metabolite mainly has an effect on opioid receptors [26]. Similarly to codeine, a lower efficacy of tramadol is observed in poor metabolisers of CYP2D6, in whom there is an increased risk of nausea and vomiting [9, 26].

As much as 90% of tramadol and its metabolites are eliminated by the kidneys and in small amounts by the gastrointestinal tract [9, 26]. In the case of renal failure, the half-life of tramadol and its active metabolite is 2–3 times longer [26]. Therefore, it seems reasonable to increase the interval between doses of the drug to 8 or 12 hours in patients with renal failure. When the creatinine clearance is below 30 mL/min, a dose of 200 mg/day, and in the case of end-stage chronic kidney disease — a dose of 50 mg twice a day, should not be exceeded. A decrease in GFR below 10 mL/min is a contraindication for the administration of tramadol [19, 29]. The controlled-release form of this drug should not be used in patients with severe renal failure either [21].

Morphine

Morphine is a pure μ-opioid receptor agonist and a weak κ- and δ-opioid receptor agonist. It undergoes metabolic processes in the liver, the intestinal wall, the kidneys, and the CNS, mainly through conjugation with glucuronic acid [9]. Approx. 60–80% of morphine is glucuronidated to morphine-3-glucuronide (M3G) and 10% to morphine-6-glucuronide (M6G), approx. 5% of morphine is metabolised to normorphine, and 10% is excreted unchanged in the urine. A small amount of morphine is metabolised to codeine [6]. After oral administration, due to the first-pass effect, the ratio of M3G to M6G and morphine concentrations is significantly higher than in patients receiving morphine parenterally. M6G has analgesic effects 10–60 times stronger than morphine; M3G has adverse — neurotoxic — effects causing opioid hyperalgesia [30]. Under normal conditions, up to 30% of morphine is metabolised outside the liver. The excretion of morphine glucuronides is directly dependent on creatinine clearance. As much as 90% of conjugated morphine can be excreted in the urine and the remainder in bile, sweat, and milk [6].

Morphine is not nephrotoxic, but it is not recommended in patients with renal failure. The drug and its active metabolites (glucuronides) are excreted by the kidneys, which may lead to their accumulation, adverse effects, and unstable analgesia. In patients with renal failure, the half-life of morphine glucuronides is extended from 4 to 14–119 hours. In addition, the accumulation of metabolites also occurs [6, 14, 19]. In the case of renal failure, apart from the accumulation of M6G, the hydrolysis of glucuronides to parent compounds is also possible. Uraemia can exacerbate CNS symptoms (apathy, decreased level of consciousness, drowsiness, impaired concentration and ability to think in a complex manner) and increases the permeability of the blood-brain barrier, which is why patients with renal failure are at higher risk of experiencing the adverse effects of morphine, including respiratory depression, sedation, nausea, and vomiting [6, 8, 19]. To reduce the risk of their occurrence, apart from reducing the dose of the drug, the interval between doses should be increased from 4 to 6 or 8 hours [19, 29].

Oxycodone

It is a semi-synthetic opioid derived from the opium alkaloid — thebaine. It is a μ- and κ-receptor agonist that has an analgesic effect approx. 1.7 times

stronger (0.25–12) than that of morphine [31]. Oxycodone is metabolised by CYP3A4 to noroxycodone and by CYP2D6 to oxymorphone. Unchanged oxycodone and its metabolites are mainly excreted by the kidneys. A small proportion of the drug is excreted in faeces.

In impaired renal function, the concentration of oxycodone increases by approx. 50% and that of noroxycodone by 20% [19]. Most authors believe that the half-life of the drug in patients with severely impaired renal function is extended and, therefore, the metabolites accumulate in their case [15, 32]. As a result, in this group of patients, oxycodone should be used with caution and at a lower dose; however, the analgesic effect of oxycodone mostly depends on the parent drug, whereas the effect of metabolites is not relevant [29]. Uraemia may lead to the suppression of the activity of CYP2D6, which may prolong the elimination of the drug [33].

Buprenorphine

Buprenorphine is a semi-synthetic opioid drug that is a derivative of thebaine. It is a μ-opioid receptor agonist and κ-and γ-receptor antagonist [24, 34]. Buprenorphine has an agonistic effect on opioid receptor-like 1 (ORL-1) and through receptors for nociceptin. This partial μ agonist is characterised by the strongest affinity for receptors out of traditional opioids, but the degree of binding is low (< 50%) [26]. This leaves a significant receptor reserve allowing buprenorphine to be used in combination with other opioids. Despite being a partial agonist in the therapeutic dose range (< 7 mg/24 h), the drug acts as a pure agonist [26]. The ceiling effect can only be achieved at very high doses, exceeding 16 mg/24 h, which are not used for the treatment of pain [26]. Unlike other "strong" opioids, buprenorphine has a ceiling effect within the range of the depressive effect on the respiratory centre and is therefore unlikely to cause respiratory depression [26].

Buprenorphine is metabolised by CYP3A4 to norbuprenorphine, which has analgesic properties but many times weaker than those of buprenorphine. Then, both compounds are glucuronidated and excreted: 70–80% unchanged by the gastrointestinal tract and 10–30% as norbuprenorphine and glucuronides in the urine. The transdermal form is the preferred form of this drug as the first-pass effect is omitted and stable therapeutic concentrations of the drug in the blood are ensured [35]. In the dose range of up to 70 μg/h buprenorphine can be safely used at an unchanged dose in patients with impaired renal function and haemodialysis patients because the pharmacokinetic properties of the drug are not altered [19]. It was considered that the drug can be safely used in patients with renal failure [26, 34, 36].

Fentanyl

It is a pure μ-opioid receptor agonist. Due to its low molecular weight and significant lipophilicity, it rapidly passes from the bloodstream through the blood-brain barrier into the CNS where it binds to the receptors [1]. Fentanyl is metabolised by cytochrome CYP3A4, mainly to inactive norfentanyl, and then excreted in the urine as inactive metabolites (approx. 75%) and faeces (approx. 9%). As much as 7–10% of the drug is excreted unchanged in the urine [6, 26].

In patients with compensated hepatic and renal failure, no significant extension of half-life is observed for fentanyl, whereas, in severe renal failure, this parameter is doubled after the first pass through the liver [1]. Fentanyl is metabolised in the liver in more than 90% to inactive metabolites. Hepatic clearance is high and depends on the blood supply to the liver and on the degree of hepatic extraction, i.e. the proportion of the substance eliminated from the blood when it passes through the liver. Fentanyl administered orally enters the bloodstream almost exclusively through the portal system and, as a result, the entire dose of the drug passes through the liver first. As much as 60% of fentanyl is inactivated during the first pass, which is why the drug has no effect after oral administration [1]. In the case of transmucosal administration, its bioavailability varies depending on the form of the drug (intranasal, sublingual, buccal) [24, 32, 37]. Fentanyl is biotransformed to inactive metabolites, the clearance of which may vary in patients with advanced CKD, but it is not of clinical significance. Such patients often suffer from excessive sleepiness and have an increased risk of respiratory depression [29]. Fentanyl is considered to be a reasonably safe opioid in patients with renal failure [26].

Remifentanil

Similarly to fentanyl, remifentanil is a pure μ-opioid receptor agonist that is characterised by poorer lipid solubility compared to fentanyl and its derivatives. As a result, the balance between the blood and the CNS is established more quickly [1]. The degradation of remifentanil occurs continuously in blood and tissues under the influence of non-specific plasma and tissue esterases and is independent of renal and hepatic function [1]. Remifentanil is mainly deesterified to carboxylic acid and 90% of the drug is excreted in the urine in this form [6]. Renal failure does not affect the pharmacokinetics of remifentanil. During anaesthesia,

the major metabolite excreted by the kidneys is accumulated and the half-life is extended from 1.5 hours to 26 hours, but this effect is of no importance [1].

Sufentanil

Sufentanil is a derivative of fentanyl. It has a 7–10 times stronger effect that occurs more quickly and lasts shorter [1]. Compared to fentanyl, it is much more lipophilic. Sufentanil also binds more strongly to opioid receptors but weakly and non-specifically in the brain tissue. It has a high hepatic extraction rate (0.8). Its major metabolites include N-phenylpropanamide. A small proportion of the drug is excreted unchanged in the urine [1].

Alfentanil

Alfentanil is a derivative of fentanyl. The potency of a single dose of the drug is about 1/4 of that of fentanyl and the duration of action is shorter. Compared to fentanyl, alfentanil is less lipophilic. This drug is mainly metabolised by CYP3A4, and it is rapidly inactivated in the liver [6]. A small proportion is excreted unchanged in the urine [1].

To sum up, fentanyl, sufentanil and alfentanil are mainly metabolised in the liver, and small amounts of these drugs pass unchanged into the urine. Inactive metabolites are excreted in the urine. Unlike the above-mentioned drugs, remifentanil is rapidly metabolised by non-specific plasma and tissue esterases [6]. In renal failure, the clearance of fentanyl analogues does not change significantly, although a reduction in plasma proteins may potentially affect the proportion of the free fraction of the opioid [6]. It appears that fentanyl and sufentanil may be used in patients with renal disease, but such individuals should be monitored for symptoms of opioid accumulation [14].

Nalbuphine

Nalbuphine is a semi-synthetic opioid that is a derivative of morphinan. It is a κ-receptor agonist and μ-receptor antagonist. Due to its antagonistic effect on the μ-receptor, nalbuphine has minimal addictive potential and does not affect the smooth muscles of the gastrointestinal tract or the urinary system. The drug is easily absorbed from the gastrointestinal tract, but it is subject to the first-pass effect to a large extent. Therefore, the drug is characterised by low bioavailability (20–25%) after oral administration. Nalbuphine is metabolised in the liver and excreted by the kidneys in the form of metabolites, such as glucuronic acid glycosides [21, 38]. Due to the lack of data on the pharmacokinetics of nalbuphine in individuals with impaired renal function and in those who are at risk of metabolite accumulation, it is recommended to reduce the opioid dose in this group of patients [21]. The use of nalbuphine is not recommended in patients with severe renal and hepatic failure and in those who are treated with μ-receptor agonists [38]. The concomitant use of nalbuphine and μ-opioid receptor agonists does not seem advisable. This drug is mainly used for the short-term treatment of pain and in the perioperative period.

Pentazocine

Pentazocine is a κ-opioid receptor agonist. In addition to its analgesic effect that is 5–10 times weaker compared to morphine, it also has hallucinogenic and dysphoric effects. For this reason, this drug should not be used in pain management [32].

Meperidine

The majority of the metabolism of meperidine involves hydrolysis to meperidine acid. A small amount (approx. 5%) is excreted unchanged in the urine and approx. 30% is metabolised to normeperidine [6]. Repeated doses of meperidine have an accumulation phenomenon associated with the short analgesic effect of meperidine and the long half-life of the neurotoxic metabolite, which increases the risk of symptoms such as agitation, confusion, movement disorders, dizziness, nausea and vomiting, especially in patients aged over 65 years [32]. The use of meperidine in renal failure can lead to accumulation of normeperidine with its toxic effects on the CNS (seizures), tachycardia and a significant increase in blood pressure [6, 8]. These toxic effects are not caused by stimulation of opioid receptors and are not reversed by naloxone [6]. According to the standards of acute and postoperative pain management prepared by the Polish Society for the Study of Pain, the use of meperidine in pain treatment is not recommended due to neurotoxic effects of metabolite of meperidine, especially at repeated doses [32, 39]. Adverse effects of this drug include anticholinergic effects.

Methadone

Methadone is a synthetic opioid drug, μ- and γ-receptor agonist. It is also an NMDA receptor antagonist and serotonin and norepinephrine reuptake inhibitor (SNRI). Only 1% of methadone occurs in the blood, the remainder forms a reservoir in tissues, hence the very long elimination time (ca. 15–60 hrs) [24].

Methadone is metabolised in the liver and intestinal wall to inactive metabolites and then excreted via the kidneys (25–50%) and gastrointestinal tract (10–45%). Impaired renal and hepatic functions do not affect the elimination time of the drug from the system. In cases of anuria, the drug is excreted almost entirely through the gastrointestinal tract as pyrrolidine [14, 40]. Methadone can be safely used in CKD patients. Halving the dose is recommended in patients whose serum creatinine levels exceed 8 mg/dL (700 μmol/L) or whose GFR is reduced to 10–15 ml/min [19, 26, 29].

Tapentadol

Tapentadol is a μ-opioid receptor agonist in the CNS with an affinity 50 times lower than morphine and a norepinephrine reuptake inhibitor [41, 42]. This drug is metabolised mainly in the liver by glucuronidation (97%), the metabolites have no analgesic effect. It is excreted almost entirely as metabolites in urine, 1% of the drug is excreted in faeces. There is very little metabolism involving cytochrome P450 isoenzymes, which limits the potential for tapentadol to interact with other drugs [43].

In patients with slightly to moderately impaired renal function, there is no need to adjust the dose of tapentadol which, in the form of extended-release tablets, can be a first-line drug for painful diabetic neuropathy that often coexists with CKD. No data are available for ESRD patients and haemodialysis patients [11].

Differences related to route of administration should be considered when using opioids (Table 2, 3). Some opioids administered by the subcutaneous or intramuscular route show 100% bioavailability; however, peak plasma concentrations may vary by up to 5-fold according to body temperature, site of administration and cardiovascular status. After opioid administration via the intravenous route, the plasma concentration range is more limited, whereas opioids administered orally are distinguished by a first pass effect that is related to metabolism in the liver and intestinal wall (up to 50%) [6].

Patient in intensive care unit (ICU) vs. patient in advanced stage of disease

Pain should be adequately treated in each patient individually, taking into account comorbidities. There is a belief that the most important element in patient care is not to save lives, but to relieve pain and suffering. Contrary to popular belief, patients experiencing pain are ICU patients [54]. In the ICU, 71% of patients experience pain during hospitalisation [55]. In addition to hypoxaemia, hypotension, hypoglycaemia, CNS damage, sepsis and uraemia, pain is one of the most common factors that cause agitation in patients [56]. A different and special group of patients who experience pain in a significant proportion are dying patients. It is estimated that up to 60–90% of such patients can be affected by pain [57, 58]. Pain at the end of life is experienced virtually every day by most patients and may exhibit a circadian rhythm (e.g. 80% of episodes between 8.00 a.m. and 0.00 a.m.), both in terms of baseline and episodic (breakthrough) pain [59–61].

It is important to select an effective treatment that does not cause progression of the underlying disease, has the intended effect, with acceptable or absent adverse effects. It is important to know the pharmacokinetics and pharmacodynamics of opioid analgesics. Patients with kidney disease and undergoing renal replacement therapy require special attention. In this group of patients, drug doses should be modified (reduced) and dosing intervals lengthened, according to the functional status of these organs [19]. Given the lack of studies and the possibility of coexistence of other factors that determine the appropriate choice of opioid, recommendations for dose reduction based only on calculated GFT are not entirely conclusive/advisable [14].

Conclusions

CKD patients require analgesic treatment with caution both during the stable phase and during periods of exacerbation. At different stages of the disease, according to GFR, reduction of opioid doses and prolongation of dosing intervals should be considered in each case. If drugs used in CKD patients — especially extended-release drugs — do not cause adverse effects, they should stay on a consistent regimen. Lipophilic drugs are considered safe opioid analgesics. The use of fentanyl or buprenorphine in transdermal systems appears to be the treatment of choice. When initiating treatment, especially in patients with advanced renal failure, half the dose should be considered compared to patients with normal renal function. In the case of insufficient analgesia, the same rules of titration apply to determine the optimal dose as in patients with normal renal function. The use of opioid analgesics in end-stage CKD requiring renal replacement therapy, including the use of opioid receptor antagonists, will be discussed in a separate paper.

Table 2. Recommended dosing of opioid drugs according to GFR [9, 11, 14, 19, 23, 44–46]

Drug	GFR 20–50 mL/ /min	GFR 10–20 mL/min	GFR < 10 mL/min	Safety
Codeine	According to the source: 75–100% dose	According to the source: — 50–75% dose — should be avoided	According to the source: — 25–50% dose (use low initial doses, extend intervals between doses, use for short periods) — should be avoided	Use with caution
Dihydrocodeine	100% dose	According to the source: — 50% dose — use low initial doses, titrate — should be avoided	According to the source: — 25% dose — use low initial doses, titrate — should be avoided	Use with caution
Tramadol	100% dose	According to the source: — 50% dose — 50–100 mg, every 8 or 12 h (increase dose according to tolerance) max. 200 mg/day	According to the source: — 50% dose — 50 mg, every 8 h (increase dose according to tolerance) — do not use max. 200 mg/day	Use with caution
Morphine	75% dose	50% dose (use low initial doses, extend intervals between doses)	25% dose (use low initial doses, extend intervals between doses)	Use with caution
Fentanyl	According to the source: 75–100% dose	75% dose	50% dose	Safe
Remifentanil	100% dose	100% dose	100% dose	Safe
Alfentanil	100% dose	100% dose	100% dose	Safe
Sufentanil	100% dose	100% dose	100% dose	Safe
Oxycodone	According to the source: 50–100% dose	According to the source: 50–100% dose	According to the source: — 50% dose — use low initial doses — not to be used due to increased risk of sedation	Use with caution
Buprenorphine	100% dose	100% dose (avoid high doses)	TTS 100% dose SL 25–75% dose according to the source (avoid single high doses)	Safe
Methadone	100% dose	According to the source: 75–100% dose	50% dose	Safe
Tapentadol	100%	Not recommended — no studies in patients with severe renal impairment	Not recommended — no studies in patients with severe renal impairment	Use with caution

TTS — transdermal; SL — sublingual

Table 3. Half-life of selected opioids [19, 21, 29, 32–34, 38, 45–53]

Drug	Half-life $T_{1/2}$ [h]	Notes
Codeine	2–4 ESRD: 13	Time of onset of maximum action (PO): 1 h Dur.: 3–4 h
Dihydrocodeine	3.5–5 ESRD: > 6	Time of onset of maximum action (PO): 60–80 min Dur. of modified-release tablets: 12 h
Tramadol	5–6 ESRD: 11	Time of onset of maximum action (IV): 1 h Time of onset of maximum action PO tablets): 1.5 h Time of onset of maximum action (PO drops): 1 h
Morphine	1.5–4.5 (2–3 h on average) ESRD: 50	Onset of action: 15 min Time of onset of maximum action: 30 min Dur.: 4–5 h Dur. of modified-release tablets: 12 h
Fentanyl	IV 3.1–6.6, SC 6–16, TTS 13–22, TM 2–44 ESRD: possible extension of half-life	Time of onset of maximum action (IV): 5–8 min Dur. (IV): 1–2 h Dur. after peeling off the patch: 12–24 h Dur. (SL): 5–12 h
Remifentanil	3–10 min ESRD: u.d.s.	Time of onset of maximum action: 1.5–2 min Dur.: 20 min
Alfentanil	1–2 (90 min on average) ESRD: u.d.s.	Time of onset of maximum action: 1 min Dur.: 30–60 min
Sufentanil	2.2–4.6 ESRD: u.d.s.	Time of onset of maximum action: 2–4 min Dur.: 100–150 min
Nalbuphine	2.93 ± 0.795 No studies in patients with renal impairment	Onset of action: IV 2–3 min, IM/SC 15 min Dur.: 3–6 h
Oxycodone	3.5 ± 1.43 (1.5–5.4), extended-release tablets: 4.5 ESRD: 3.9 (1.8–26), extended-release tablets: 5.5	Time of onset of maximum action (IV): 20 min Dur.: 3.5–7 h Dur. of prolonged-release preparations: 11–14 h
Buprenorphine	IV 20–25 TTS 25–36 TM 24–69 ESRD: u.d.s.	Onset of action: IV 15–25 min, IM 30 min, SC 12–24 h Dur.: 6–8 h with a residual effect of up to 24 h, SC 72–96 h TTS — minimum effective concentration: 12–24 h, dur.: 60–96 h, excreted after patch removal with $T_{1/2}$ 30 h TM — onset of action: 15–30 min, effect after 6–9 h, $T_{1/2}$ 32 h
Methadone	5–75 (SmPC: in patients without developed tolerance, the average half-life after a single dose is ca. 15 h, with prolonged administration: 22 h)	Onset of action: IV 2–5 min, IM 10–20 min, PO 30–60 min Time of onset of maximum action (PO): 3–4 h, dur.: 4–8 h
Tapentadol	4 (extended-release tablets 5–6)	Time of onset of maximum action (PO): 85 min (extended-release tablets 3–6 h)

ESRD — end-stage renal disease; PO — per os; dur. — duration; IV — intravenous; SC — subcutaneous; TTS — transdermal; TM — transmucosal; SL — sublingual; u.d.s. — unchanged disease status; IM — intramuscular; SmPC — Summary of Product Characteristics

Declaration of conflict of interests

The authors declare no conflict of interest.

Funding

The article has no funding source.

References

1. Larsen R. Anestezjologia. Volume 1. Edra Urban & Parter, Wrocław 2020: 9–16, 65–82.
2. Wordliczek J, Kotlińska–Lemieszek A, Leppert W. et al. Farmakoterapia bólu u chorych na nowotwory — zalecenia Polskiego Towarzystwa Badania Bólu, Polskiego Towarzystwa Medycyny Paliatywnej, Polskiego Towarzystwa Onkologicznego, Polskiego Towarzystwa Medycyny Rodzinnej, Polskiego Towarzystwa Anestezjologii i Intensywnej Terapii. Ból. 2017; 18: 11–53.
3. Kocot-Kępska M, Dobrogowski J, Wordliczek J, et al. Stosowanie silnie działających opioidów u osób z bólem przewlekłym pochodzenia nienowotworowego — praktyczne wskazówki z wytycznych polskich i europejskich. Med Prakt. 2018; 3: 51–63.
4. Chmielewski M. Jakimowicz–Tylicka M, Rutkowski B. Leki analgetyczne — wciąż poważny problem w nefrologii? Forum Nefrol. 2015; 8(2): 63–68.
5. Kuźniar–Placek J, Jaroszyński A. Nefropatia analgetyczna. Family Medicine & Primary Care Review. 2014; 16(4): 370–371.
6. Smith T, Pinnock C, Lin T. Podstawy anestezjologii. Wydanie 3. DB Publishing, Warszawa 2012: 584–608.
7. Kuźniar–Placek J, Dereziński T, Wofl J, et al. Ocena funkcji nerek u osób w podeszłym wieku. Forum Medycyny Rodzinnej. 2015; 9(2): 112–114.
8. Miller RD. Miller's Anesthesia. Seventh edition. Churchill Livingstone, Philadelphia. 2010; 1: 769–824.
9. Ciałkowska-Rysz A, Dzierżanowski T. Medycyna paliatywna. Termedia, Poznań 2019: 106–120, 253–261, 420–430.
10. Murtagh FEM, Chai MO, Donohoe P, et al. The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. J Pain Palliat Care Pharmacother. 2007; 21(2): 5–16, indexed in Pubmed: 17844723.
11. Coluzzi F, Caputi FF, Billeci D, et al. Safe Use of Opioids in Chronic Kidney Disease and Hemodialysis Patients: Tips and Tricks for Non-Pain Specialists. Ther Clin Risk Manag. 2020; 16: 821–837, doi: 10.2147/TCRM.S262843, indexed in Pubmed: 32982255.
12. Bailie GR, Mason NA, Bragg-Gresham JL, et al. Analgesic prescription patterns among hemodialysis patients in the DOPPS: potential for underprescription. Kidney Int. 2004; 65(6): 2419–2425, doi: 10.1111/j.1523-1755.2004.00658.x, indexed in Pubmed: 15149355.
13. Murtagh FEM, Addington-Hall JM, Edmonds PM, et al. Symptoms in advanced renal disease: a cross-sectional survey of symptom prevalence in stage 5 chronic kidney disease managed without dialysis. J Palliat Med. 2007; 10(6): 1266–1276, doi: 10.1089/jpm.2007.0017, indexed in Pubmed: 18095805.
14. Dean M. Opioids in renal failure and dialysis patients. J Pain Symptom Manage. 2004; 28(5): 497–504, doi: 10.1016/j.jpainsymman.2004.02.021, indexed in Pubmed: 15504625.
15. Osowicka M. Niewydolność nerek a leki przeciwbólowe. Psychoonkologia. 2007; 11: 24–30.
16. Kapłon-Pasionek K, Tabin Ł, Woroń J, et al. Opioidy i interakcje z innymi lekami siła działania i bezpieczeństwo stosowania. Poster Session. Conference of the Polish Association for the Study of Pain, Warsaw, 2019.
17. Małyszko J. Przewlekła niewydolność nerek — problem tylko nefrologów? Choroby Serca i Naczyń. 2005; 2(2): 78–83.
18. Ficek J, Chudek J. Przewlekła choroba nerek jako czynnik zwiększający ryzyko nefrotoksycznego działania leków oraz metody wykrywania polekowych uszkodzeń nerek. Choroby Serca i Naczyń. 2015; 12(4): 233–239.
19. Szkutnik-Fiedler D, Kazanowska P, Szałek E, et al. Stosowanie leków opioidowych u pacjentów z niewydolnością nerek i wątroby. Farm Współcz. 2010; 3: 117–123.
20. National Institute for Health and Clinical Excellence. Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care. Clinical guideline CG73. NICE, London 2008.
21. Porażka J, Karbownik A, Szałek E, et al. Zmiany w farmakokinetyce analgetyków u pacjentów z niewydolnością nerek. Farm Współcz. 2015; 8: 1–9.
22. King S, Forbes K, Hanks GW, et al. A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: a European Palliative Care Research Collaborative opioid guidelines project. Palliat Med. 2011; 25(5): 525–552, doi: 10.1177/0269216311406313, indexed in Pubmed: 21708859.
23. Kotlińska-Lemieszek A, Deskur-Śmielecka E. Bezpieczna farmakoterapia objawów u pacjentów ze schyłkową przewlekłą chorobą nerek — wnioski z ankiety przeprowadzonej wśród lekarzy pracujących w ośrodkach opieki paliatywnej. Med Paliat. 2017; 9(3): 139–151.
24. Malec-Milewska M, Woroń J. Kompendium leczenia bólu. Wydanie 3. Medical Education, Warszawa 2017: 43–66, 577–588.
25. Leppert W, Wordliczek J, et al. Zalecenia postępowania diagnostyczno–terapeutycznego u chorych na nowotwory z bólem. Onkol Prakt Klin – Edukacja. 2018; 4(1): 1–15.
26. Malec-Milewska M, Krajnik M, Wordliczek J. Chory na nowotwór. Kompendium leczenia bólu. Wydanie 2. Medical Education, Warszawa 2014: 77–93.
27. Davison SN. Clinical Pharmacology Considerations in Pain Management in Patients with Advanced Kidney Failure. Clin J Am Soc Nephrol. 2019; 14(6): 917–931, doi: 10.2215/CJN.05180418, indexed in Pubmed: 30833302.
28. Cherny NI. Opioid analgesics: comparative features and prescribing guidelines. Drugs. 1996; 51(5): 713–737, doi: 10.2165/00003495-199651050-00002, indexed in Pubmed: 8861543.
29. Graczyk M, Zylicz Z. Co powinniśmy wiedzieć o stosowaniu leków opioidowych u pacjentów z przewlekłą chorobą nerek? Med Paliat Prakt. 2007; 1(2): 54–60.
30. Kotlińska-Lemieszek A, Bączyk E, Ciałkowska-Rysz A, et al. Morfina w leczeniu bólu u pacjentów z zaawansowaną chorobą nowotworową. Czy dobrze znamy ten lek? Jak go bezpiecznie stosować? Med Paliat. 2010; 2: 67–80.
31. Riley J, Ross J, Rutter D, et al. No pain relief from morphine? Supportive Care in Cancer. 2005; 14(1): 56–64, doi: 10.1007/s00520-005-0843-2.
32. Wordliczek J, Dobrogowski J. Leczenie bólu. Wydanie 3. PZWL, Warszawa 2017: 54–83, 629–633, 641–693.
33. Dzierżanowski T, Ciałkowska-Rysz A. Oksykodon — lek pierwszego rzutu w leczeniu silnego bólu nowotworowego. Med Paliat. 2010; 3: 123–131.
34. Dzierżanowski T, Ciałkowska-Rysz A. The principles of management of pain exacerbations in cancer patients. Med Paliat/Palliative Medicine. 2016; 8(1): 1–8.
35. Nalpain 10 mg/ml. Solution for injection. Summary of Product Characteristics.

36. Wordliczek J, Zajączkowska R, Dziki A, et al. Uśmierzanie bólu pooperacyjnego w chirurgii ogólnej — zalecenia Towarzystwa Chirurgów Polskich, Polskiego Towarzystwa Anestezjologii i Intensywnej Terapii, Polskiego Towarzystwa Badania Bólu oraz Polskiego Towarzystwa Znieczulenia Regionalnego i Leczenia Bólu. Pol Przeg Chir. 2019; 91(1): 47–69.
37. Kocot-Kępska M, Przeklasa-Muszyńska A, Dobrogowski J. Buprenorfina — opioid o unikalnych właściwościach. Med Paliat Prakt. 2016; 10(3): 77–88.
38. Szałek E. Buprenorfina — wyjątkowy opioid. Geriatria. 2017; 11: 209–214.
39. Zylicz Z. Buprenorfina w plastrach. Szereg odpowiedzi na dręczące pytania. Med. Paliat. Prakt. 2012; 6(2): 46–53.
40. Graczyk M, Krajnik M, Stróżecki P, et al. Analiza skuteczności przeciwbólowej i działań niepożądanych metadonu u pacjentów hemodializowanych z powodu przewlekłej choroby nerek. Pol Med Paliat. 2006; 5(4).
41. Schröder W, Tzschentke TM, Terlinden R, et al. Synergistic interaction between the two mechanisms of action of tapentadol in analgesia. J Pharmacol Exp Ther. 2011; 337(1): 312–320, doi: 10.1124/jpet.110.175042, indexed in Pubmed: 21262850.
42. Kress HG. Tapentadol and its two mechanisms of action: is there a new pharmacological class of centrally-acting analgesics on the horizon? Eur J Pain. 2010; 14(8): 781–783, doi: 10.1016/j.ejpain.2010.06.017, indexed in Pubmed: 20659810.
43. Dzierżanowski T, Ciałkowska-Rysz A. Tapentadol w leczeniu przewlekłego bólu związanego z nowotworem. Med Paliat. 2016; 8: 157–163.
44. Adaptation of Palliative Care drugs in renal failure by Yorkshire Palliative Medicine Guidelines Group, 2006.
45. Ashley C, Currie A. The Renal Drug Handbook. Third edition. Radcliffe Publishing Ltd, Abingdon 2009.
46. Lizakowski S. Leki w przewlekłej chorobie nerek. Serwis Edukacyjny Polskiego Towarzystwa Nefrologicznego.
47. Efferalgan Codeine 500 mg + 30 mg. Effervescent tablets. Summary of product characteristics.
48. Methadone Hydrochloride Molteni 1 mg/ml. Syrup. Summary of product characteristics.
49. Bunondol 0.3 mg/ml. Solution for injection. Summary of product characteristics.
50. Larsen R. Anestezjologia. Volume 2. Edra Urban & Parter, Wrocław 2020: 700–705.
51. Tramal 50 mg/1ml. Solution for injection. Summary of product characteristics.
52. DHC Continus 60 mg, 90 mg, 120 mg. Modified-release tablets. Summary of product characteristics.
53. Kołodziej D. Tapentadol – nowy analgetyk opioidowy. Farm Współcz. 2015; 8: 1–9.
54. Marino PL. Intensywna Terapia. 4th Edition. Elsevier Urban & Partner, Wrocław 2019: 961–985.
55. Weisbrot M, Kwiecień-Jaguś K, Mędrzycka-Dąbrowska W. Analiza dolegliwości bólowych pacjentów wentylowanych mechanicznie w oddziale intensywnej terapii. Ból. 2019; 20(3): 23–31.
56. Rybicki Z. Intensywna Terapia Dorosłych. Kompendium. 1st Edition. Makmed, Lublin 2011: 209–228.
57. Lesage P, Portenoy R. Trends in Cancer Pain Management. Cancer Control. 2017; 6(2): 136–145, doi: 10.1177/107327489900600202.
58. van den Beuken-van Everdingen MHJ, Hochstenbach LMJ, Joosten EAJ, et al. Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. J Pain Symptom Manage. 2016; 51(6): 1070–1090.e9, doi: 10.1016/j.jpainsymman.2015.12.340, indexed in Pubmed: 27112310.
59. Alarcón MªD, Estévez FV, Cabezón-Gutiérrez L, et al. Expert consensus on the management of breakthrough cancer pain in older patients. A Delphi study. J Geriatr Oncol. 2019; 10(4): 643–652, doi: 10.1016/j.jgo.2019.03.012, indexed in Pubmed: 31036463.
60. Campagna S, Sperlinga R, Milo A, et al. The Circadian Rhythm of Breakthrough Pain Episodes in Terminally-ill Cancer Patients. Cancers (Basel). 2018; 11(1), doi: 10.3390/cancers11010018, indexed in Pubmed: 30586878.
61. Gonella S, Sperlinga R, Sciannameo V, et al. Characteristics of Breakthrough Pain and Its Impact on Quality of Life in Terminally Ill Cancer Patients. Integr Cancer Ther. 2019; 18: 1534735419859095, doi: 10.1177/1534735419859095, indexed in Pubmed: 31220961.