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The use of opioid receptor agonists and antagonists in the treatment of patients with advanced chronic kidney disease and undergoing renal replacement therapy

The basic principles of pharmacotherapy and changes in pharmacokinetics of drugs in this patient group are discussed in another article: Sołtysik A, Graczyk M, Woroń J. Use of opioid analgesics in chronic kidney disease. Palliat Med Pract 2022; 16(3): 156–166; DOI: 10.5603/PMPI.2022.0010

Abstract

Patients suffering from chronic kidney disease (CKD) are a special group of patients, especially those with advanced renal failure/end-stage renal disease (ESRD) before dialysis and renal replacement therapy (RRT). CKD causes many therapeutic problems. The pharmacokinetics of drugs used, including opioid analgesics, is influenced by the degree of kidney damage and, ultimately, by RRT. The choice of opioid analgesic is crucial to ensure an optimal analgesic effect in relation to possible side effects. For dialysis patients, several important factors must additionally be taken into account, such as molecular weight of a drug, water solubility and volume of distribution. In the management of chronic pain in ESRD patients and dialysis patients, there are in practice limitations in terms of the use of lipophilic drugs. The drugs of choice seem to be opioids administered via transdermal route, such as buprenorphine and fentanyl, and in the next line of treatment — methadone for opioid rotation.

On the other hand, opioid antagonists that were previously used only in the case of opioid overdose are currently being used in the treatment of opioid-induced bowel dysfunction, especially in opioid-induced constipation.

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Table 1. Properties of selected opioids [2, 3, 6–10]

	Volume of distribution (L/kg)	Degree of binding to proteins (%)	Water solubility (mg/mL)	Molecular weight (Da)
Codeine phosphate	According to the source: 2.6 or 3–6	7–10	0.57	406.4
Tramadol hydrochloride	According to the source: 3 or 2.6–2.9	20	0.75	299.8
Morphine sulphate	According to the source: 3.2 or 3–5	20–35	10.2	758.8
Fentanyl citrate	4	80–85	0.024	336.5
Remifentanil hydrochloride	0.35	70	0.591	412.9
Alfentanil hydrochloride	0.4–1	92	0.252	453
Sufentanil	2.5–3	91–93%	0.012	386.5
Oxycodone hydrochloride	According to the source: 2.6 or 1.2–6.31	45	5.59	405.9
Buprenorphine	According to the source: 2.5–8.3	96	0.0168	467.6
Methadone hydrochloride	According to the source: 3.8 or 3–6	According to the source: 89 or 69–90	0.0059	309.5
Tapentadol hydrochloride	6.7	20	0.78	221.3

Introduction

The pharmacokinetics of drugs is affected by both renal failure and RRT. Patients with renal failure most commonly show decreased binding of drugs to proteins, impaired activity of certain drug-metabolising enzymes and transporters [1]. The molecular weight of a drug, its water solubility and volume of distribution are extremely important factors in the course of RRT. Also important is the degree of binding to proteins, which can be impaired in uremia [2]. For opioids that bind highly to proteins, changes in plasma protein levels significantly affect the unbound fraction of opioids, which can increase significantly in the case of opioids (e.g. alfentanil) that bind to the acute phase protein alpha-1-acid glycoprotein during inflammation, infection, cancer and pregnancy [3]. The basic principles of pharmacotherapy and changes in pharmacokinetics of drugs in this patient group are discussed in another article [4].

Basic principles of dialysis:

1. The lower the molecular weight of a drug, the more likely its molecule will pass through the filter of a RRT device.
2. The greater the degree of binding to proteins, the less likely the drug will be removed in significant amounts.
3. The greater the water solubility, the more likely the drug will be removed during dialysis.
4. The higher the volume of distribution, the less the drug is removed per unit time [2].

The low molecular weight, good water solubility and low volume of distribution favour drug release during dialysis [1]. More commonly, however, there are differences in terms of the process of elimination, with a consequent increase in plasma drug concentrations, which results in an increased risk of side effects [1]. The removal of a drug from plasma is the sum of its renal and extra-renal excretion. Consequently, if such a drug is not predominantly excreted by the kidneys, RRT will have little effect on the removal of the drug from the body [2]. Given the technical aspect of dialysis, drug elimination depends on the dialysis efficiency, which is a product of the surface area of the dialysis membrane and its permeability, the flow rate of blood and dialysis fluid, and the technique used [2]. The elimination of drugs during peritoneal dialysis is much poorer compared to haemodialysis, which is due to the low dialysis flow rate. In patients undergoing peritoneal dialysis, the clearance rates of drugs used are constant and the timing of subsequent doses does not play a significant role [5].

The properties of opioids should be interpreted according to the patient's clinical status (Table 1). For example, a patient with advanced cancer, in addition to liver failure or kidney failure, may suffer from abdominal dropsy and/or massive peripheral oedema, resulting in a change in the volume of distribution of hydrophilic drugs and the need to modify the dose size and frequency of drug administration. Hypoalbuminaemia causes an increased unbound fraction of some drugs [11]. An extremely different group such

as critically ill patients in the intensive care unit (ICU) will manifest similar problems. A patient in septic shock can be expected to have impaired organ perfusion, low albumin levels, endothelial dysfunction, the need for fluid resuscitation or catecholamines, which ultimately increases the volume of distribution of some drugs and increases their clearance. Moreover, increased elimination of hydrophilic drugs, especially in patients with hypoalbuminaemia, is to be expected in patients on continuous RRT as a result of increased unbound fraction of the drug.

Codeine

Codeine is not eliminated from the body during peritoneal dialysis or haemodialysis. Codeine, as a parent drug, does not show a therapeutic effect but, paradoxically, can cause side effects. During haemodialysis, active metabolites of morphine are eliminated, which may worsen the analgesic effect during dialysis [12]. Some sources recommend that codeine be avoided in CKD patients and dialysis patients due to the risk of metabolite accumulation [2, 9, 13]. Metabolism of codeine is dependent on the cytochrome P450 2D6 isoenzyme, which may consequently lead to further therapeutic complications, especially for slow and ultrarapid CYP2D6 metabolisers.

Dihydrocodeine

No data are available on the effect of peritoneal dialysis and haemodialysis on serum drug levels [12].

Tramadol

This drug is eliminated from the body during haemodialysis [12]. In dialysis patients, after the initial loading dose, the daily oral dose should be gradually adjusted to the optimal dose (usually up to 50 mg twice daily). The maximum dose in dialysis patients is 100 mg twice daily. Controlled release products should be avoided [13]. There is no information on the effect of peritoneal dialysis on blood levels of tramadol and metabolites [12].

Morphine

Both morphine and its metabolites are removed during dialysis, whereas they are not removed during peritoneal dialysis. If a patient suffers from ascites in the course of cancer or cirrhosis, this does not represent contraindication to the use of morphine [14]. An additional dose of morphine may be necessary during or after dialysis. The use of morphine is not a preferable choice for the treatment of pain in dialysis patients. It is therefore best to avoid it, due in part to changes in the drug's steady-state concentration (Css), which can consequently cause unstable analgesia [2]. Morphine should be administered with extreme caution and the patient should be monitored — although morphine and metabolites are removed during dialysis, there is a risk of metabolite accumulation between dialyses [15].

Oxycodone

Oxycodone shows a significant volume of distribution and is completely soluble in water. Its physicochemical properties indicate that it may be removed to some extent during dialysis. However, due to insufficient data, it is recommended that this drug be avoided in dialysis patients [2, 14–16]. Oxycodone reaches peripheral and central equilibrium in a short time, which is related to the rapid penetration of this drug through the blood-brain barrier (BBB) (11 minutes) [17]. More recent data indicate that both oxycodone and its metabolites are completely removed during haemodialysis [9, 12].

Fentanyl

Fentanyl binds to a significant extent to proteins, has low water solubility, a significant volume of distribution and a moderately high molecular weight [2]. Fentanyl is not easily removed during therapy and thus does not usually require additional doses. It may deposit, however on the surface of some types of filters [2]. In such a situation, the filter should be changed immediately or, when this is not possible, fentanyl should be replaced with methadone. Fentanyl is slightly affected by haemodialysis [12].

Buprenorphine

The use of buprenorphine does not need dose modification in patients with renal failure or dialysis patients. The use of buprenorphine in transdermal systems (TTS) up to a dose of 70 μg/h did not result in accumulation of this drug and its metabolites, nor symptoms of toxicity, while leaving analgesia intact [18, 19].

Methadone

Methadone is lipophilic, binds well to plasma proteins and shows a significant volume of distribution. Less than 1% of the daily dose is removed during haemodialysis or peritoneal dialysis. Dialysis should not

significantly affect serum methadone levels, so that there is no need for additional doses during or after RRT [2, 14]. However, in this patient group, it should be noted that the potential pharmacokinetic interactions of methadone with CYP3A4 inhibitors, which in practice can significantly alter the methadone profile, especially when CYP3A4 is eliminated by the kidneys.

Tapentadol

There is no data concerning the effect of haemodialysis on serum tapentadol levels. There is a possibility that tapentadol is highly dialysable due to its low molecular weight, low binding to proteins and moderate water solubility [9].

The use of opioid analgesics in the course of RRT is presented in Table 2.

Opioid receptor antagonists

The use of opioid drugs predisposes to gastrointestinal side effects (nausea, emesis, constipation) and other symptoms such as dizziness, drowsiness, urinary retention, dry mouth, risk of respiratory depression [9]. Opioid-induced constipation, the most common side effect of opioids, affects patients with chronic non-cancer pain (60%) and cancer patients (85%) [9, 21, 22]. Opioid analgesics inhibit propulsive peristalsis and secretory functions of the gastrointestinal tract by acting on μ-, κ- and δ-opioid receptors in the myenteric and submucosal plexuses of the small and large intestine, modulating opioid receptor function at the level of the spinal cord [23, 24].

The effects of opioids can be abolished by opioid receptor antagonists [6], which include classical antagonists — such as naloxone and naltrexone — and peripherally acting μ-opioid receptor antagonists (PAMORAs). The latter group includes N-methylnaltrexone, naloxegol, alvimopan and naldemedine [25]. PAMORAs are modified derivatives of naloxone or naltrexone, whose molecules have lost their ability to penetrate the BBB, blocking opioid receptors in the gastrointestinal tract without impairing analgesia [26, 27].

Naloxone

Naloxone is a derivative of oxymorphone, a competent, non-selective antagonist out of all three opioid receptors. It has the highest affinity for μ-receptors [6]. Due to its very high affinity for opioid receptors, naloxone displaces both opioid agonists and partial antagonists [28]. Naloxone reverses central and peripheral effects of opioids as well as abolishes the analgesic effect, the depressive effect of opioids on the respiratory center and the sedative effect [13]. It can be administered parenterally or orally in a controlled release product in combination with oxycodone. It is also used in the treatment of alcohol dependence [29].

Naloxone has significant lipophilicity and is rapidly distributed to tissues and fluids, particularly the brain, following parenteral administration. After its oral administration, naloxone is 90% absorbed, followed by its almost complete elimination in the liver by glucuronidation. Hence, the bioavailability is approximately 2–3% [30, 31], and the effect of naloxone is almost exclusively limited to the intestines [25]. This drug is excreted in the urine [28].

According to the summary of product characteristics (SmPC), there have been no clinical trials evaluating the safety and efficacy of naloxone in patients with renal impairment. Therefore, caution and close observation are recommended when administering this drug [28]. This drug is not recommended in patients with renal failure and impaired hepatic clearance function (liver failure, post-infection damage and drug-induced damage, during therapy with drugs that induce liver damage). The first pass effect after naloxone administration is then reduced, which may result in reversal of analgesia.

Naltrexone

The binding of naltrexone to receptors, both in the central (CNS) and peripheral nervous system, is competent [32]. Compared to naloxone, naltrexone is several times more potent and longer acting [29]. Naltrexone is effective when administered orally, as it has a small first pass effect [3]. It is metabolised mainly in the liver and eliminated by the kidneys [33]. In Poland, this drug is approved for the adjunctive treatment of opioid-dependent patients and for reduction of the risk of alcohol relapse [34]. According to SmPC, the administration of naltrexone is contraindicated in patients with severe hepatic and/or renal diseases [33].

N-methylnaltrexone

N-methylnaltrexone is a naltrexone derivative, a preferential, non-selective, peripheral μ-opioid receptor antagonist [27]. This drug is used for the treatment of opioid-induced bowel dysfunctions (OIBD) in patients with an inadequate response to laxatives. N-methylnaltrexone does not penetrate the BBB, can reverse the effects of opioids on peripheral receptors, and does not affect the effects of opioids in the central nervous system (CNS) [7]. It undergoes little metabolism and is excreted in the urine and faeces,

Table 2. The use of opioid analgesics in the course of RRT [2, 8, 9, 14, 20]

Drug	Removal during dialysis	Dosage during dialysis				Notes
		CAPD	HD	HDF high flux	CVVHD	
Codeine	No: HD, CVVHD Unlikely: CAPD No data: HDF	As for GFR < 10	As for GFR < 10	As for GFR < 10	As for GFR 10–20	Use with caution, on a short-term basis
Dihydrocodeine	No data: CAPD, HD, HDF, CVVHD	As for GFR < 10	As for GFR < 10	As for GFR < 10	As for GFR 10–20	No data available: use with caution
Tramadol	Yes: HD, HDF, CVVHD No data: CAPD	As for GFR < 10	As for GFR < 10	As for GFR < 10	As for GFR 10–20	An additional dose after haemodialysis may be necessary
Morphine	No: CAPD Yes: HD, HDF, CVVHD	As for GFR < 10	As for GFR < 10	As for GFR < 10	As for GFR 10–20	Use low initial doses, extend intervals between doses
Fentanyl	No: CAPD, HD, HDF, CVVHD	As for GFR < 10	As for GFR < 10	As for GFR < 10	As for GFR 10–20	The removal rate depends on the filter, flow rate and type of dialysis, individual reports indicating that the CT190 filter allows fentanyl to be removed by adsorption onto its surface
Remifentanil	No: HD Unlikely: CAPD, HDF, CVVHD	As in normal kidney function	As in normal kidney function	As in normal kidney function	As in normal kidney function	The half-life of metabolites increases to 30 hours in patients with renal failure, compared to 90 min. in those with normal renal function; 25–35% of metabolites are removed during dialysis
Alfentanil	No: CAPD, HD, CVVHD No data: HDF	As in normal kidney function	As in normal kidney function	As in normal kidney function	As in normal kidney function	No change in dosage is needed
Sufentanil	No data	As in normal kidney function	As in normal kidney function	As in normal kidney function	As in normal kidney function	No change in dosage is needed
Oxycodone	Yes: HD, HDF No data: CAPD, CVVHD	As for GFR < 10	As for GFR < 10	As for GFR < 10	As in normal kidney function	
Buprenorphine	No: CVVHD Yes: CAPD, HD, HDF	As for GFR < 10	As for GFR < 10	As for GFR < 10	As for GFR 10–20	
Methadone	No: CAPD, HD No data: HDF, CVVHD	As for GFR < 10	As for GFR < 10	As for GFR < 10	As in normal kidney function	No additional doses are needed after HD; QT interval monitoring is necessary; increased risk of cardiac arrhythmias due to decreased potassium levels and magnesium levels after HD
Tapentadol	No data	No data	No data	No data	No data	Significantly dialysed

CAPD — continuous ambulatory peritoneal dialysis; CVVHD — continuous veno-venous haemodialysis; GFR — glomerular filtration rate; HD — intermittent haemodialysis; HDF — intermittent hemodiafiltration

mostly unchanged [25]. It is administered subcutaneously in a single dose, every 2 days or at longer intervals as needed. The dose of this drug should be reduced in patients with creatinine clearance < 30 mL/min [25].

According to SmPC, there are no data concerning dialysis patients due to advanced renal failure. Hence, N-methylnaltrexone is not recommended in this patient group [35].

Table 3. Properties of opioid antagonists [9, 26, 28, 33, 35–39]

Drug	Elimination half-life time [hours]	Volume of distribution	Degree of binding to proteins [%]
Naloxone hydrochloride	1–1.5	2 L/kg	32–45
Naltrexone hydrochloride	4	14.2–16.1 L/kg	21
Methylnaltrexone bromide	8	1.1 L/kg	11–15.3
Naloxegol oxalate	6–11	968-2140 L (apparent volume of distribution in the final phase)	4.2 (80–100% unbound fraction)
Naldemedine tosylate	11	155 L (apparent volume of distribution in the final phase)	93.2

Naloxegol

Naloxegol is a derivative of the μ-opioid receptor antagonist — naloxone. Penetration of naloxegol through the BBB into the CNS is 15-fold less than that of naloxone, and it does not affect central analgesia [25]. Naloxegol blocks μ-opioid receptors in the gastrointestinal tract without affecting opioid receptors in the brain, thereby reducing opioid-induced constipation [29]. It is administered orally and is metabolised by CYP3A4 enzyme to six metabolites that are mainly excreted in the faeces (68%) and urine (16%) [25, 27]. Pharmacokinetic interactions with CYP3A4 inhibitors are possible, especially when they are eliminated by the kidneys and their pharmacokinetics may be significantly altered in patients with renal failure.

In patients with moderate to severe renal failure, naloxegol was well tolerated at a single dose of 25 mg; however, the initial dose in these patients is 12.5 mg [9]. According to SmPC, no dose adjustment of naloxegol is necessary in patients with mild renal failure, whereas the initial dose of this drug in patients with moderate to severe renal failure is 12.5 mg [36]. In haemodialysis patients with ESRD, exposure to naloxegol was similar to healthy volunteers with normal renal function [36]. Due to its low molecular weight, this drug is effectively removed during haemodialysis [9].

Alvimopan

Alvimopan is a μ-receptor antagonist that is approved in the United States for the short-term treatment of patients with postoperative intestinal obstruction [26, 27].

Naldemedine

Naldemedine is a naltrexone derivative, an antagonist of μ-, κ-, δ-opioid receptors [22, 23, 27, 37]. Its penetration into the CNS is negligible [26, 27]. This drug, which is metabolised mainly by CYP3A4 to naldemedine, undergoes significantly less coupling to glucuronic acid [26]. Naldemedine is rapidly absorbed from the gastrointestinal tract, 57% is excreted in the urine and 35% in the faeces [25].

The excretion of naldemedine in patients with renal impairment, including ESRD patients who need haemodialysis, is not affected and the pharmacokinetics is similar to that in individuals with normal renal function, in whom 16–18% is excreted unchanged in the urine. Naldemedine is eliminated to a small extent (2.7%) during haemodialysis [26]. Plasma concentrations of this drug in ESRD patients who need dialysis are similar following naldemedine administration before or after haemodialysis, indicating that naldemedine is not removed during haemodialysis [37]. Unlike other PAMORAs, naldemedine does not require dose adjustment in CKD patients and haemodialysis patients [9]. Nevertheless, clinical observation should be made when initiating naldemedine treatment in patients with severe renal impairment, due to limited experience in treating this patient group [37]. Patients with uraemia in the course of CKD may have lower expression of CYP3A4 — the main enzyme involved in PAMORA metabolism [9].

Properties of opioid antagonists and the use of them in CKD patients are summarized in Table 3 and Table 4.

Patient in the ICU *vs.* patient with advanced disease

Effective treatment of the underlying pain in haemodialysis patients is important, and lipophilic drugs (buprenorphine or fentanyl in TTS or methadone as a further choice, under the supervision of a specialist in palliative medicine or pain management) should be used as an option. The overriding aim is to achieve satisfactory analgesia during and after haemodialysis, which ensures patient comfort and preserves regular RRT [9].

If hydrophilic drugs are used, there is a risk of pain during or after haemodialysis. If there is a need for

Table 4. The use of opioid antagonists in CKD patients [8, 9, 28, 33, 35–37]

Drug	Dosage in the general population	Dosage in CKD patients	Dosage in haemodialysis patients
Naloxone	In the case of opioid overdose, 0.4–2 mg intravenously, every 2–3 min	According to the source: • Irrespective of GFR level 100% dose • No studies, use caution	No data available, dose as in normal GFR function
Naltrexone	25–50 mg per os	No data available, this drug should be contraindicated in patients with severe renal disease	No data
Methylnaltrexone	8 mg (38–61 kg) 12 mg (62–114 kg) 0.15 mg/kg (> 114 kg) subcutaneously	Dose reduction needed in patients with moderate or severe renal failure (GFR < 30 mL/kg): 4 mg (≤ 61 kg), 8 mg (62–114 kg)	Not recommended due to lack of data
Naloxegol	25 mg/day per os	Dose reduction needed in patients with moderate or severe renal failure; initial dose of 12.5 mg	Removed during haemodialysis
Naldemedine	200 μg/day per os	No dosage changes are needed in CKD and ESRD patients	It is not removed during haemodialysis, no change in dosage is needed

CKD — chronic kidney disease; GFR — glomerular filtration rate

morphine, analgesia is sometimes impaired during or after haemodialysis. In this situation, and when episodic pain occurs, patients need short-acting morphine via the oral route (in the form of an aqueous solution or immediate-release tablets, or alternatively via the subcutaneous route, 50% less dose than that administered via the oral route). Moreover, the administered dose of this drug should be taken into account before the next scheduled dose (according to the "clock" rule), which should be rescheduled, thus avoiding toxicity induced by subsequent doses of morphine [14, 40].

When drugs are administered intravenously, e.g. in patients with acute stage of disease, emergency patients and patients treated in the ICU, optimal drug selection is essential. In a patient with stable CKD, hydrophilic drugs via the parenteral route (morphine, oxycodone) may be considered when glomerular filtration rate (GFR) > 30 mL/min. On the other hand, with a decrease in GFR < 30 mL/min, the lipophilic drug of choice, fentanyl, should be considered unless there are contraindications and limitations due to comorbidities. Fentanyl, however, is ineffective in the treatment of neuropathic pain. In emergencies, the use of TTS is not recommended due to the long time to achieve an analgesic effect (12–24 h after patch application). This is possible after evaluation of demand for opioids, during a stability period of the patient's clinical status. The use of a lipophilic drug (buprenorphine, fentanyl) may then be considered, taking into account the time required to achieve the effect (together with continuation of the current treatment for at least further 12 h). In addition to renal failure, other factors modify the pharmacokinetic profile of opioid analgesics in patients hospitalised in the ICU (Table 5).

Summary

Advanced renal failure is a challenging situation for both the patient and the treatment team. Pharmacotherapy should take into account the therapeutic possibilities of individual drugs and their optimal dosage. Treatment should be individualised, considering the patients' needs and preferences regarding the route of administration of a drug. A favourable choice for patients with renal failure before and during dialysis is the use of lipophilic drugs via the transdermal route (buprenorphine, fentanyl), which can be a convenient and simple form of treatment for the patient and their carers. The above-mentioned drugs are first-choice drugs, especially in elderly patients with signs of dementia and in patients who do not adhere to recommendations regarding the regular use of drugs. Methadone is distinguished by its opioid and non-opioid mechanisms of analgesic effect, so it can provide effective analgesia in terms of a variety of pain types, including those with a neuropathic component. Methadone may be useful for rapid escalation of doses of other opioids, hyperalgesia (in addition to buprenorphine) or in cases of hypersensitivity/allergic reactions to the adhesive contained in TTS.

Declaration of conflict of interests

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Table 5. The most important factors that modify the pharmacokinetic profile of opioid analgesics in patients hospitalised in the ICU [41]

Factor modifying the pharmacokinetics of analgesics in patients with renal failure	Effects on the pharmacokinetic profile of analgesics, therapeutic conclusions
Patient with sepsis — the third-space effect	There is an increase in the volume of distribution (V_d), which may require dose adjustments of hydrophilic analgesics
Augmented renal clearance	Clearance parameters may be changed, which often necessitates an adjustment of the dosage interval for drugs used
Pharmacotherapy — furosemide in fractionated doses	This drug is distinguished by a "wave effect", which in practice means that it rapidly achieves a maximum serum concentration and there is then a rapid decrease in the concentration resulting from the pharmacokinetic profile of furosemide; furosemide may alter the clearance of opioid analgesics, particularly those that are eliminated by kidneys
Pharmacotherapy — pressor amines, particularly agonists of vascular alpha-1 receptors, acting to a lesser extent via vasopressin receptors	Centralisation of the circulation may induce an increase in the distributional loss of opioid analgesics, which may directly affect instability of analgesia
Pharmacotherapy — linezolid	Should not be combined with fentanyl and methadone due to the possibility of cumulative serotonergic effect
Other methods of extracorporeal elimination	
Abdominal dropsy	

References

1. Porażka J, Karbownik A, Szałek E, et al. Zmiany w farmakokinetyce analgetyków u pacjentów z niewydolnością nerek. Farm Współcz. 2015; 8: 1–9.
2. 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.
3. Smith T, Pinnock C, Lin T. Podstawy anestezjologii. Wydanie III. DB Publishing, Warszawa 2012: 584–608.
4. Sołtysik A, Graczyk M, Woroń J. Use of opioid analgesics in chronic kidney disease. Palliat Med Pract. 2022; 16(3): 156–166, doi: 10.5603/PMPI.2022.0010.
5. Russon L, Mooney A. Palliative and end-of-life care in advanced renal failure. Clin Med (Lond). 2010; 10(3): 279–281, doi: 10.7861/clinmedicine.10-3-279, indexed in Pubmed: 20726463.
6. Larsen R. Anestezjologia. Tom 1. Edra Urban & Partner, Wrocław 2020: 9-16, 65-82.
7. Miller RD. Miller's Anesthesia. Seventh Edition, Vol. 1. Churchill Livingstone, Philadelphia 2010: 769–824.
8. Ashley C, Currie A. The Renal Drug Handbook. Third Edition. Radcliffe Publishing Ltd, Abingdon 2009.
9. 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.
10. Drug Bank Online. https://go.drugbank.com/drugs (7.04.2022).
11. Woroń J. Farmakoterapia u kresu życia. Onkologia po Dyplomie. 2019(4).
12. Ciałkowska-Rysz A, Dzierżanowski T. Medycyna paliatywna. Termedia, Poznań 2019: 06–120, 253–261, 420–430.
13. Smyth B, Jones C, Saunders J. Prescribing for patients on dialysis. Aust Prescr. 2016; 39(1): 21–24, doi: 10.18773/austprescr.2016.008, indexed in Pubmed: 27041803.
14. 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.
15. 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.
16. Wordliczek J, Dobrogowski J. Leczenie bólu. Wydanie III. PZWL, Warszawa 2017: 54–83, 629–633, 641–693.
17. Lötsch J, Dudziak R, Freynhagen R, et al. Fatal respiratory depression after multiple intravenous morphine injections. Clin Pharmacokinet. 2006; 45(11): 1051–1060, doi: 10.2165/00003088-200645110-00001, indexed in Pubmed: 17048971.
18. Filitz J, Griessinger N, Sittl R, et al. Effects of intermittent hemodialysis on buprenorphine and norbuprenorphine plasma concentrations in chronic pain patients treated with transdermal buprenorphine. Eur J Pain. 2006; 10(8): 743–748, doi: 10.1016/j.ejpain.2005.12.001, indexed in Pubmed: 16426877.
19. Böger RH. Renal impairment: a challenge for opioid treatment? The role of buprenorphine. Palliat Med. 2006; 20 Suppl 1: s17–s23, indexed in Pubmed: 16764217.
20. Lizakowski S. Leki w przewlekłej chorobie nerek. Serwis Edukacyjny Polskiego Towarzystwa Nefrologicznego.
21. Webster LR, Hale ME, Yamada T, et al. A renal impairment subgroup analysis of the safety and efficacy of naldemedine for the treatment of opioid-induced constipation in patients with chronic non-cancer pain receiving opioid therapy. J Pain Res. 2020; 13: 605–612, doi: 10.2147/JPR.S237833, indexed in Pubmed: 32280263.
22. Coluzzi F, Scerpa MS, Pergolizzi J. Naldemedine: a new option for OPID. J Pain Res. 2020; 13: 1209–1222.
23. Woroń J, Wordliczek J. Opioid-induced gastrointestinal side effects, the roleof naldemedine in their therapy. Ból. 2020; 21(2): 54–58, doi: 10.5604/01.3001.0014.5100.
24. Galligan JJ, Sternini C. Insights into the role of opioid receptors in the GI tract: experimental evidence and therapeutic relevance. Handb Exp Pharmacol. 2017; 239: 363–378, doi: 10.1007/164_2016_116, indexed in Pubmed: 28204957.
25. Dzierżanowski T. The role of peripherally acting mu-opioid receptor antagonists (PAMORA) in the treatment of constipation in palliative care. Palliative Medicine. 2019; 11(2): 51–57, doi: 10.5114/pm.2019.86528.

26. Dzierżanowski T. The role of naldemedine in the treatment of opioid-induced constipation. Palliative Medicine. 2020; 12(4): 167–173, doi: 10.5114/pm.2020.101700.
27. Leppert W. Rola naldemedyny w leczeniu zaparcia stolca wywołanego opioidami. Palliat Med Pract. 2019; 13(4): 237–247.
28. Naloxonum Hydrochloricum WZF 400 μ/ml. Roztwór do wstrzykiwań. Charakterystyka Produktu Leczniczego.
29. Malec–Milewska M, Woroń J. Kompendium leczenia bólu. Wydanie III. Medical Education, Warszawa 2017: 43–66, 577–588.
30. Meissner W, Schmidt U, Hartmann M, et al. Oral naloxone reverses opioid-associated constipation. Pain. 2000; 84(1): 105–109, doi: 10.1016/S0304-3959(99)00185-2, indexed in Pubmed: 10601678.
31. Smith K, Hopp M, Mundin G, et al. Single- and multiple-dose pharmacokinetic evaluation of oxycodone and naloxone in an opioid agonist/antagonist prolonged-release combination in healthy adult volunteers. Clin Ther. 2008; 30(11): 2051–2068, doi: 10.1016/j.clinthera.2008.11.008, indexed in Pubmed: 19108793.
32. Skrzypacz M. Niskie dawki naltreksonu jako lek przeciwbólowy w terapii zesztywniającego zapalenia stawów kręgosłupa (ZZSK) – opis przypadku. Ból. 2018; 29(2): 47–50.
33. Adepend 50 mg. Tabletki powlekane. Charakterystyka produktu leczniczego.
34. Mundzik-Janczarska E, Stańczak A. Terapia naltreksonem w niskiej dawce – skuteczność i bezpieczeństwo terapii stosowanej poza wskazaniami. Farm Klin. 2019; 75(12): 676–686, doi: 10.32383/farmpol/116846.
35. Relistor 12 mg/0,6ml. Roztwór do infuzji. Charakterystyka produktu leczniczego.
36. Moventig 12,5 mg. Tabletki powlekane. Charakterystyka produktu leczniczego.
37. Rizmoic 200 μg. Tabletki powlekane. Charakterystyka produktu leczniczego.
38. Gonzalez J, Brogden R. Naltrexone. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. Drugs. 1988; 35(3): 192–213, doi: 10.2165/00003495-198835030-00002.
39. Garnock-Jones KP. Naloxegol: a review of its use in patients with opioid-induced constipation. Drugs. 2015; 75(4): 419–425, doi: 10.1007/s40265-015-0357-2, indexed in Pubmed: 25666542.
40. Broadbent A, Khor K, Heaney A. Palliation and chronic renal failure: opioid and other palliative medications — dosage guidelines. Progress in Palliative Care. 2013; 11(4): 183–190, doi: 10.1179/096992603225002627.
41. Woroń J, Kutaj–Wąsikowska H, Drygalski T, et al. Bezpieczeństwo farmakoterapii w Oddziale Intensywnej Terapii, jak to realizować w praktyce. Anestezjologia i Ratownictwo. 2001; 15: 199–203.