Diplomarbeit

Schmerztherapie bei Nierenversagen

Der Einsatz des WHO Stufenschemas bei Nierenversagen

eingereicht von

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Zusammenfassung

Niereninsuffiziente Patienten bedürfen häufig einer adäquaten Schmerztherapie. Die Wahl der passenden Medikamentendosierung bei diesen Patienten ist meist eine schwierige Aufgabe. Die folgenden Empfehlungen wurden anlehnend an das WHO-Stufenschema geschaffen, um die Grundlage einer sicheren medikamentösen Schmerztherapie zu gewährleisten und Arzneimittelnebenwirkungen zu vermeiden. Dazu wurde die vorhandene Literatur auf pharmakokinetische und pharmakodynamische Eigenschaften diverser Analgetika und Co-Analgetika in Bezug auf Nierenversagen untersucht.

Paracetamol, Buprenorphin, Remifentanil, Lamotrigin, Carbamazepin, Ketamin und Kortikosteroide sind vorrangig zu empfehlen. Diese Medikamente scheinen unter Standarddosierungen bei Niereninsuffizienz gefahrlos anwendbar.

Vorsicht, Dosisanpassung und Überwachung des Patienten sind bei Tramadol, Metamizol, Fentanyl, Hydromorphon, Oxycodon, Methadon, Gabapentin, Pregabalin, Amitriptylin und Nortriptylin geboten.

Sufentanil scheint bei Nierenversagen sicher anwendbar, diesbezüglich ist derzeit jedoch nur wenig Evidenz verfügbar.

Definitiv vermeiden sollte man Nicht-steroidale Antirheumatika, COX-2-Hemmer, Codein, Dihydrocodein und Morphin, da deren Anwendung bei eingeschränkter Nierenfunktion schwerwiegende Komplikationen mit sich bringen kann.

Aufgrund fehlender Daten bezüglich Duloxetin, Oxcarbazepin, Topiramat und Bisphosphonaten wird deren Anwendung derzeit nicht empfohlen. Diesbezüglich werden noch weitere Forschungsarbeiten benötigt.

Zusammenfassend sind Daten über Schmerztherapie bei Nierenversagen unzureichend vorhanden, weshalb die gebotenen Empfehlungen im Einzelfall durch individuelle Anpassungen an den Patienten ergänzt werden sollen.

Abstract

Adequate pain treatment is a frequent necessity in renally impaired patients. It is accompanied by the challenging problem of dose modification. Hence, this guidance has been created in reference to the WHO-pain relief ladder to provide basic knowledge for safe analgesic use and the avoidance of adverse effects. For that purpose, the existing literature concerning pharmacokinetics and pharmacodynamics of several analgesics and co-analgesics pertaining to renal failure has been reviewed.

Paracetamol, buprenorphine, remifentanil, lamotrigine, carbamazepine, ketamine and corticosteroids are primarily recommended. Their use seems to be safe in renally impaired patients at standard doses.

Substances like tramadol, metamizole, fentanyl, hydromorphone, oxycodone, methadone, gabapentin, pregabalin, amitriptyline and nortriptyline may be given cautiously, if dose adjustments are made and close patient monitoring is ensured.

Sufentanil appears to be safe in renal impairment, although there is currently only little data available.

NSAIDs, COX-2-inhibitors, codeine, dihydrocodeine and morphine must be avoided due to the risk of severe adverse-effects.

Due to the lack of data it is suggested, that duloxetine, oxcarbazepine, topiramate and bisphosphonates are best to be avoided. In this regard, further research needs to be made.

Summing up, the existing data is often insufficient and therefore, the following recommendations should always be individually adjusted according to the patients' needs.

List of abbreviations

AM404	N-(4-hydroxyphenyl)arachidonoylethanolamide
AUC	area under the curve
B3G	buprenorphine-3-glucuronide
bid	two divided doses
BN	buprenorphine
C6G	codeine-6-glucuronide
CKD	chronic kidney disease
CNS	central nervous system
COX	cyclooxygenase
CRCL	creatinine-clearance
EDDP	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine
eGFR	estimated glomerular filtration rate
ESRD	end-stage-renal-disease
GABA	gamma-aminobutyric acid
GFR	glomerular filtration rate
H3G	hydromorphone-3-glucuronide
HD	haemodialysis
HM	hydromorphone
i.v.	intravenously
M1	O-demethyl-tramadol
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide
MHD	10,11-dihydro-10-hydroxycarbamazepine
MAAP	4-methylaminoantipyrine
NBN	norbuprenorphine
NMDA	N-methyl D-aspartate
p.o.	orally
qd	single daily dose
tid	three divided doses

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Introduction

Preface

„Pain is inevitable, suffering is optional.“, is postulated by an unknown author. Nowadays state of the art medical treatment requires the best pain treatment possible. Pain is always subjective (1) and pain medication shows broad inter-patient variability in effects and thus needs to be individually adjusted.

Renal failure has a great influence on the pharmacokinetics and pharmacodynamics of several analgesic substances. Consequently, adaptations need to be made to achieve adequate pain therapy in patients with renal insufficiency and to avoid potentially fatal complications. It is important for the pain treating physician to have a clear overview of the usability of painkillers in such patients. The following narrative review has been accomplished in order to give clinicians and general practitioners summarized recommendations towards a practicable pain therapy in the situation of renal impairment.

Definition of Pain

Pain is defined as „an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” (1) Hence, the sensation of pain is a subjective matter, that only occurs within our consciousness and that each of us experiences differently (2).

Pain can be diverse in its duration, its intensity as well as in its character. Pain rating scales are the most objective methods to evaluate the degree of pain intensity. In the last years, there has been a dramatic increase in the use of pain rating scales, especially the visual analogue scale (VAS) (3). Concerning pain-character, there are two major types of pain, which are differently experienced and derive either from the tissue (nociceptive pain) or from neural structures (neuropathic pain). Distinguishing between these types is essential for the process of diagnosis, as well as finding the appropriate therapeutic treatment.

WHO's pain ladder

To provide a practical model for the treatment of cancer-pain, the WHO developed a three-step ladder (figure 1), that was firstly made public in 1986 and revised in 1996. It turned out to be an easily applicable model for the treatment of non-cancer-pain . In the first stage mild to moderate pain is treated with non-opioid analgesics like NSAIDs, metamizole or paracetamol. If the pain still persists or aggravates, second step analgesics, like codeine or tramadol are applied. In the case of further inadequate analgesia, strong opioids (such as morphine) can be initiated. The combination of strong and weak opioids is obsolete, but due to the different mechanisms of action, opioids can be well combined with non-opioid drugs. Special adjuvant drugs, so called co-analgesics, can be given additionally in each stage for the treatment of chronic pain in order to reduce opioid dosage and enhance analgesia.

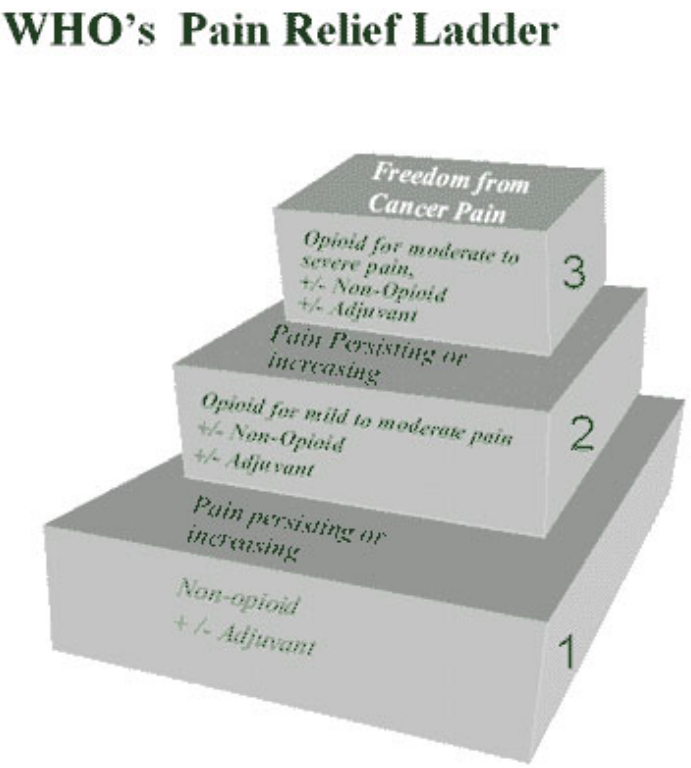

figure 1 WHO's Three Step Pain Relief Ladder (4)

Complementary, further psychological or physiotherapeutical activities (e.g. Transcutaneaous electrical nerve stimulation=TENS, psychotherapy, spinal-cord-stimulation, biofeedback and physiotherapy) can be used to achieve enhanced pain relief.

In order to maintain a painless state, analgesics should be given “by mouth”, or in some cases transdermally to achieve a smoother blood concentration curve and onset of action. Analgesics should be given “by the clock”, preferably rather every three to six hours, than on demand (5) and “by the ladder”. Barakzoy and Moss found the WHO three-step analgesic ladder to effectively relieve pain in renally impaired patients, undergoing haemodialysis (HD) (6).

Renal failure

Renal failure describes a medical state, in which the kidneys are unable to filter toxins and waste products sufficiently from the blood. The National Kidney Foundation defines kidney failure as “either a level of GFR to <15mL/min/1.73 m², which is accompanied in most cases by signs and symptoms of uremia, or a need for initiation of kidney replacement therapy (dialysis or transplantation) for treatment for complications of decreased GFR, which would otherwise increase the risk of mortality and morbidity” (7).

Renal impairment by chronic kidney disease and the decline in renal function due to increasing age are important issues in pain management (8). Recent literature has demonstrated that the prevalence of pain is much higher among chronic kidney disease (CKD) patients compared with healthy subjects (9-10). Pain was found in over 70% of pre-end-stage-renal-disease (pre-ESRD) patients. This is particularly concerning, because pain in the CKD population is associated with poor quality of life (9). Chronic pain in CKD is typically classified as moderate to severe in the degree of severity and it is often undertreated (10).

Depending on the stage of renal impairment, the reduced function can affect the elimination of analgesics causing changes in absorption, distribution, protein binding, renal excretion and non-renal clearance. Hence, blood levels of the parent drugs or their metabolites can be augmented with increasing risk of adverse effects, if toxic concentrations are reached (11). The renal function represents one of the most important

factors influencing a patient's susceptibility to the adverse effects of opioids and other analgesic drugs. Some analgesics like NSAIDs, if used in the case of renal insufficiency, may also aggravate pre-existing renal disease (11). Thus, the kidney function should be assessed before beginning a medicamentous analgesic treatment. The following parameters can be used to evaluate kidney function: serum creatinine, glomerular filtration rate (GFR)≙creatinine clearance and estimated glomerular filtration rate (eGFR). However, secrum creatinine is not an optimal and sensible marker in the clinical practice. GFR in healthy subjects is considered to be in the range of 90-130mL/min/1.73 m² (12). Creatinine clearance can be overestimated due to increased tubular secretion of creatinine, as glomerular filtration rate falls (8). Therefore, the eGFR seems to be the most reliable parameter of kidney function (except in acute renal failure) and can be calculated using the Cockroft-Gault- and MDRD-formula (8). J.P. Koonman found a good correlation between results of the MDRD equation and the gold standard method of inuline clearance (12).

Stage	eGFR
1	> 90mL/min
2	60 – 89mL/min
3	30-59mL/min
4	15-29mL/min
5	<15mL/min

Table 1 Stages of Renal Impairment (1)

Haemodialysis

Dialysis is generally started at stage 5 of renal impairment with glomerular filtration rates below 15mL/min/1.73 m² (12). Patients who are managed with haemodialysis require special adjustments concerning the administration of analgesic drugs. Balie et al. found analgesics more likely to be underprescribed in haemodialysis patients (13).

The degree of extraction of a certain substance during haemodialysis depends on several factors, such as molecular weight, plasma protein binding, volume of distribution, but also the special type and size of filters used. However, these parameters cannot predict dialyzability of drugs reliably (14). Therefore, studies examining the effects of haemodialysis on analgesic substances need to be made. Depending on the medication applied, haemodialysis can reduce the blood concentration and additional dose adjustments may be necessary after the dialysis process. At present, there exists a considerable lack of evidence concerning analgesics and their use in haemodialysis patients.

Material and Methods

Due to the scattered evidence concerning analgesia in renal failure the following narrative review was accomplished. The aim was to summarize the existing evidence in order to give a practicable overview over the mostly applied pain medications.

Fundamental knowledge was gathered in textbooks and online articles. Existing evidence was extracted via database-screening from articles in Pubmed, Ovid and Chochrane Library. The specific search terms included: analgesia, analgesics, acetaminophen, acetylsalicylic acid, amitriptyline, anticonvulsants, benzodiazepines, bisphosphonates, buprenorphine, calcitonin, carbamazepine, celecoxib, co-analgesics, codeine, cortisone, COX-inhibitors, dexamethasone, diclofenac, dihydrocodeine, dipyrone, dronabinol, duloxetine, fentanyl, gabapentin, haemodialysis, hydromorphone, ibuprofen, fetamine, kidney failure, lamotrigine, lornoxicam, mefenamic acid, metamizole, methadone, mianserin, mirtazapine, morphine, nortriptyline, NSAIDs, oxcarbazepine, oxycodone, paracetamol, piritramide, prednisolone, pregabalin, remifentanil, renal disease, renal failure, renal impairment, renal insufficiency, SNRIs, sufentanil, topiramate, tramadol, trazodone, tricyclic antidepressants, triptans and valproat.

Insufficient or no data was found concerning the following substances: benzodiazepines, calcitonin, mianserin, mirtazapine, piritramide, trazodone and triptans.

The collected literature was filtered and significant information was extracted and summarized in table form and subsequently processed.

Results

Non-Opioid Analgesics

Non-Opioids	Recommendations	Comments	References
Paracetamol	recommended, no dose adjustment required	step 1 analgesic of first choice, can deteriorate previous CKD	(10-11, 15)
Metamizole	appears safe	more evidence needed	(16-17)
NSAIDs	avoid	negative effects on renal perfusion	(11, 18-19)
COX-2-Inhibitors	avoid	negative effects on renal perfusion	(2, 19-21)

Table 2 Non-Opioid Recommendations in Renal Dysfunction,

green = recommended, orange = more evidence needed, red = avoid

Metamizole

Metamizole (dipyrone) is a prodrug that exerts analgesic, antipyretic, slightly antiphlogistic and spasmolytic effects after its biotransformation. Until now, its exact mechanisms of action are unknown. After oral administration the parent compound is transformed to 4-methylaminoantipyrine (MAAP) in the intestine via non-enzymatic hydrolysis. MAAP is then rapidly and almost completely absorbed (16). After oral administration metamizole is not detectable in the blood. Its clinical effects are mainly exerted by MAAP, which is the primary pharmacologically active metabolite of metamizole. Oxidation of MAAP leads to N-formylaminoantipyrine (FAAP) and demethylation of MAAP results in aminoantipyrine (AAP), which undergoes acetylation to N-acetylaminoantipyrine (AcAAP). None of the metabolites are extensively bound to plasma proteins (16).

MAAP is mainly eliminated via hepatical metabolism. Its renal excretion accounts for about 8% after i.v. administration. All metabolites deriving from MAAP are predominantly excreted by the kidney (16). At dosages over 1500mg, the elimination kinetics of MAAP become dose dependent (17).

In current literature, diverse comments on the influence of renal impairment on the elimination of metamizole have been found. Acute renal failure was shown to have different effects than chronic renal failure. There is a definitive need for further studies and evidence before detailed dosage recommendations can be made. Moreover, no significant data concerning the effects of haemodialysis on metamizole and its metabolites could be found, declaring it a point of focus for further researches. However, if patients with impaired renal function need to be treated with metamizole, it is recommended that the dosage should be titrated regarding the clinical response (16).

Paracetamol

Paracetamol (acetaminophen) exerts analgesia by elevating the pain threshold (2), has antipyretic effects and lacks in anti-inflammatory potential (22). Its mechanism of action still remains unclear, but it is considered to inhibit the COX-enzymes, though to a lesser degree than NSAIDs and COX-2-inhibitors. Furthermore, there is evidence that the active metabolite N-(4-hydroxyphenyl)arachidonoylethanolamide (AM404) acts on the endogenous cannabinoid system and thus exerts analgesic effects (23). Moreover, Paracetamol is described to interact with the serotonergic system, reinforcing descending inhibitory pain pathways (24). Paracetamol is metabolized primarily in the liver into non-toxic products via glucuronidation, sulfation and N-hydroxylation.

In a study on nine patients with chronic renal failure that received a daily dose of 40mg/kg for three days paracetamol plasma concentrations were not altered, but sulphate and glucuronide metabolites substantially accumulated (25). These metabolites are yet nontoxic and inactive and their elevated serum levels seem to be of minor importance. Paracetamol is less likely to induce acute renal failure than NSAIDS or COX-2-inhibitors (11). However one study found, that the exposure to paracetamol in a dose-dependent manner is associated with the deterioration of previously existing CKD (15). Therefore kidney function has to be monitored in such patients.

Literature reports, that paracetamol does not require dose adjustment in the presence of ESRD and therefore it is recommended as the step 1-analgesic of first choice in such patients (10-11).

Non-Steroidal Anti-Inflammatory Drugs

In the case of renal insufficiency, the kidneys depend on local synthesis of vasodilating prostaglandins to maintain renal perfusion (11). Conversely, NSAIDs risk an acute ischemic insult to the kidney by inhibiting these prostaglandins causing vasoconstriction (11, 18). Due to vasoconstriction NSAIDs can reduce the glomerular filtration rate and increase the likelihood of impaired potassium handling and bleeding (11, 19).

Therefore the use of NSAIDs for analgesia should be avoided in the presence of chronic renal failure. In absence of alternatives it is mandatory, that dosages are minimized, hypotension and hypovolaemia are prevented and renal function is strictly monitored (11). Side-effects are most likely to occur within the first few days of NSAID-therapy and therefore follow-up monitoring within days, not weeks is recommended (18). Moreover episodic application of NSAIDs is said to be beneficial in terms of reducing adverse events (19). In order to avoid hypotension, calcium-antagonists should be the preferential agents used in those patients requiring NSAID therapy (19).

COX-2-Inhibitors

COX-2-inhibitors act by inhibiting the prostaglandin synthesis, primarily via inhibition of cycloocygenase-2 (COX-2) without inhibiting the cyclooxygenase-1 (COX-1) isoenzyme at therapeutic concentrations (2). They were found to have the same effects on renal perfusion as NSAIDs due to the reduction in prostaglandin levels and consequently in renal blood flow. This may lead to secondary renal decompensation (2, 19-21).

Celecoxib is a commonly used COX-2-inhibitor. It is highly protein bound within the clinical dose range (97%) and has a very high volume of distribution, suggesting extensive tissue-distribution (2). The parent compound is primarily metabolized in the liver by CYP 450 2C9 to inactive metabolites. Only less than 3% of the unchanged drug can be recovered in the urine and faeces (2). The main metabolite in urine and faeces is the carboxylic acid metabolite.

Celecoxib should be avoided in patients with advanced kidney disease, because of the risk of sodium retention and decreased GFR similar to NSAID-therapy (2, 21).

Opioids

Opioid	Recommendations	Comments	References
Buprenorphine	recommended, no dose adjustment required	-	(8, 11, 26-27)
Remifentanil	recommended, no dose adjustment required	-	(11, 28-31)
Tramadol	recommended, dose adjustment required	avoid modified release preparations or when CRCL<10 mL/min	(2, 11, 26)
Fentanyl	recommended, dose adjustment required in long-term application	uraemia may prolong clearance and requires dosage decrease, safe in acute pain treatment	(8, 11, 26, 30, 32)
Hydromorphone	recommended, dose adjustment and monitoring required	metabolite accumulation may induce neuroexcitation and cognitive impairment	(8, 10-11, 26, 33)
Oxycodone	recommended, monitoring, strict dose and interval adjustment required	avoid sustained release preparations, CNS side effects may appear in case of accumulation	(8, 32, 34-35)
Methadon	recommended, dose adjustment required	wide inter-patient variability of response, should be individually adjusted	(8, 11, 26, 31, 36)
Sufentanil	appears safe	more evidence needed	(8, 32, 37)
Codein Dihydrocodein	avoid	metabolite accumulation may lead to severe adverse effects	(26, 38)
Morphine	avoid	use alternative strong opioids preferably	(8, 11, 32)

Table 3 Opioid Recommendations in Renal Dysfunction

green = recommended, yellow = dose reduction required, orange = more evidence needed, red = avoid

Weak Opioids

Tramadol is a peripherally and centrally acting agent with one third of its activity due to μ-agonism and two thirds due to inhibiting the reuptake of serotonin and norepinephrine in the raphe nucleus (8, 22). Its analgesic potency shows significant benefits in neuropathic pain (39). The oral dose of 50mg tramadol is equianalgesic to 10mg oral morphine (2, 40). Given orally, tramadol is rapidly and extensively absorbed (41) and has a bioavailability of about 75% (2). It is metabolized in the liver by numerous pathways with just one active metabolite, O-demethyl-tramadol (M1) (11).

Ninety percent of the oral dose is excreted via the kidneys and therefore accumulates in renal failure (11, 26). The elimination half-life was found to be 6.3h (±1.4) for tramadol and 7,4h (±1.4) for M1 (2) and can increase up to twofold in patients with renal impairment (26). The total amount of tramadol and M1 removed during a 4h dialysis period was found to be less than 7% (2). Tramadol demonstrated to have epileptogenic potential in ESRD-patients due to drug and metabolite accumulation. Moreover a higher incidence of drowsiness, confusion and lethargy was described (26). One case of a 75-year-old male with chronic renal failure was found, who suffered from respiratory insufficiency after an applied dose of 100mg four times daily. Respiratory depression disappeared following naloxone treatment (42). Care should be taken in combination with other drugs that influence serotonin drug level, because serotonin syndrome might be induced (22).

Tramadol is described to be the least problematic step 2 opioid analgesic for patients with ESRD. However, literature recommends that modified release preparation is best to be avoided (26). In patients with creatinine clearance less than 30mL/min the dosage interval should be increased from 4-6h to 12h (2, 11, 26) and lower dosages with a maximum of 200mg daily should be applied (2, 26). Product manufacturers' literature recommends avoiding where creatinine clearance is less than 10mL/min. Dialysis patients can receive their regular dose on the day of dialysis, as less than 7% is removed during dialysis.

Codeine is a centrally active analgesic acting as a μ-receptor agonist. It is a potent cough-suppressant and has modest analgesic effects. The oral dose of 90-100mg codeine is equianalgesic with 10mg oral morphine (2, 40). After oral application the bioavailability is

around 35% and the duration of action is 4-6h (2). Five to ten percent of the substance is metabolized to morphine (2, 11, 43). 80% of a codeine dose is conjugated with glucuronic acid to codeine-6-glucuronide (C6G), which was found to exert the main clinical activity. Furthermore codeine's analgesic effect does not depend on the formation of morphine (43).

Five to fifteen percent of codeine in the unchanged form, morphine, C6G and multiple active metabolites are renally excreted and therefore accumulate in case of renal impairment (38). Elimination half-life was found to be increased from 4h to 18,69h in renally impaired patients (8). Thus this may lead to severe side-effects such as hypotension, respiratory arrest, profound narcolepsy and constipation (2, 26, 44-45). Patients with ultrarapid CYP2D6 metabolism are endangered by intoxication due to metabolite accumulation, especially when renal function is impaired (46).

Codeine cannot be extensively dialyzed due to its moderately large volume of distribution and molecular weight. Its chronic use leads to accumulation of toxic tissue levels in most HD patients (26, 38). Due to the risk of metabolite-accumulation and serious side-effects, codeine is recommended to be avoided whenever possible (26).

Dihydrocodeine is a prodrug and semisynthetic derivate of codeine, with slightly superior analgesic efficacy. The oral dose of 60mg dihydrocodeine is equianalgesic with 10mg oral morphine (2).

Its metabolism and elimination are similar to codeine and therefore it is recommended to avoid dihydrocodeine in renal failure (26).

Strong Opioids

Fentanyl is a full μ-receptor agonist with an approximately 80-fold analgesic potency of morphine. Fentanyl is commonly used as an adjunct to general anaesthesia (30). Interestingly, the pharmacokinetic properties of fentanyl vary greatly within healthy patients (30). This highly lipid soluble synthetic drug is also available as a transdermal application system. Its steady-state plasma concentration is reached approximately after 12-24h and lasts for about 72h (2, 8). Additionally, the oral transmucosal form of fentanyl citrate allows rapid absorption and is mostly used to control breakthrough pain in cancer patients and as pre-emptive analgesia in painful diagnostic procedures. The systemic bioavailability of the oral-transmucosal form of application lies between 25% (8) and 50% (2) and its plasma-protein binding accounts for about 80-85% (30-32).

The duration of action in this substance is dose dependent. Therefore repeated doses lead to higher plasma concentrations and an increased cumulative half-life. As a consequence, dose reduction of fentanyl in repeated administration is necessary. Following a single i.v. dose, the half-life is approximately 2-4 hours, increasing up to 6.4h (±3.4) in renal failure (30-31). In critically ill patients with continuous infusion the half life turned out to be augmented up to 25 hours (30).

Fentanyl is hepatically metabolized to norfentanyl (>99%) and some other metabolites, which are all non toxic, inactive (8, 26, 47) and eliminated by the kidneys (31). Only five to ten percent is excreted unchanged in the urine (30, 47). Literature states that high levels of uraemia may significantly prolong fentanyl clearance and require individual dosage decrease to 1/2 -1/3 of usual commencement doses (11). Thus, the normal elimination half-life of 3-4h (30, 41) may be prolonged in renal impairment (30, 48). Interestingly, there is no existing evidence for increased likelihood of adverse effects. Due to its high molecular weight, high protein binding, low water solubility and the high volume of distribution, fentanyl is not expected to be dialyzable (49-50), but at present only scarce evidence related with haemodialysis is available.

Fentanyl seems to be safely manageable in short term. If used in long-term in patients with renal failure, careful monitoring and dose reduction is advised due to the cumulative

tendency of the substance and the current lack of evidence (30, 32). However, the existing evidence described the substance to have no additional risk of adverse effects, when used in case of renal failure (51).

Hydromorphone (HM) is a semi-synthetic opioid, which acts primarily on μ-opioid receptors and to a lesser degree on delta-receptors (52). HM was found to have similar analgesic properties to morphine and a similar side effect profile (52). Therefore it is an effective alternative to morphine in treatment of moderate to severe pain (2). When given by the oral route, HM is five times as potent as morphine. Given i.v., it has 5-8.5 times the analgesic potency of morphine (8, 52-54). HM is absorbed in the upper small intestine and extensively metabolized in the liver. Over 60% of the oral dose is eliminated as first pass effect. The oral bioavailability was found to be in the range of 1:2 to 1:8 (49). At therapeutic plasma levels HM is approximately 8-19% bound to plasma proteins (2). The normal elimination half-life of HM in a healthy population has been reported to be about 2.3-2.6 hours (2, 55).

More than 95% of HM are metabolized to hydromorphone-3-glucuronide (H3G) (2), which is devoid of analgesic activity and opioid-related side-effects (8). H3G is renally excreted and accumulates in renal impairment, possibly causing neuroexcitatory effects (8, 26). HM does not substantially accumulate in renal failure, likely because of its rapid conversion to H3G (55). Two studies reported the removal of HM by haemodialysis to approximately 40% of predialysis levels, but there is still a lack of confirming evidence and further research needs to be done (55-56). H3G accumulates between haemodialysis procedures, but is effectively removed during haemodialysis (53).

Literature found its use to be safe in patients with renal failure and also in patients receiving haemodialysis treatment (8, 10). However, caution and careful monitoring are recommended and a dose adjustment is required, because the accumulation of H3G may cause neuroexcitation and also cognitive impairment is postulated (11, 33).

Morphine is by far the most studied opioid. It acts as a full μ-receptor agonist and is mostly used for the treatment of moderate to severe cancer pain. It can be administered by virtually all routes (8). When given orally the bioavailability is 25%-35% (2, 8) and peak

plasma levels are reached approximately after one hour, with s.c. application after 15-30 minutes (57). The elimination half-life of morphine is approximately 120 minutes (41). Morphine is conjugated in the liver to morphine-3-glucuronide (M3G) (55%), morphine-6-glucuronide (M6G) (10%) and normorphine (4%), all of which are excreted renally together with 10% of the unchanged parent compound (32).

Morphine excretion is not altered significantly in renal insufficiency, but its metabolites are affected and can accumulate (51). M3G is essentially inactive, but it is neurotoxic in animals and it is thought to antagonise the analgesic effects of morphine and M6G (26, 30). Moreover it has been found to stimulate respiration and cause behavioural excitation, especially with accumulation (51). M6G has a more potent analgesic effect and a longer half-life than morphine and it is also known to depress the CNS. As M6G accumulates in renal failure, it can intensify analgesia and sedation and moreover induce severe neurotoxicity (8, 32). This can cause somnolence, dizziness and hallucinations that can persist, even after morphine is discontinued, as M6G crosses the blood-brain barrier slowly (51). Furthermore, increased M6G-levels were also found to exert respiratory depression (58). The retention of M6G leads to a progressive accumulation in the cerebrospinal fluid, which may explain the elevated susceptibility to morphine in renally impaired patients (59).

Morphine and its metabolites have low protein binding and moderate water solubility and can be significantly dialyzed, depending on the type of dialysis membrane used (32, 51). M6G is also removed by HD (a mean of 48%) but diffuses out of the CNS very slowly, which delays the response to dialysis (30, 60).

Where renal failure and epilepsy co-exist, morphine treatment should probably be avoided (11). Even though dose reduction proposals for reduced glomerular filtration rate can be found in the literature (32), these adjustments need further confirmation. Therefore it is recommended to avoid the use of morphine when kidney function is lowered and preferably alternative strong opioids should be used (8).

Oxycodone is a semisynthetic derivate of thebaine acting as a μ-, kappa- and delta-receptor agonist. It has an analgesic efficacy of 1:1-1:2 compared to morphine with a superior side-effect profile (2, 8). When orally applied, the systemic availability is around

60-90% (57), with a half-life of 2.5-3 hours (41). Oxycodone has a large volume of distribution and a plasma protein binding of 45% (32). The parent drug undergoes biotransformation in the liver forming its main metabolites, noroxycodone and oxymorphone (11). Oxymorphone is active and has a higher analgesic activity than noroxycodone, which only exerts some analgesic effect. The metabolites are primarily excreted in the urine (41). Oxycodone is eliminated mainly through hepatic metabolism and only to some degree via the kidney.

However, its excretion and the elimination of oxymorphone and noroxycodone are significantly impaired in patients with renal failure (34). In uremic patients the mean elimination half-life is prolonged as the volume of distribution increases and the clearance is reduced. Due to the prolonged half-life (up to 4,5h) (8, 34), the accumulation of the parent compound and its metabolites can exert toxic and CNS-depressant effects (32).

Therefore it is recommended to avoid the use of oxycodone in patients with an eGFR less than 60ml/min (8). The physico-chemical properties of oxycodone suggest, that it is dialyzable, but there is very few existing evidence. In only one study, oxycodone and its metabolites were found to be removable with haemodialysis (61). Therefore caution is advised when oxycodone is used in dialysis patients as blood levels are potentially influenced by HD (32). If used in patients with impaired renal function without haemodialysis careful patient monitoring, dose reduction and adjustment of administration intervals are recommended (8, 34). Sustained release preparations of oxycodone should generally be avoided (35). More research in the setting of renal failure and haemodialysis is mandatory, before profound and concrete recommendations can be made.

Buprenorphine (BN) is a semisynthetic highly lipophilic opioid that acts as a partial agonist at the μ-receptor and exerts kappa-receptor antagonistic activity (26, 62). BN has an antihyperalgesic effect and its analgesic efficacy is variably discussed to be in the range of 30-100 times the one of morphine (2, 8, 30, 63). Interestingly, BN was found to have a ceiling effect to respiratory depression but not to analgesia in humans (64). Moreover, BN produces adequate analgesia via any administration route. Given orally, only 10% of the dose are systemically available (30) and the mean elimination half-life is 37 hours (2). BN is metabolized in the liver via CYP P450 3A4 to norbuprenorphine (NBN). In an animal

study it was shown, that NBN has a 40 times less analgesic potency than BN but a 10 times higher respiratory depressant efficacy (27). Both BN and NBN undergo rapid glucuronidation to the inactive substances buprenorphine-3-glucuronide (B3G) and norbuprenorphine-3-glucuronide (65). Unchanged BN is predominantly excreted via the biliary tract and the metabolites are renally excreted (8, 11, 26).

Hence BN does not accumulate in the presence of renal failure but the metabolite blood levels are augmented. In one study, NBN was found to be increased by a median of four times, B3G concentrations by a median of 15 times (66). However, this accumulation has been claimed to be of minor importance, but caution should be taken due to the respiratory depressive potential of NBN (26-27).

Because of its good safety- and tolerability profile in patients with renal impairment, no dose-adjustment is required (8). Hence BN is a safely usable drug in the circumstance of renal impairment, although caution and close patient monitoring are recommended (8, 11).

Remifentanil is a fentanyl-derivate that is mostly used as a supplement for general anaesthesia. Remifentanil acts as a μ-receptor agonist and has rapid analgesic effects in onset and offset after intravenous application. New steady-state concentrations occur within 5-10 minutes after changes in infusion rate (2). The protein binding of remifentanil is 92% (30). The parent compound undergoes rapid metabolism by nonspecific blood- and tissue-esterases (2, 11) and results in the production of carboxylic acid metabolite as the principal metabolic pathway (>95%) (2). This prevailing metabolite is essentially inactive and is excreted by the kidneys. The high clearance of remifentanil combined with a relatively small volume of distribution results in a short elimination half-life of approximately 3-10 minutes. The elimination half-life of the main metabolite is approximately 90 minutes (2). In case of patients undergoing haemodialysis, the carboxylic acid metabolite is removed with a dialysis extraction ratio of approximately 30% (2).

Renal impairment can change serum levels and in anephric patients the metabolite half-life is increased up to 30 hours. However, renal failure does not have a significant effect on the pharmacokinetics of remifentanil (11, 28-29). Thus, it is suggested to be a suitable agent for the use in patients with renal dysfunction (11, 30-31). Regular assessment of sedation levels and respiratory function, as well as a reliable infusion device under the control of a

skilled clinician are demanded (11). Dose adjustment is not required in renal failure (31).

Sufentanil is a highly potent analogue of fentanyl with 5-10 times fentanyl's analgesic efficacy (2). Sufentanil is rapidly distributed in most tissues; it is highly protein bound and has a large volume of distribution (30). The parent compound is extensively converted by the liver by N-dealkylation and O-demethylation to almost inactive metabolites. Metabolites are eliminated via the urine and faeces, only 2% is excreted as an unchanged drug (30). The elimination half-life of sufentanil is approximately 3 hours (30).

Due to the high molecular weight, the high degree of protein binding, the high volume of distribution and the low water solubility sufentanil is not expected to be dialyzable, but no current data was found concerning haemodialysis and sufentanil (32).

One case report indicated prolonged postoperative respiratory depression as a result of sufentanil accumulation in a patient with chronic renal failure (37), but the authors state that there might have been other factors contributing to the respiratory depression.

Summarizing the scarce evidence, the use of sufentanil appears to be safe in the case of renal impairment but further data needs to be evaluated before exact recommendations can be made. If used in the setting of renal failure, careful monitoring is advised (8).

Methadone is a synthetic racemic opioid exerting its effects via μ-receptor-agonism (L-methadone) and N-methyl-D-aspartate (NMDA) -antagonsim (D-methadone). It is used for analgesia, sedation, detoxification and maintenance in opioid addiction (2). Its analgesic potency shows large interindividual differences and ranges between 1-10 times the one of morphine (40). Methadone is effective for the relief of moderate-to-severe pain and opioid-refractory pain states (8). Due to its NMDA antagonistic effect it is potent in relieving neuropathic pain (39) and it is optionally used in opioid rotation (8). This highly lipophilic substance has a bioavailability that ranges between 41%-99% (11, 67-68) and is highly protein bound to alpha-1-acid-glycoprotein (89% in average) (2, 30, 32, 68). The large tissue distribution causes its long, unpredictable half-life, which shows broad inter-patient variability following repeated administration (7-80h) and also increases with age (2, 8). Moreover, considerable differences between acute and chronic phase dosing have been found. The elimination of methadone occurs mainly by metabolism (36), whilst 20% of the unchanged drug are renally excreted of an administered single dose. Methadone is

primarily metabolized by N-demethylation in the liver and intestine with predominantly inactive metabolites (2, 8), that are mostly excreted via the urine (2, 68). The major metabolite EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) is pharmacologically inactive (36) and is excreted in the faeces (26).

In renal failure, the parent compound and the metabolites undergo compensatory elimination via the gut (69) although inter-patient variability can be found (32). Hence methadone does not accumulate extensively in renal failure (8, 36). However, the risk of elevated concentrations and toxicity with methadone also exists in patients with normal renal function and therefore experienced specialist supervision in pain treatment with methadone is required (26). The chief hazard with administrating methadone is respiratory depression and this can lead to life-threatening situations in case of overdosage or accumulation. In one study methadone was poorly removed by haemodialysis, which is in agreement with its pharmacokinetic properties. The more hydrosoluble metabolite EDDP was found to be extracted during haemodialysis, but this does not have clinical effects due to its inefficacy (36). With patients undergoing haemodialysis during methadone-treatment, no supplemental application is required (36).

Dose reduction is recommended in patients with impaired renal function. When the eGFR is below 15mL/min, the dose should be reduced by 50%-75%, also taking into consideration the wide inter-patient variability of response (26). Clinicians should be aware of the risk of overdose with lethal ending. Thus, literature recommends a specialized setting, especially because the analgesic activity can disappear though methadone still remains in the body. Methadone is not suitable for the initial treatment of acute pain (11, 31). Taking all of this into account, methadone appears to be safe in the setting of renal failure.

Co-analgesics

Co-Analgesics	Recommendations	Comments	References
Lamotrigine	appears safe at standard dose	more evidence needed	(73)
Carbamazepine	appears safe at standard dose	more evidence needed	(11, 74)
Ketamine	appears safe at standard dose	more evidence needed	(11, 75-76)
Corticosteroids	appears safe at standard dose	more evidence needed	(74)
Pregabalin	recommended, dose adjustment required	-	(2, 77)
Gabapentin	recommended, dose adjustment required	-	(78-81)
Amitriptyline Nortriptyline	-	close montoring recommended due to potential side effects, more evidence needed	(70-72)
Duloxetine	ambivalent recommendations	more evidence needed	(82-84)
Oxcarbazepine	ambivalent recommendations	more evidence needed	(85-87)
Topiramate	ambivalent recommendations	more evidence needed	(2, 88-89)
Bisphosphonates	-	controversial results, more evidence needed	(74)

Table 4 Co-Analgesic Recommendations in Renal Dysfuncion

green = recommended, yellow = dose reduction required, orange = more evidence needed, red = avoid

Antidepressants

Amitriptyline belongs to the group of tricyclic antidepressants and is also used as a co-analgesic in the treatment of neuropathic pain. It acts primarily as a serotonin-norepinephrine reuptake inhibitor and also has negligible influence on the dopamine transporter. The doses used in pain treatment are mostly lower than those used in the treatment of depression (11, 22). After oral administration amitriptyline is rapidly absorbed and metabolized (2). Subsequently it undergoes demethylation in the liver to the active metabolite nortriptyline (11).

Nortriptylin is a second-generation tricyclic antidepressant, which is sometimes additionally used in the treatment of chronic pain and migraine. It inhibits the reuptake of norepinephrine and to a lesser degree serotonin. It also strongly antagonizes histamine H1 receptors and shows some antagonistic effect to 5-hydroxytryptamine and acetylcholine. Nortriptyline is extensively hepatically metabolized into unconjugated and glucuronide-conjugated 10-hydroxy-nortriptyline, which are said to have some activity and these metabolites are renally excreted (71).

The half-life of the metabolites was reported to be significantly longer in patients with renal failure than in healthy subjects (70). Nortriptyline does not seem to accumulate in renal failure and its pharmacokinetics are not altered in patients with CKD (90). One study found significantly increased concentrations of the conjugated metabolites (500-1500%) in patients undergoing haemodialysis (70), in another study concentrations were even higher (1000-2000%) (71). This metabolite accumulation was said to increase the likelihood of unwanted side-effects (70).

Nevertheless no recommended dose adjustments for nortriptyline and amitriptyline in renal failure were found, but further research is indicated and increased caution giving these substances is recommended due to the possibility of metabolite accumulation and unwanted side effects (70-72). Interestingly, the value of haemodialysis was found to be negligible concerning the clearance of nortriptyline and its metabolites in overdosed patients (71).

Duloxetine acts selectively as a potent dual serotonin and norepinephrine reuptake inhibitor and is approved in various countries for treating major depressive disorder, generalized anxiety disorders and stress urinary incontinence (91). It is also approved as a co-analgesic mainly for alleviating pain associated with diabetic neuropathy and fibromyalgia (22, 39). For treating diabetic peripheral neuropathic pain in patients with normal kidney function, it is recommended to apply 60mg once daily orally (82). The absorption of duloxetine begins after two hours after oral administration, reaching its peak plasma levels in six hours. Duloxetine is highly bound to plasma proteins (>90%), has a large volume of distribution (1640 L) and its half-life in healthy subjects is approximately 12 hours (92). The majority (70%) of the duloxetine dose is recovered in the urine as conjugated metabolites and approximately 20% is recovered in the faeces as the unchanged drug, unconjugated metabolites or unidentified compounds (83). Duloxetine is mainly metabolized via CYP450-mediated oxidation (89) followed by methylation and conjugation resulting in two major conjugated metabolites that are mainly renally excreted (84).

Dose recommendations are diverse for patients with severe renal impairment. Recent literature found that mild or moderate renal impairment with a creatinine-clearance ≥30mL/min does not affect duloxetine pharmacokinetics and therefore standard dosing recommendations are appropriate (82). For patients with ESRD or severe renal impairment (creatinine-clearance <30mL/min) duloxetine is not recommended (82), or if applied in such patients, the dosage should be bisected (83).

Anticonvulsants

Gabapentin is a structural analog of GABA and exerts its pharmacological actions similar to pregabalin by selectively binding to the alpha2delta-subunit of voltage-dependent calcium channels, modulating the calcium influx and influencing GABAergic neurotransmission. Thereby gabapentin executes peripheral and central analgesic action (2). Importantly, gabapentin needs slow individual titration (39). The bioavailability of gabapentin is not dose proportional. As dose increases, bioavailability decreases (2). Less than 3% of gabapentin is bound to plasma protein and unlike GABA, gabapentin crosses the blood brain barrier after systemic administration (2, 93). Gabapentin is only

metabolized to a minor amount. It is solely renally excreted in the unchanged form with a half-life in healthy subjects of 5-7 hours, which is unaltered by dose (2, 94).

Gabapentin half-life in anuric humans undergoing HD is about 132 hours (94). HD removes gabapentin effectively with a half-life during HD of four hours.

It was found that gabapentin application without dose reduction can lead to serious toxicity in patients with renal impairment (79). Treatment with gabapentin was related to asterixis, which subsided on the discontinuation of gabapentin (80-81). Dosage adjustment recommendations for subjects with renal impairment over the age of twelve can be found in Table 5.

CRCL (mL/min)	**Total Daily Dose Range (mg/day)**	**Dose Regimen (mg)**				
≥ 60	900-3600	300 tid	400 tid	600 tid	800 tid	1200 tid
30-59	400-1400	200 bid	300 bid	400 bid	500 bid	700 bid
15-29	200-700	200 qd	300 qd	400 qd	500 qd	700 qd
<15 *	100-300	100 qd	125 qd	150 qd	200 qd	300 qd
Post-Haemodialysis Supplemental Dose (mg)						
HD		125	150	200	250	350

Table 5 (78) modified, Gabapentin Dosage Adjustments based on Renal Function

For patients with CRCL <15mL/min it is recommended, that the daily dose is reduced in proportion to CRCL (patients with CRCL of 7,5mL/min should receive one-half the dose of patients with CRCL of 15mL/min) (78) bid = two divided doses, tid = three divided doses, qd = single daily dose

Pregabalin is an anticonvulsant drug that is commonly used for treating neuropathic pain (39). Pregabalin binds to the alpha2delta-subunit of voltage-dependent calcium channels in the CNS with a consequential reduction in the calcium influx and a decrease in release of several excitatory neurotransmitters (95). However, it does not completely block calcium channel function or transmitter release, which is an important safety implication in the case of overdosage (95). After oral administration the bioavailability is about 90% and pregabalin reaches the maximal plasma concentration in one hour. Steady state plasma levels are achieved within 24-48 hours after repeated administration (2, 95-96). Pregabalin does not bind to plasma proteins and has a volume of distribution of 0.5 L/kg (2).

Interestingly, pregabalin is only negligibly metabolized (<2%) (95). It is largely eliminated by renal excretion as the unchanged compound (90%), whereas its main metabolite accounts for only about 0.9% in the urine (2). Recommended doses for healthy subjects begin at 150mg/day (50mg three times a day) and may be increased to 300mg/day within one week, based on efficacy and tolerability (2, 95).

As pregabalin clearance is nearly proportional to creatinine-clearance, it accumulates in renal failure and can exert dose-dependent adverse reactions (77). Recommended dose adjustments for patients undergoing haemodialysis based on renal function (creatinine-clrearance) can be found in table 6. Patients with a CRCL of >60mL/min receive a dose of 150mg/day for a certain treatment. Hence for the same treatment a patient with a CRCL of 50mL/min will receive 75mg/day.

CRCL (mL/min)	Total Pregabalin Daily Dose (mg/day)*				Dose Regimen
>60	150	300	450	600	bid or tid
30-60	75	150	225	300	bid or tid
15-30	25-50	75	100-150	150	qd or bid
<15	25	25-50	50-75	75	qd

Table 6 (77) modified, Pregabalin Dosage Adjustments based on Renal Function

bid = two divided doses, tid = three divided doses, qd = single daily dose, * Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose

Pregabalin is effectively removed from plasma by HD, about 50% are removed in a dialysis treatment lasting 4 hours (2). Therefore, supplementary dosages should be applied following HD treatment as can be seen in Table 7.

Total Pregabalin Daily Dose	Supplemental Dose following HD
25	1x 25-50
25-50	1x 50-75
50-75	1x 75-100
75	1x 100-150

Table 7 (77), Pregabalin Post-Haemodialysis Supplemental Dose (mg)

Lamotrigine is an antiepileptic drug for the treatment of partial and secondary generalised seizures (73). Its precise mechanisms of action are unknown, but it was in vitro found to inhibit voltage-sensitive sodium channels consequently modulating the release of excitatory amino acids like glutamate and aspartate (2). It is said to be an alternative for painful diabetic neuropathy and trigeminal neuralgia. However, the literature is ambivalent concerning the benefit of lamotrigine in the treatment of neuropathic pain (97-98). Lamotrigine is completely absorbed after oral dosing and is eliminated primarily by metabolism. It is largely glucuronidated and forms its main metabolite lamotrigine N^2-glucuronide, which accounts for 90% of the eliminated substance in the urine (73).

The limited evidence available indicates that impaired renal function has little effect on the plasma concentrations of lamotrigine (73). However, this was only studied for a daily single oral dose of 200mg. Care should be taken, if lamotrigine is used in renally impaired patients and further studies concerning its efficacy and safety need to be made.

Carbamazepine is an anticonvulsant drug that exerts its efficacy through stabilizing the inactivated state of sodium channels and thereby reducing the excitability of neuron cells. Carbamazepine is mainly indicated in the treatment of epilepsy and bipolar disorder. In pain management it is used for treating trigeminal neuralgia (2, 22) and as an alternative for diabetic neuropathy (97). Its analgesic potential is only light, but it is able to modify pain by reducing synaptic transmissions along nerve fibres (74). Carbamazepine undergoes primarily hepatic metabolism to the clinically active carbamazepine-10,11-epoxide, which is further metabolized into an inactive metabolite trans-10,11-dihydroxy-10,11-dihydrocarbamazepine (99). The metabolites are excreted in the urine mainly in an unconjugated form together with less than 1% of the parent compound (11).

However literature recommends no dose adjustment for patients with CKD (74), although potentially serious side-effects, such as agranulocytosis, cardiac arrhythmia, hepatitis and renal failure have been reported (11, 74). For this reason it is recommended to monitor drug blood levels, erythrocyte count and liver and renal function during carbamazepine therapy (11, 74). However, the existing evidence is currently sparse.

Oxcarbazepine is an antiepileptic drug with a similar chemical structure to carbamazepine, but with different metabolism and a more favourable side-effect profile (85-86). Together with carbamazepine it is considered the first choice for trigeminal neuralgia (22) and it can be alternatively given for diabetic neuropathy (97). It is rapidly absorbed after oral administration and the bioavailability is >95% (85, 100). After a single dose, the peak plasma concentration is reached after 1-3 hours. Oxcarbazepine is rapidly reduced to an active monohydroxy-metabolite, 10,11-dihydro-10-hydroxycarbamazepine (MHD), that peaks in plasma concentration within 4-12 hours after a single dose (85, 101). Oxcarbazepine has an elimination half-life of 1-5h in healthy subjects, whereas the half-life of MHD was found to be between 7-20h (85) and 8-9h (87)

Focusing on pharmacokinetics in renal failure, the limited literature found a 2-2.5-fold increase of the AUC of oxcarbazepine and MHD in patients with severe renal impairment and a doubled half-life of the main metabolite (101).

Therefore it is suggested, that patients with a CRCL under 30mL/min do not need dose adjustment, whereas patients with a CRCL of 10-30mL/min should receive at least 50% dose reduction (85-87). For subjects with severe renal impairment (CRCL<10mL/min) detailed dose adjustment recommendations were not found. Thus more research needs to be made to create profound oxcarbazepine dosage guidelines in pain therapy.

Topiramate is an anticonvulsant drug, which is alternatively used for neuropathic pain treatment (102). Its mechanisms of action imply the potentiation of GABA responses, the impairment of AMPA/kainate glutamate receptors and the suppression of high frequency action potential firing (100). Topiramate is quickly absorbed after oral application and its steady-state concentration is reached in about 4 days in patients with normal renal function (2). Protein binding is said to be somewhere between 15-41%. As blood concentration rises, the protein bound fraction decreases. Elimination half-life in humans after single or multiple doses is about 21 hours. Most of the side effects of topiramate are dose dependent, thus the principle “start low, go slow” should be utilized and thereby tolerance is more easily achieved (102). With topiramate six metabolites have been identified in humans, but none of them accounts for more than 5% of the applied dose (2). The majority of topiramate (70%) is renally excreted as the unchanged drug.

In renally impaired patients with a CRCL of 30-69mL/min the topiramate clearance was found to be reduced by 42% and in subjects with a CRCL of under 30mL/min the clearance reduction was even higher (54%) (2).

Therefore topiramate can accumulate in patients with impaired renal function and dose reduction of 50% or more is recommended, if CRCL falls under 70mL/min (88-89). Furthermore haemodialysis treatment reduces topiramate blood levels to a significant degree, 4-6 times greater than in normal individuals. Thus extra doses should be applied after HD treatment (2), but due to the current lack of data no profound supplement recommendations can be made. As a consequence further research concerning topiramate therapy in haemodialysis patients is needed.

Ketamine

Ketamine is a rapid-acting general anaesthetic with profound analgesic potential (2) and therefore can be used in the treatment of acute and chronic pain states (103). Ketamine acts as a NMDA receptor antagonist and even binds to opioid μ receptors and sigma receptors, when high doses are applied.

There is currently only limited evidence concerning ketamine use in renally impaired patients. One study found a slightly increased ketamine steady-state plasma levels in patients with acute renal failure and ketamine long-term analgosedation (1.1-1.3mg/kg/h), but concluded that this difference was not significant. However, in this study the dehydronorketamine plasma levels were found to be significantly increased, but this metabolite only has little potency (75). In the same study only a minor fraction of ketamine (10%) was eliminated during haemodialysis treatment (75). One case report stated that ketamine was successfully used to ameliorate severe pain associated with calciphylaxis in a haemodialysis patient (76).

The limited literature recommends dose adjustment to be unnecessary when ketamine is applied in higher infusion rates in the presence of renal failure (11). However, ketamine needs to be further analyzed before definitive statements concerning its use in renally impaired patients can be made.

Corticosteroids

Corticosteroids are commonly used to treat certain pain states, such as relief nerve compression pain, headaches associated with increased intracranial pressure and bone pain (74).

Patients with CKD that are treated with corticosteroids do not need dose adjustments, although high doses may lead to increasing hypertension, water and salt retention and deterioration in bone disease (74).

Bisphosphonates

Bisphosphonates act by inhibiting osteoclast-activity by binding to calcium phosphate crystals and therefore reduce osteolysis (74). Their efficacy in the long term-treatment of cancer induced bone pain is well known.

However, evidence referring to the optimal dosage is unclear and data referring to the application in renal impairment is very scarce. It is said, that bisphosponates may deteriorate underlying renal failure (74).

At present, bisphosphonate-therapy in CKD patients should be cautiously approached due to the controversial and insufficient data existing.

Conclusion

Finding the adequate pain treatment for patients with renal failure can be demanding, taking into consideration, that analgesia needs to be optimized, while adverse effects should be kept to a minimum. Focusing on analgesic drug treatment, the WHO offers practicable and helpful guidelines for the step-wise selection of analgesics based on pain severity.

For mild to moderate pain in patients with renal dysfunction paracetamol is the step 1 analgesic of first choice, as it does not require any dose adjustment. NSAIDs and COX-2-inhibitors seem to have the same negative effects on renal perfusion in underlying renal failure and thus should be avoided in such patients. Metamizole appears to be safe, but there is a definitive need for further studies and evidence concerning its use in renally impaired subjects.

Concerning step 2 analgesics tramadol is described to be the least problematic opioid analgesic for patients with ESRD, although dose adjustments are needed. Codeine and dihydrocodeine should be avoided due to the risk of metabolite-accumulation and serious side-effects.

For the management of severe pain strong opioids may become mandatory. In this case buprenorphine and remifentanil can be preferably recommended. Buprenorphine offers effective pain relief combined with a good safety and tolerability profile. Remifentanil represents a suitable agent for general anaesthesia and does not require dose adjustment. Sufentanil seems to be safe, however further data needs to be evaluated. Fentanly appears safe at standard doses in acute pain treatment, but requires dose reduction if given repeatedly due to its potential of accumulation. Other strong opioids like hydromorphone and methadone appear safe, if dose-adjustments are made and close patient monitoring is given. Oxycodone can be used with strict dose reduction in absence of CNS side effects. Importantly, the use of morphine should be avoided when kidney function is lowered and preferably alternative strong opioids should be used.

The value of co-analgesics seems to be special in renally impaired patients, as opioid dose can be reduced and specific pain-states are more effectively treated. Lamotrigine and

carbamazepine seem to be safely applicable at standard dose, but close monitoring is recommended due to potential side-effects. Definitively further research is required, because only short application data is currently available. Diverse recommendations have been found for duloxetine, oxcarbazepine and topiramate, which all tend to accumulate in renal failure. In summary, they are best to be avoided in patients with moderate to severe renal impairment due to the lack of profound evidence, or at least 50% dose reduction is necessary. Amitriptyline and nortriptyline have an increased likelihood of unwanted side effects due to metabolite accumulation, but no detailed dose recommendations were found and therefore further studies are required. The anticonvulsants pregabalin and gabapentin can be used, if dose adjustment recommendations are utilized and drug levels are monitored.

Concerning the available literature, ketamine and corticosteroids at standard doses seem to be safe in renal impairment and dose adjustment is unnecessary, but these substances also need to undergo further analysis. Regarding the use of bisphosphonates, preexisting renal failure may be deteriorated and the available data concerning appropriate dosage is insufficient and controversial.

The lack of data makes the application of analgesic substances in CKD patients and their dose adaptations related with HD a point of focus for further research. Future studies should always clearly define their results and give detailed recommendations related to renal impairment and its stages. Larger patient groups need to be analyzed, as the existing data is mostly based upon studies with few participants and cannot conclusively guide analgesic use for all degrees of renal failure and haemodialysis.

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