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What Every Doctor Should Know about Drug Safety in Patients with Chronic Kidney Disease

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Abstract

Drug safety is a very relevant issue when dealing with patients with chronic kidney disease (CKD) who need vascular access procedures and interventions. Drug dosage adjustments are needed for patients with acute or chronic kidney disease. In CKD patients, the estimated glomerular filtration rate is used to guide dose adjustments. Determining the influence of renal replacement therapies on drug dosage adjustment is also very important. Safety issues for the following drugs used for situations related to vascular access are reported: anticoagulants and antiplatelet agents, antibiotics, antimicrobials for catheter lock therapy, thrombolytics, local anesthetics, and painkillers. General principles of the interactions of drugs in CKD are also reported.

Recommendations to Improve Patient Safety

- The assessment of kidney function with estimated glomerular filtration rate (eGFR) using CKD-Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) formulas is key for correct and safe drug prescribing.
- Dosing adjustments are generally required when eGFR is below 60 ml/min/1.73 m^2.
- When choosing drugs for use in chronic kidney disease (CKD) patients, consider pharmacokinetics (PK) and pharmacodynamics (PD) characteristics for the best efficacy/safety profile.

- Drug interactions in CKD patients are more frequent for the large number of prescribed drugs and for the altered PK.
- Avoid (or use with extreme caution) drugs that have not been proved effective and safe in CKD.

Background

Introduction to the Use of Drugs in Chronic Kidney Disease Patients: Assessment of Kidney Function

Dialysis access procedures, from central venous catheter insertion to arteriovenous fistula and grafts placement, are performed in patients with different degrees of renal insufficiency, including patients with acute kidney injury (AKI) and chronic kidney disease (CKD) in different stages. AKI and CKD can change the pharmacokinetics (PK) and the pharmacodynamics (PD) of many drugs [1]. Moreover, drug removal by intermittent and continuous renal replacement therapies determines the need for evaluating drug transport across biological (the peritoneum) and artificial membranes. Identifying drugs for which individualization of the treatment regimen will be necessary and consequently adjusting drug dosage regimens is important to avoid overdosage and toxicity of the drugs and/or their metabolites in renally impaired patients. Therefore, prior to treating patients with CKD, one must define kidney function (fig. 1).

Which Is the Most Accurate and Reliable Index to Assess Kidney Function for Drug Dosing, Thus Improving Drug Safety?

Determination of GFR based on the administration of exogenous substances is not practical for routine individual drug dose calculations. Therefore, urinary clearance of inulin (the gold standard) is rarely performed except for research purposes. Moreover, determination of GFR using an endogenous substance (creatinine), based on the urinary clearance of creatinine derived from a 24-hour urine collection is of limited clinical value because of frequent urine collection errors and analytical interferences with the serum or urine creatinine assays as the result of concomitant diseases and drug therapies. Therefore, estimated glomerular filtration rate (eGFR) obtained in clinical practice from the measurement of endogenous substances such as serum creatinine (Scr) and then combined with patient factors is the most commonly used measure to define kidney function [2]. eGFR can be measured in several different ways (table 1). However, in those clinical

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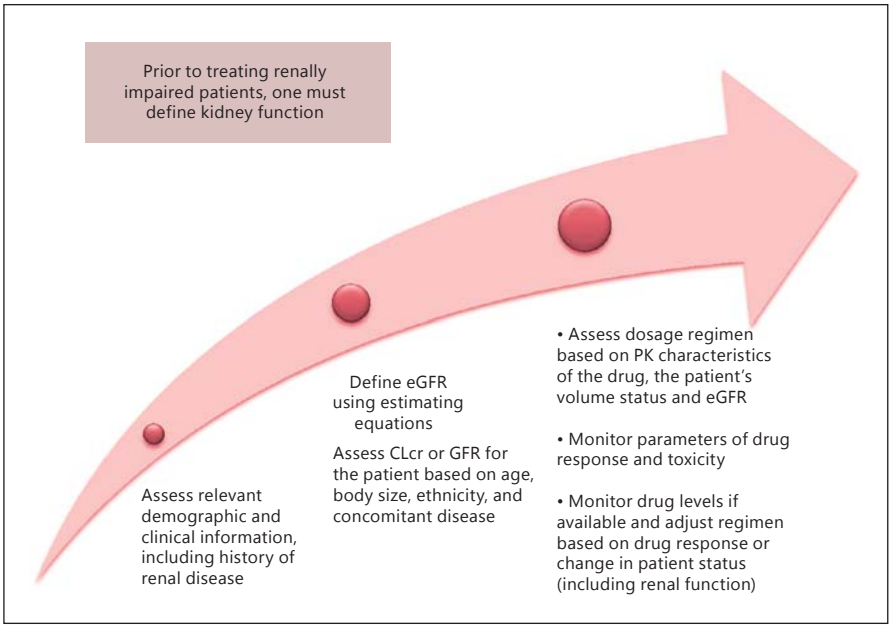

Fig. 1. Clinical algorithm for drug prescribing in CKD patients. CLcr = Urinary clearance of creatinine.

Table 1. List of the most common formulas for eGFR used for guiding drug dosage adjustment (see www.mdrd.com)

Cockcroft and Gault [6]	
MDRD-four variables [4]	(Modification of Diet in Renal Disease)
CKD-EPI [3, 5]	(Chronic Kidney Disease-Epidemiology Collaboration)

situations and for those drugs with a narrow therapeutic index for which dosing individualization is required, where any creatinine-based estimation equation is not likely to provide a good estimate of GFR, measured creatinine clearance or measured GFR using exogenous markers should be considered.

Which eGFR Equation Should Be Used for Assessment GFR as the Guide to Drug Dosage Regimens?

Several considerations regarding methods to estimate eGFR may guide us to choose the best option:

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- Estimating equations are more accurate than measured creatinine clearance, given the errors in urine collection [3].
- Variability in Scr assays is a major source of bias, leading to differences in reported Scr values among laboratories as well as within laboratories over time. Use of isotope dilution mass spectroscopy (IDMS), a method to standardize creatinine assays, leads to less variation in eGFR and theoretically more consistent drug dosing recommendations across institutions and clinical settings. The MDRD Study [4] and CKD-Epidemiology Collaboration (CKD-EPI) [3, 5] equations should be preferentially used with IDMS-standardized creatinine.
- Keep in mind that in addition to the effect of GFR, Scr may be influenced by differences in muscle mass, diet and tubular secretion. Estimating equations capture the average differences in the rate of creatinine generation due to age, sex, race, and weight, but they do not capture all factors. Therefore, some individuals will have substantially different values of Scr than expected and eGFR will be higher or lower than the true GFR.
- In the past, before the availability of standardized approaches, variations of the Scr assays affected PK/PD drug studies. This may still determine difficulties in interpretation of product label drug dosing recommendations. However, it is not conceivable repeating all of the PK studies with standardized creatinine: considering that the MDRD equation has a similar performance at lower levels of GFR, where drug dose adjustment is frequent, it is still reasonable to use drug dosing adjustments suggested in the product labeling.
- The Cockcroft and Gault (CG) equation [6] has been shown to overestimate GFR with the use of standardized creatinine assays. The CG equation is reported in units not adjusted for body surface area (BSA), which is appropriate for drug dosage adjustment. However, it is worth noting that the CG equation considers the body weight in the mathematical approach.
- The Modification of Diet in Renal Disease (MDRD) equation was developed from an extensive sample of patients with known CKD, all of whom had a measured GFR <90 ml/min/1.73 m^2 [4]. This equation is now widely reported by clinical laboratories around the world whenever Scr is measured. Since the MDRD equation overestimates measured GFR in subjects with values >60 ml/min/1.73 m^2, values are only reported for GFR <60 ml/min/1.73 m^2 [3]. Use of IDMS-traceable creatinine values in the IDMS-MDRD Study equation results in a more accurate eGFR.
- The CKD-EPI equation, derived from studies including people with and without CKD, is more accurate than the MDRD equation, particularly at higher levels of GFR [5, 7].

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- Formulas for eGFR are not accurate in individuals with extremes of body size or muscle mass, including the frail, elderly, critically ill, and subjects with unusual dietary habits. Kidney function is proportional to kidney size, which is proportional to BSA. BSA of 1.73 m^2 is the normal mean value for young adults. The eGFR ml/min/1.73 m^2 adjusted for BSA is necessary in patients whose body size is markedly different than average. If using eGFR in very large or very small patients, multiply the eGFR ml/min/1.73 m^2 by the BSA in order to obtain adjusted eGFR in units of ml/min.

In summary, it is very important to assess the GFR based on Scr levels. All the formulas considered in this chapter may give an acceptable estimate of GFR. The CKD-EPI equation appears to be preferable.

Drug Safety

Antimicrobial Drugs

Many antimicrobial agents are eliminated by the kidneys, and they require dosing adjustments in patients with CKD; however, several commonly used drugs do not require adjustments. Antibiotics should be used at the correct dose (see the section Drug Dosing in Patients with Renal Failure) to avoid undertreatment or, more commonly, drug toxicity.

Infectious complications are relevant causes of morbidity and mortality in hemodialysis patients [8, 9]. Of particular concern, vascular access has emerged as a major risk factor for infection and bacteremia [10]. Furthermore, the majority of these bacteremias are caused by staphylococci, associated with high rates of mortality (8–25%), recurrence (14.5–44%), and serious metastatic complications (14.5–44%) [11, 12]. When the source of fever is suspected to be vascular access (catheter or graft) related, antimicrobial therapy must reliably cover Gram-positive species (including methicillin-sensitive *Staphylococcus aureus*) since these organisms account for about two thirds of HD access-related bacteremias. Enterococci and Gram-negative organisms account for the majority of the remaining bacteremias, and antimicrobial therapy should target these organisms as well [12]. It has become common practice to treat the febrile HD patient empirically with a combination of parenteral vancomycin plus gentamycin or vancomycin plus a third generation cephalosporin [12]. With the emergence of vancomycin-resistant enterococci, the empiric use of vancomycin in the febrile patient on HD has been challenged: CDC published guidelines for the prudent use of vancomycin in an attempt to prevent the spread of vancomycin resistance [13]. In accordance with these guidelines, empiric treatment with

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vancomycin is appropriate in patients with β-lactam allergy or when serious infections with β-lactam-resistant Gram-positive bacteria are likely [12]. Continuing treatment, however, depends on culture results.

The appropriate management of catheter-related infections has become a major challenge for physicians, and the initial empiric antibiotic therapy should take into consideration the frequency of the bacterial isolates in such settings. Staphylococcal species are the most prevalent (60–100%) bacterial isolates in HD patients with catheter-related bacteremia [14, 15]; in some patients, both Gram-positive and Gram-negative organisms have been isolated from the bloodstream, indicating mixed bacteremia [16, 17]. These data mandate that empiric antibiotic therapy should target both Gram-positive and Gram-negative organisms.

For infections with documented sensitivity to cefazolin in anuric HD patients, intravenous postdialysis dosing of cefazolin is both safe and effective. Moreover, empiric treatment of non-life-threatening infections with cefazolin alone or in combination with gentamicin may be appropriate in HD patients pending culture results [18, 19].

Exit site infections are common and are recognized by redness, exudation and crusting. Topical agents applied to catheter exit site, such as povidone iodine, mupirocin, bacitracin zinc and polymixin B sulphate ointments have been proven effective [20, 21]. Oral rifampin or nasal mupirocin ointment reduced the incidence of *S. aureus* bacteremia [22].

Patient safety issues regarding the use of antibiotics are largely debated [23]. The WHO suggests that prescribing antibiotics without regard for the patient's underlying condition and whether antibiotics will help the patient, or administering multiple drugs without attention to the potential for adverse drug reactions, all have the potential for harm and patient injury. When considering CKD patients with end-stage renal disease, it should be kept in mind that if we want to avoid safety issues, use of the right antibiotic at the right dose is the ultimate goal.

Catheter Lock Therapy

Catheter-related bacteremia is the most relevant CVC-related complication, which can lead to catheter removal because bacteria colonize the catheter and may be difficult to eradicate.

Antibiotic-lock therapy (ALT) is used in addition to systemic treatment for CVC-related infections. After filling both catheter lumens with a mix of antibiotic and anticoagulant at the end of dialysis (catheter locking), antibiotic concentrations inside the catheter reach very high levels, much higher than the con-

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centration reached during conventional treatment. The catheter lock can remain in place for many hours when the catheter is not in use, and it may limit biofilm formation. ALT is particularly important in central venous catheter-related infection of intraluminal origin, especially in patients with coagulase-negative staphylococci infections.

Published guidelines on the management of catheter-related infections are in favor of the use of ALT for the treatment of catheter-related infections [24]. The in vitro stability of antibiotic-heparin combinations in CVCs was studied by Vercaigne et al. [25]. While ciprofloxacin produced immediate precipitation with heparin, cefazolin, vancomycin and ceftazidime at 10 mg/ml and gentamycin at 5 mg/ml were successfully incubated with heparin (5,000 U/ml) for 72 h in the central venous catheter lumen. Although free antibiotic in CVC solution was reduced, the final concentration was still sufficient for an effective antibiotic-heparin lock [25]. Good evidence is available to support ALT in the prevention of catheter-related bacteremia in patients on hemodialysis [26, 27]. However, others have reported that the use of ALT may be limited due to antibiotic toxicity and the appearance of antibiotic-resistant microbial isolates [28, 29].

Sodium citrate locks are effective for prophylaxis against catheter-related infections [30], although increased rates of catheter thrombosis have been reported [31].

Catheter-related bloodstream infections are reduced by interdialytic locking with taurolidine, a nontoxic antimicrobial agent. Although the use of a formulation of 1.35% taurolidine in 4% citrate, compared to 5,000 U/ml heparin, was associated with a greater need for thrombolysis to maintain catheter patency [32], the addition of 500 U/ml heparin to taurolidine-citrate solution avoided the need for thrombolysis without increasing bacteremia, with catheter patency comparable to heparin 5,000 U/ml [33]. A taurolidine-citrate (4%)-urokinase (25,000 U) lock solution is now available.

Locking of catheters with ethanol is a promising technique: the agent is bactericidal, has low toxicity, is unlikely to produce resistant organisms, is able to disinfect organisms in biofilms and is cheap; ethanol is bactericidal by protein denaturation and is active against a wide variety of organism including Gram-positive bacteria, Gram-negative bacteria and fungi. A study has been designed comparing ethanol lock (70%) once a week versus standard heparin lock [34], but it recruited a limited number of patients and could not demonstrate a benefit of ethanol [35].

In patients with vascular access, the probability of dialysis access-related infection is considerably less for patients with native arteriovenous fistulae than for those with synthetic grafts [36]. Postoperative wound infection as well as poor aseptic technique at dialysis may cause infection of the fistula; silent infec-

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tion in old nonfunctional clotted prosthetic arteriovenous grafts has been recognized as a frequent cause of bacteremia and morbidity among HD patients [12]. Patient safety, with the aim of avoiding infectious complications, should always be considered, even in the absence of a catheter.

Thrombolytics

Catheter thrombosis is another relevant problem for patients dialyzed with a CVC, leading to the use of thrombolytic therapy. Urokinase is used in Europe, and recombinant tissue plasminogen activator in the US for prevention and treatment of thrombosis.

Locking of the catheter with urokinase (5,000 IU instilled to each lumen for 30 min) may be used to open occluded CVCs [37], but in some patients is ineffective and is suggested in those patients who have contraindications to systemic urokinase. High-dose intradialytic urokinase (250,000 IU infused into the venous chamber over 3 h) is safe and effective in almost all instances of nonpositional malfunction of hemodialysis catheters without signs of sepsis; contraindications to high-dose systemic urokinase are rare in stable hemodialysis outpatients [38]. However, it is not indicated in patients with recent trauma or surgery.

The recombinant tissue plasminogen activator alteplase has recently been shown to be an effective alternative for restoring line patency [39]. In addition, a recent randomized trial demonstrated that the use of alteplase instead of heparin once weekly, as compared with the use of heparin three times a week, as a locking solution for central venous catheters significantly reduced the incidence of catheter malfunction and bacteremia [40]. It is also significantly more expensive than heparin and urokinase, but it can reduce the costs of unblocking or replacing clotted CVCs [41].

Analgesics

In CKD patients, analgesic drugs are difficult to handle, and pain is often undertreated as renal failure modifies the PK and PD of analgesics. In addition, most analgesics and their active metabolites are distributed in different tissues and their distribution volume is frequently altered in renal failure. Therefore, it is possible to observe side effects even at low doses of analgesics. In addition, many patients with CKD follow complex polypharmacy therapies for which there is a high risk of drug interactions.

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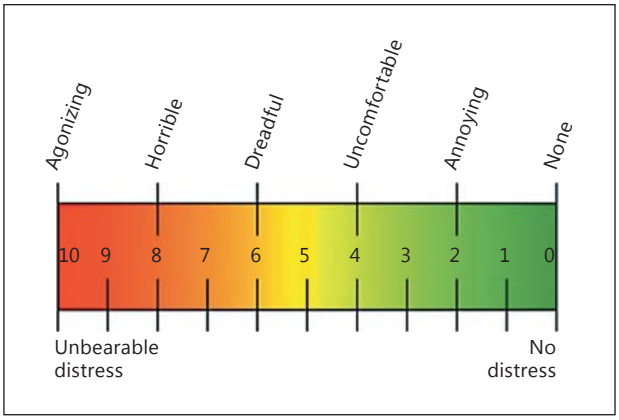

Fig. 2. Example of a VAS, where 0 is no pain and 10 is agonizing pain. Pain is a subjective sensation, and patients can adequately express the level of pain they are feeling and the level of pain they consider acceptable using the VAS.

Before starting treatment of pain, it is always necessary to understand its cause. In the general population, different drugs are available for the treatment of acute and chronic pain: peripherally acting analgesics (paracetamol and non-steroidal anti-inflammatory drugs, NSAIDs), centrally acting analgesics (opioids), clonidine, adjuvants (anticonvulsants, antidepressants, ketamine), peripheral neuronal blocking. NSAIDs are known for their renal toxicity and they should be avoided in renal failure. In addition, local anesthetics are generally used for control of surgery-related acute pain prevention and treatment.

Somatic pain responds well to NSAIDs and narcotics. Visceral pain, deep and poorly localized, caused by irritation of the serous or distension or ischemic tissue (for example pain associated with nephrolithiasis or pancreatitis) responds better to narcotics. In some cases, however, the narcotics themselves can exacerbate the problem (for example in case of bile duct obstruction). Neuropathic pain is characterized by excruciating burning pain, and is frequently associated with hypersensitivity. It may be more responsive to anticonvulsants and antidepressants than to opioids.

The knowledge of formulations, PK, potency and duration of analgesics is required for optimal analgesic therapy practice.

For a good treatment plan, one must first establish visual-analogue scale pain intensity (fig. 2), which is broadly classified as follows: mild pain (visual analogue scale, VAS, 1–4), moderate pain (VAS 5–6), and severe pain (VAS 7–10).

Barakzoy and Moss [42] validated in patients with renal failure the three-step scale of the World Health Organization for the treatment of pain, achieving ad-

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Table 2. General principles for the treatment of chronic pain in CKD patients

Pain level	Recommended analgesic	Safety issues
Mild pain: VAS 1–3	Paracetamol (±adjuvant) is the nonnarcotic agent of choice NSAID are not indicated (topical gels may be used in small amounts)	Paracetamol: at high doses (over 4 g/day), liver toxicity is possible, especially in patients with chronic liver disease (viral or alcohol related) NSAID: increased risk of gastrointestinal bleeding; oliguria/anuria due to sodium and water retention; hyperkalemia; worsening of renal function
Moderate pain: VAS 4–6	Tramadol (with dose adjustment according to residual renal function)	Side effects are similar to those observed with opioids: constipation; nausea; central nervous system depression; seizures (in conditions with lower seizure threshold) May precipitate excess serotonin activity (serotonin syndrome), when patients are concomitantly treated with serotonergic drugs
Severe pain: VAS 7–10	Fentanyl (mostly cleared by the liver; inactive metabolites) Buprenorphine (with dose adjustment according to residual renal function; mostly cleared by the liver; inactive metabolites) Methadone (mostly cleared by the liver; inactive metabolites)	Safe for treatments over short periods; all may accumulate in the long term Reassess the need and dose of opioids every 24–48 h Use caution in opioid-naïve patients (monitor for central nervous system and respiratory effects) Fentanyl and methadone are highly protein bound and not dialyzable Constipation; nausea; central nervous system depression; seizures (in conditions with lower seizure threshold) May precipitate excess serotonin activity (serotonin syndrome), when patients are concomitantly treated with serotonergic drugs

equate analgesia in 96% of patients. However, this scheme is not applicable to acute pain for the long kinetics of tramadol, methadone and fentanyl; for the treatment of acute pain, rapid action and easy handling therapy is necessary. With this understanding, the general principles for the treatment of chronic pain in CKD are summarized in table 2, while in table 3 a treatment algorithm is proposed for acute pain [42, 43].

Analgesic drugs can be administered intravenously or orally. It is a doctor's duty to prevent the onset of severe pain by early administration of an analgesic rather than waiting until the patient has severe pain. The goal is the absence of pain, but also the limitation of side effects.

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Table 3. Treatment of acute pain in CKD patients

Severity of pain	CKD EPI 50–10 ml/min[1]	CKD EPI <10 ml/min or dialysis[2]
Mild pain	paracetamol 1 g × 4; tramadol 100 mg may be added	paracetamol 1 g × 3; tramadol 50 mg may be added
Moderate pain	paracetamol 1 g × 4 + tramadol 100 mg × 2; buprenorphine 0.15 mg may be added	paracetamol 1 g × 3 + tramadol 50 mg × 2; buprenorphine 0.15 mg may be added
Severe pain[3]	buprenorphine 0.3 mg × 2 + paracetamol 1 g × 4; buprenorphine (3rd dose)	buprenorphine 0.3 mg × 2 + paracetamol 1 g × 3; buprenorphine (3rd dose)

[1] An eGFR of 50–10 ml/min calculated with the CKD-EPI formula usually corresponds to an Scr level between 1.5 and 5 mg/dl for males and between 1.25 and 4 mg/dl for females.
[2] An eGFR <10 ml/min or dialysis calculated with the CKD-EPI formula usually corresponds to an Scr level >5 mg/dl for males and >4 mg/dl for females.
[3] The combination oxycodone/naloxone is an opioid analgesic which may also be used for severe pain in CKD patients. Oxycodone is responsible for the pain-relieving effects, while naloxone reduces opioid-induced constipation.

Anesthetics

The anesthetist treating CKD patients is confronted with a number of clinical challenges related to altered drug handling, the production and accumulation of active metabolites and difficulties with vascular access and fluid balance [44]. CKD is a risk factor for serious postoperative complications, such as acute renal failure and cardiovascular complications, which are associated with an increased morbidity and mortality [45].

Dose adjustments are not usually necessary until GFR falls below 50 ml/min. CKD may influence both the PK and the PD of a drug [44].

Local anesthetics have two plasma protein-binding sites: a high-affinity and low-capacity site, and a low-affinity high-capacity site on albumin; the albumin-binding site becomes increasingly important as the plasma concentration of the local anesthetic increases. Metabolic acidosis increases the percentage of unbound drug, and this effect is more pronounced with bupivacaine [46].

Local anesthetics, such as lidocaine, are metabolized in the liver and excreted by the kidneys. Acute or chronic deterioration of renal function can lead to their inadequate clearance. Use of local anesthetics is not contraindicated in CKD patients with eGFR <50 ml/min, but dosages should be kept to a minimum and the interval between injections adequately extended.

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Local anesthesia and regional blocks, commonly used in vascular access surgery, may affect vein diameter and fistula blood flow rates, which are important predictors of fistula failure. Regional block anesthesia (brachial plexus block) is associated with vasodilation in both the cephalic and basilic veins and with increased fistula blood flow.

Intravenous Anesthetic Agents

- Propofol PK are unaltered by established renal failure; the time interval between cessation of a propofol infusion and eye opening is significantly shorter in renal failure patients than controls, although blood propofol concentrations are not significantly different on waking [47].
- Thiopental has an increased volume of distribution and reduced plasma protein binding in renal failure, and the brain is exposed to a higher free drug concentration, so the rate of administration should be reduced [48].

Potent Inhalation Agents

- Methoxyflurane anesthesia may determine elevated serum inorganic fluoride levels and polyuric renal failure (serum fluoride levels >50 μmol/dl were associated with an increased risk of renal damage) [49].
- Enflurane: case reports of renal failure after enflurane anesthesia suggest that it is best avoided in patients with renal dysfunction [50].
- Desflurane and isoflurane are not associated with renal toxicity and appear safe to use in patients with CKD [51].

Anticoagulants and Platelet Aggregation Inhibitors

The prevalence of atrial fibrillation (AF) in end-stage renal disease is high, with an increased risk of stroke among these patients with AF compared with the AF population without severe renal impairment. Many trials have shown the clinical benefit of oral anticoagulation therapy for primary and secondary prevention of stroke in patients with AF. However, current stroke risk stratification schemes are based on studies that have deliberately excluded patients with severe renal impairment. Indeed, there are no large randomized controlled trials assessing the real risk/benefit of full intensity anticoagulation in patients with severe renal impairment. In addition, rates of major bleeding episodes in anticoagulated hemodialysis patients with AF are high [52].

Using data from the international Dialysis Outcomes and Practice Patterns Study (DOPPS) studying patients with AF, Wizemann et al. [53] found that warfarin use was associated with an overall significantly higher stroke risk due to an

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increased risk of bleeding, particularly in those over 75 years of age. This study shows that AF is common and associated with elevated risk of adverse clinical outcomes, and this risk is even higher among elderly patients prescribed warfarin. The effectiveness and safety of warfarin in hemodialysis patients require additional investigation [53].

Many physicians prescribe anticoagulants and antiplatelet medications to prevent thromboembolic events and access thrombosis in dialysis patients despite limited evidence of their efficacy in this population. Chan et al. [54] concluded that warfarin, aspirin, or clopidogrel prescription is associated with higher mortality among hemodialysis patients [54].

Recently, several novel oral anticoagulants (NOACs; rivaroxaban, dabigatran, apixaban) have been tested in large trials involving patients with AF and venous thromboembolism (VTE). All of these new anticoagulants are partially eliminated by renal clearance. In CKD patients, therefore, the half-lives of these novel anticoagulants may be prolonged, resulting in enhanced antithrombotic activity. On the other hand, there might be a higher risk of bleeding in CKD patients with these compounds.

The ROCKET-AF study [55] tested the efficacy and safety of rivaroxaban, a novel factor Xa inhibitor, in 14,264 patients with nonvalvular AF and additional stroke risk factors compared with standard warfarin therapy aiming at an international normalized ratio (INR) of 2.0–3.0. Rivaroxaban is predominantly metabolized by the liver, but approximately one third of the drug is cleared by the kidneys. The ROCKET-AF trial excluded patients with an eGFR <30 ml/min, whereas the daily dose of rivaroxaban was reduced from 20 to 15 mg in patients with an eGFR of 30–49 ml/min based on available PD data and PK modelling [55].

In the setting of chronic nonvalvular AF or venous thromboembolism, a recent systematic review of 8 randomized controlled trials among patients with CKD who received NOACs compared with those who received vitamin K antagonists (VKAs) identified no difference in the risk of stroke and systemic thromboembolism, recurrent thromboembolism or thromboembolism-related death, or bleeding. CKD was defined as a creatinine clearance between 30 and 50 ml/min [56]. Collectively, the NOACs have demonstrated efficacy and safety similar to those of the VKAs in patients with moderate CKD (CrCl 30–50 ml/min); however, trials evaluating the effect of these agents on important clinical outcomes in patients with more severe CKD, including patients undergoing dialysis, are lacking [56].

When planning vascular access interventions, one important safety aspect is the management of already established anticoagulant and antiplatelet treatments. Oral anticoagulation should be substituted with unfractionated heparin,

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which can be easily monitored with activated partial thromboplastin time and stopped the day before surgery. Low-molecular-weight heparins, on the other hand, pose an increased risk of bleeding because they accumulate in patients with CKD, unless their activity is monitored by the anti-factor Xa assay, which currently is not widely available.

Patients with CKD, including dialysis patients, are often prescribed platelet aggregation inhibitors. However, safety with antiplatelet therapy is a major concern in patients with renal impairment because they are at increased risk of bleeding compared with the general population for the concurrent uremia-related platelet dysfunction [57]. Therefore, understanding strategies of antiplatelet management in patients with CKD is of key importance. The most commonly used agents are ticlopidine, clopidogrel, and aspirin, which sometimes are combined.

A systematic review identified 16 studies including 40,676 patients, and found an increased bleeding risk for hemodialysis patients treated with combination antiplatelet therapy, while there are mixed results for studies using a single antiplatelet agent [58]. The study also suggested that antiplatelet agents appear to be effective in preventing shunt and central venous catheter thrombosis, but not for preventing thrombosis of arteriovenous grafts. Considering risks and benefits, the usefulness of antiplatelet agents for the prevention of access thrombosis in dialysis patients remains poorly defined. Individual risk stratification taking into account the increased risk of bleeding should be considered before initiating antiplatelet agents, especially in combination therapy [58].

Ongoing treatment with antiplatelet agents is generally stopped before planned vascular access surgery because they might increase the bleeding and the overall surgical risk in CKD patients. A recent retrospective study in renal transplantation, however, highlighted that these drugs are associated with a low risk of bleeding during renal transplantation, and their use does not seem to be a contraindication for renal transplant surgery [59]. The same might be true for vascular access surgery, especially when considering risks in patients needing urgent interventions for vascular access dysfunction.

Martinez Salazar et al. [60] reported no bleeding complications after 53 tunneled hemodialysis catheter procedures performed in dialysis patients on clopidogrel therapy, indicating that cardiologic indications to continue clopidogrel after cardiac procedures can be followed with low risks of complications during dialysis catheter procedures.

After vascular access surgery, benefits and risks of antithrombotic medications should be considered. The aim of such treatment is increasing the access duration, but its suitability for needling is also an important outcome to be considered.

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Antiplatelet agents represent a logical strategy to prevent vascular access failure. Clopidogrel activity has been studied in patients with renal function impairment [61], although no data are reported in the drug prescribing information. Dose adjustment in patients with severe renal failure (GFR 5–15 ml/min) and moderate renal impairment (GFR 30–60 ml/min) does not appear to be required [61].

Clopidogrel has been evaluated for prevention of AV fistula nonmaturation [62] in a multicenter randomized clinical trial. Patients received either clopidogrel or placebo for 6 weeks after surgery. Although the frequency of access thrombosis within 6 weeks was significantly lower in patients receiving clopidogrel (12.2 vs. 19.5%), AV fistula nonmaturation was similar (and surprisingly very high) in both groups (61.8 vs. 59.5%). Antithrombotics for prevention of stenosis or thrombosis of AV grafts have also been evaluated with randomized trials. Neither warfarin nor aspirin plus clopidogrel prevented AV graft thrombosis, but unfortunately they increased the risk of bleeding complications [63, 64]. Dipyridamole plus aspirin produced a modest, although significant, prolongation of primary unassisted AV graft survival [65].

Interestingly, long-term fish oil ingestion (four 1-gram capsules/day) in patients with new hemodialysis grafts decreased by 22% (although statistically nonsignificant) the proportion of grafts with loss of native patency within 12 months [66]. In addition, fish oil improved some relevant secondary outcomes such as graft patency (RR 0.58), rates of thrombosis (RR 0.50), and angioplasty (RR 0.59). Unexpected benefits on cardiovascular events were also observed: improved cardiovascular event-free survival (hazard ratio, 0.43) and lower mean systolic blood pressure, indicating a favorable risk/benefit ratio for this pharmacological approach [66].

Systemic anticoagulation for the prevention of dialysis catheter thrombosis is controversial for its inherent risk-benefit issues: while it may improve catheter survival, it can also increase the risk of side effects, such as bleeding and cardiovascular calcifications due to inhibition of vitamin K-dependent proteins such as MGP (Matrix Gla protein) [67, 68].

Warfarin at the mini-dose of 1 mg/day was not effective in preventing thrombus formation with hemodialysis catheters, although catheter survival improved in patients with an INR greater than 1.00 [69]. A retrospective study found a significantly reduced thrombosis rate of tunneled catheters using anticoagulation at therapeutic levels [70]. Similar results were reported in patients anticoagulated after treatment with urokinase for thrombosis [71] and in patients at high risk for thrombosis with the maintenance of target INR in the range of 1.5–2.0 [72]. Twardowski [73] proposed a stepwise anticoagulation strategy in which the warfarin dose, started at 1 mg/day, is titrated upwards until thrombotic episodes resolve.

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Thus, anticoagulation appears to be effective in preventing catheter thrombosis, but the available evidence is based on retrospective and noncontrolled studies, where the risks of bleeding, vascular calcification and bone side effects were not assessed. This raises a relevant safety issue, and in the absence of controlled prospective studies confirming the overall benefits of anticoagulation use, its general use cannot be currently recommended [74].

Interactions of Drugs: General Principles

CKD patients are affected by many comorbidities that require multiple pharmacological treatments. One of the factors that can modify the response to drugs is the concurrent administration of other drugs. This phenomenon is defined as drug interaction. Drug interactions may lead to adverse effects and occasionally to fatal outcomes [75]. Adverse effects due to drug interactions are often predictable from previous reports and careful knowledge of pharmacologic principles, but many clinicians have a low awareness of these possible adverse events.

Drug interaction is a condition of pharmacological incompatibilities, in which a drug affects the activity of another drug when they are administered together (drug-drug interaction, DDI); moreover, this reaction may also happen between drug and food, or between drug and medical plants.

Potential DDIs have been frequently reported, but only few studies have been conducted on actual interactions. Some data are available about drug interactions among elderly patients hospitalized for drug toxicity [76]. In a recent review [77], differences between actual and potential DDIs were outlined: the incidence of actual DDIs resulted lower than that of potential DDIs; important adverse effects occur only in the presence of specific risk factors, such as age or genetic polymorphisms.

There are several mechanisms by which drugs may interact; they can be classified as PK, PD, or combined interactions [78, 79]. Drug action can be synergistic (when the drug's effect is increased), antagonistic (when the drug's effect is decreased), or it may produce new effects. Drug interactions depend on both patient-specific factors (intrinsic drug clearance, genetics, gender, concurrent diseases, diet), and drug-specific factors (dose, route of administration, drug formulation, and the sequence of drug administration).

PD Interactions

PD interactions can occur through pharmacological receptors or signal transductor mechanisms [79]. The drugs may or may not act on the same receptor to

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produce pharmacological effects. When drugs with similar pharmacologic effects are concurrently administered, an additive or synergistic response is usually seen.

If the drugs act on the same receptor, they in turn can be:

- Pure agonists, binding to the receptor's main locus and causing a similar effect.
- Partial agonists, binding to one of the receptor's secondary loci, causing the same effect, but with a lower intensity in contrast to the principle drug.
- Antagonists, binding the receptor's main locus but with an opposite effect to that of the main drug. If they compete with the main drug to bind with the receptor, they are defined as competitive antagonists; but, when the antagonist irreversibly binds to the receptor and it is not released until the receptor is saturated, it is called uncompetitive antagonist.

PK Interactions

Different basic PK parameters must be considered for obtaining a careful drug management [78]. The most important are clearance, distribution volume, amount bound in plasma, half-life. Clearance is the measure of capacity to eliminate the drug, while volume of distribution is the measure of the apparent body space available to contain the drug. Moreover, half-life represents the time required to reduce the amount of drug in the body by one half during elimination and attain 50% of steady state. Finally, the renal eliminated fraction of a drug is the key to predict its PK.

PK interactions may modify drug concentrations by interfering with different mechanisms such as absorption, distribution, metabolism, and excretion of the drug [78].

Absorption is strictly related to gastric pH, drug solubility or gastrointestinal motility, while distribution is influenced by competition of plasma protein binding, displacement from tissue-binding sites, or alterations in local tissue barriers.

Metabolism is regulated by metabolizing enzymes, which are typically activated through nuclear receptors. It primarily occurs in liver tissue and small intestine, followed by other sides, such as plasma, lung and kidney. The most important of this enzymatic system is the system of cytochrome P450 isozymes. A result of interactions between endogenous or exogenous factors on enzymatic systems may stimulate the function of the enzyme (enzyme induction) or inhibit it (enzyme inhibition) [80]. The final action is a modification in drug metabolism.

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Table 4. Potential effects of kidney failure on drug PK

Absorption
Diabetic or uremic gastroparesis may alter gastrointestinal transit time and modify drug absorption
A drug able to alter gastric pH (e.g. antacids ad phosphate binders) can reduce the absorption of other drugs
Gastrointestinal tract edema caused by congestive heart failure or nephrotic syndrome can slow drug absorption
Distribution
Edema or ascites may increase the distribution volume for protein-bound and water-soluble drugs
Uremia can alter plasma protein binding, affecting acidic drugs
Hypoalbuminemia and altered plasma protein binding increase free or unbound concentrations of drugs
Tissue protein drug binding is reduced in uremic states
Metabolism
Renal failure may affect liver function, increasing or decreasing hepatic bio-transformations
Excretion
Reduced excretion and prolonged half-life; renal failure may alter glomerular filtration, tubular secretion, reabsorption

Finally, the excretion interactions principally depend on renal function. Drugs are removed from the plasma by the kidney with different mechanisms: passive filtration, reabsorption and active secretion. Filtration depends on urine pH, so that renal excretion of certain drugs that are weak acids or weak bases may be influenced by other drugs that affect urinary pH (for example, drugs acting as weak bases are more easily excreted with acid urine pH; the inverse it is true for weak acids). Finally, secretion is a process based on saturability of the transported molecule and competition between substrates. P-glycoprotein, organic anion and cation transporters are involved in active tubular secretion of some drugs, and inhibition of these transporters can reduce renal elimination of the drugs, causing an increase in their serum levels [81].

Considering the key role of the kidneys in drug metabolism and excretion, kidney failure obviously modifies drug PK (table 4).

Drug Dosing in Patients with Renal Failure

The standard dose of a drug derives from studies in healthy volunteers and patients with normal capacity to metabolize and eliminate drugs [78]. However, the effective dose may be different from patient to patient. Pathologic conditions

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Table 5. Drug dosage individualization in patients with CKD

eGFR should be calculated for evaluating the stage of CKD and drug dosing purposes
Dosing adjustments are generally required when GFR falls below 50 ml/min/1.73 m^2
The impact of interactions of all drugs commonly used in CKD patients (e.g. phosphate binders) should be evaluated
The volume of distribution (VD) of many drugs is increased in patients with moderate to severe CKD as well as in those with pre-existing CKD who develop AKI; the increase in VD may be the result of decreased protein binding or fluid overload; obese CKD and AKI patients and those with large variations in serum protein levels should have their drug dosage individualized
Dosing changes can involve dose reduction, increasing the interval between doses or both
Loading doses may be required if a drug has a long half-life and there is a need to rapidly achieve the desired steady-state concentrations or if the VD of a drug is significantly increased
Maintenance dose: most commonly, prolonging the dosing interval but maintaining the same dose will result in the achievement of similar peak and trough concentrations as well as area under the curve and thus may be preferred
A more accurate drug dosage adjustment is recommended for agents that have a narrow therapeutic index; when available, measurement of therapeutic drug levels may optimize therapeutic regimens; hypoalbuminemia may influence the interpretation of drug concentrations

(heart, liver or renal failure) may demand dosage adjustment in individual patients because they modify specific PK parameters of the drugs.

For the predominant role of the kidneys in drug metabolism and excretion, patients affected by renal failure require an adjustment of dosing for substances cleared and metabolized by the kidney. The principles for drug dosage individualization in CKD patients are summarized in table 5.

Dose adjustment is based on a combination of PK and PD effects, determining the relationship between the concentration of a drug and its final effect on organs [82]. In case of a marked reduction of glomerular filtration, certain drugs should no longer be given, either because they may further damage the kidneys or because they are insufficiently eliminated and will accumulate, causing adverse events.

Dosages of drugs cleared by kidney should be adjusted according to creatinine clearance or GFR calculated using online or electronic calculators [83], as previously outlined.

A careful assessment of renal function is necessary before starting a drug. It is necessary to evaluate if a drug should be administrated or not, and/or if a dosing adjustment is required according to GFR.

Attention in the use of antibiotics is particularly important. Patients with fluid overload may require a larger loading dose, in contrast to dehydrated pa-

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tients. Patients with renal insufficiency generally need a higher starting dose, and then the maintenance dose is adjusted according to renal function, depending on drug half-life. The starting dose is important for both types of antibiotic, those whose effect is concentration dependent and those whose effect is time dependent. For adjusting the maintenance dosage in patients affected by kidney failure, it is possible to reduce the dose or to increase the intervals between doses, keeping the dose size normal. In clinical practice, a combination of the two methods is often useful. Finally, in patients requiring dialysis, many drugs are given at the end of the dialysis session, minimizing removal during dialysis. As a clinical alternative, it is often useful to search for drugs that are similar to the principal drugs but not metabolized by the kidney [83].

Detailed dosing recommendations for individual drugs are available in specific textbooks [84, 85]. Nevertheless, although guidelines are available, indications and regimens must be always individualized according to patient response and serum drug concentrations.

Problematic Drugs in CKD

Many drugs are commonly administered in CKD and dialysis patients. Here, we focus our attention on drugs required for management of vascular access: antimicrobials, anticoagulants, analgesics and anesthetics. PK parameters may be modified in kidney failure and dosing adjustment based on GFR may be required, especially for antimicrobials (table 6). Again, we want to emphasize that patients affected by renal failure are at high risk of adverse events induced by NSAIDs [86]. The most frequent are acute kidney failure, nephritic/nephrotic syndrome, papillary necrosis. In patients with preexisting renal damage, the use of NSAIDs can lead to permanent renal damage. The risk of renal damage is increased if NSAIDs are administrated together with ace inhibitors, in dehydrated conditions and for prolonged time. They should be avoided in renal failure.

Measurement of Therapeutic Drug Levels

Measuring drug concentrations is one way to optimize therapeutic regimens and account for changes between individuals. Therapeutic drug monitoring mainly involves antibiotics (i.e. vancomycin, gentamicin), immunosuppressives (cyclosporine), anti-seizure drugs (carbamazepine, phenytoin and valproic acid), mood stabilizers (lithium), and antipsychotics.

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Table 6. PK parameters for selected drugs used in CKD/dialysis patients and dosing adjustment according to GFR

Drug	Urinary excretion, %	Bound to plasma proteins, %	Volume of distribution, l/kg	Half-life normal/ESRD, h	Dose for normal renal function	Dosing adjustment for eGFR	
						30–15 ml/min (CKD IV)	<15 ml/min (CKD V)
Antiplatelet and anticoagulant drugs							
Acetylsalicylic acid (aspirin) for prophylaxis of thrombosis	5–80% (highly variable: increases with increased urinary pH)	80–90	0.1–0.2	2 (salicylate)/unchanged	75–325 mg q24 h	75–325 mg q24 h	not recommended[a]
Warfarin	3	99	0.15	34–45/unchanged	2–10 mg[b]	100%	10%
Ticlopidine	2	98	no data	12/no data (single dose) 24–33/no data (repeat dosing)	250 mg q12 h	100%	100%
Clopidogrel	50	98	no data	6–8/no data	75 mg q24 h	100%	100%
Heparin	–	90	0.06–0.1	0.3–2/unchanged	50–75 IU/kg per day	100%	100%[c]
Low-molecular-weight heparin	–	no data	0.06–0.13	22.6/4–10	30–40 mg q12 h[d]	100%	50%[d]
Pain medications/analgesics							
Paracetamol (acetaminophen)	3	20–30	1–2	2/2	500–1,000 mg q4 h	500–1,000 mg q6 h[e]	500–1,000 mg q8 h[e]
Tramadol	95	20	2–3	5–7/11 (range up to 20 h)	50–100 mg q12–4 h depending on severity of pain	50–100 mg q12 h[f]	50 mg q12 h[f]
Buprenorphine	30 (inactive metabolites)	96	2.8	37/unchanged	0.3 mg q6 h (initial dose)	0.15–0.3 mg q12 h	0.15–0.3 mg q12 h
Fentanyl	10	84	3–4	i.v.: 6/no data sublingual: 6.6/no data transdermal: 20–27/no data	sublingual: 100 µg (initial dose) transdermal: 25 µg/h (initial dose)	75%	50%
Codeine	>90	7	3–4	2.5–3.5/no data	30–60 mg q4–6 h	avoid[g]	avoid[g]

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Table 6 (continued)

Drug	Urinary excretion, %	Bound to plasma proteins, %	Volume of distribution, l/kg	Half-life normal/ESRD, h	Dose for normal renal function	Dosing adjustment for eGFR	
						30–15 ml/min (CKD IV)	<15 ml/min (CKD V)
Methadone	highly variable (reduced with increased urinary pH)	85–90	1–8	30/unchanged	2.5–10 mg q8–12 h	75%[g]	50%[g]
Morphine	8%	20–30	3.5	1–4/unchanged	20–25 mg q4 h	avoid[g]	avoid[g]
Antimicrobial drugs							
Gentamicin	76	10	0.23–0.28	1.8–3/20–60	1.7 mg/kg q8 h	100% q12–24 h	100% q48 h
Ciprofloxacin	65	40	2.5	3–6/6–9	500–750 mg q12 h	50–75%	50%
Levofloxacin	60–80	24–38	1.1–1.5	4–8/76	250–750 mg q24 h	250–750 mg q24–48 h[h]	250–500 mg q48 h[h]
Vancomycin	80	30	0.4–1.1	4–6/200–250	1 g q12 h	1 g q24–96 h	1 g q4–7 days[i]
Amoxicillin	50–70	15–25	0.26	0.9–2.3/5–20	250–500 mg q8 h	250–500 mg q8–12 h	250–500 mg q24 h
Ampicillin	30–90	20	0.17–0.31	0.8–1.5/7–20	250 mg to 2 g 6 h	250 mg to 2 g q6–12 h	250 mg to 2 g q12–24 h
Cefazolin	90	80	0.13–0.22	2/40–70	0.25–2 g q6 h	100% q12 h	50% q24–48 h
Ceftazidime	60–80	5–24	0.18–0.31	1.2/13–25	1–2 g q8 h	1–2 g q12–24 h	1–2 g q24–48 h
Ceftriaxone	30	90	0.12–0.18	7–9/12–24	0.25–2 g q12–24 h	100%	100%
Meropenem	70	2	0.35	1.1/6–10	1–2 g q8 h	100% q12 h	100% q24 h
Imipenem	70	13–21	0.17–0.3	1/4	0.2 mg to 1 g q6 h	50%[j]	25%[j]
Local anesthetics							
Lidocaine 0.5 – 1%	<10	70	1.1	1.8/5.0	5–300 mg (1–60 ml)	75%	75%

Modified from Holford [78], Berns and Aronoff [84], and Gilbert et al. [85].
[a] Nephrotoxic at high doses (a potential GFR reduction when renal blood flux is supported by prostaglandins); dose of 100 mg when administrated as antiplatelet action. [b] According to INR, reduced binding to plasma protein in CKD. [c] Increased risk of bleeding – measure activated partial thromboplastin time. [d] 1 mg = 100 IU; monitored by anti-Xa factor activity; reduced elimination in renal failure. Avoid in renal failure if anti-Xa factor activity cannot be monitored. [e] Safe in CKD. [f] 100 mg extended-release tablets should not be used. [g] Opioid use causes adverse events in CKD patients. [h] Loading dose 500 mg. [i] Measure serum levels. [j] Administered together with cilastatin to prevent nephrotoxicity.

Therapeutic drug monitoring requires availability of rapid, specific, and reliable assays and known correlations of drug concentration to therapeutic and adverse outcomes. Hypoalbuminemia may influence the interpretation of drug concentrations as the total drug concentration may be reduced even when the active unbound drug concentration is not. Unbound drug concentrations are often not clinically available, and therefore clinicians must empirically consider the impact of hypoalbuminemia in their interpretation of measured total drug concentrations.

Conclusions

Safety of pharmacologic therapy in CKD patients is a major concern. Therefore, understanding strategies of drug management in this patient population is of key importance. The lack of studies performed specifically in patients with impaired renal function, particularly those with AKI or end-stage renal disease, who are generally excluded from many large-scale clinical trials, often leads to either no recommendation on the most appropriate pharmacologic treatment regimen or to opinion-based indications. Overall, the choice and combination of drugs prescribed to CKD patients should be balanced against the individual risk of adverse events. More data from large-scale clinical trials including CKD patients or even better from dedicated studies in patients with CKD are warranted in order to define the most effective and safe drugs for CKD patients.

Disclosure Statement

The authors have no conflicts of interest to declare.

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