Abstract

Due to the increasing incidence of acute kidney injury (AKI) and chronic kidney disease (CKD), nurses in most healthcare settings are likely to care for patients with some degree of impaired kidney function. Impaired kidney function can adversely affect the way the body excretes, absorbs, distributes and metabolises medicines (pharmacokinetics), potentially resulting in a wide range of drug-related complications. This article provides an overview of the effects of impaired kidney function on pharmacokinetics and the importance of accurate drug dose adjustments for patients with related conditions. It also discusses various aspects of medicines use in patients with AKI, the pharmacological management of patients with CKD and the use of immunosuppressive therapy in patients who have had a kidney transplant. The authors consider the role of the nurse in ensuring safe medicines use for patients with impaired kidney function throughout the article.

Impaired kidney function: supporting the safe use of medicines for patients

Kathrine Parker and Janette Chu

Significant kidney function impairment can result in a range of complications, including fluid retention, hypertension, electrolyte imbalances (for example high potassium or low calcium levels) and build-up of toxins (National Institute for Health and Care Excellence (NICE) 2021). All of these complications alter the aspects of pharmacokinetics – the way in which the body excretes, absorbed, distributes and metabolises medicines – in which the kidneys are involved (Lea-Henry et al 2018). This means that patients with conditions such as acute kidney injury (AKI) or chronic kidney disease (CKD) are at increased risk of experiencing adverse effects of medicines and drug interactions. Therefore, consideration must be given to the types and doses of medicines that are prescribed and administered in this population (Joint Formulary Committee 2024).

AKI refers to rapid deterioration of kidney function in both kidneys, either through direct injury or acute functional deterioration (Kellum et al 2012, Ostermann et al 2019). The incidence of AKI is increasing, potentially due to an ageing population with multiple comorbidities and improved identification of the condition (NICE 2023a). Around one in five emergency hospital admissions in the UK is associated with AKI, while the estimated cost of AKI-related inpatient care to the NHS in England is around £1.2 billion per year (NICE 2023a). People at risk of developing AKI include those with long-term conditions such as diabetes mellitus, cardiac failure, liver failure or CKD (NICE 2023a).

CKD, which has been defined as ‘a reduction in kidney function or structural damage (or both) present for more than three months, with associated health implications’ (NICE 2024), is also an increasing issue for healthcare services. In 2023, an estimated 3.25 million people in the UK were living with stages 3-5 of the condition (from mild or moderate kidney damage to established renal failure) (Kidney
The kidney excretes drugs and in people with diabetes mellitus who take exogenous insulin, the kidney may metabolise up to 80% of the drug. The effects of impaired kidney function on pharmacokinetics and the importance of accurate drug dosing in patients with associated conditions. The authors also discuss various aspects of medicines use in patients with AKI and the pharmacological management of patients with CKD. Medicines use in patients with renal-related critical illness, or those who require intensive care and/or continuous renal replacement therapy, is beyond the scope of this article.

**Effects of kidney impairment on pharmacokinetics**

There are four stages of pharmacokinetics: absorption of a drug into the body (unless the drug is given intravenously); distribution to the site of action; metabolism into smaller components; and excretion from the body (Lea-Henry et al 2018). While the kidney has a fundamental role in the excretion of medicines and metabolites from the body, all four stages of pharmacokinetics can be adversely affected in patients with altered kidney function (Lea-Henry et al 2018). Table 1 details some of the effects of impaired kidney function on the four stages of pharmacokinetics.

**Drug dose adjustments**

Reduced excretion of medicines in patients with impaired kidney function may result in increased drug levels with predictable adverse effects (Joint Formulary Committee 2024), so careful consideration must be given to the choice and dose of medicines prescribed and/or administered.

Understanding how drug dose adjustments are made in patients with impaired kidney function will enable the nurse to check dose calculations when they are administering medicines, which facilitates early identification of potential dosing errors and enhances patient safety. Furthermore, the ‘10 Rs’ of safe medicines administration emphasise that nurses or other healthcare professionals should follow the ‘5 Rs’ (right patient, drug, route, time and dose) and understand the causes of drug errors, how to implement strategies to reduce drug errors and how to ensure safe medicines practice (Edwards and Axe 2015). This is supported by the Royal Pharmaceutical Society and Royal College of Nursing (2019) joint guidance on the administration of medicines in healthcare settings.

Drugs excreted via the renal system, where small differences in blood concentration can cause adverse effects, are likely to require a dose reduction when this system is impaired. There are two ways of making drug dose adjustments in patients with impaired kidney function: by increasing the dosing interval but using the same dose, or by decreasing the dose but using the same dosing interval (Joint Formulary Committee 2024).

The British National Formulary provides information on renal dosing for individual medicines, expressed in terms of estimated glomerular filtration rate (eGFR) (Joint Formulary Committee 2024). eGFR is a calculation used to estimate how well the kidneys are functioning by measuring how well they are filtering serum creatinine, a waste product of muscle and protein metabolism and breakdown. Using eGFR is appropriate for prescribing and dose adjustments for most patients and with most medicines; however, in some circumstances dose adjustments should be determined by creatinine clearance, calculated using the Cockcroft-Gault formula (Medicines and Healthcare products Regulatory Agency (MHRA) 2019).

**Table 1. Effects of impaired kidney function on the four stages of pharmacokinetics**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Effect of impaired kidney function</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Drug absorption is reduced due to gastrointestinal side effects, for example vomiting</td>
<td>Decreased absorption of oral iron</td>
</tr>
<tr>
<td></td>
<td>Patients with stages 4 and 5 chronic kidney disease (CKD) (severe kidney damage or established renal failure) and those on renal replacement therapy will require intravenous iron</td>
<td></td>
</tr>
<tr>
<td>Distribution</td>
<td>Reduction in drug binding to albumin, which increases the concentration of active drug in the body</td>
<td>Patients taking medicines such as phenytoin (used in the treatment of seizures) may be exposed to increased phenytoin levels, so will require monitoring and potentially a lower dose of the medicine</td>
</tr>
<tr>
<td></td>
<td>Patients who require warfarin sodium may require a low starting dose and regular international normalised ratio (blood clotting time) monitoring</td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>Reduction in the activity of metabolic enzymes, therefore the drug remains active for longer</td>
<td>In people with diabetes mellitus who take exogenous insulin, the kidney may metabolise up to 80% of the drug, so smaller doses may be required in those with reduced kidney function to avoid hypoglycaemia</td>
</tr>
<tr>
<td>Excretion</td>
<td>The kidney excretes drugs and metabolites in the urine, therefore impaired kidney function can reduce the clearance of some drugs, potentially resulting in drug accumulation and toxicity</td>
<td>Accumulation of opioids, particularly morphine and codeine phosphate, can result in opioid toxicity, so should be avoided in people with severe kidney function impairment, such as those with stage 4 and 5 CKD or acute kidney injury</td>
</tr>
<tr>
<td></td>
<td>Pregabalin and gabapentin are fully excreted by the kidney, so patients taking these medicines may require a significant dose reduction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Accumulation of anticoagulants, such as direct oral anticoagulants, can result in bleeding complications</td>
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</tbody>
</table>

(Adapted from Lea-Henry et al 2018, Renal Drug Database 2024)
An online calculator is available at: www.mdcalc.com/calc/43/creatinine-clearance-cockcroft-gault-equation

Examples of circumstances where dose adjustments should be determined by creatinine clearance calculated using the Cockcroft-Gault formula include (MHRA 2019):

- Nephrotoxic medicines (medicines that are harmful to the kidneys), such as gentamicin.
- Medicines that are renally excreted with a narrow therapeutic index (a narrow difference between a medicine being effective or toxic), such as digoxin.
- Anticoagulants, such as direct-acting oral anticoagulants or low molecular weight heparin.
- For older patients (aged >75 years).
- For patients at extremes of body weight, since their body surface area may differ from the standard (laboratory reported eGFR is normalised to a body surface area of 1.73m²), leading to an overestimation or underestimation of kidney function and subsequent drug dosing.

No method for estimating kidney function has been validated for use in pregnancy, where the circulating blood volume is significantly increased, or in patients with AKI, where there is a delayed increase in serum creatinine following renal injury (Waikar and Bonventre 2009). However, in practice, creatinine clearance trends based on the Cockcroft-Gault formula, and changes in urine output, are reviewed regularly in patients with AKI (Kellum et al 2012).

Drug dosing in patients with impaired kidney function should be individualised, based on tolerability of side effects, outcomes of drug-level monitoring (where applicable) and patient and disease characteristics (Joint Formulary Committee 2024). Resources that provide information on drug dosing in kidney impairment include the British National Formulary (bnf.nice.org.uk), Electronic Medicines Compendium (www.medicines.org.uk/emc) and The Renal Drug Database (www.renaldrugdatabase.com/s).

### Medicines use in patients with acute kidney injury

The causes of AKI are categorised as pre-renal, intra-renal and post-renal (NICE 2023a) and affect how the condition is managed. All patients with AKI should have their medicines reviewed, regardless of the cause.

Most AKI episodes are caused by an insult that reduces blood flow to the kidney, referred to as pre-renal AKI (NICE 2023a). Pre-renal AKI may be caused by blood loss, dehydration, sepsis, burns, cardiac failure, liver failure or use of certain medicines, and is usually reversible if identified early (Makris and Spanou 2016). Intra-renal AKI, which is usually caused by structural damage inside the kidney (NICE 2023a), is mainly caused by shock (inability of the body to deliver adequate oxygen to the tissues), infection or the effects of certain medicines (Makris and Spanou 2016). Post-renal AKI is related to a blockage of the flow of urine from the kidney, resulting in an increase in intra-tubular pressure and reduction in eGFR (Makris and Spanou 2016). Box 1 lists some of the risk factors for AKI.

Evidence suggests that mortality is higher with increasing severity of AKI (UK Renal Registry 2020) – severity is classified based on the increase in serum creatinine levels and reduction in urine output (Table 2) (Kellum et al 2012). However, early identification of AKI can improve prognosis (Prescott et al 2012). Therefore, the condition should be considered in any patient who presents with: nausea and vomiting, diarrhoea or signs of dehydration; reduced urine output or change in urine colour; and/or confusion, fatigue or drowsiness (NICE 2023a).

Nurses can support early identification of AKI by raising concerns based on the signs and symptoms described by the patient and by recognising the significance of reduction in urine output and increase in serum creatinine levels in patients’ blood results, then escalating this to the appropriate colleague.

### Key points

- Impaired kidney function can affect all four stages of pharmacokinetics, absorption, distribution, metabolism and excretion
- Reduced excretion of medicines in patients with impaired kidney function may result in increased drug levels and adverse effects, so choice and dose of medicines must be carefully considered
- Nurses have a crucial role in supporting the safe and effective use of medicines in patients with impaired kidney function through understanding drug dose adjustments and recognising potential prescribing errors

### High-risk medicines

Pharmacological considerations in patients with AKI include whether the person is taking medicines that could exacerbate their condition and should therefore be withheld, whether a dose adjustment is required and whether newly prescribed medicines are appropriate.

Medicines to consider withholding during an episode of AKI include (Think Kidneys 2018):

- Angiotensin-converting enzyme (ACE) inhibitors, for example ramipril, if the patient has a high potassium level or low blood pressure, as these types of medicines can exacerbate these symptoms. It is important to consider when to re-start ACE inhibitors, which should ideally be before discharge if the patient’s kidney function is stable.

### Box 1. Risk factors for acute kidney injury

- Aged over 65 years
- History of acute kidney injury
- History of long-term conditions, such as diabetes mellitus, cardiac failure or liver failure
- Chronic kidney disease
- Cancer or receiving cancer treatment
- Neurological or cognitive impairment
- Symptoms or history of urological obstruction
- Sepsis, hypovolaemia or oliguria
- Use of specific medicines within the previous week, such as:
  - Non-steroidal anti-inflammatory agents
  - Angiotensin-converting enzyme inhibitors
  - Angiotensin II receptor blockers
  - Diuretics
  - Antibiotics, including aminoglycosides

(Adapted from National Institute for Health and Care Excellence 2023a)
Nurses have an important role in identifying medicines that may not be appropriate for patients with AKI and escalating this information to the appropriate colleague. For nurse prescribers, reviewing and withholding medicines is an important part of their initial medicines review with the patient, supported by the multidisciplinary team.

**Nephrotoxic medicines**

Some medicines are classified as nephrotoxins, which cause a rapid deterioration in kidney function due to their toxic effect (Al-Naimi et al 2019). One such medicine is gentamicin, a highly effective aminoglycoside antibiotic commonly used in the UK for the treatment of serious infection (Joint Formulary Committee 2024), but which is also one of the most common causes of drug-induced nephrotoxicity (Campbell et al 2023). Patients with AKI who develop sepsis may be given a one-off dose of gentamicin (Cobussen et al 2020).

Monitoring pre-dose gentamicin levels, and once-daily dosing of gentamicin, have been shown to reduce nephrotoxicity in patients with renal insufficiency (Parker and Pogson 2023). Nurses caring for patients receiving gentamicin should ensure that the appropriate monitoring is undertaken, in accordance with local protocols, and escalate elevated gentamicin levels to the appropriate clinical team for review before further administration of the medicine.

Other examples of nephrotoxic medicines include contrast media such as iodine contrast (used in imaging), intravenous bisphosphonates such as zoledronic acid (used in the treatment of osteoporosis, for example) and chemotherapy agents such as cisplatin (Perazella and Rosner 2022, Parker and Pogson 2023).

### Pharmacological management of patients with chronic kidney disease

Patients with CKD experience a gradual deterioration of kidney function over time, classified by five stages (Table 4) (NICE 2024). The rate of progression to kidney failure varies depending on the severity of disease and comorbid conditions (Major et al 2019). Patients at high risk of disease progression, which can be calculated using the Kidney Failure Risk Equation (Tangri et al 2011) – available at: kidneyfailurerisk.co.uk – can be prescribed pharmacological treatment to slow kidney function decline (NICE 2021).

Hypertension can both cause kidney damage and occur as a result of kidney disease (NICE 2021). The recommended target blood pressure for adults with CKD is <140/90mmHg, or <130/80mmHg in those with an albumin to creatinine ratio of ≥70 mg/mmol (NICE 2021, 2023b). Fluid retention secondary to impaired kidney function and over-activation of the renin-angiotensin-aldosterone system.
system due to inadequate renal blood flow can cause hypertension in people with CKD (Parker et al. 2015). Severe fluid retention can be life-threatening if it accumulates in the lungs. Therefore, patients with CKD may need fluid and salt restrictions, alongside high doses of diuretics, to manage fluid levels and blood pressure (Parker et al. 2015).

CKD mineral bone disorder – a condition caused by phosphate, calcium and parathyroid hormone imbalances – can result in abnormal bone turnover, leading to bone damage and calcification of blood vessels (Martin and González 2007). Therefore, patients may require vitamin D supplementation. Reduced erythropoietin secretion, inadequate iron absorption and blood loss on renal replacement therapy can all contribute to renal anaemia, for which patients may be prescribed an erythropoiesis-stimulating agent (Ogden 2018, NICE 2021). Table 5 shows some of the medicines used to treat complications associated with CKD.

Prescribing errors are common when prescribing for patients with CKD (Dunleavy 2012). Nurses have a role in identifying and escalating potential prescribing errors to the medical team and reporting near-miss events. Nurses working in acute settings also have an important role in ensuring medicines such as phosphate binders (Table 5) are administered at the appropriate times to improve treatment efficacy.

Immunosuppressive agents

Kidney transplantation is the preferred option for renal replacement therapy in patients with end-stage renal disease (Tonelli et al. 2011) and has been shown to improve mortality and morbidity, as well as quality of life (Kaballo et al. 2018).

Almost all people who receive a kidney transplant are required to have immunosuppressive therapy to avoid rejection of the donor kidney (National Kidney Foundation 2024). Calcineurin inhibitors, such as tacrolimus, are used as immunosuppressive agents in many UK transplant centres. Small differences in the concentration of tacrolimus in the blood can cause graft rejection or toxicity, so it is important to know that different brands of this medicine are not interchangeable and to ensure that the brand prescribed is the medicine dispensed. Tacrolimus is available in once-daily and twice-daily preparations. Twice-daily preparations should be administered 12 hours apart, with routine monitoring of calcineurin inhibitor levels (MHRA 2017).

Nurses have an important role in supporting timely administration of these medicines.

Calcineurin inhibitors are subject to interactions with other medicines due to their metabolism by cytochrome P450 enzymes in the liver. For example, rifampicin can cause a reduction in calcineurin inhibitor levels that increases the risk of organ rejection and potential kidney failure. Medicines such as erythromycin, clarithromycin, voriconazole and fluconazole can

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**Table 4. Stages of chronic kidney disease**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Estimated glomerular filtration rate (eGFR)  (mL per minute per 1.73m²)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>Normal or high eGFR, with other evidence of kidney damage</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Mild reduction in eGFR, with other evidence of kidney damage</td>
</tr>
<tr>
<td>3a</td>
<td>45-59</td>
<td>Mild to moderate or severe reduction in eGFR, with or without other evidence of kidney damage</td>
</tr>
<tr>
<td>3b</td>
<td>30-44</td>
<td>Established renal failure</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Severe reduction in eGFR, with or without other evidence of kidney damage</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>Renal failure</td>
</tr>
</tbody>
</table>

(Adapted from National Institute for Health and Care Excellence 2022)

**Table 5. Medicines used to treat complications associated with chronic kidney disease**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Medicine</th>
<th>Comments on use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>» Angiotensin-converting enzyme inhibitors, for example ramipril</td>
<td>First-line antihypertensives in adults with diabetes mellitus and/or albuminuria</td>
</tr>
<tr>
<td></td>
<td>» Angiotensin II receptor blockers, for example candesartan cilexetil</td>
<td>Slows renal decline and the risk of cardiovascular events. May cause some kidney function impairment on initiation</td>
</tr>
<tr>
<td>Renal anaemia</td>
<td>Erythropoiesis-stimulating agents, for example darbepoetin alfa</td>
<td>Frequency of administration varies depending on the agent prescribed</td>
</tr>
<tr>
<td></td>
<td>» Hypoxia-inducible factor prolyl hydroxylase inhibitors, for example roxadustat</td>
<td>Often given intravenously during haemodialysis sessions</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Vitamin D, for example alfalcacidol</td>
<td>Approved by the National Institute for Health and Care Excellence (2022) for the treatment of renal anaemia in patients with non-haemodialysis chronic kidney disease</td>
</tr>
<tr>
<td>mineral bone disorder</td>
<td>» Phosphate binders, such as calcium acetate, sevelamer, lanthanum</td>
<td>Stimulates erythropoietin and improves iron bioavailability</td>
</tr>
<tr>
<td></td>
<td>» Sodium zirconium cyclosilicate, which acts as a selective potassium binder in the gastrointestinal tract</td>
<td>Non-absorbed binder that captures potassium throughout the gut</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>Loop diuretics, such as furosemide</td>
<td>A high dose may be required to achieve the desired effect (Parker et al. 2015)</td>
</tr>
</tbody>
</table>

(Adapted from National Institute for Health and Care Excellence 2024)
increase calcineurin inhibitors levels, causing adverse reactions. For example, clarithromycin can increase calcineurin inhibitors levels by around five to six times, resulting in patients experiencing severe sickness, seizures and arrhythmias (Joint Formulary Committee 2024). Having an awareness and understanding of drug interactions can assist nurses in recognising potential issues and escalating their concerns to the appropriate colleague (Edwards and Aye 2015).

Conclusion
The incidence of conditions such as AKI and CKD is increasing so nurses in all healthcare settings may care for patients with kidney function impairment. All four stages of pharmacokinetics can be adversely affected in patients with altered kidney function, therefore consideration must be given to the types and doses of medicines that are prescribed and administered. For patients with AKI, some medicines may need to be withheld or avoided, while patients with CKD can be prescribed pharmacological treatment to slow the decline in kidney function. Nurses can identify early deterioration in patients' kidney function by recognising the signs and symptoms, as well as the significance of reduced urine output and laboratory blood test results. In addition, nurses have a vital role in supporting the safe and effective use of medicines in patients with impaired kidney function through understanding drug dose adjustments and recognising potential prescribing errors.

References


