Drug management in patients with reduced kidney function

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Renal impairment can reduce drug excretion and increase the risk of adverse drug reactions. This article discusses the factors to consider when prescribing for patients with reduced kidney function or acute kidney injury.

The kidneys play a fundamental role in an individual's health, with functions ranging from regulating blood pressure and balancing electrolytes to activating vitamin D and producing urine.

Numerous factors can reduce a patient's kidney function, including medical conditions such as diabetes, hypertension and chronic kidney inflammation, along with advanced age. Commonly prescribed and over-the-counter (OTC) medication such as NSAIDs, ACE inhibitors, proton-pump inhibitors (PPIs), diuretics and antibiotics can also reduce kidney function.

Reduced kidney function results in slower elimination of renally excreted drugs, causing increased levels in the blood and an increased risk of adverse drug reactions (which may or may not go noticed), acute kidney injury or hospital admissions.

Nephrotoxic drugs

Nephrotoxic drugs are agents that are harmful to the kidneys and can potentially cause pre-, intra- or post-renal damage.[1,2] Pre-renal damage is defined as damage caused to the kidney or glomerulus usually when blood flow to the kidney is restricted, intra-renal damage is defined as damage caused by a process within the kidney and post-renal damage is harm caused to the kidney caused by obstruction of the urinary tract.[1,2] Some examples of nephrotoxic drugs and agents are shown in Table 1.

Drugs such as NSAIDs can cause pre-renal damage and should be avoided in patients with reduced kidney function as even short courses could potentially cause acute kidney injury (AKI) due to renal underperfusion.[2] Toxic effects on renal tubules from drugs such as aminoglycosides or ciclosporin are examples of intra-renal damage, as are hypersensitivity reactions.[2] Anticholinergic drugs, *eg* amitriptyline, can cause post-renal damage due to retention of urine in the bladder.[2] It is generally accepted that nephrotoxic drugs should be avoided in patients with impaired renal function as the consequences of renal toxicity can prove to be fatal.[3]

Drug accumulation

Impaired renal function can negatively influence drug excretion along with drug absorption, distribution and clearance.[4]

NSAIDs
Chemotherapeutic drugs
Aminoglycosides
Amphotericin B
Calcineurin inhibitors
ACE inhibitors
Loop and thiazide diuretics
Penicillins and cephalosporins
Angiotensin II-receptor blockers
Methotrexate
Warfarin
Anticholinergic drugs

Table 1. Examples of nephrotoxic drugs and agents. Adapted from Dashti-Khavidaki S, *et al*.[1]

When reduced kidney function is suspected, baseline renal function should be assessed prior to prescribing any therapy that requires dose modification, as drug dosing errors are common in patients with impaired kidney function.[3,4] The challenges associated with patients suffering from reduced kidney function can potentially be averted by using alternative medication or by adjusting the dose according to level of kidney function.[3,4]

A number of approaches can be taken to modify doses of renally cleared drugs, including reducing the dose or lengthening drug dosing interval.[3,4] For example, in the summary of product characteristics (SmPC) for pregabalin, which can be found on the electronic Medicines Compendium (www.medicines.org.uk), it states that "as pregabalin clearance is directly proportional to creatinine clearance, dose reduction in patients with compromised renal function must be individualised according to creatinine clearance", and a table is provided for prescribers.

Alternatively, instead of lowering the dose for patients with reduced kidney function, other therapy could be prescribed. For example, prescribing linagliptin, whose dosing is not affected by renal impairment, rather than other gliptins, which have dose change recommendations for low kidney function.

Drugs that lose efficacy in reduced kidney function

Some drugs have decreased efficacy when kidney function is reduced, including commonly prescribed drugs such as thiazide diuretics. For example, the SmPC for indapamide indicates that in patients suffering from severe renal impairment (creatinine clearance [CrCl] below 30ml/min), treatment is contraindicated. Thiazide and related diuretics are fully effective only when renal function is relatively normal or marginally impaired. Nitrofurantoin is ineffective at a CrCl <45ml/min, but the risk of adverse reactions is increased.

How should kidney function be calculated?

The most commonly used and frequently calculated estimates of glomerular filtration rate (GFR) for drug dosing are from the Cockcroft-Gault equation.[5-6] It is worth noting that estimates of GFR can be significantly affected by patient bodyweight. There are various other equations like the Modification of Diet in Renal Disease (MDRD) to calculate estimated GFR (eGFR), which does not require weight measurements. MDRD is useful in estimating GFR in stable chronic kidney disease (CKD) but is not validated in acute kidney injury (AKI), older or younger age, extremes of weight, or for drug dosing. CKD is split in to five stages with a subdivision of stage 3 and classified based on GFR and albumin:creatinine ratio (ACR).[7-8] This tool can be used to help identify and manage disease progression.

$$\text{Estimated creatinine clearance (ml/min)} = \frac{(140 - \text{age in years}) \times \text{weight* (kg)} \times \text{Constant a}}{\text{Serum creatinine (in µmol/L)}}$$

Constant a = 1.23 for men; 1.04 for women
*Use ideal body weight if excess body fat,[3] calculated as follows:
Ideal body weight (kg) = Constant b + 0.91 (height in cm – 152.4cm)
Constant b = 50 for men; 45.5 for women

Figure 1. The Cockcroft-Gault equation for estimating kidney function[3]

Mr A Hart, newly diagnosed with atrial fibrillation agrees to anticoagulation with dabigatran
75 years old, 60kg, history of stroke and essential hypertension
Serum creatinine = 100µmol/L
eGFR = 55ml/min/1.73m^2

$$\text{Estimated creatinine clearance (ml/min)} = \frac{(140 - 75) \times 60 \times 1.23}{100} = 47.97$$

If eGFR is used, a dosage of 110–150mg twice daily for prophylaxis of stroke in non-valvular atrial fibrillation is recommended. If using estimated creatinine clearance, a maximum dose of 110mg twice daily is recommended

However, if his weight was 40kg and serum creatinine = 120µmol/L, then estimated creatinine clearance = 26.65ml/min – dabigatran is contraindicated at <30ml/min and so should be avoided

Figure 2. Example of different drug dosing recommendations resulting from use of eGFR or estimated creatinine clearance (Cockcroft-Gault equation)

The results of several retrospective studies suggest that the use of the MDRD equation (eGFR) in place of the Cockcroft-Gault method will often lead to prescribing of higher doses.[9-10] This is most marked in the elderly and those with extremes of body mass (body builders, those with muscle-wasting disorders, frail elderly). For drugs that are high risk and have a narrow therapeutic window or for high-risk individuals, the most conservative figure should be used.[11-12] There is no universal method for drug dosing in all patient populations.

The *BNF* quotes renal function recommendations as eGFR and for most patients of younger age, average build and height, this is sufficient. However, a key point to note when prescribing

for older people as well as with low-range/high-risk drugs, the *BNF* recommends using CrCl, *ie* the Cockcroft-Gault equation.[3]

The Cockcroft-Gault formula is shown in Figure 1; this is the preferred method for estimating renal function when calculating drug doses in patients with renal impairment who are elderly or at extremes of muscle mass. Using dabigatran as an example, Figure 2 shows how drug dosing recommendations are different depending on whether eGFR or estimated CrCl is used. Caution is needed when prescribing in individuals who are elderly or at extremes of body weight. Using the example in Figure 2, the risk of a bleed becomes higher if the correct dosage based on renal function is not used.

How big is the problem of prescribing outside recommendations in reduced kidney function?

Drug-induced nephrotoxicity is a serious and prevalent problem in clinical practice. Drugs are potentially the cause of 60% of cases of AKI.[13] Drug-induced renal disorders are more common in patients with reduced kidney function such as patients over 65 years.[13,14] In a study of 594 patients aged over 65 years with an eGFR <60ml/min/1.73m^2, Wood *et al*. found that 25% of patients were prescribed medication that needed to be altered due to the level of each patient's kidney function.[14] Overall, 70 medicines were found that needed reviewing, their doses altering or to be stopped. Drug classes that accounted for the most errors were lipid-lowering agents (30%) and ACE inhibitors/angiotensin-receptor blockers (26%), followed by thiazides (17%) and osteoporosis drugs (14%). The authors concluded that clinicians may not be aware of the importance of taking renal function into account when prescribing drug therapy.

A more recent cross-sectional study conducted by Wood *et al*. aimed to explore the extent of prescribing outside recommendations for patients aged over 65 years with reduced kidney function in primary care.[15] Data for this cohort of patients were recorded from 80 general practices and two drug types were identified in each category that needed to be avoided (metformin, alendronic acid); required a dose reduction (gabapentin/pregabalin, simvastatin); would be ineffective if the patient had reduced kidney function (thiazides, nitrofurantoin); or were associated with frequent adverse drug reactions in reduced kidney function (NSAIDs, ACE inhibitors/angiotensin-receptor blockers). This study identified that reduced kidney function was not considered when prescribing and recommended prescribing guidance (*eg BNF*) was not adhered to in 4–40% of patients aged over 65 years, and 24–80% of patients aged over 85 years, even though the majority of these patients had recent kidney function tests. Ultimately, this could have had a negative effect on patient safety, leading to increased sensitivity to these drugs, increases in drug blood levels or alternatively rendered the treatment ineffective. In these cases, clinicians could have either reduced the dose of the drug using *BNF* or SmPC recommendations or prescribed alternative therapy to reduce the likelihood of any adverse events that could result in patient harm.[15]

- Aged over 65 years
- Urinary blockage, *eg* kidney stones, prostate-related conditions
- Chronic kidney disease
- Dehydration
- Drugs
- Heart failure
- Diabetes
- Liver disease
- Sepsis
- Temperature
- Hypovolaemia
- Hypotension

Table 2. Risk factors for acute kidney injury[17]

- Is the heating on and is the temperature set at the right level?
- Are the residents wearing the correct amount of clothing for the temperature?
- Are they drinking adequate fluid? Encourage drinks, keep disposable cups nearby
- Monitor residents' bowel habits and continence pads; are they showing signs of dehydration?
- Are they taking diuretics? If so, adjust dose/omit during periods with hotter temperatures

Table 3. Measures to reduce the risk of acute kidney injury in frail elderly in residential and nursing homes

Drugs and acute kidney injury

AKI is defined as a sudden drop in renal function leading to an increase in the concentration of serum creatinine and other waste products.[16] With an estimated cost to the NHS of £620 million, AKI is seen in 13–18% of all hospital admissions.[17] Table 2 lists the risk factors that can predispose an individual to suffer from AKI.[17] Some drugs, for example NSAIDs and ACE inhibitors, can cause AKI and have the potential to become harmful if renal function is impaired. Drugs that are cleared via the kidneys can accumulate to high plasma levels, potentially leading to toxicity or further exacerbating negative effects on the kidneys.[18,19] Measures to prevent AKI for those that are most vulnerable, particularly the frail elderly, are listed in Table 3; these may be helpful for those living in residential and nursing homes.

Which drugs need adjustment in reduced kidney function?

A list of commonly prescribed medicines and their recommended management in kidney disease is shown in Table 4.[18,20,21] This is not an exhaustive list but provides an idea of the kind of decisions that should be made and things to consider relating to drug therapy. Extra precautions should be taken if contrast media is required for imaging. The European Society of Urogenital Radiology has issued guidance on this, stating that for certain patients, metformin should be withheld 48 hours prior to contrast media being used and restarted 48 hours after.[22]

How can prescribers be reminded about drug dosage adjustment and avoidance in kidney disease?

Prescribers should get into the habit of thinking about kidney function, particularly for every patient aged 65 years or over, when initiating new treatments or reviewing medication. It is vital that an up-to-date CrCl is recorded. There are several tools that can be utilised on the general practice clinical information system (CIS), which can aid clinicians in making appropriate prescribing decisions with regard to reduced kidney function. The built-in renal calculators in EMIS and TPP SystmOne populate and use ideal body weight. There is also a web/app-based calculator that can be used called MDCalc.[23]

Patients who have chronic kidney disease should have a clinical code added to their record, making it easier to identify them with a simple report and ensuring they are having regular monitoring as part of the Quality and Outcomes Framework (QOF). Recalls can be added to patient records where ongoing monitoring is required. A team member can then take responsibility to ensure these patients are being contacted and blood tests are taking place to maintain the provision of safe and effective prescribing.

A reminder can be set up on the patient record. This will be displayed on the home screen when the patient record is accessed. Turning it into a high-priority reminder will allow it to be visible to services outside the GP surgery, for instance, an out-of-hours clinic. A disadvantage of using reminders could be the accumulation of data on the home screen, which may lead to overlooking vital information. It is recommended that only relevant and applicable data should be added to the home screen and anything no longer needed should be removed. A similar option is the use of patient plans within SystmOne. These are yellow pop-up boxes that appear on the bottom right corner of the screen; however, these only appear if the individual user has them turned on in their settings.

The use of decision support tools has its place in general practice. Examples of such software currently available include ScriptSwitch and OptimiseRx. These are integrated into the CIS and are useful for informing prescribers about numerous pre-programmable alerts, including prescribing from the formulary and alerts when prescribing drugs to patients with impaired renal function where dose adjustment is required or when drugs are contraindicated and should be stopped. However, these tools do rely on accurate and up-to-date coding. Another software programme is STOPP/START, which can be integrated into SystmOne and can aid medication reviews. An example of an alert would be a patient on long-term digoxin at a dosage greater than 125µg daily with an eGFR less than 30ml/min/1.73m^2. This protocol can be accessed by joining the Frailty Organisation Group.[24]

Summary

Care and caution is needed when prescribing for patients with reduced kidney function as well as for the elderly/those with extremes of body weight. To reduce the risk of toxicity, estimated CrCl should be used to assess the level of renal function. This should aid prescribing/dosing decisions and help where medication adjustments are needed in cases of temporary (*ie* AKI) or permanently reduced kidney function.

Stop/withhold
• NSAIDs
• Potassium-sparing/thiazide diuretics: reduced efficacy, increased risk of adverse drug reactions
• Metformin: avoid if eGFR less than 30ml/min/1.73m^2 – risk of lactic acidosis
• ACE inhibitors/angiotensin II-receptor blockers: depending on indication, if prescribed in heart failure, restart when safe to do so, titrate up and monitor closely. If hypertensive, consider alternative agents
• Lercanidipine: avoid if eGFR less than 30ml/min/1.73m^2
• Methotrexate
• Fibrates and statins: risk of rhabdomyolysis – stop if acute kidney injury develops due to rhabdomyolysis, reduce dose and monitor
• Contrast media
Review dose
• Opioids: avoid MR/XL preparations, use short-acting preparations at the minimum required dose
• Benzodiazepines: reduce dose and monitor for excess sedation
• Penicillins: accumulation leading to CNS toxicity – reduce dose
• Antiepileptic drugs: reduce dose and monitor serum drug levels
• Loop diuretics
• Trimethoprim
• Antianginal drugs, *ie* nitrates and nicorandil: can lead to renal hypoperfusion
• Sulfonylureas: care needed to use the lowest possible dose; gliclazide is metabolised by the liver and can be used in renal impairment
• Gliptins: adjust dose and monitor closely; linagliptin OK to use
• Gabapentin/pregabalin: dose adjustment necessary
• Allopurinol: reduce to 100mg daily
Ongoing monitoring required
• Warfarin
• Ciclosporin
• Digoxin
• Lithium

Table 4. Recommended management of commonly prescribed medicines in kidney disease[18,20,21]

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Declarations of interest

None to declare.

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