Prescribing principles for patients with chronic kidney disease

The definition and classification of chronic kidney disease (CKD) has changed in recent years following international acceptance of guidance from the US Kidney Disease Outcomes Quality Initiative (K\DOQI) programme.[1] This classification identifies five stages of CKD, defined in part, by an estimate of glomerular filtration rate or eGFR (Table 1). Following the UK adoption of the K\DOQI classification, the Department of Health recommended routine reporting of eGFR by all NHS clinical biochemistry laboratories by 1 April 2006. This has done much to improve the recognition of early CKD in patients in whom reported serum creatinine levels alone would have missed.

With the growth in recognition of CKD, there is inevitably an increase in demand for specialist referral. UK guidelines for CKD in adults[2] have been developed to promote the optimal management of patients with CKD, many of whom do not necessarily require referral to a nephrologist and can be managed suitably in primary care. While the vast majority of early CKD patients do not progress to established renal failure (ERF)[2] the guidelines clearly identify patients with progressive CKD who would benefit from timely referral and, therefore, avoid the adverse consequences of late referral.

Although much of the prescribing for the symptoms and complications of ERF is undertaken by the specialist renal physician, at some point most primary care clinicians will encounter a CKD patient for whom they will prescribe. This may be early pharmacological intervention for cardiovascular disease (CVD) risk factors in CKD stages 1–3 for example (CKD being an important risk factor for CVD[2]) or perhaps as part of a shared care arrangement for anaemia, or renal bone disease seen later in CKD stage 3. It may even be that a prescription will be needed for a co-morbidity in a CKD patient of any stage, for whom special consideration to the drug choice or prescribed dose may be required. This article outlines the principles that will ensure safe and effective prescribing for these patients, whether seen as part of the everyday routine or the occasional encounter.

Table 1. K\DOQI Classification for chronic kidney disease[1]

Stage	GFR (ml/min/1.73m²)	Description
1	GFR ≥ 90	Normal GFR but with other evidence of chronic kidney damage*
2	GFR 60–89	Mild impairment with other evidence of chronic kidney damage*
3	GFR 30–59	Moderate impairment
4	GFR 15–29	Severe impairment
5	GFR <15 or dialysis	Established renal failure (ERF)

Notes:

Chronic kidney *disease* is defined as **either** kidney *damage* **or** GFR<60ml/min/1.73m² for ≥3 months[1]

*Chronic kidney *damage* is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies such as:

- Persistent microalbuminuria; proteinuria or haematuria (without urological disease)[2]
- Structural abnormalities of the kidneys such as polycystic kidney disease, reflux nephropathy[2]
- Biopsy-proven chronic glomerulonephritis (most of these patients will have microalbumuria or proteinuria, and/or haematuria).[2]

A patient with a GFR of 60–89ml/min/1.73m² *without* one of these markers **should not be considered to have CKD** and should not be subjected to further investigation unless there are additional reasons to do so.[2]

How to prescribe safely, rationally and effectively in CKD

When prescribing for patients with CKD, many considerations have to be made. The introduction of a nephrotoxic drug for example, may further insult the kidneys and tip the balance towards the need for renal replacement therapies. As renal function declines, so does the clearance of renally-cleared drugs or drug metabolites. The array of uraemic manifestations that accompany CKD can alter other pharmacokinetic drug characteristics and when coupled with the electrolyte disturbances commonly seen in CKD may increase the sensitivity to pharmacological and toxic effects.

Many of the kidney's endocrine, synthetic and metabolic functions are lost or compromised in CKD. This often involves a high degree of pharmacological intervention and creates the potential for many clinically significant drug-drug interactions. Furthermore, many drugs are unlicensed or even contraindicated in CKD. A practical based approach on how to address these considerations is discussed individually.

Prescribing considerations when pharmacokinetics are altered

When a patient has alterations in their drug handling ability — either through changes in absorption, distribution, metabolism or excretion of their medicines — this must be taken into account when prescribing.

Dosage adjustment for reduced drug excretion

The kidney plays a vital role in drug excretion, either in the form of glomerular filtration or active tubular secretion[3] and provides the final common route of elimin-

Table 2. Prescribing decisions, underlying rationale and their consequences in CKD

Consider:	Rationale:	Clinical example:
1. Is the drug in question the most appropriate choice in CKD?	The drug may be nephrotoxic or contraindicated in CKD or may augment uraemic manifestations.	NSAIDs may worsen renal impairment or increase uraemic gastrointestinal (GI) bleeding risk.
2. If the drug/ drug metabolite is renally excreted is modification to the dosage necessary?	If elimination is dependent on the kidney then the dose will need to be reduced relative to the degree of renal impairment. Alternatively if the elimination half-life is prolonged in the presence of CKD an increase in the dosing interval may be more appropriate.	Gabapentin may need both dose reduction and extension of dosage intervals as renal impairment progresses. Dose reduction may not be necessary for drugs with wide safety margins (eg. flucloxacillin) despite the reliance on the kidney for elimination.
3. Is a rapid clinical response needed?	With a reduced 'renal' dose, and a prolonged elimination half-life, time to steady state is delayed and therapeutic effect may not be observed as quickly as normal.	See example for digoxin and teicoplanin below.
4. Is there a parameter such as INR or a therapeutic drug level that can be monitored?	When achieving therapeutic effect is paramount or avoiding toxic effect is vital, monitoring drug levels can tailor an individual's dosage requirement.	Vancomycin is renally cleared and extremely toxic in overdose. Doses are not repeated until plasma levels indicate trough levels <10–15mcg/ml.
5. Is there a potential for drug interaction?	The polypharmacy of CKD increases the potential for drug interactions. Uniquely, displacement interactions that are not clinically significant in 'normal' patients may be clinically significant in the renally impaired patient.	The insoluble chelates formed by oral ciprofloxacin and phosphate binders commonly used in CKD means that absorption of the antibiotic is reduced significantly unless administration is separated.

ation for many drugs or drug metabolites.[4] While some drugs, such as gentamicin, are excreted by the kidney in the unchanged, active form, other drugs, like morphine, require hepatic metabolism to increase water solubility before elimination by the kidney.[5] These metabolites may exert an active pharmacological or toxic effect and may accumulate in the presence of reduced renal function (as occurs, for example, with morphine-6-glucuronide).[5,6] For drugs that rely on renal elimination, the prescribed doses often require adjustment relative to the degree of renal impairment. This is particularly important for toxic drugs or for drugs with a narrow therapeutic window. The degree of renal impairment is usually quantified by an estimate of the patient's glomerular filtration rate (GFR).

Estimating GFR: The convention in determining this estimate until now has been to use creatinine clearance (CrCl) as a surrogate marker for GFR. CrCl can be measured from of a 24-hour urine collection. However, more routinely in clinical practice, GFR can be estimated from serum creatinine by applying the Cockcroft and Gault (C&G) equation.[7]

Cockcroft & Gault equation[7]

$$\text{CrCl (ml/min)} = \frac{F \times (140 - \text{age in years}) \times \text{weight (kg)}}{\text{serum creatinine (mcmol/l)}}$$

where F = 1.23 in males or 1.04 in females

Standard reference texts like the *British National Formulary* (*BNF*)[8] or the *Renal Drug Handbook*[6] classify kidney function based on CrCl values and arbitrarily grade renal function on CrCl ranges. The *BNF* uses the same qualitative descriptors of impairment as the K\DOQI classification of CKD — mild, moderate and severe — and qualifies these with a quantitative estimate of GFR. However, the fundamental difference in these two nomenclatures is three-fold. Firstly, the quantitative values used to qualify the descriptors in each system has different numerical ranges (see Table 3). Secondly, the estimates for GFR in the K\DOQI classification (the eGFR) are derived not from the Cockcroft & Gault equation, but from the Modification of Diet in Renal Disease (MDRD) equation. A version of the MDRD equation is given in the box below. An important point to note is that the equation used by local laboratories to report eGFR will account for local variation in creatinine assays and may produce slightly different, but more accurate, values to this calculator. Always use locally reported value preferentially. The third reason is that the C&G equation predicts *non-normalised* creatinine clearance, whereas the MDRD equation predicts a *normalised GFR to a body surface area* (BSA) *of 1.73m²*, which is why laboratories do not need to know the patients body weight for the calculation, and is the main advantage of the equation.

Modification of Diet and Renal Disease equation*

$$\text{eGFR (ml/min/1.73m}^2\text{)} = 186 \times (\text{serum creatinine mcmol/l}/88.4)^{-1.154} \times (\text{age})^{-0.203}$$

then multiply by 0.742 if female or 1.21 if black

**available as an online calculator at www.renal.org/eGFRcalc/GFR.pl*

CrCl vs eGFR for drug dosing: For the three reasons described above, the *BNF* 'grading' and K\DOQI 'classification' are not interchangeable. Although the introduction of routine reporting of eGFR by NHS laboratories has done much to improve recognition of CKD, and indeed in identifying patients who may need dosage reduction, it does present a potential for error when used for estimating drug doses.

The bottom line message to bear in

Table 3. *BNF* grading and K\DOQI classification of renal impairment

BNF grading		K\DOQI classification	
Descriptor	Quantitative estimate (based on CrCl)	Descriptor	Quantitative estimate (based on eGFR)
Mild	20–50 ml/min	Mild	60–89 ml/min/1.73m^2
Moderate	10–20 ml/min	Moderate	30–59 ml/min/1.73m^2
Severe	<10 ml/min	Severe	15–29 ml/min/1.73m^2
—		ERF	<15 ml/min/1.73m^2 or on dialysis

mind *when adjusting doses for CKD* is the non-normalised C&G CrCl is the gold standard to date, because CrCl will be the basis by which manufactures will have established their dosage recommendation in CKD. When using the C&G equation it is important to remember that body weight is used as a marker for muscle mass (creatinine being a breakdown product of muscle). Therefore, it is prudent to use ideal body weight (IBW) for the obese patient (see Table 4) who typically weighs >20% above IBW, because the use of actual body weight (ABW) will overestimate GFR and potentially result in a drug overdose (see Table 5). Conversely, it is important to use ABW in the heavily muscle-bound patient (Table 4), because substituting ABW with IBW will underestimate GFR and potentially result in drug under-dosing. For patients who are underweight (Table 4) the situation becomes more complicated and practices vary.

More commonly in clinical practice, eGFR values are used for drug dosing. However, it essential that the reported normalised eGFR is converted to the patient's actual, non-normalised eGFR (especially at extremes of weight) using the following equation:[7,8]

$$GFR_{ACTUAL} = eGFR \times (BSA^{*}{}_{ACTUAL}/1.73)$$

**BSA = body surface area*

When using this correction equation, the actual, non-normalised eGFR more closely resembles the C&G CrCl using IBW for CKD stages 3–5 (see Table 5) and is more likely to guide correct dosage adjustment until such time as the standard text is able to make recommendations based on normalised eGFR.[5,7,8] Failure to correct to actual, non-normalised GFR in patients with a BSA smaller than 1.73m^2 will overestimate GFR and potentially result in drug over-dosing. Similarly, failure to correct to actual, non-normalised GFR in patients with a BSA greater than 1.73m^2 will underestimate GFR and potentially result in drug under-dosing.

Table 5 gives a clinical example of where using a standard normalised eGFR for dosage adjustment can lead to error. This example shows how the recommended dosage of the same drug for the same patient can vary fourfold depending on the equation used. The bottom-line is the estimate of GFR for drug-dosing should be obtained from *either* a calculated CrCl or a *corrected non-normalised* GFR (GFR_{ACTUAL}) for:

- patients at extremes of body weight
- renally cleared drugs for which the clinical consequences of under- or over-dosing would be serious.

Dosage adjustment in cases of altered absorption, distribution and metabolism

When prescribing drugs for the renally impaired patient much of the dosing emphasis is correctly placed on alterations in drug clearance. However, this is not the only pharmacokinetic change observed in CKD; as renal function declines the absorption, distribution and metabolism of drugs can also be affected, and this is often overlooked in clinical practice.

Absorption: The presence of oedema can affect the gastric absorption of some drugs. Limited evidence suggests that oral bumetanide has a better bioavailability compared to oral furosemide in the oedematous patient[9] and may be a possible alternative to intravenous (IV) furosemide when wanting to avoid the IV route.[5,10]

Distribution: The presence of oedema can increase the volume of distribution (Vd) of water-soluble drugs.[10] However, drug doses are rarely, if ever, increased to accommodate this. More significantly, drug distribution can be affected by the uraemic manifestation of the failing kidney. Phenytoin is the classic example of where this can occur. Although the elimination of phenytoin is not reliant on the kidney (with a maximum 5% excreted unchanged in the urine[6]), the high degree of plasma protein binding (around 90%[6]) is reduced significantly in CrCl <25ml/min as a result of the accompanying uraemia and hypoalbuminaemia.[3] This reduced binding affinity increases the fraction of free (unbound) drug[3] that is responsible for both pharmacological and toxic effects.

Phenytoin has a narrow therapeutic index and demonstrates saturation kinetics. Small increases in dose can, therefore, create a disproportionate increase in serum levels, which may result in toxicity. Therapeutic drug monitoring is essential to ensure that prescribed doses are both safe and effective. The concentration range required for therapeutic effect is 10–20mg/L,[11] but when interpreting phenytoin levels in renal

Table 4. Summary of actions needed for people with different body masses

Patient	Weight for C&G eqn.	Why	Consequence
Obese	IBW	ABW will overestimate GFR	Potential for drug overdose
Underweight	*		
Muscle bound	ABW	IBW will underestimate GFR	Potential for drug under-dose

** If underweight C&G can not reliably estimate GFR. If patients are slightly underweight but not catabolic it may be prudent to use actual body weight (ABW), otherwise ideal body weight (IBW) may be a better estimate but C&G is not valid in these circumstances and local customs and practices vary.*

Table 5. Dosing based on MDRD eGFR vs Cockcroft & Gault CrCl

Mr I P Freely requires a prescription for IV ganciclovir. He is 53-years old and obese, weighing 110kg. His serum creatinine is stable at 155mcmol/L. He is of white ethnic origin, has an IBW of approximately 79kg and a BSA of 2.34m². Four different GFR values are presented below:

1. Cockcroft & Gault using actual body weight
   CrCl = **76ml/min (at 110kg)**
2. Cockcroft & Gault using ideal body weight
   CrCl = **55ml/min (at 79kg)**
3. MDRD eGFR normalised BSA
   43ml/min/1.73m²
4. MDRD eGFR actual non-normalised BSA
   58ml/min/2.34m²

IV ganciclovir dosage in CKD from *Renal Drug Handbook*[6]

CrCL (ml/min)	Dose		
>70	**5mg/kg**	**12 hourly**	(method 1)
50–69	**2.5mg/kg**	**12 hourly**	(methods 2,4)
25–49	**2.5mg/kg**	**24 hourly**	(method 3)
10–24	1.25mg/kg	24 hourly	
<10	1.25mg/kg	24 hourly	

give after haemodialysis on dialysis days

impairment it is important to make a clear distinction between *free* and *total* plasma levels, since raised free plasma levels account for the reduced protein-binding. The therapeutic reference range for free plasma levels (1–2mg/L)[13] is the same in all patients[12,13] but not all clinical laboratories are able to report these. This is a problem when CrCl is between 10–25ml/min because binding affinity is *unpredictably* altered and total plasma phenytoin concentrations cannot be interpreted accurately for this group of patients.[11] However, in patients receiving intermittent haemodialysis a mathematical equation can be used to correct for reduced protein binding (see *Renal Drug Handbook*[6]). When the reported total plasma levels are within the 'target' range of 10–20mg/L this misleadingly suggest they are within the therapeutic range.

Bearing in mind that the unbound fraction of phenytoin will be disproportionately elevated, aiming for this target total plasma level can result in serious toxic effects. Conversely, in the same patients, seizure control can be accomplished with an apparent 'sub-therapeutic' total plasma level as low as 5mg/l.[12]

Consider a haemodialysis patient for whom total plasma levels are reported to be 15mg/L (within the 'target' range) but for whom albumin level is only 3.8g/dL. When adjusted for hypoabluminaemia and renal failure the corrected level is almost 32mg/l, a value often associated with CNS symptoms.[11] If the dose is reduced to accommodate this, a subsequent apparently sub-therapeutic total level of 7mg/L, when adjusted mathematically, would produce a level of 15mg/L.

Metabolism: The kidney has an important role in the metabolism of insulin, especially in diabetics receiving insulin therapy, because this exogenous source enters the systemic circulation without the first-pass effect of the liver. Although the uraemia of CKD may create a degree of insulin resistance, as renal impairment progresses the decreased insulin degradation may lead to a significant decrease in insulin or oral antidiabetic drug requirements. This might even involve stopping therapy altogether.

Other prescribing considerations for CKD

Nephrotoxicity: The vast majority of early CKD patients do not progress to established renal failure.[2] It is vitally important, therefore, that nephrotoxic drugs are avoided in CKD. Drugs commonly seen to induce or contribute to acute renal failure include NSAIDs, aminoglycosides, vancomycin, ACE inhibitors, aggressive diuretic use, ciclosporin and drugs used for rheumatoid arthritis. A distinction to the exact cause of CKD may also be significant when deciding whether a drug is appropriate or not. ACE inhibitors for example can have a cardio- and nephroprotective effect in patients with diabetic nephropathies, but can precipitate acute or chronic renal failure in patients with renovascular disease.

Product license: Some drugs, such as metformin, may be contraindicated in the presence of renal impairment, while others may be used outside the terms of their product licenses. Metformin is contraindicated when CrCl is <60ml/min or indeed any acute condition with the potential to alter renal function such as dehydration or severe infection, because drug accumulation may result in lactic acidosis. Although rare, this condition is serious and associated with high mortality in the absence of prompt intervention. Despite this some clinicians, experienced in treating diabetes, will balance the risks and benefits and actively start metformin in patients with serum creatinine of up to 150mcmol/L, with an awareness of an increased possibility of lactic acidosis. This raises many medico-legal considerations but the legitimacy of such a decision falls to a body of expert medical opinion in the event that any adverse events are pursued. Drugs may also be used for non-licensed indications, such as aspirin and dipyridamole in combination for the maintenance of an AV fistula. Alternatively, drugs may be used 'off licence', such as phosphate binders in early CKD, which are only licensed in dialysis dependency. The manufacturer's Summary of Product Characteristics (SPC) reflects the clinical trials that lead to a product's marketing authorisation. Patients with renal failure — by and large — fall into trial exclusion criteria, so drugs are often not licensed for this population.

Initial or loading doses: Drugs that require reduced maintenance doses to accommodate reduced renal function will almost invariably require loading doses if an immediate therapeutic effect is needed. A common analogy used to explain this is a bucket with a hole. Consider that a bucket may represent the human body and that renal function is determined by a hole in that bucket; the smaller the hole, the greater the degree of renal impairment. The volume needed to fill the bucket, which is the same regardless of the size of the hole, represents the loading dose. The maintenance dose is represented by the amount of water needed to maintain a full bucket; the larger the hole (or better the renal function) the greater the volume of water needed (or the larger the drug dose needed). In scientific terms this is explained by the time to steady state, which is achieved only after 4 to 5 elimination half-lives. With drug half-lives already prolonged in renal failure it takes a good deal longer for the reduced 'renal' doses to achieve therapeutic levels. An example of where there is a need to

establish rapid clinical response is with the antimicrobial teicoplanin. Unlike many other drugs, teicoplanin is licensed for use in renal impairment and the manufacture's SPC provides precise directions for dosing in renal failure. The options are to reduce the daily dose or alternatively to extended the dosage interval, but only on the fourth day of therapy using the conventional loading regimen. Failure to load would mean the immediate antimicrobial effect, governed by the need to reach the minimum inhibitory concentration would not be achieved, because the reduced 'renal' doses and prolonged elimination half-life would create a delay in achieving steady state. Similarly, the prolonged half-life and reduced excretion necessitates a reduction in the maintenance dose or an extension to their dosage intervals. Failure to do this would result in a steady state level being achieved well above the concentrations where a patient experiences toxic effects.

Alterations to pharmacodynamics: The known pharmacological or toxic effects of drugs may augment the uraemic complications of CKD, namely oedema, hyperkalaemia, metabolic acidosis and hypertension. For example, NSAIDs may increase the uraemic GI bleeding risk or complicate fluid overload. ACE inhibitors or potassium-sparing diuretics may precipitate life-threatening hyperkaleamia on a background of elevated potassium levels. As discussed, metabolic acidosis may be complicated by the introduction of metformin, or the presence of uraemia may induce a state of insulin resistance. Hypertension and hyperkalaemia can be worsened by rapid correction of anaemia with erythropoiesis stimulating agents. Many of the ureamic manifestations of CKD result in an increased sensitivity to the pharmacological and toxicological effects of digoxin. Consider the use of digoxin for the correction of atrial fibrillation. Clearly clinical circumstances dictate that a rapid therapeutic effect is needed. The principles described above for loading doses in CKD do, in theory, apply to digoxin. However, if conventional loading (or digitalisation) doses are used in patients with renal impairment then an increased sensitivity to its pharmacological and toxic effect is observed. Digoxin has complex kinetics in renal impairment and the increased sensitivity may be a result of uraemia, a reduced volume of distribution and total body clearance, or simply because of the electrolyte disturbances seen in these patients[12] (hypokalaemia, hypomagnesaemia, marked hypercalaemia or hypothyroidism). More conservative doses or increased dosage intervals are used for digitalisation, with the option to repeat if necessary, to achieve therapeutic effect. The increased sensitivity, prolonged half-life and reduced excretion also means smaller maintenance doses are usually needed and are often directed by drug level monitoring in addition to clinical parameters.

Conclusion

Prescribing for patients with CKD can be a difficult and daunting task. Many considerations have to be made about the correct choice of drug, the appropriate dose and whether the interval between doses needs to be lengthened. Additionally, interpretation of drug levels may be complicated in CKD. Over-cautious dose reductions can result in therapeutic failure, whereas failure to reduce doses can result in drug accumulation and toxicity. Prescribing for this population will often involve a series of complex calculations and routinely specialist reference sources will need to be consulted. If this is not intimidating enough, all too often prescribing for CKD patients will involve using licensed drugs outside the terms of the product license (or marketing authorisation). The unconventional drug regimens and anomalous doses found in any renal unit, requires a sound comprehension and application of the first principles of pharmacokinetics.[5] Good prescribing will accommodate the effectual magnitude of the failing kidney, any further alterations to the pharmacokinetic profile that may result from CKD, or any uraemic manifestation that may alter a drug's pharmacodynamic response. Bear in mind that under the Bolam principle, professionals will be held accountable for their prescribing decisions, and potentially be found negligent if a body of expert medical opinion does not support their actions.[5] The *Renal Drug Handbook*[6] represents this body of medical opinion and is the invaluable reference source for providing a practice-based guide to the dosing of drugs in the renally impaired adult. The handbook is the reference of first choice in most renal units. With the correct reference source and an understanding the principles outlined in this article the reader will be able to individualise the dose of drugs they prescribe to optimise patient outcomes.

Declaration of competing interests

The author declares he has no competing interests.

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