

Calculating GFR is crucial when determining drug dosage requirements in reduced renal function

Renal function status affects dosage requirements of renally excreted medicines and this is particularly important in the elderly, who are often receiving multiple medicines. Pharmacists can make a large contribution to informing appropriate prescribing by considering a patient's renal function and age when these medicines are prescribed, as Su Wood explains

Introduction

In 2003 the UK adopted the US Kidney Disease Quality Outcomes Initiative leading to the new chronic kidney disease (CKD) guidelines describing the degree of renal function in five stages and detailing clinical care for each of the stages of renal impairment (see Box 1).¹ The *National Service Framework (NSF) for renal services*² was introduced in 2005. In 2006 quality and outcome framework (QOF) markers³ led to the formation of registers of patients in stages 3, 4 and 5 of CKD as determined from calculating their estimated glomerular filtration rate (eGFR) from the MDRD (modification of diet in renal disease) equation. The MDRD equation estimates GFR from serum creatinine normalised for a body surface area of 1.73m². This has already greatly improved awareness of kidney function by health professionals, but there are two areas where we, as pharmacists, need to be aiding and informing prescribers regarding the use of medicines for these patients. These are:

1. Using the most appropriate formula to calculate GFR

Historically the most well established formula to estimate renal function for informing on drug dosing is that of Cockcroft and Gault⁴ (C&G) which calculates creatinine clearance (CrCl) in ml/min (described in Box 2). Most dosage recommendations for use of drugs in

Stages of chronic kidney disease¹

Stage 1:	eGFR >90ml/min/1.73m ² with other evidence of chronic kidney damage
Stage 2:	eGFR 60–89ml/min/1.73m ² with other evidence of chronic kidney damage
Stage 3:	eGFR 30–59ml/min/1.73m ²
Stage 4:	eGFR 15–29ml/min/1.73m ²
Stage 5:	eGFR <15ml/min/1.73m ²

Box 1. The stages of chronic kidney disease (CKD) taken from the CKD guidelines¹

reduced renal function are based on the Cockcroft and Gault formula.

The *British National Formulary (BNF)*⁵ appendix 3 lists the licensed recommendations for drug use and dosage in renal impairment; these are based on the C&G estimates used by the drug industry.

Therefore, the C&G formula needs to be calculated for these recommendations to be valid when applying to patients. The UK Renal Pharmacy Group has stated that the C&G formula should remain the gold standard when adjusting drug doses to an individual's renal function; eGFR should not be used to adjust drug doses.⁶

The Cockcroft and Gault formula⁴

$$\text{Creatinine clearance (CrCl) ml/min} = \frac{F \times (140 - \text{age}) \times \text{LBW (KG)}}{\text{Serum creatinine (micromol/L)}}$$

where F = 1.23 for males or 1.04 for females

LBW = lean body weight – ideal body weight or actual body weight (whichever is the lower) can be used (creatinine is formed from muscle turnover so the weight is needed as a marker of muscle mass not excess body fat)

Box 2: the Cockcroft and Gault formula

Basic pharmacy skills

By calculating the creatinine clearance using the C&G formula and applying the recommendations in appendix 3 of the *BNF*, risk of side-effects and nephrotoxicity can be reduced.

2. Considering patients' age: Calculating GFR is even more crucial for elderly patients when informing about dosage requirements

Both the MDRD and C&G formulae give less reliable estimates of renal function at the extremes of age. We know that renal function reduces with increasing age — trends of natural decline are estimated at 1ml/min/year from the age of 40 years. The elderly are more likely to be taking regular medications and with the reduced renal function they have less reserve to counter any nephrotoxic effects of drugs, disease, acute illness or over/under hydration. This means that it is more important that we estimate renal function when prescribing drugs for our very elderly patients. Despite the limitations, the C&G formula will give us the best estimate to apply the dosage recommendations from the drug industry.

Case study

You are a practice pharmacist in a GP surgery doing computer-based medication reviews for patients in care homes. Mrs Crumbly is an 89-year-old lady and at her last GP review she was well and her blood pressure was within normal limits.

Medical history: Non-insulin dependent diabetes mellitus, hypertension, osteoarthritis, polymyalgia rheumatica

Weight: 54kg

Serum creatinine: 113micromol/L

eGFR: 42ml/min/1.73m²

HbA1c: 7.6%

Medication list:

aspirin 75mg od
bendroflumethiazide 2.5mg om
paracetamol 2qds prn
lisinopril 10mg od
lansoprazole 15mg od

risedronate 35mg wkly
prednisolone 4mg od
simvastatin 40mg od
cetirizine 10mg od.

From the information provided above, consider the following questions:

1. Based on the eGFR, what dose adjustments would you recommend and which medicines should be avoided?
2. Now work out the creatinine clearance for this lady using the Cockcroft and Gault formula (see box 1)
3. Using the *BNF* appendix 3, what recommendations would you now make for changing any of the medications based on your findings in question 2?

Take a moment to try to answer these questions before you read on. The answers are provided below:



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1. The eGFR is 42ml/min/1.73m² and as we do not have the height of this patient we cannot estimate her body surface area. We therefore have to use the figure of 42 to make our recommendations. From appendix 3 of the *BNF*, there would be no changes needed to be made to the medications based on the eGFR — except to be cautious with any dose increases of the lisinopril and to regularly monitor the renal function and electrolytes (see answer to question 3 for more on the renal effects of

angiotensin-converting enzyme inhibitors).

2. Using the C&G formula to calculate the creatinine clearance (CrCl):

$$\text{CrCl} = F \times (140 - \text{age}) \times \text{LBW} / \text{serum creatinine}$$

Thus, $\text{CrCl} = 1.04 \times (140 - 89) \times 54 / 113$
Giving: $\text{CrCl} = 25\text{ml/min}$.

3. Based upon the CrCl value calculated from the C&G equation of 25ml/min for each of Mrs Crumbly's medications:

Aspirin — *BNF* states to avoid the low dose if renal function is 'severe' (which is defined as <10ml/min) so this patient can continue taking aspirin at 75mg/day. It should be emphasised that any additional non-steroidal anti-inflammatory (NSAID) including cyclo-oxygenase-2 inhibitors (COX-2s) would not be recommended. For NSAIDs the *BNF* recommends that in mild renal impairment (20–50ml/min) the lowest possible dose should be used and the renal function monitored; NSAIDs may cause sodium and water retention and deterioration in renal function possibly leading to renal failure. For moderate to severe renal impairment (<20ml/min) NSAIDs should be avoided. Even Summary of Product Characteristics for topical NSAIDs caution their use in patients with renal impairment.

Bendroflumethiazide — *BNF* states to avoid if <30ml/min. Thiazides (except metolazone) are ineffective at this level of renal function.

Paracetamol — there are no problems with the use of paracetamol in renal impairment. However, all opioid analgesics in moderate to severe renal impairment (<20ml/min) will have increased and prolonged effects, and increased cerebral sensitivity so we need to be cautious with any use of combination analgesics or opioids on their own in this situation.

Lisinopril — *BNF* chapter 2.5.5.1 details the renal effects of angiotensin-converting enzyme inhibitors (ACEIs). They can cause renal impairment, which may progress and become severe — and at particular risk are

the elderly. Renal function and electrolytes should be checked before starting ACEIs (or before increasing the dose) and should be monitored during treatment. Starting doses should be lower for those patients found to have impaired renal function.

Looking at the pharmacokinetic properties of the ACEIs (see the individual Summary of Product Characteristics on www.medicines.org.uk) you will see that lisinopril, perindopril and enalapril's active components are all entirely renally excreted. Therefore, reduced renal function results in significantly increased plasma concentrations of the active ACEI; the paragraph relating to enalapril on www.medicines.org gives the example that a creatinine clearance of 40–60ml/min results in twice as much active component being available from each dose; for <30ml/min it is eight times as much. Ramipril elimination is only partially reliant on kidney function so renal impairment has less effect on its plasma concentration.

Lansoprazole — there is no problem with its use in renal impairment.

Risedronate — the *BNF* states for CrCl of <30ml/min avoid risedronate. For alendronate the *BNF* states to avoid if CrCl is <35ml/min. The only bisphosphonate with a recommendation for use in CrCl of <30ml/min is ibandronic acid where it is suggested to use the 50mg dose — this may be considered where it is being used for steroid osteoporosis prophylaxis, for example. Mrs Crumbly is taking prednisolone for polymyalgia rheumatica, but she only having 4mg per day and so it would be recommended to stop the risedronate.

Prednisolone — there are no specific dosing instructions, but it has a weak mineralocorticoid effect so it can cause sodium and water retention and potassium loss.

Simvastatin 40mg — the *BNF* states that at CrCl of <30ml/min doses of more than 10mg should only be used with caution. Atorvastatin does not have any dosage reduction recommendations and so if it was decided that Mrs Crumbly should continue to be taking a statin then

atorvastatin could be used.

Cetirizine 10mg — at CrCl of <30ml/min half the normal dose (ie. 5mg od) should be prescribed.

Outcome

It was decided with the GP that bendroflumethiazide and risedronate should be stopped, lisinopril changed to ramipril, simvastatin changed to atorvastatin and cetirizine reduced to 5mg.

By two months after making these changes the serum creatinine was reduced to 94micromol/L and the eGFR improved to 52ml/min (ie up by 10ml/min) giving Mrs Crumbly a greater renal reserve. The BP was still within normal limits.



Discussion

Although Mrs Crumbly was seemingly well, her impaired renal function gave her very little reserve to counter any nephrotoxic effects of drugs or disease. The changes made to her medications resulted in improved renal function giving an extra 10ml/min reserve.

The impaired renal function also meant that Mrs Crumbly was likely to have higher than recommended plasma levels of some of her medications and so could be at higher risk of iatrogenic harm. For example:

Bendroflumethiazide — as well as its lack of effect at Mrs Crumbly's level of renal function, there is increased likelihood of it producing electrolyte disturbance and of affecting her diabetes.

Lisinopril — there is an increased risk of

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nephrotoxic effects leading to a further reduction in renal function, especially in acute illness or dehydration; also hyperkalaemia, hypoglycaemia and gastrointestinal effects are more likely.

Risedronate — Mrs Crumbly may be more likely to experience gastrointestinal disturbances including oesophageal effects.

Simvastatin — higher than recommended plasma levels could lead to the statin causing muscle pains and increased incidence of myopathy; altered liver function tests may also be a consequence.

Cetirizine — a full dose would be more likely to cause side-effects, such as drowsiness and psychomotor impairment.

Generally, Mrs Crumbly was likely to have been at a greater risk of falls from the combination of the higher plasma levels of these drugs.

By calculating the creatinine clearance using the C&G formula and applying the recommendations in appendix 3 of the *BNF*, risk of side-effects and nephrotoxicity can be reduced. Examples of identification of patients at particular risk who would benefit from review are:

- patients taking NSAIDs (including COX-2s), especially those aged more than 65 years
- patients in care homes
- patients on the CKD register, especially those in CKD stages 4 and 5. Calculation of creatinine clearance with the C&G formula for patients coded as

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CKD stage 3 shows a proportion who need alterations to their medications and doses

- the very elderly.

Recent workshops on this topic have revealed that GPs frequently have never used appendix 3 of the *BNF* and do not tend to think of renal function when making drug and dose choices. With the greater awareness engendered by the CKD guidelines, the *NSF* and the QOF markers we, as pharmacists, can help improve prescribers' decisions on drug use and dosing in reduced renal function, especially

in the very elderly. Also, we are better able to highlight and review those patients at greatest risk of harm from drug use in renal impairment. ❖

Declaration of competing interests

The author declares that she has no competing interests.

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Applicants will be judged against the following criteria:

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