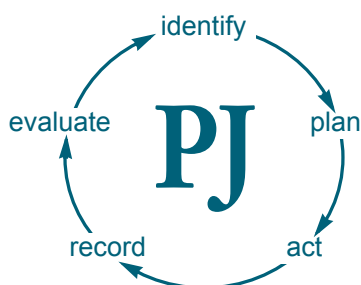


DRUG USE AND DOSING IN THE RENALLY IMPAIRED ADULT

By John Sexton, MSc, MRPharmS

This article gives an overview of how reduced renal function can affect prescribing



identify gaps in your knowledge

1. How is renal impairment defined and measured?
2. Which characteristics determine whether a drug should be used in patients with renal impairment?
3. What information sources would you consult to decide what drug and dose to recommend for a patient with renal impairment?

Before reading on, think about how this article may help you to do your job better.

The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record," (available at: www.rpsgb.org.uk/education). This article relates to "common disease states" (see appendix 4 of "Plan and record").

In addition to kidney disease, there are many causes of impaired renal function, including haemorrhage, heart failure, sepsis, prostate problems, carcinoma, calculi and drugs. Articles published in *The Journal* in 2001 looked at drugs that cause renal impairment¹ and drugs used to treat renal disease and its symptoms.^{1,2} This article focuses on how the use of drugs in general is affected by renal impairment.

The liver metabolises and conjugates drugs to more polar products that can be excreted in the urine, although metabolism is not always necessary before the kidneys can excrete a drug. Unless the liver is severely damaged, hepatic blood flow and microsomal activity are usually sufficient for the effects of liver disease on the metabolism of most drugs to be fairly minor. Renal impairment has different consequences. Many drugs pass easily through the glomeruli from the circulation, especially if they are water-soluble, and small changes in glomerular filtration can have a dramatic effect on the blood levels of renally cleared drugs or their metabolites. As the severity of renal impairment increases, the absorption, distribution and hepatic metabolism of some drugs can also be affected. For example, if the patient is oedematous, absorption of furosemide from the gastrointestinal tract is reduced and intravenous therapy may be required.

Panel 1 provides background information on how renal impairment is defined and measured.

DRUG CHARACTERISTICS

The main routes of drug excretion are via the kidneys, bile or lungs. Drugs that will be most affected by renal impairment are those that are normally substantially renally excreted or that have active or toxic metabolites which are renally excreted.

High renal clearance, wide therapeutic index Many drugs accumulate in renal impairment, but dose reduction is only necessary for some of these because the consequences of accumulation vary with each drug. A good example of this is the accumulation of different

antibiotics. Many are extensively renally cleared and have wide therapeutic windows. Most penicillins and cephalosporins are unlikely to be problematic in practice, although the high intravenous doses used in hospital can sometimes cause problems. Therefore, the individual summaries of product characteristics (SPCs) should be consulted for precise dosing instructions for each drug, especially for intravenous administration. Pharmacists also need to be prepared to discuss exceeding the manufacturers' guidelines with consultant microbiologists if the clinical situation requires.

High renal clearance, narrow therapeutic index Other antibiotics have narrower therapeutic indices and are likely to cause harm if levels rise. For example, vancomycin and gentamicin need careful dose adjustment because any accumulation is liable to be extremely toxic to the ears and kidneys. When there is pre-existing renal impairment, the likelihood of accumulation and therefore the risk of toxicity is increased. There is also an additive toxicity with other drugs used in renal failure, such as furosemide.

Digoxin is a classic example of a non-antibiotic narrow therapeutic range drug needing substantial dose reduction, but others include gabapentin, lithium, oral hypoglycaemics and allopurinol.

Low renal clearance, narrow therapeutic index Many other drugs have narrow therapeutic windows but, in general, the common ones such as theophylline, carbamazepine and phenytoin are mainly hepatically cleared with no problem metabolites and can be safely used in full doses at all degrees of renal impairment. In any event, in renal impairment some sort of monitoring, either for drug efficacy or for blood levels, is usually performed and doses can then be titrated if needed.

Drugs that are titrated against response or a physiological parameter Antihypertensive drugs can be renally cleared (eg, atenolol and most ACEIs) or hepatically cleared (eg, propranolol, most calcium-channel blockers and alpha-blockers) but, in practice, this distinction need not affect the choice of an antihypertensive. If the drug of choice is started or added at a low dose, then the dose can be adjusted until the desired response is obtained. ACEIs are renoprotective in people with diabetes but two cautions apply. If the renal impairment is caused by renovascular disease (commonly seen in people with diabetes or associated with peripheral vascular disease), the ACEI should be introduced with biochemical monitoring

Mr Sexton is principal pharmacist lecturer-practitioner at the Royal Liverpool and Broadgreen University Hospitals NHS Trust and Liverpool John Moores University Hospital

PANEL 1: MEASURING RENAL IMPAIRMENT

Glomerular filtration rate and creatinine clearance Renal function is usually expressed in terms of glomerular filtration rate (GFR), the rate at which plasma is filtered at the glomeruli. This can be derived by finding the rate at which a substance that is not reabsorbed or secreted is cleared by the kidneys. The endogenous substance creatinine (a product of muscle turnover) is only reabsorbed and secreted in small amounts so creatinine clearance is often used as a measure of GFR. It is worth noting though, that the discrepancy between creatinine clearance and GFR becomes more significant as GFR falls. Creatinine clearance is not easy to measure because urine output needs to be collected over 24 hours. Fortunately, if the patient's renal function is not changing rapidly, a population-based estimate of creatinine clearance can be derived from a single measurement of serum creatinine, using a method such as that of Cockcroft and Gault. The equation most commonly used is:

$$\text{Creatinine clearance (ml/min)} = \frac{F \times [140 - \text{Age}] [\text{Weight}(\text{kg})]}{\text{Serum creatinine } (\mu\text{mol/L})}$$

F=1.23 (male) or 1.04 (female)

The estimate of creatinine clearance relies on the assumption that a person of a particular age, weight, and sex produces a certain amount of creatinine. So the relationship between serum creatinine and creatinine clearance is only accurate in the middle of the age and weight distributions that patients fall into. The method is not reliable in children, pregnancy or catabolic states (in which creatinine production increases). It is only valid in obese patients if ideal body weight is used. This is because a 90kg obese man could carry 20kg of non creatinine producing fat. However, in most patients it can produce a surprisingly good estimation of renal function.

For the reasons mentioned above, using serum creatinine to estimate creatinine clearance may also be less accurate in patients with low levels of renal function or who are elderly. Although renal function deteriorates throughout mid-life and old-age, this may not be so apparent from serum creatinine levels because declining lean body weight and muscle mass mean that less creatinine is being produced in the body. Also noteworthy is that where renal function is changing rapidly, for example, in acute renal failure secondary to drug therapy, sepsis or dehydration, changes in serum creatinine will lag behind changes in GFR. Estimates of

renal function based on single measurements of serum creatinine will be inaccurate until the patient's condition stabilises.

Defining renal impairment For the purposes of drug dose adjustment and cautions, the British National Formulary describes renal impairment as "mild", "moderate" or "severe" and the following ranges of GFR have been used to define these terms:

- Mild 20 to 50ml/min
- Moderate 10 to 20ml/min
- Severe <10ml/min

When renal function has deteriorated to a point where dialysis or transplantation is required, the patient is considered to have reached "end-stage renal failure", a term that can alarm patients because it sounds terminal. However, it should be remembered that the other bands (mild, moderate and severe) are arbitrary. Healthy younger adults typically have GFRs between 100 and 150ml/min, but few drugs need dose reduction when GFR is more than 50ml/min, even though this may equate to the loss of more than half of glomerular filtration capacity.

Renal impairment is the most important pharmacokinetic change in ageing and is the main reason for reducing the doses of drugs in the elderly. When urine is collected or the Cockcroft and Gault equation is used, most elderly patients have creatinine clearances in the "mild renal failure" band.

By the time symptoms of renal impairment (eg, tiredness, nausea, itching or oedema) appear, a large proportion of renal function will have already been lost. Elevated serum creatinine levels must therefore be acted upon, especially in patients with diabetes or hypertension. So if the application of the Cockcroft and Gault equation results in a creatinine clearance of 40ml/min in a patient aged 80 years, this is not unusual. However, a similar result even in a seemingly healthy young or middle-aged patient, bodes ill.

in case acute renal failure is precipitated. In addition, as renal function deteriorates, the use of ACEIs may be restricted by their propensity to cause or exacerbate hyperkalaemia. Pharmacists will know that most thiazides become ineffective in moderate renal failure, but otherwise the choice of antihypertensive is the same as in other patients — based on evidence, cost, indications, contraindications and current hypertension-management guidelines.

In a similar manner, for most of the drugs used in severe renal failure (eg, sodium bicarbonate, phosphate binders, alfacalcidol, calcitriol, epoetin, unfractionated heparins) the means of elimination is irrelevant because the dose will be adjusted against a monitored parameter (eg, plasma bicarbonate, phosphate, calcium, haemoglobin or clotting time). Low molecular weight heparins such as dalteparin and enoxaparin can be a problem when used to treat deep vein thromboses or acute coronary syndromes because haemorrhage can result as they accumulate. Hospitals use them because, unlike older heparins, their effects on clotting would not normally require monitoring.

Single and initial doses Single doses of drugs are unlikely to be dangerous in renal impairment, even if the drug has a narrow therapeutic index, because accumulation is unlikely. Similarly, initial doses of a course of an antibiotic should not be reduced because otherwise it may take a long time to reach therapeutic levels. The classic example of this is teicoplanin, which, in severe renal impairment, only needs a dose administered every 72 hours. In practice, however, no reductions in dose frequency are recommended during the first four days

of treatment. If an immediate therapeutic effect is required, it is imperative that a loading dose is given and, in general, this should be the same as for patients with normal renal function — only the maintenance doses are reduced.

Other drugs Opioids and benzodiazepines are extensively hepatically metabolised, but many of their metabolites may be active and may even be toxic (eg, pethidine). They should therefore be used with caution.

Non-steroidal anti-inflammatory drugs (NSAIDs) are mostly renally cleared but can cause acute renal failure, especially when there is pre-existing renal impairment. In end-stage renal failure this may not be so much of a concern because there is little renal function left to reduce. However, the risk of gastrointestinal bleeding increases as renal function declines. NSAIDs should therefore only be used in renally impaired patients and in patients who have had a successful renal transplant if essential. The use of low-dose aspirin is rarely a cause of concern if prophylactic ranitidine or proton-pump inhibitor therapy is used.

DRUG DOSING IN END-STAGE RENAL FAILURE

If a patient has had a successful renal transplant, then the doses of drugs are simply those that the creatinine clearance achieved by the new kidney would indicate. Most of the immunosuppressant drugs used in renal transplantation, (eg, ciclosporin, tacrolimus, azathioprine, sirolimus, mycophenolate, prednisolone) are given at doses

PANEL 2: IS THE DRUG APPROPRIATE OR ONLY APPROPRIATE AFTER DOSE MODIFICATION?

Patient factors

- Has the patient got (or is he or she likely to have) impairment of renal function to a GFR of less than 50ml/min?
- What degree of renal impairment is the patient likely to have?
- Is the patient's renal function stable, or is it improving or deteriorating?
- Is the patient at any risk of developing acute renal failure?
- Is the other therapy that a patient might be taking relevant?

Drug factors

- How essential is the use of the drug?
- Is there a better alternative?
- If essential, how important is it that adequate therapeutic levels are quickly achieved?
- Is the drug renally cleared (or does it have active metabolites that are)?
- What proportion of the drug (or metabolite) is eliminated by the renal route?
- Is the drug nephrotoxic or likely to cause a further deterioration of GFR?
- Does the drug have a narrow therapeutic window (or toxic metabolites)?
- Is there a parameter that can be monitored for efficacy and safety (eg, clotting time)?
- Is the drug more likely to cause other drug-related problems in renal impairment (eg, gastrointestinal bleeding)?
- Is the drug associated with altered pharmacodynamic responses in renal impairment (eg, bumetanide can cause cramps)?

that are independent of renal function, and adjusted against blood concentrations to achieved the desired therapeutic level in light of the patient's condition. Prophylactic therapy for viral and protozoal infections may need to take renal function into account, however. It should be noted that some of these drugs have serious drug-drug interactions, including with herbal remedies, and the addition of any other drug to an immunosuppressant regimen should be preceded by some thought about whether caution is needed.

An article published in 1990³ covered the general points related to the dosing of drugs during haemodialysis and peritoneal dialysis, and the principles covered there are still valid. In summary, most drugs that would be renally cleared in a healthy kidney are removed by dialysis, with the exception of some larger drugs such as vancomycin and teicoplanin. In practice, however, because the simulated GFR in peritoneal dialysis is fairly low, and in haemodialysis only significant for four hours in every 48 to 72 hours, dose recommendations for most drugs are much the same as those for a patient with severe renal failure but not yet in need of dialysis. For drugs such as ceftazidime, which only require once daily dosing in severe renal failure, the dose is best given after any haemodialysis to avoid removing it from the circulation too soon.

CONCLUSION

Reduction in renal filtration, including that which is a normal consequence of ageing, has major effects on the therapeutic levels of drugs that are cleared through the kidneys. In practice, however, this rarely contraindicates the use of a particular drug and does not always require a dose alteration.

So what should pharmacists do when asked to suggest a drug and dose for a renally impaired adult? The BNF can give general pointers, but it is often necessary to consult a product's SPC. Hospitals will have access to specialist information, including the 'Renal drug handbook',⁴ or the American 'Drug prescribing in renal failure',⁵ which collates the available official guidance and unofficial experience for most common drugs.

action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Familiarise yourself with the section on renal impairment in the British National Formulary (Appendix 3). Use it and summaries of product characteristics whenever a patient with known or possible renal impairment has a drug prescribed.
2. Update yourself on the interactions possible with transplant medication, especially ciclosporin and tacrolimus.
3. Community pharmacists with regular patients with established renal failure under hospital care could establish a relationship with the local hospital renal pharmacist. Hospital pharmacists could ensure that any wards with Nephrology patients have easy access to the current Renal Drug Handbook or similar reference.

evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following three questions:

What have you learnt?

How has it added value to your practice? For example, have you applied this learning or had any feedback?

What will you do now and how will this be achieved?

It should be remembered that the official reduced doses recommended in product literature are often exceeded in practice, especially after lower doses have been tried. This, however, should be authorised by senior, specialist medical staff. Many companies may not have a licence for the use of their products in various degrees of renal impairment. This does not mean that the use of the drug is always inappropriate, but it does mean that the prescriber should have discussed his or her actions with the patient. In Panel 2, some of the considerations that will affect the decision to recommend a particular therapy, or otherwise, and any dose reduction, are detailed.

ACKNOWLEDGEMENT The author is grateful for the assistance of Caroline Ashley, principal pharmacist, Royal Free Hampstead NHS Trust, in the preparation of this article.

REFERENCES

1. Ashley C, Holt S. Acute renal failure. *Pharm J* 2001;266:625–8.
2. Morlidge C, Richards T. Managing chronic renal disease. *Pharm J* 2001;266:655–7.
3. Bunn RJ, Smith S. Drug dosing during renal replacement therapies. *Pharm J* 1990;244:413–4.
4. Bunn R, Ashley C (editors). *The renal drug handbook*. Oxon: Radcliffe Medical Press; 1999.
5. Aronof GR, Berns JS, Brier ME, Golper TA, Morrison G, Singer I, et al. *Drug prescribing in renal failure: dosing guidelines for adults*. 4th edition. Philadelphia: American College of Physicians; 1999.

RESOURCES

- For those who wish to read about this topic in more depth, there is an excellent website on renal failure containing many useful links at www.pharminfotech.co.nz/adept/RenalF.pdf
- The second edition of the 'Renal drug handbook', published by the Radcliffe Medical Press for the United Kingdom Renal Pharmacy Group, is due for publication in December 2003.