Pharmacology and the Kidney

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The kidney plays an important role in the handling of drugs in the body; therefore patients with renal impairment will invariably require different dosage regimes to those with normal renal function [1]. Unfortunately, there are no absolute guidelines on how to adjust doses in renal impairment, and pharmaceutical company literature often excludes patients with renal impairment in the dosage guidelines. Where information can be found, the advice may not be specific and different texts may give different advice [2]. Therefore, it is important to have an understanding of the potential effects of renal impairment on the pharmacodynamic and pharmacokinetic properties of a drug so that appropriate dosing decisions can be made. Although a reduced GFR is the primary reason for reduced excretion of drugs in renal failure, absorption, distribution, protein binding, metabolism and pharmacodynamics are all relevant.

Absorption

Absorption of orally administered drugs may be reduced in patients with renal impairment as a result of:
1. Nausea, vomiting or diarrhoea associated with uraemia.
2. Hypoproteinaemic oedema of the gastrointestinal tract, e.g. in nephrotic syndrome.
3. Reduced intestinal motility and gastric emptying time, e.g. in uraemic neuropathy.
4. An increase in pH in the gut from increased gastric ammonia production in uraemia; this reduces the bioavailability of drugs requiring an acidic environment for absorption, such as ferrous sulphate [3, 4].

5. Co-administration of drugs which increase gastric pH, e.g. H_2 antagonists.
6. Co-administration of chelating agents such as those used as phosphate binders.

It is also speculated that the absorption of some drugs is increased as a result of (1) reduced activity of drug-metabolising enzymes in the intestine, although this increase may be offset by increased first-pass metabolism in the liver [4] and (2) co-administration of drugs which increase gastric pH, this will increase the bioavailability of weakly acidic drugs [4].

Drug doses are not routinely altered to allow for these factors alone but if therapeutic levels of drugs are not being achieved or if a fast onset of action is required, a change of dose or a different route of administration may be required.

Distribution

Changes to distribution of drugs in the body in patients with renal impairment may occur as a result of (1) changes in the hydration state of the patient, (2) alterations in protein binding and (3) alterations in tissue binding.

The state of hydration of a patient is only important for drugs with a small volume of distribution (Vd) (<50 l), e.g. gentamicin [5]. In the presence of oedema, the Vd will be increased; conversely in the presence of dehydration, the Vd will be reduced.

Protein binding is altered due to (1) hypoalbuminaemia, (2) uraemia and the accumulation of metabolites and endogenous substances which will compete with the drugs for binding to albumin and (3) altered structural arrangement of albumin possibly reducing the affinity or number of binding sites for drugs [3, 4]. Alterations in protein binding are clinically important for highly protein bound drugs (>80 %) [3]. A reduction in bound drug in the plasma will result in a higher proportion of unbound, and therefore active, drug in the plasma. However, as there is more unbound drug available for metabolism, this effect is usually transient.

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For highly bound drugs, such as phenytoin, interpretation of drug level measurements can be problematic as total drug concentrations (bound and unbound) are usually reported, rather than free active drug. So a reported low phenytoin level may not necessarily be subtherapeutic, and free phenytoin levels should be measured where possible.

Where creatinine clearance is <10 ml/min or the patient is undergoing haemodialysis, phenytoin levels can be interpreted using an equation incorporating factors which take into account both altered serum albumin concentration and decreased binding affinity for this patient group:

$$Cp_{normal} = Cp_{observed} \frac{\left[\left(0.48\right)\times\left(1-0.1\right)\times\text{serum albumin}\left(g/dl\right)\right]}{4.4\left(g/dl\right)} + 0.1$$

where Cp_{normal} is the plasma drug concentration that would have been observed if the patient's serum albumin concentration had been normal and $Cp_{observed}$ is the observed plasma concentration reported by the laboratory.

Alterations in tissue binding may affect a drug's Vd. For the majority of drugs, this is not clinically relevant, although it is for digoxin [4]. The Vd of digoxin may be reduced by up to 50 % in patients with CKD stages 4–5, and so both the loading and maintenance doses will need to be reduced to prevent toxicity.

Metabolism

Both phase I and phase II metabolism are generally slower in chronic kidney disease [4, 7]. The effect of this is to increase serum drug concentrations of the parent drug. Where drugs are usually metabolised to inactive metabolites, a slowing of biotransformation may lead to a higher prevalence of side effects and toxicity. The kidney itself is also the site of metabolism for some drugs, two important examples being the hydroxylation of 25-hydroxycholecalciferol to active vitamin D (1,25-dihydroxycholecalciferol) and the metabolism of insulin.

Elimination

The kidney eliminates drugs and metabolites by a combination of glomerular filtration, renal tubular secretion and resorption [4]. In renal impairment all these functions are reduced, and while the reduction in glomerular filtration and tubular secretion results in higher plasma drug levels, reduced resorption will result in higher urinary concentrations of drug. The extent to which the profiles of drugs are affected depends on the percentage of active drug or active metabolite that would normally be excreted renally. For some drugs accumulation of active metabolites with different effects to the active parent may change the pharmacological response, a classic example being pethidine. In common with most opiates, pethidine produces CNS depression as a toxic effect, but accumulation of the renally excreted, pharmacologically active metabolite norpethidine produces CNS stimulation and seizures [7].

Pharmacodynamics

Although there is a paucity of literature on changes in the body's response to drugs in renal impairment, it is known that patients with uraemia have (1) an increased sensitivity to drugs acting on the central nervous system, e.g. antipsychotics, opiates and benzodiazepines; (2) a reduced sensitivity to some endogenous hormones such as growth hormone; (3) an increased sensitivity to cholinesterase inhibitors; (4) an increased risk of gastrointestinal bleeding with irritant drugs such as nonsteroidal antiinflammatory drugs; and (5) an increased risk of hyperkalaemia with drugs such as potassium-sparing diuretics, ACE inhibitors and angiotensin receptor blockers [8].

Drug Metabolism in Normal and Impaired Kidney Function

In the normal kidney, molecular size, protein binding, lipid solubility and charge are all important factors in determining elimination of drugs by the kidney.

Nonprotein-bound compounds up to a molecular size of 60 kD are filtered through the glomerulus. Smaller molecules are filtered more freely. Highly protein-bound substances may be filtered only if the protein binding is saturated, for example, in salicylate poisoning. Once filtered into the renal tubule, reabsorption may occur if the compound is nonpolar or lipid soluble allowing it to diffuse readily across tubular cell membranes back into the plasma. Polar or water-soluble drugs remain in the glomerular filtrate and are excreted in the urine.

Urine pH can enhance or retard drug elimination from the normal kidney as acidic compounds become less ionised and more soluble in alkaline urine with the same applying to basic compounds in acidic urine.

Four other concepts are important in drug excretion by the kidney:
1. Volume of distribution (Vd)
2. Half-life ($t_{1/2}$)
3. Elimination rate constant (ke)
4. Steady-state concentration (Css) of a drug

Table 56.1 Comparison of Cockcroft and Gault equation with MDRD equation for estimated GFR

Cockcroft and Gault equation	$$Clcr = \frac{\left[140 - Age\left(years\right)\right] \times Weight\left(kg\right)}{Plasma\ creatinine\left(\ mol\ /\ l\right)}$$
	NB.
	1. For males, multiply above equation by 1.23
	For females, multiply above equation by 1.04
	2. Use ideal body weight in obesity (i.e. if patient's weight is >15 % over IBW)
	3. This equation can only be used if the plasma creatinine is stable (i.e. not varying by >40 μmol/l per day)
	4. Do not use if:
	(i) Patient is <15 years or >90 years of age
	(ii) Patient has rapidly changing renal function
	(iii) Patient has a serum creatinine >350 μmol/l
	(iv) Patient is pregnant
	(v) Patient is an amputee
	(vi) Patient is severely wasted
MDRD equation	$$GFR\left(ml\,/\,min\,/\,1.73\ m^2\right) = 175 \times \left\{\left[serum\ creatinine\left(mmol\,/\,l\right)/88.4\right] - 1.154\right\} \times \left\{age\left(years\right) - 0.203\right\}$$ $$\times 0.742\ if\ female\ and \times 1.21\ if\ African\ American\ or\ African\ Caribbean$$
	Validated in Caucasians and African Americans
	Not yet validated in Asians and transplants
	Normalised GFR – reported as/1.73 m^2
	Incorporated into Renal NSF and Renal Association guidelines
	Can be calculated from on-line websites, e.g. http://www.renal.org/eGFRcalc/GFR.pl

The relationship between these variables is discussed below. Finally, drugs present in tubular fluid may affect the elimination of other compounds, for example, aspirin reduces methotrexate removal.

In considering the likelihood that excretion of an individual drug may be affected by kidney failure, the following factors need to be considered:

- *Size*: <60 kD filtered by the glomerulus.
- *Protein binding*: Only unbound drug can be filtered, the more protein bound a drug is, the less that drug is available for filtration; proteins can become saturated leaving unbound drug to be filtered depending on its size.
- *Polarity or water/lipid solubility*: Polar/water-soluble drugs are usually not reabsorbed once filtered.
- *Charge*: Acidic drugs are excreted more efficiently in alkaline urine and basic compounds in acidic urine.
- *Volume of distribution* (*Vd*): A measure that relates the amount of drug in the body to the concentration in the blood. It is the theoretical volume required to distribute a drug at a defined concentration (measured in blood) throughout the body.
- *Half-life* ($t_{1/2}$): Time taken for the plasma concentration to fall by half after absorption and distribution are complete.
- *Elimination rate* (*ke*): The proportion of the total amount of drug removed per unit time.
- *Proportion of the drug excreted by the kidney*
- *Extent of liver metabolism and renal excretion of metabolites*
- *Active secretion or reabsorption by the kidney*

In considering drug metabolism in CKD, the most important point to remember is that both filtration and secretion of drugs fall in parallel and in proportion to the GFR. It is important to note that although serum creatinine is widely used as a surrogate measure of renal function, it is not sufficiently accurate and at the very least eGFR should be used to adjust dosing.

Table 56.1 outlines the commonly used formulae for calculating eGFR. The Cockcroft and Gault formula, though crude, is based on age, sex and weight and current creatinine measurement and can be easily calculated at the bedside. It should not be used for patients in end-stage renal disease or receiving RRT. The ideal body weight is used for patients who are obese and is calculated as follows:

$$Ideal\ body\ weight\left(men\right) = 50 + 2.3\ kg\ for\ every\ inch\ over\ 5\ ft\ in\ height$$

$$Ideal\ body\ weight\left(women\right) = 45.5 + 2.3\ kg\ for\ every\ inch\ over\ 5\ ft\ in\ height$$

The MDRD (modified diet in renal disease) equation is more sophisticated and cannot be calculated so readily.

Table 56.2 Approximate GFR for renal replacement modalities

Renal replacement therapy	Typical theoretical GFR achieved during therapy (ml/min)
Intermittent haemodialysis	150–200 during dialysis (0–10 between dialysis periods)
Continuous arteriovenous haemofiltration (CAVH)	10–15
Continuous venovenous haemodiafiltration (CVVH)	15–25
Continuous arteriovenous haemodiafiltration (CAVHD)	20
Continuous venovenous haemodiafiltration (CVVHD)	30–40
Continuous ambulatory peritoneal dialysis (CAPD) (4 exchanges daily)	5–10

Data from Industry Submission, Renal National Service Framework (Acute Renal Failure) October 2003

However, there are websites that can perform the calculation within seconds, and as a result of the Renal NSF, most laboratories in the UK now routinely report MDRD eGFR both in primary and secondary care.

Elimination of Drugs by Haemodialysis/Filtration and Peritoneal Dialysis

The same principles of drug elimination apply to dialysis and filtration membranes as to native kidneys. Drug removal follows first-order kinetics, and the amount of drug removed is determined by plasma concentration, the sieving coefficient or permeability of the membrane, the molecular weight of the drug and the extent to which it is bound to plasma proteins.

Newer "high-flux" dialysis membranes can remove larger molecules and are particularly useful when trying to remove middle molecules including β_2 microglobulin responsible for dialysis amyloid. Haemofilters remove molecules smaller than inulin (average molecular weight 5,200 Da). This difference is especially important as most drugs which are not protein bound are removed by haemodialysis including most antibiotics, but drugs such as vancomycin (1,800 Da), amphotericin (960 Da) and erythromycin (734 Da) behave differently in haemodialysis, "high-flux" haemodialysis and haemofiltration. Just as in the native kidney, water-soluble drugs are more readily filtered than fat soluble ones. When deciding on drug dosing regimens for patients on renal replacement therapy (RRT), it is essential to ascertain which mode of RRT the patient is receiving. This is because the different modalities all have differing solute clearance rates, which has major implications for drug dosing to ensure the patient is neither overdosed nor underdosed (see Table 56.2).

The plasma concentration of a drug is determined by its volume of distribution and tissue binding characteristics. Digoxin, phenytoin and antidepressants, for example, have large volumes of distribution with only very low plasma

Table 56.3 Antibiotics that still achieve therapeutic levels when given three times a week on haemodialysis

1. Vancomycin
2. Gentamicin
3. Amikacin
4. Meropenem
5. Ceftazidime
6. Temocillin
7. Teicoplanin
8. Ertapenem

concentrations and are therefore hardly influenced by dialysis or filtration. Conversely, gentamicin has a very small Vd and negligible protein binding, so is removed extremely efficiently by dialysis.

Drugs are eliminated much less efficiently by the peritoneal membrane than by synthetic dialysis or filtration membranes. This poor permeability is used to advantage in treating peritonitis in peritoneal dialysis (PD) patients where antibiotics are injected into the peritoneal fluid.

There is one small advantage of ESRD in that reduced dosing of some antibiotics means that some patients can be easily managed with three times a week administration of antibiotics on haemodialysis, thus facilitating early discharge or avoiding daily outpatient administration of antibiotics (see Table 56.3).

Handy Hints for Prescribing for Patients with Renal Impairment

- A number of published tables that provide dosing guidelines exist to assist in dose modification (www.globalrph.com/renaldosing2.htm). Individualisation of therapy should be based on pharmacokinetic principles whenever possible [8].
- Most texts use creatinine clearance (as calculated using Cockcroft and Gault) as an estimation of GRF for recommending doses [6].

- For most drugs there is a broad creatinine clearance range for guidance on dosage and so in practice the variations of measurement will not change the recommendations [7] but it is important to consider the implications of under and over dosing for patients with GFR levels which are borderline.
- If non-renal clearance accounts for elimination of more than 50 % of a drug, then no adjustments need be made to dose or frequency of administration.
- Dosages of toxic drugs which are mainly excreted in active form by the kidney (i.e. as unchanged drug or active metabolites) may need to be modified to avoid accumulation.
- In renal failure, potentially toxic drugs should only be used if there is a specific indication for their use and if therapy can be monitored appropriately.
- If dose adjustment is required, then dose, dose interval or both can be adjusted to achieve the desired therapeutic profile.
- If dose amendment is required, then dose, dose interval or both can be adjusted to achieve the desired therapeutic effect. For example, with antibiotics, particular peak concentrations are required for optimal bacteriocidal or bacteriostatic effects, so typically the normal dose given less frequently is prescribed. Conversely, with digoxin, a steady plasma concentration is desirable, so the dosing interval remains at 24 h, and the dose is reduced.
- If the drug is unaffected by renal impairment, it may be used in usual doses and the patients should be monitored for signs of increased sensitivity to the effects of the drug or to the side effects.
- Drugs that require therapeutic levels quickly may require a loading dose as the time taken to reach steady state will be prolonged for drugs where the metabolism and excretion is slowed in renal impairment.
- Supplementary doses for RRT – some texts quote supplementary doses to be given after intermittent RRT. They will only be important for drugs with a low Vd and a narrow therapeutic range which are cleared efficiently by dialysis. In practice, it is better to adjust the timings of doses so that the next dose falls after the RRT session rather than add in extra doses.
- A number of sources are now available to provide drug dosing guidelines for the adjustment of doses for the severity of renal impairment or stage of chronic kidney disease (CKD).
- Electronic prescribing systems may assist in the use of medications in AKI and such systems have been developed in University Hospitals Birmingham Foundation Trust and Vanderbilt University Hospital, USA.

Prescribing in Acute Kidney Injury

From a drugs perspective, it is essential in AKI to review all the medications that a patient is taking, including those for co-morbidities.

- Temporarily, or permanently, withdraw drugs that affect kidney haemodynamics especially NSAIDs and drugs blocking the renin-angiotensin system.
- Stop any nephrotoxic drugs and avoid prescribing nephrotoxic therapy.
- Review drugs that may have adverse effects in patients with AKI, for example, antihypertensives, metformin, statins and any drugs which may exacerbate hyperkalaemia.
- Ensure drug dosing is appropriate for the level of renal impairment or the type of renal replacement therapy used.
   Caution should be taken with drug dosing in AKI. The use of eGFR and Cockcroft and Gault is unreliable in AKI as serum creatinine levels are regularly changing and their rate of change might not reflect current renal function. However, the daily assessment of renal function using eGFR or GFR may be an appropriate estimation for drug dosing, as long as the patient's prescription is reviewed each day.

In addition, review doses of medications as AKI resolves. This may happen quickly in a patient with dehydration where fluids are given to resolve the cause of AKI. Underdosing of drugs such as antibiotics may have an adverse impact on the management of sepsis, and doses of low molecular weight heparins may need to be increased in VTE prophylaxis.

It is also worth bearing in mind that drugs are very commonly the primary or contributing cause of AKI (see Table 56.4); an obsessional medication history (prescribed and over the counter) with start dates, courses, dose increments and potential drug interactions is important and may involve contacting prescribers such as the patients family practitioner.

Summary

Drug dosing in patients with impaired renal function is a complex area. It is important to have an understanding of how drug handling may be altered in renal impairment and RRT and on the limitations of the calculations used to estimate renal impairment in order to help make informed decisions on drug doses. Where possible, textbooks on drug dosing in renal impairment should be consulted and in addition, liaise with pharmacists with a special interest in the field who have clinical experience with these patients. In all cases once a drug regimen has been prescribed, monitor the patient for efficacy, side effects and signs of toxicity.

Table 56.4 Medication well documented to cause renal injury

Drugs that can cause glomerulonephritis

Allopurinol	Captopril
Dapsone	Gold
Halothane	Hydralazine
NSAIDs	Penicillamine
Penicillins	Phenindione
Probenecid	Rifampicin
Sulphonamides	Procainamide
Tolbutamide	Psoralen
Thiazide diuretics	Levamisole

Drugs that can cause acute tubular injury

Aciclovir	Furosemide
Aminoglycosides	Gold
Amphotericin	Ifosfamide
Cephalosporins	Lithium
Cisplatin	Mannitol
Contrast media	NSAIDs
Ciclosporin	Paracetamol
Ethylene glycol	Tacrolimus
Foscarnet	Vancomycin

Drugs that can cause interstitial nephritis

Allopurinol	Erythromycin	Phenobarbitone
Aminosalicylates	Furosemide	Phenytoin
Amlodipine	Gentamicin	Proton pump inhibitors
Azathioprine	Gold	Quinolones
Bumetanide	Interferon	Ranitidine
Carbamazepine	Isoniazid	Rifampicin
Cephalosporins	Lithium	Sulfonamides
Cimetidine	Mesalazine	Thiazides
Cotrimoxazole	NSAIDs	Vancomycin
Diltiazem	Penicillins	

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