Drug dosing in patients with renal impairment and during renal replacement therapy (RRT) by the Renal Pharmacy Group March 2019

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Introduction

The kidney plays an important role in the handling of drugs in the body. Patients with renal impairment may therefore require different dosage regimes to patients with normal renal function. 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 [1]. Even in texts where information can be found the advice may not be specific and different texts may give different advice [2]. It is important, therefore, for pharmacists to have an understanding of the potential pharmacokinetic and pharmacodynamic changes in renal impairment so that appropriate dosing decisions can be made.

Drug handling considerations in patients with renal impairment

Changes to the way drugs are handled in the presence of impaired renal function will affect both the choice of drug and the method of administration. Renal impairment can affect the absorption, distribution, metabolism and elimination of a drug. There may also be pharmacodynamic changes.

Absorption

Absorption of orally administered drugs may be reduced in patients with renal impairment as a result of:

(i) nausea, vomiting or diarrhoea associated with uraemia [3];
(ii) hypoproteinaemic oedema of the gastrointestinal tract eg in nephrotic syndrome [3] An example of this is furosemide;
(iii) reduced intestinal motility and gastric emptying time eg in uraemic neuropathy [3], this can reduce the time taken for the drug to be absorbed but does not generally affect the extent of absorption [4];
(iv) 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 [3,4];
(v) co-administration of drugs which increase gastric pH eg. Antacids, H_2 antagonists and proton pump inhibitors. This also reduces the bioavailability of drugs requiring an acidic environment for absorption.
(vi) co-administration of chelating agents such as those used for binding phosphate. An example of this is ciprofloxacin given with calcium acetate results in reduced absorption of ciprofloxacin

It is also speculated that the absorption of some drugs is increased as a result of:

(i) reduced activity of drug-metabolising enzymes in the intestine, although this effect may be offset by increased first-pass metabolism in the liver [4] and
(ii) 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 must be considered in the whole picture. 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. For example the route of furosemide can be changed to intravenous if oral absorption is thought to be impaired and ciprofloxacin should be routinely given at least 2 hours apart from phosphate binders such as calcium acetate.

Distribution

Changes to the distribution of drugs in the body in patients with renal impairment may occur as a result of;

i.) Changes in the hydration state of the patient

The state of hydration of a patient is only important for drugs with a small volume of distribution (Vd) eg. Gentamicin. In the presence of oedema the Vd will be increased and in the presence of dehydration the Vd will be reduced. It is important to note the state of hydration when blood samples are taken for therapeutic drug monitoring (TDM) and to use this knowledge when interpreting the results. This is particularly important when the state of hydration is fluctuating with the use of intravenous fluids, diuretics or intermittent RRT.

ii.) Alterations in protein binding

Protein binding is altered due to (i) hypoalbumineamia; (ii) uraemia and the accumulation of metabolites and endogenous substances which will compete with the drugs for binding to albumin and (iii) 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 (>80%) acidic drugs as these drugs bind to albumin. The protein binding of basic drugs which bind to acid glycoprotein is largely unchanged in renal impairment [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 this effect is usually transient because there is more unbound or '' drug available for metabolism and for drugs with a large volume of distribution the increased unbound drug will equilibrate into tissues [5].

For highly bound drugs care must be taken in interpreting TDM results as total drug concentrations (bound and unbound) are usually reported and not free active drug. In this instance low TDM levels may not necessarily be sub-therapeutic. The most important example of this is phenytoin. Free phenytoin levels should be measured where possible. However, as free levels are not usually readily available it is important to know how to interpret a total plasma level. Equation 1 from Winter M E. *Basic clinical pharmacokinetics* [5] may be used to adjust a total plasma level.

Figure 1: Phenytoin equation to adjust a total plasma level

$$C_{\text{Normal Binding}} = \frac{C'}{(1-fu)\,[P'/P_{NL}] + fu}$$

Where: $C_{\text{Normal Binding}}$ is the plasma drug concentration that would have been observed if the patient's serum albumin concentration had been normal; C' is the observed plasma

concentration reported by the laboratory; fu is the normal free fraction of phenytoin quoted as 0.1 for patients with a CrCl>25 mL/min and 0.2-0.35 for uraemic patients; P' is the patient's serum albumin in units of g/dL; and P_{NL} is the normal serum albumin (4.4g/dL).

Where creatinine clearance is <10mL/min and the patient is undergoing haemodialysis treatment an equation incorporating a factor which takes into account both altered serum albumin concentration and decreased binding affinity for this patient group should be used (equation 2)

Figure 2: Phenytoin equation to adjust levels for haemodialysis patients

$$C_{\text{Normal Binding}} = \frac{C'}{(0.48)(1\text{-}fu)\,[P'/P_{NL}] + fu}$$

For this equation fu has a value of 0.1 because it corrects for both serum albumin and renal dysfunction [5]. Although these equations can help us determine TDM results more accurately, they are still only an estimation and various authors have validated this and derivative equations with conflicting conclusions on the accuracy in different patient populations [6]. Therefore clinical signs and symptoms must also be used, and free levels of phenytoin should be specifically requested. It should also be noted that in patients with CrCl <25mL/min and not undergoing haemodialysis, binding affinity is unpredictably altered and neither of the above equations can be used to interpret plasma phenytoin concentrations[5]. In these patients free phenytoin levels must be requested.

Before taking samples for TDM consideration must be given to the time taken for equilibrium to be reached ($4^1/_2$ half-lives). For some drugs the half-life is increased in renal impairment so unless a loading dose is given it will take longer to reach steady-state.

iii.) Alterations in tissue binding

Alterations in tissue binding may affect the Vd of a drug. For the majority of drugs this is not clinically relevant [4]. One drug for which it is relevant is digoxin. The Vd of digoxin is reduced by up to 50% in patients with stage 5 chronic kidney disease (CKD) [7] due to a decrease in the uptake of digoxin by the myocardial tissue [3]. The loading dose will need to be reduced to prevent toxicity. Maintenance doses of digoxin must also be reduced because it is predominantly excreted via the kidneys (see 'elimination' below).

Metabolism

Chronic kidney disease and acute kidney injury (AKI) have an impact on non-renal metabolism of drugs as well as renal metabolism [7 & 8] Animal studies have shown downregulation of hepatic and intestinal metabolism via cytochrome (CYP) p450,. and clinical studies have shown increases in plasma drug levels for some drugs metabolised by CYP2C9 and CYP2C19 in patients with CKD. The transporters p-glycoprotein (Pgp) and anion transporting peptide (OATP) have also been shown to have reduced activity in CKD. This would also reduce the first pass metabolism for hepatically metabolised drugs. It is thought the mechanism of the reduced activity is mainly due to uraemic toxins but high levels of cytokines and parathyroid

hormone have also been shown to reduce CYP activity [8]. The effect of this reduced metabolism is to increase serum drug concentrations of the parent drug. This may lead to higher prevalence of adverse effects and toxicity where drugs are usually metabolised to inactive metabolites.

The kidney itself is also the site of metabolism for some drugs, two important examples are the hydroxylation of 25-hydroxycholecalciferol to active vitamin D (1,25-dihydroxycholecalciferol) and metabolism of insulin. For patients requiring vitamin D either the active drug (calcitriol) or a preparation requiring metabolism to active drug by the liver (alphacalcidol) should be used. For diabetic patients insulin requirements will be reduced as CKD progresses.

Elimination

The kidney is involved in the elimination of drugs and metabolites by glomerular filtration, renal tubular secretion and resorption [4]. As kidney disease progresses the ability of the kidney to carry out these functions is progressively reduced. The reduction in glomerular filtration and tubular secretion results in higher plasma levels of drug, and the reduction in resorption results in higher concentrations of drug in the urine (and lower concentrations in the plasma). The extent to which drugs are affected depends on the percent of active drug or active metabolite that would normally be excreted by this route. For some drugs accumulation of active metabolites with different properties to the active parent drug may change the pharmacological response in renal impairment. An example of this is pethidine. An excess of pethidine produces CNS depression, but an accumulation of the renally excreted metabolite norpethidine produces CNS stimulation and seizures [9].

In order to make decisions on doses of drugs excreted by the kidney an assessment of renal function needs to be made (see below).

Pharmacodynamic alterations.

Although there is not as much literature on changes in the body's response to drugs in renal impairment it is known that patients with uraemia have (i) an increased sensitivity to drugs acting on the central nervous system such as benzodiazepines; (ii) a reduced sensitivity to some endogenous hormones such as growth hormone; (iii) an increased sensitivity to cholinesterase inhibitors; (iv) an increased risk of gastrointestinal bleeding with irritant drugs such as non-steroidal anti-inflammatory drugs and (v) an increased risk of hyperkalaemia with drugs such as potassium-sparing diuretics [10].

Assessment of renal function

Assessing the degree of renal impairment usually involves a measurement of glomerular filtration rate (GFR). GFR cannot be measured directly so it is estimated from the clearance of a solute present in a stable concentration in the plasma and freely filtered by the kidney [11]. The solute ideally should not be secreted or reabsorbed by the renal tubule. Exogenous products which have been used include inulin, isotopes and iohexol. Naturally occurring solutes which have been used are cystatin C, urea and creatinine. The merits of each will be considered in turn.

Exogenous solutes

Inulin

Inulin used to be considered the gold standard in measuring GFR [11]. It is an inert polymer of fructose that is freely filtered and is not secreted nor reabsorbed by the tubules. Measurement was by infusion of inulin to produce steady state plasma levels and an accurately timed urine collection. The disadvantages of inulin are that it is not readily available in the UK and it is difficult to assay.

Isotopes

Radioactive chromium-51-ethylenediaminetetraacetic acid (51Cr-EDTA), Technetium-99-diethylenetriamine pentaacetic acid (DTPA) and 125-I-iothalamate have been used to estimate GFR. Following injection of the isotope assays, GRF can be measured by dynamic renal scanning to measure the rate of disappearance of the isotope or by blood samples or collection of urine samples. The method measures disappearance from the plasma rather than renal clearance [12]. The disadvantages are: the patient is exposed to radiation; in patients with advanced renal failure the samples need to be taken for a several hours after injection and the assays are expensive [11]. Also differences in the clearance of these substances have been highlighted [13] questioning the accuracy of the GFR estimation.

Iohexol

Iohexol is a contrast medium that can be measured with high performance liquid chromatography following a single injection. It avoids the problems of assaying associated with inulin and avoids exposure to radiation with using isotopes. It is excreted exclusively by the kidneys, the total amount injected is recovered in the urine 12 hours after injection [13]. It shows good correlation with inulin techniques as a filtration marker.

Although measurement of GFR using exogenous solutes are not routine they should be considered for patients requiring highly accurate GFR measurement, for example during chemotherapy or to assess living donors [14].

<u>Endogenous solutes</u>

Cystatin C

Cystatin C is a low molecular weight protein that is produced at a constant rate and freely filtered by the glomerulus [11]. After filtration it is reabsorbed and catabolised by the tubular epithelial cells which means that it is only present in the urine in small amounts. Plasma levels of cystatin C correlate well with GFR and may be more accurate than creatinine estimations in mild renal impairment [15]. Cystatin C levels are not affected by muscle mass or diet but do show high interpatient variability. Factors shown to affect cystatin C levels include age, gender, weight, height, smoking, steroid therapy and thyroid disease [13]. Equations using both cystatin C and serum creatinine have also been derived [16] but are not in routine use. Currently cystatin C levels are not routinely monitored. The National Institute of Clinical Excellence (NICE) recommends considering using cystatin C levels to estimate GFR to diagnose CKD in patients who have an eGFR (using creatinine) of 45–59 mL/min/1.73m^2 sustained for at least 90 days and no proteinuria or other marker of kidney disease [14].

Urea

Urea is used with other results as a guide to the severity of renal impairment but its use to calculate GFR is limited by external factors that affect urea production. These include alterations

in protein intake by the patient (which alters production throughout the day); catabolism caused by sepsis or treatment with corticosteroids; hyperthyroidism; liver disease; gastrointestinal bleeding and muscle injury. Another problem with using urea as a filtration marker is that it undergoes resorption by the renal tubules as well as being filtered, therefore it gives an underestimate of GRF and at low urine flow rates its clearance is independent of GFR [11].

Creatinine

Creatinine is a product of muscle breakdown formed by metabolism of creatine and phosphocreatine in skeletal muscle [13]. It is a good marker of renal function because it is mainly filtered by the kidneys and creatinine production is relatively constant in any individual with a stable diet [11]. However there are some limitations to using creatinine: (i) The production of creatinine varies between individuals as it is proportional to muscle mass and meat intake. It is therefore important to take into account the age, sex, race and weight of each individual, and to ensure the individual has a stable diet; (ii)Creatinine is actively secreted in the proximal tubule as well as being filtered, so estimating renal function using creatinine leads to an overestimate of GFR by 10-20mL/min/1.73m^2 [15]. (iii)Creatinine secretion in the tubules is blocked by some drugs (e.g. cimetidine, trimethoprim, probenecid, amiloride, spironolactone, triamterene). Administration of these drugs in patients with renal impairment can produce a reduction in excretion of creatinine without a change in the GFR. (iv)The method used to assay serum creatinine can vary between laboratories depending on the method of assay [17]. To minimise this problem NICE have recommended that all laboratories now use assays that are zero-biased compared with isotope dilution mass spectrometry (IDMS) [14]. Despite these limitations creatinine is the most commonly used marker for assessment of renal function. The ready availability of serum creatinine levels means it is easy to make an estimation of renal function without the need for cumbersome and expensive tests. The methods used for estimating renal function using creatinine are given below.

<u>Estimation of renal function using creatinine</u>

Albumin:Creatinine Ratio (ACR)

Measurement of urine creatinine and urine albumin is used to calculate an albumin:creatinine ratio which can be used in combination with GFR to classify CKD [14]. This method is not used in isolation to estimate GFR.

Calculation of creatinine clearance

A 24 hour urine collection can be performed. This entails the patient emptying their bladder first thing in the morning and then collecting all urine produced upto and including emptying the bladder the following morning.

If a 24 hour urine collection has been carried out then a creatinine clearance can be calculated using equation 3 which has been adapted from Stevens LS & Levey AS [15].

Figure 3: Equation to calculate creatinine clearance from a 24hour urine collection

$$\text{CrCl (mL/min)} = \frac{UV}{P}$$

Where: U is the urine creatinine concentration in micromol/L; V is the urine flow rate in mL/min (ie volume of urine collected divided by the time over which it was collected) and P is the average plasma creatinine concentration during the 24 hour collection period in micromol/L. When conducted properly this is a very accurate way of determining creatinine clearance, however inaccuracies in collection often occur and it is cumbersome to perform.

An alternative method is to calculate the creatinine clearance using serum creatinine levels. The most widely used method for is the Cockcroft-Gault equation derived by Cockcroft and Gault in 1976 [18]:

Figure 4: Cockcroft-Gault equation to calculate creatinine clearance

$$\text{CrCl (mL/min)} = \frac{F \times (140 - \text{age [years]}) \times \text{Weight [Kg]}}{\text{Serum Creatinine [micromol/L]}}$$

Where: F is1.23 for men and 1.04 for women.

The authors suggested that a correction factor should be used for people at extremes of body weight and ideal body weight (IBW) was often used for obese patients. However the use of IBW had not been proven to give a more accurate estimation of GFR [19,20]. In 2012 Winter et al found the most accurate weight to use in obese patients was the adjusted body weight, and that actual body weight should be used in underweight patients and ideal body weight for normal weight patients [21]

Underweight	BMI < 18.5	Use actual body weight
Normal weight	BMI 18.5 – 24.9	Use ideal body weight
Overweight	BMI >25	Use adjusted body weight

Ideal Body Weight (men)	50Kg + 2.3Kg for every inch over 5feet in height
Ideal Body Weight (women)	45.5Kg + 2.3Kg for every inch over 5feet in height
Adjusted body weight	0.4(actual body weight – ideal body weight) + ideal body weight

The Cockcroft and gault equation takes into consideration the differences in muscle mass (and therefore creatinine production), gender and age, however it does not take into account variations

between different races. The equation was derived at a time when creatinine assays were not standardised and it can't be adjusted for the current standard IDMS-traceable creatinine [19,22]. It therefore has inherent limitations in accuracy. It can only be used if the renal function is stable, and it becomes inaccurate as the GFR falls because creatinine excretion is not solely by filtration (see above). It should not be used for patients with established kidney failure or receiving renal replacement therapy (RRT). Despite these limitations the Cockcroft -Gault equation is still routinely used to calculate creatinine clearance for drug dosing.

Estimated GFR (eGFR)

There are several equations used to calculate eGFR. The Modification of Diet in Renal Disease (MDRD) study group compared different methods for calculating GRF and found the equation in equation 5 to give a good prediction of GFR [23]:

Figure 5: MDRD equation for calculating eGFR

$$GFR = 170 \times (P_{cr})^{-0.999} \times (age)^{-0.176} \times (0.762 \text{ if female}) \times (1.180 \text{ if African American}) \times [SUN]^{-0.170} \times [Alb]^{+0.318}$$

Where: eGFR is expressed in mL/min/1.73m^2, P_{cr} is plasma creatinine concentration in mg/dL, age is in years, SUN is serum urea nitrogen concentration in mg/dL and Alb is serum albumin concentration in g/dL. This equation also has limitations: (i)The equation was developed in patients with CKD that were predominantly white and did not have diabetic kidney disease or a kidney transplant. (ii)The equation has been validated for African Americans but no other ethnic groups. (iii)The equation assumes that all patients have a body surface area (BSA) of 1.73m^2. For patients with a BSA less than 1.73m^2 the eGFR is likely to overestimate their kidney function and for patients with a BSA greater than 1.73m^2 the eGFR is likely to underestimate their kidney function. Use of the patient's actual BSA will overcome this problem (see below). Despite these limitations The authors reported that this method was more accurate at estimating GFR than the Cockcroft-Gault equation [23] and further studies have confirmed this finding [24. Since the publication of the first equation, the MDRD equation has been modified to include a correction factor for IDMS creatinine and simpler versions of the equation using four variables are also in use.

As discussed above the MDRD study equation was developed in people with CKD and has been shown to underestimate GFR in people with higher GRF (>60mL/min/1.73m^2) [25]. A study published in 2009 showed a new equation - The CKD-EPI equation - had better correlation with GFR than the MDRD study equation especially in people with higher GFR [26]. The CKD-EPI equation is given below:

Figure 6: CKD-EPI equation for calculating eGFR

$$eGFR = 141 \times \min(S_{Cr} / k, 1)^{\alpha} \times \max(S_{Cr}/k, 1)^{-1.209} \times 0.993^{Age} \times 1.018[\text{if female}] \times 1.159[\text{if Black}]$$

Where eGFR (estimated glomerular filtration rate) = mL/min/1.73m^2, S_{Cr} (standardised serum creatinine) = mg/dL, k = 0.7 (females) or 0.9 (males) α = -0.329 (females) or -0.411 (males) min = indicates the minimum of S_{Cr}/k or 1, max = indicates the maximum of S_{Cr}/k or 1 and age = years. As for the MDRD study equation, this equation can be adjusted using the patient's actual BSA to give a more accurate eGFR.

Figure 7: Equation to calculate absolute GFR from MDRD eGFR and body surface area

GFR(Absolute) = eGFR x [individual's body surface area(m^2) /1.73(m^2)]

If the patient's BSA is not known this can be calculated using the Mosteller formula [27]:

Figure 8: Mosteller formula for body surface area

$$\text{Body Surface Area } (m^2) = \sqrt{\frac{\text{height (cm)} \times \text{Weight(Kg)}}{3600}}$$

The CKD-EPI is now the standard method for laboratories to report eGFR, as recommended by NICE [14]

Adjusting doses for patients with renal impairment

It can be seen from the information above that assessing the degree of renal impairment is not an exact science. The same is applicable to drug dosing in these patients. There are many literature sources available with suggested doses for patients with renal impairment (see further reading) but the advice in different sources is not always consistent [2]. It is important therefore to be able to apply your pharmaceutical knowledge to each individual case.

Choice of drug

In order to limit the potential problems with adverse effects and toxicity, as far as possible drugs with the characteristics listed in the table below should be used.

Table 1

'Ideal' Characteristics for drugs prescribed in renal impairment
Not nephrotoxic
Has a large therapeutic index

Does not require renal metabolism to an active form
Does not require renal excretion of active drug or active metabolites
Has a low adverse effect profile
Is not highly protein bound
Has an action unaffected by altered tissue sensitivity
Is unaffected by fluid balance changes
Is able to reach the site of action in high enough concentrations in the presence of renal impairment

In addition if a drug is to be given by the intravenous route it is preferable to use a drug with a low sodium content and requiring a small infusion volume.

It is rarely possible to find a drug fitting all these criteria but where a drug has potential kidney toxicity, serious dose-related adverse effects, or a narrow therapeutic range with no potential to monitor, an alternative drug should be sought.

Dosing regimen

Once a drug has been selected a decision on the dose needs to be made. Ideally one or more of the available renal drug dosing reference sources should be consulted (see further reading) along with the summary of product characteristics, and advice should be sought from a renal pharmacist who may have clinical experience of using the drug.

The drug dosing sources will give dose ranges for GFR estimated using one of the methods given above. It is important to remember: (i) Serum creatinine can only be used to estimate renal function in patients with stable function ie. in patients with CKD. It is not an accurate reflection of function in patients whose function is rapidly changing. Therefore it is not appropriate to use serum creatinine to calculate renal function in AKI. (ii) None of the equations using serum creatinine to calculate a GFR can be used in extremes of muscle mass (eg. Body builders or amputees or people with muscle wasting disorders).

Recent changes to the way renal function is assessed has brought about some confusion when interpreting drug dosing texts. Different terminology used for the degree of renal impairment refers to different methods of assessment. The term ‘creatinine clearance’ (measured in mL/min) is not interchangeable with ‘eGFR’ (measured in mL/min/1.73m^2) and different methods of estimating GFR can give different results for the same patient [20,22]. Creatinine clearance is the method that has been used to assess drug dosage in renal impairment for many years and so most texts use creatinine clearance and not eGFR in their guidance for dosing [28]. Despite the discrepancies in the calculations for GFR, for most drugs there is a broad range for guidance on dosage and so in practice the variations of measurement will not change the recommendations [29]. The British National Formulary (BNF) states that ‘for most drugs and for

most adult patients of average build and height, eGFR (rather than CrCL) can be used to determine dosage adjustments'[30]. However it is appropriate to use the Cockcroft-Gault equation if: the patient is elderly (>75 years) [30]; the drug has a narrow therapeutic range; where treatment may fail if too low a dose is given (eg antibiotics); and, where side effects or toxicity may occur if too high a dose is given (eg opiates). As none of the above forms of assessment are accurate, knowledge of the drug side effect profile and the clinical condition of the patient should aid decisions on appropriate doses. For very potent drugs such as chemotherapy, GFR should be assessed using an exogenous product for a more accurate prediction of kidney function (see above) [14].

Care should also be taken in interpreting texts which give dosing information in terms of disease severity – either in the form of the CKD classification or the older classification of 'mild' 'moderate' or 'severe'. In these instances clarity on the GFR value should be sort.

If information about the drug required is not in a reference text the following principles should also be applied: (i)If the drug and/or any active metabolites are unaffected by renal impairment (ie not renally metabolised or excreted) it may be used in usual doses and the patient should be monitored for signs of increased sensitivity to the effects of the drug or to the adverse effects.(ii)Drugs that require therapeutic levels quickly may require a loading dose as the time taken to reach steady state will be prolonged for any drug where the half-life is extended in renal impairment.(iii) Maintenance doses and frequency will depend on the extent of renal impairment and the drug to be used. (ix) If the drug adverse effect profile includes nephrotoxicity, avoid its use in CKD or patients at risk of AKI.

Loading doses

Equation 9 can be used to calculate a loading dose [31]:

Figure 9: Loading dose equation

Loading Dose (mg) = Target plasma concentration (mg/L) x Volume of distribution (L)

There will be variations in the loading dose calculated depending on the target concentration chosen (most drugs have a target range) and depending on the volume of distribution figure used (this can vary between literature sources and may again be quoted as a range). Knowledge of the adverse effect and toxicity profile will be important in choosing the loading dose.

Maintenance Doses

Equation 10 can be used to calculate maintenance doses [31]:

Figure 10: Maintenance dose equation

DRrf = DRn x [(1-Feu) + (Feu x RF)]

Where: DRrf is the dosing rate in renal failure, DRn is the normal dosing rate, RF is the extent of renal impairment (calculated as patient's CrCl(mL/min) divided by the ideal CrCl of

120mL/min), and Feu is the fraction of drug normally excreted unchanged in the urine (available in literature sources and the summary of product characteristics).

Once a dosing regime has been decided it is important to monitor the patient's progress, even if the drug does not appear to be metabolised or eliminated by the kidney, as other factors may affect the response to the drug (see above). For drugs with a narrow therapeutic range serum drug levels should be monitored and the physiological response to the drug should also be monitored. The patient and their carers should be informed of potential adverse effects or signs of toxicity so that they can report any they experience.

Drug handling considerations in patients undergoing renal replacement therapy (RRT)

Once a patient is requiring RRT their own kidney function is negligible and so removal from the body of a drug dependent on renal excretion is also negligible. It is therefore important to know whether a drug is likely to be removed by RRT. The factors to consider during RRT fall into two categories;

(i) the drug characteristics which will affect drug removal in RRT and
(ii) (ii) the RRT characteristics that will affect drug removal.

i.) Drug characteristics affecting drug removal in RRT.

A list of the drug characteristics likely to affect drug removal by RRT are given in table 2.

Table 2

Drug Characteristics affecting removal by RRT
Molecular Weight
Percentage of drug bound to plasma proteins
Volume of distribution
Water solubility
Percentage of renal clearance in normal subjects
Steric hindrance

Knowledge of the molecular weight will help determine if a drug is likely to be removed by the RRT system being used. Systems using artificial dialysis membranes have varying pore sizes. Solutes (including drugs) with a molecular weight <500Daltons will be removed by any RRT system but for solutes of larger molecular weight removal will vary depending on the system used (see below). Protein binding also affects drug removal. Only unbound drug will be available for removal by RRT so drugs with low protein binding potential are more likely to be removed. It is also important to remember that changes in protein binding occur in patients with low serum albumin levels and uraemia as discussed above. The volume of distribution of each drug is

important as only free drug in the plasma is available for removal by RRT. This is more important with intermittent haemodialysis where drugs with a low Vd (<1L/Kg) are likely to be removed effectively [32] but only a small fraction of a drug with a high Vd is likely to be removed. During continuous RRT drugs with a high Vd are more effectively removed because the equilibrium between the plasma and tissue levels is constantly changing. Vd is therefore less important for continuous RRT. Care must be taken in interpreting literature on Vd as alterations in protein binding in renal impairment will alter the volume of distribution of highly protein bound drugs (see above). The water solubility of a drug will reflect the level of drug usually in the plasma and therefore available for removal by RRT. The higher the water solubility the more likely the drug is to be removed [32]. Another reflection of a whether a drug is likely to be removed is the amount of drug usually removed by filtration in the kidneys. Although RRT cannot mimic completely the role of the kidneys it is more likely to remove drugs usually filtered by the kidney in normal subjects. Lastly steric hindrance is important. Even if a molecule appears small enough to be removed by the RRT process the atomic arrangement of the drug molecule will affect its ability to pass through the RRT membrane.

ii.) RRT system characteristics affecting drug removal

The system characteristics affecting drug removal will vary depending on the type of RRT used. The characteristics important to each system are listed in tables below.

Table 3

System characteristics important for drug removal by haemodialysis
Duration of the dialysis procedure
Blood flow rate in the dialyser
Dialysate flow rate
Composition of the dialysate
Permeability of membrane used
Surface area of membrane used
Reuse of dialyser membrane

Table 4**System characteristics important for drug removal by continuous peritoneal dialysis**
Volume of exchange of dialysate
Frequency of exchange of dialysate

Composition of the dialysate
Osmotic gradient between dialysate and plasma
Pathology of the peritoneum

Table 5

System characteristics important for drug removal by continuous haemofiltration and haemodiafiltration
Type of membrane used
Surface area of membrane used
Selection of Arterio-Venous or Veno-Venus system used
Pump pressure (if used)
Administration site of replacement fluid (pre- or post- filter)

For dialysis, solutes (including drugs) are removed mainly by diffusion. For haemodialysis and peritoneal dialysis the composition of the dialysate used will affect the concentration gradient for solutes and therefore solute removal, the higher the concentration gradient the more effectively solute will be removed. The concentration gradient will also be affected by the blood flow rate and dialysate flow rate for haemodialysis and the length of time between exchanges for peritoneal dialysis. Increasing the flow rate during haemodialysis will increase the concentration gradient as will shorter periods of time between exchanges in peritoneal dialysis.

For intermittent haemodialysis, haemodiafiltration and continuous RRT ie. Continuous arterio-venous haemodialysis (CAVHD), continuous veno-venous haemodialysis (CVVHD), continuous arterio-venous haemofiltration (CAVHF), continuous veno-venous haemofiltration (CVVHF), continuous arterio-venous haemodiafiltration (CAVHDF) and continuous veno-venous haemodiafiltration (CVVHDF) the characteristics of the synthetic membrane are important. Firstly pore size will determine the size of the solute that can pass through. For haemodialysis two filter types are in use; ‘low flux’ membranes which have a small pore size and allow solutes upto 500Daltons to pass through and ‘high flux’ membranes which have a much larger pore size allowing solutes of upto 20,000Daltons to pass though [33] Solutes pass through the dialysis membrane mainly by diffusion. Continuous RRT involving filtration use membranes with large pore size, and solutes are removed mainly by convection resulting in larger solutes (>20,000Daltons) being removed [34]. Intermittent Haemodiafiltration will remove solutes by

diffusion (dialysis) and convection (filtration). Changes in membrane composition can affect adsorption, which is when molecules adhere to the surface of the membrane without penetration [35]. Adsorption onto the synthetic polymer membrane will reduce the drug clearance. Adsorption is dependent on blood pH and type of drug as well as membrane composition, these are complex interactions and cannot always be predicted. The surface area of the membrane affects solute removal, the larger the surface area the more solute is removed. Lastly, whether the haemodialysis filter is reused or not also affects the solute clearance as the effectiveness of the filter decreases with use [33].

The membrane used for peritoneal dialysis is the peritoneal membrane and the health of this membrane is important for solute removal. During peritonitis the membrane becomes more porous and will remove a larger proportion of solutes. Solutes are removed by diffusion and convection between the capillary blood and the dialysis solution. Removal of fluid is by osmosis (see learning package on Renal replacement therapy).

The duration of the RRT will affect the amount of solute removed. More solutes will be removed during a four hour haemodialysis session than will be removed during a three hour session and continuous RRT will clear more solutes over a 24 hour period than intermittent haemodialysis. Continuous RRT will also be more efficient at removing drugs with a high Vd because the drug is constantly equilibrating between body compartments (see above). The pressure used in continuous RRT is important, the higher the transmembrane pressure gradient, the more efficient the solute removal by convection. For arterio-venous systems arterial pressure is used and for veno-venous systems a pump is used. The pumped system produces higher transmembrane pressure gradient and hence a higher solute clearance. For haemofiltration systems the site of the fluid replacement will affect drug removal. If the fluid is replaced before the filter the solutes will be diluted and less will be removed than if the fluid is replaced after the blood has been through the filter [34].

Adjusting drug doses for patients undergoing renal replacement therapy (RRT)

Once again the dosing of drugs for patients requiring RRT is not an exact science. Decisions about drug doses are difficult due to the variability of the RRT systems and the lack of specific information for individual drugs. For patients receiving RRT a creatinine clearance cannot be calculated using the equations discussed above. Table 4 gives a guide to the clearance provided by each system.

It is important to know the type of dialysis and membrane used as clearances will vary as described above. The manufacturer of the machine and filters should be able to give an estimate of creatinine clearance by their system. Haemodialysis is more effective than peritoneal dialysis at removing fluid and solutes. However, because the procedure is intermittent (often every 2-3 days) drugs should be dosed as if for a creatinine clearance of <10mL/min unless the SmPC or other specialist texts state differently. If a drug is likely to be removed by dialysis it should be given after the procedure and not before. For continuous peritoneal dialysis doses for creatinine clearance < 10mL/min are also used. Continuous renal replacement therapy not involving the use of a pumped circuit (CAVHF, CAVHD and CAVHDF) will allow drug doses for a clearance in

the range of 10-20mL/min to be used. However, those utilising pumped systems (ie. CVVHF, CVVHD and CVVHDF) have an even better solute clearance, and in the case of CVVHDF, clearances can be in the range of 30-40mL/min, allowing for much larger drug doses to be prescribed. Most systems currently used are pumped systems. For haemofiltration systems dosage decisions can also be made using a calculation involving the sieving coefficient of the drug. The sieving coefficient is a measure of the proportion of drug that will pass through the haemofiltration membrane during ultrafiltration [3]. A drug which passes freely through the membrane will have a sieving coefficient of 1 and a drug which does not pass through the membrane will have a sieving coefficient of 0. Knowledge of the ultrafiltration rate of the RRT system and the sieving coefficient can be combined to calculate the drug clearance for that system (see equation 11) [37].

Figure 11. Equation to calculate drug clearance by RRT
Drug clearance = ultrafiltration rate x sieving coefficient

The sieving coefficient can be found in specialist texts but is dependent on the type of haemofiltration and membrane used. Once an idea of the rate of drug clearance in RRT has been established literature sources such as renal drug dosing textbooks and the summary of product characteristics may be consulted to find information on dosing (see further reading).

However, care is needed in interpreting the data from published literature and texts. Patients requiring continuous RRT often have AKI and may also have multi-organ failure therefore other non-renal elimination may be affected. This may mean lower doses are required as the non-renal elimination is reduced. Conversely for patients with AKI the patient's own kidneys may still have some function or their kidney function may improve as treatment progresses. Drug doses calculated solely on the removal by continuous RRT would then result in under dosing. The improvement in dialysis filters over the last few years means that information in the literature published about drug dosing in haemodialysis and haemofiltration must also be interpreted with caution, as the low flux filters were not as efficient at removing drugs as high flux filters which are more commonly used currently.

It is therefore once again important to monitor treatment for patients on RRT. Where possible, and especially for drugs with a narrow therapeutic index, blood levels should be monitored. For all other drugs signs of efficacy and toxicity should be monitored throughout treatment. This is especially important for patients who are critically ill on continuous RRT.

Loading doses

For drugs requiring therapeutic doses quickly and with a prolonged half-life in renal failure a loading dose may be required. Equation 9 above can be used to calculate the loading dose.

Supplementary Doses for intermittent RRT

Some texts quote supplementary doses to be given after intermittent RRT. These will only be important for drugs with a low Vd and a narrow therapeutic range. It is better to adjust the

timings of the regular doses so that the next dose falls after the RRT session rather than add in extra doses.

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 function in order to help make informed decisions on drug doses. Where possible, textbooks on drug dosing in renal impairment (see further reading) should be consulted and also make use of the 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, adverse effects and signs of toxicity.

Case Study 1:

Mr PT is a haemodialysis patient. He dialyses three times a week via a tunnelled line. The haemodialysis registrar has admitted him to the renal ward suffering with rigors and fever (39^{o}C) and has prescribed him intravenous(iv) flucloxacillin.

Current medication:

Flucloxacillin iv 1g qds
Alfacalcidol 0.25micrograms po 3 x weekly
Calcium acetate 2 tablets with meals
Atenolol 50mg daily
Lisinopril 5mg daily
Erythropoietin 2,000units iv 3 x weekly
Iron sucrose 100mg iv weekly

Blood results pre dialysis on the day of admission:

Cr = 505 micromol/L (70-120micromol/L)
U = 26 mmol/L (3.7 – 8.4 mmol/L)
Na = 138 mmol/L (134 – 148 mmol/L)
K = 5.5 mmol/L (3.5 – 5 mmol/L)

Question 1:

Is the dose of flucloxacillin reasonable for a haemodialysis patient?

Question 2:

Should supplementary doses be given on dialysis days?

Question 3:

How should Mr PT be monitored?

Case study 1 answers:

Question 1:

The summary of product characteristics (SmPC) for flucloxacillin states that its use in patients with renal impairment does not usually require a dose reduction [38]. However, it also states that in the presence of severe renal failure (creatinine clearance <10mL/min) a reduction in dose or extension in dosage interval should be considered. As described in the text previously, patients undergoing intermittent haemodialysis should be considered in the category of CrCl < 10mL/min when choosing drug doses. Although it has stipulated a creatinine clearance for 'severe' renal failure the SmPC does not indicate how to reduce the dose or change the dosage interval. From the SmPC we can also see that the usual iv dose for flucloxacillin is 250mg – 1g four times a day , doubled in severe infection. 60-76% of an iv dose is recovered in an active form in the urine in 8 hours [38]. Excretion of flucloxacillin is slowed in the presence of renal failure (half-life increases from 60mins to between 135 and173 mins [39]).

Evidently the excretion of flucloxacillin will be affected by renal failure but as specific dosage instructions are not given in the SmPC it is prudent to consult other available texts. The Renal Drug Handbook suggests dosing for haemodialysis patients should be the same as those for normal renal function up to a maximum of 4g per day [39].

As Mr PT has sepsis and the source is thought to be the tunnelled line needed for haemodialysis it is important to treat quickly and to get high therapeutic levels. The consequences of under treating are a deterioration of Mr PT's health due to sepsis and the removal of his haemodialysis line. It would therefore seem appropriate to use the dose of 1g four times a day..

Question 2:

Supplementary doses should only be used in haemodialysis if significant drug removal takes place during haemodialysis and where there is a long delay before the next dose is due. The SmPC states 'flucloxacillin is not significantly removed by dialysis and hence no supplementary dosages need to be administered either during or at the end of the dialysis period'. This could also have been predicted from the pharmacokinetic data as flucloxacillin is 95% protein bound

and therefore significant removal is unlikely. Even if flucloxacillin was significantly removed by haemodialysis because the dose is given 4 times a day the doses could be timed so that a regular dose is given after dialysis.

Question 3:

Mr PT has been prescribed a high dose of flucloxacillin for someone receiving haemodialysis, therefore he should be monitored for signs of toxicity and adverse effects. The SmPC can be consulted for the whole list of side effects but the most important ones are; CNS toxicity including convulsions; blood disorders e.g. neutropenia, haemolytic anaemia, prolongation of bleeding time, defective platelet function; electrolyte disturbances;.hepatits and cholestatic jaundice and diarrhoea and antibiotic-associated colitis. Any of these would necessitate a change in therapy. It is also important to note that the flucloxacillin injection has a sodium content of 2.26mmol/g [38]. This will be important in his fluid assessment and interpretation of blood results.

As important as measuring toxicity, Mr PT needs to be monitored for therapeutic efficacy. His temperature and white blood cell count should be regularly monitored as well as the clinical symptoms. If he does not improve a change of antibiotic and/or removal of his haemodialysis line will be required.

The administration of iv iron to Mr PT during his illness should also be reviewed as iv iron is not recommended in bacteraemia [38].

Case Study 2:

Mr PM is a 60 year old man of weight 51.2Kg and height 170cm
PC: planned admission for a urology procedure.
PMH: CKD, Ureteric stenosis, nephrostomies, recurrent UTI
NKDA

Medication on admission:
Alfacalcidol 0.25 micrograms po daily
Atorvastatin 20mg at night
Diltiazem MR 120mg daily
Doxazosin 8mg daily
Omeprazole 20mg daily
Sodium bicarbonate 1g three times a day
Erythropoietin alpha 6,000 units weekly

Pre-admission blood results:
SrCr = 240micromol/L
Urea = 10.5mmol/L
eGFR = 24mL/min/1.73m^2
BMI 18Kg/M^2

Additional medication prescribed post-op:
Dalteparin 2,500 units sc daily
Paracetamol 1g po four times a day
Ibuprofen 400mg po three times a day when needed
Tramadol 100mg four times a day when needed
Cyclizine 50mg iv three times a day when needed

Post-op blood results:
SrCr = 247micromol/L
Urea = 10.9.mmol/L
eGFR =23mL/min/1.73m^2

Question:
Comment on the appropriateness of the additional medication prescribed to Mr PM and any changes that should be made.

Case study 2 answers:

Mr PM has CKD, his reported eGFR is 24mL/min/1.73m^2 pre-operatively and 23mL/min/1.73m^2 post-operatively. This shows that Mr PM has stable renal function at present and so it is appropriate to use equations that utilise serum creatinine to estimate his renal function, eg CKD-EPI and Cockcroft-Gault (see above). Mr PM has a low BMI (18Kg/m^2) and so the eGFR will have over-estimated his renal function. The BNF states that for patients with a BMI below 18 an absolute GFR should be calculated. As Mr PM's BMI is 18 and some of his new medication is potentially harmful calculating an absolute l GFR to use for drug dosing would be prudent. Mr PM weighs 51.2Kg and his height is 170cm. Using the Mosteller equation (Figure 8) Mr PM's actual body surface area can be calculated as follows:

Body Surface Area(m^2) = square root of $\frac{170 \times 51.2}{3600}$ = 1.55m^2

His eGFR can therefore be adjusted using equation as follows:

GFR(Absolute) = eGFR x [individual's body surface area(m^2) /1.73(m^2)]

GFR(Absolute) = 23 x (1.55/1.73)

GFR (Absolute) = 20.6mls/min (round to 21mls/min)

This GFR can be used to aid dosing decisions for Mr PM's medication.
(i) Daltepatin: The half-life of dalteparin is extended in renal impairment because it is primarily eliminated through the kidneys. It is therefore likely to accumulate in patients with renal impairment and increase the risk of bleeding complications. This is more of a problem when dalteparin is used at full dose for anticoagulation but care should still be taken at prophylactic doses continued for long periods. Follow any local policies for DVT prevention but if the use in renal impairment it not addressed in these use a specialist text for advice. The renal drug handbook recommends that for prophylaxis normal doses can be given with monitoring of anti-factor Xa levels[39]. The SmPC recommends monitoring anti-factor Xa levels every 3-4 doses for patients with CrCL < 30mL/min. For Mr PM no dose adjustment is required at present but factor Xa levels should be measured after 3-4 days or as per local policy.

(ii) Paracetamol: Paracetamol is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol in the urine and the half-life is unchanged in renal impairment [39]. The SmPC states 'care is advised' in patients with severe renal impairment but makes no further recommendations. The renal drug handbook [39] advises to give the same doses as patients with normal renal function for patients with a GFR >10mL/min. No dosage adjustment is therefore required for Mr PM.

(iv) Ibuprofen: Non-steroidal anti-inflammatory drugs can potentially cause renal failure due to inhibition of prostaglandins which are responsible for vasodilation. Inhibiting these prostaglandins can lead to vasoconstriction and hypo-perfusion of the kidney. This is more likely to be a problem in people with pre-existing renal impairment and those with volume depletion (such as may occur post –operatively). Ibuprofen is therefore not a good choice of analgesic for Mr PM and should be stopped. As Mr PM also has regular paracetamol prescribed and tramadol 'when needed' he may not require an alternative. His pain control should be monitored and changes to his analgesia made if needed.

(v) Tramadol: Tramadol and the metabolites of tramadol (one of which is active) are eliminated via the kidney so the half-lives are prolonged in renal impairment. The usual dose is 50mg – 100mg 4-6 hourly the SmPC recommends increasing the dosage interval to 12 hourly if the CrCl is <30mL/min (and recommends that tramadol is avoided if the CrCl <10mL/hour). More specific guidance is given in the Renal Drug Handbook [39]. These recommendations are based on CrCl using the Cockcroft-Gault equation and categorised as CrCl 20-50mL/min, CrCl 10-20mL/min and CrCl<10mL/min. Mr PM has a GFR of 21mL/min using the CKD-EPI equation,

as this is on the border of two dosing regimens it would be prudent to also calculate Mr PM's kidney function using the Cockcroft-Gault equation (see equation 10.4). Mr PM's CrCl using the Cockcroft-Gault equation is calculated as follows:

CrCl = [(140-60) x 1.23 x 51.2] / 247
CrCl= 20.3 (rounded to 20mls/min)

A CrCL of 20mL/min is between two dosing regimens in the renal drug handbook, CrCl 20-50mL/min states 'dose as in normal renal function' and CrCl 10-20mL/min recommends 50mg – 100mg 8-hourly. It is important to assess the risks and benefits of tramadol. Too low a dose would be a dose that does not control the pain in Mr PM. Too high a dose would risk effects such as convulsions and in extreme cases sedation, miosis, and respiratory depression. For tramadol the lowest effective dose should be used. It would therefore be prudent to start with a lower dose (recommended for CrCl 10-20 mL/min) and increase if needed and as tolerated rather than starting with a high dose and risk side effects.

(vi) Cyclizine: Cyclizine does not require any dose adjustment in renal impairment [39] as it is metabolised to inactive metabolites in the liver. This is a good choice of anti-emetic in Mr PM. If cyclizine does not control the nausea and vomiting, ondansetron or metoclopramide could also be used. There is no dose reduction required for ondansetron in patients with renal impairment. Metoclopramide is renally excreted however and can potentially accumulate. The SmPC recommends reducing the dose by 50% in patients with CrCl 15-60mL/min. In practice 'normal' doses can be used [39] but patients should be monitored for signs of extra-pyramidal side effects which are more common in renal impairment [37,38].

Case study 3.

Mrs SA is a patient with end stage renal failure for which she is having peritoneal dialysis (PD), four exchanges per day. Her dry weight is 64.9Kg. She has had several previous episodes of peritonitis and has presented again feeling unwell and with cloudy PD bags. The blood cultures have grown staphylococcus aureus sensitive to teicoplanin and the decision is taken to remove the PD catheter and start haemodialysis. The doctors ask your advice on the dose of iv teicoplanin.

Question 1:

What dose of teicoplanin should Mrs SA receive?

Question 2:

How should Mrs SA be monitored?

Case study 3 answers

Question 1:

Teicoplanin has a long half-life (100-170 hours in normal subjects [38]) and is mainly excreted unchanged in the urine. The elimination is therefore decreased in renal impairment and the half-life is further prolonged. As steady state levels are achieved after $4^1/_2$ half-lives, teicoplanin requires a loading dose even in patients with normal kidney function to achieve therapeutic levels quickly. For patients with renal impairment the SmPC states that a dose reduction is not required until day 4 of treatment. The recommendation for patients with CrCl<30 mL/min or requiring dialysis is that after day 4 the dose should either be reduced by one third or the initial dose should be given every 3 days [38]. This is also the dose regimen recommended in the Renal Drug Handbook [39].

With this dosing regimen it is easier to give the normal dose of teicoplanin every 3 days than to give one third of the dose daily because of the vial sizes and the difficulty in making up the vials. The dosing interval of every 3 days also has the advantage that it can be given on the days when the patient comes in for dialysis and there is no need for a prolonged inpatient stay if they are clinically well enough to go home.

The usual dose of teicoplanin is 6mg/Kg every 12 hours for 3 doses then 6mg/Kg daily. So Mrs SA should receive: 400mg iv 12 hourly for 3 doses, then 400mg iv daily until day 4, then 400mg iv every 3 days. Even though teicoplanin is primarily eliminated unchanged by the kidneys it is not removed by haemodialysis [38] because it is highly bound to plasma proteins (87.6 to 95% [38,39]). A supplementary dose is not required after dialysis. However if the dose is due on a dialysis day it would be prudent to give the dose after dialysis.

Question 2:

If available, levels should be monitored to ensure therapeutic efficacy. Trough levels should be not less than 10mg/L when measured by high performance liquid chromatography or at least 15mg/L when measured by Fluoresence polarisation immunoassay [39] If levels are not available Mrs SA should be monitored for signs of teicoplanin toxicity: thrombocytopenia and ototoxicity. Nephrotoxicity has also been reported with teicoplanin use in renally impaired patients. however as Mrs SA is already dialysis dependent and any residual kidney function will be affected by the introduction of haemodialysis, reduction in urine output will not be a reason for stopping treatment. Treatment efficacy should also be monitored: CRP, WCC and temperature will all give an indication of whether the teicoplanin is effective.

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