PHARMACOKINETIC VARIATIONS IN KIDNEY DISORDERS AND ITS CLINICAL IMPLICATIONS

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Introduction

Many drugs and their metabolites are excreted by the kidney by glomerular filtration, tubular secretion, or in some cases both. Renal impairment has a significant effect on clearance of these drugs, with important clinical consequences. These are most obvious in patients with overt renal failure. Although in theory changes in dosage and dose interval of all drugs, which are affected by renal impairment, should be considered, in practice dose adjustment is necessary for relatively few drugs, the most important of which are those with a narrow therapeutic index or adverse effects related to drug or metabolite accumulation. The corollary is that drugs are often prescribed in greater doses than are necessary to achieve therapeutic plasma concentrations. This is less likely to occur when the drug is started at a low dose and titrated against a ther-apeutic effect (antihypertensives). Although renal impairment has its important effect upon excretion, other aspects of pharmacokinetics (absorption,distribution including protein binding, metabolism, and renal haemodynamics) and pharmacodynamics may be altered. The major determinant of alteration in dosage of a drug is the change in clearance[1] ,which can be estimated by measuring the GFR. The adjustment of dosage are derived from measurement or estimation of changes in clearance,half life(t1/2) and volume of distribution(Vd). However, the determination of these pharmacokinetic variables is very model dependent and its applications has limitations. It has even been suggested that calculated half lives are often wrong[2],but may be a useful guide in prescribing.

Pharmacokinetics

Absorption

Gastrointestinal

Ammonia production occurs in the stomach in chronic renal failure, concomitant with urea accumulation and hydrolysis. Ammonia buffers hydrochloric acid, causing an increase in gastric pH. Consequently, there may be reduced absorption of drugs such as ferrous sulfate, folic acid, pindolol, and cloxacillin whose absorption is greater at acid pH. Aluminium hydroxide, which is used as a phosphate binding agent may also bind several drugs including ciprofloxacin, aspirin, and iron, and therefore should not be administered simultaneously with these agents. D-xylose. absorption is reduced by renal failure[3]. Diuretic resistance is reported to occur in the nephritic syndrome and with congestive cardiac failure as a consequence of poor intestinal absorption[4].

Peritoneal

The peritoneum is used as an absorptive surface during peritoneal dialysis during peritoneal dialysis in patients with peritonitis. The transfer of some antibiotics is bidirectional although it is primarily from the peritoneum to the circulation; absorption of gentamicin is unidirectional from peritoneum to plasma[5].During peritonitis insulin requirements may decline as absorption increases with mesothelial damage.

Distribution: Protein binding is affected by renal impairment, which is accompanied by increased concentrations in plasma of a number of acidic compounds that compete for binding sites on albumin and other plasma proteins[6,7]. Some of these have been identified: indoxyl sulfate and 2-hydroxyhippuric acid[8],3-carboxy-4-methyl-5propyl-2-furanpropanoic acid which inhibits phenytoin binding[9], 2-hydroxybenzoylglycine[10] and free fatty acids[11]. Serum albumin concentration is low in patients with the nephrotic syndrome and may also decline in cachectic patients and in elderly people, reducing the number of drug-binding sites. As a consequence, the proportion of free to bound drug is increased, and there is greater fluctuations in the free drug concentration following the administration of each dose. This could be responsible for an increased susceptibility to adverse drug reactions[12].

Table 1 - Alteration in drug binding in renal impairment

Reduced	Unaltered	Increase
Theophylline	Indomethacin	Imipramine
Phenytoin	Metoclopramide	
Methotrexate	Trimethoprim	
Diazepam	D-Tubocurarine	
Frusemide	Quinidine	
Dicloxacillin	Dapsone	
Warfarin		
Barbiturates		
Clofibrate		

Routine measurement of the plasma drug concentration includes both bound and unbound (free) drug. Binding of phenytoin to plasma protein is reduced in direct proportion to the reduction in GFR. The proportion of free (active) drug increases for a fixed total plasma concentration. Furthermore, this free fraction can be removed by dialysis [13] .These factors should be noted when prescribing phenytoin; any adjustments should be small (50 mg at a time) to avoid adverse effects. Tissue binding of digoxin (and consequently its volume of distribution) declines in renal failure and a smaller loading dose is needed. The effect of reduced digoxin clearance as GFR diminishes is even more important, and a lower maintenance dose is required than in patients with normal renal function. Monitoring the plasma concentration is often of use especially if digoxin is being used for its inotropic action (which is relatively difficult to gauge clinically), in contrast to its effect on ventricular response in patients with atrial fibrillation. In the anephric patient, the elimination of digoxin by non-renal mechanisms usually permits a dose of approximately 0.125 mg on alternate days[14] .Volume of distribution may alter in renal failure because of fluid retention and expansion of the circulating blood volume, alteration in protein and tissue binding, and alterations in the proportion of fat and muscle in the body.

Metabolism: The majority of drugs are excreted by the kidney either as the original compound or after metabolism in the liver to more polar (water-soluble) substances. Uraemia may affect drug metabolism and reduces the non-renal clearance of drugs such as acyclovir, aztreonam, moxolactam, cefotaxime, captopril, cimetidine, and metoclopramide. This alteration in clearance is minor in comparison to the retention in renal impairment of metabolites that have therapeutic or adverse effects [15].

Table 2 - Parent drugs, metabolites, and possible adverse effects

Drug	Metabolite	Effect of metabolite
Allopurinol	Oxypurinol	Causes rashes
Clofibrate	Chloro phenoxy isobutyric acid	Muscle damage, neuropathy
Nitroprusside	Thiocyanate	Toxic symptoms
Primodone	Phenobarbitone	Active drug
Procainamide	N-acetyl procainamde	Antiarrhythmic Rashes
Sulfonamides	Acetyisulfonamides	Rashes
Pethidine	Norpethidine	Causes seizures
Morphine	Morphine -6-glucuronide	Prolongs analgesia
Codeine	Morphine	Prolongs analgesia and respiratory depression
Propoxyphene	Norpropoxyphene	Cardiotoxic
Acebutalol	N-acetyl analogue	Confers selecticity
Nitrofurantion	Nitrofurantoin metabolite	Peripheral neuropathy

It is of significance when metabolites of drugs are retained in the plasma in the presence of renal impairment. The retention of these metabolites appears to reduce the proportion of active drug available; for example, the area under the curve for celecoxib specific cyclo-oxygenase 2 inhibitor (COX-2 inhibitor) is reduced in renal impairment[16].The situation may be more complex. Mycophenotic and mycophenolic acid (MPA), the active form of mycophenolate mofetil (MMF) is avidly protein bound and only the free portion is active. This binding may be reduced in uraemia and in addition MPA may also be displaced by its metabolite MPA-glucuronide (MPAG), which is renally excreted and therefore retained in the presence of renal impairment[17]. Metabolites may not only cause adverse effects but also indirectly affect drug concentrations. Renal failure may reduce drug metabolism, for instance, the conversion of sulindac to its sulfide metabolite is reduced in uraemia[18], which has been invoked as a partial explanation for the lower incidence of adverse effects as compared to indomethacin[19].

Effects Of Renal Disease on Drug Metabolism:

Type of metabolism	**EFFECT**
1. **Oxidation**	normal or increased
Eg. Phenytoin	
2. **Reduction**	slowed
Eg. Hydrocortisone	
3. Hydrolyses	
Plasma esterase	slowed
Eg.Procaine	
Plasma peptidase	normal
Eg.Angiotensin	
Tissue peptidase	slowed
Eg.Insulin	
4. Synthesis	
Glucuronide formation	normal
Eg.Hydrocortisone	
Acetylation	slowed
Eg.Procainamide	
Glycine conjugation	slowed
Eg.p-Aminosalicylic acid	
O-Methylation	normal
Eg.Methyldopa	
Sulfate conjugation	normal
Eg.Acetaminophen	

It is stated that creatinine clearance must fall below 25ml/ min before the acetylation rate of procainamide is impaired.

Renal excretion:

Renal excretion of drugs depends upon

(1) Glomerular filtration;
(2) active tubular secretion and reabsorption;
(3) passive diffusion.

Renal clearance of drugs can be expressed as function of GFR, the fraction of the drug that is unbound or free in plasma, secretion, and reabsorption. Compounds with a molecular weight below 60,000 Da are filtered to a variable extent (depending on molecular size) through the glomerulus unless they are protein bound, in which case only the unbound portion is filtered.

$ClR = f_u$ X GFR + secretion — reabsorption

where, $C1_R$ is the renal clearance and f_u the fraction of unbound drug (available for filtration). Therefore, if $C1_R$ is lower than GFR X f_u, then reabsorption (usually passive) must be taking place, and if C1R is greater than GFR X /u then secretion must be taking place.

Compounds with a molecular mass of less than 60,000 Da are filtered through the glomerulus to a variable extent, depending on molecular size, unless they are protein bound when only the unbound portion is altered. Non-polar (lipid soluble) drugs diffuse readily across tubular cells, whereas polar (water soluble) compounds do not. Since less than 1 per cent of the volume filtered is usually excreted as urine, drugs in tubular fluid become concentrated relative to plasma as water is reabsorbed. Polar drugs generally remain in the tubular fluid and are excreted in the urine, while non-polar drugs are reabsorbed by passive diffusion down their concentration gradient into plasma. Some polar drugs are eliminated in the urine as a result of active of facilitated transport mechanisms that transport organic acids or bases.

Organic acids (e.g. penicillins, cephalosporins, salicylates, frusemide, and thiazides) and organic bases (e.g. amiloride, procainamide, and quinidine) have active tubular secretion. In addition, some drugs interact to inhibit tubular secretion of others (e.g. probenecid with penicillins, with cephalosporins, and with frusemide). Elimination of organic acids (AH) or bases (B) is affected by the H+ ion concentration of the tubular fluid with any change of urinary pH that favours ionization leading to more drug excretion:

$$H^+ + B \underset{pKB}{\rightleftharpoons} BH^+$$

$$AH \underset{pKA}{\rightleftharpoons} H^+ + A^-$$

The amount of ionized drug at any particular pH is determined by its pK. The The pK is the pH at which 50 per cent of the drug is ionized. If an organic acid has a pK_A less than 7.5, making the urine alkaline (i.e. increasing its pH) increases the amount of ionized drug (A^-) and therefore its excretion. The converse is true for organic bases with a pK_B greater than 7.5, which are eliminated as the charged (BH+) form favoured by acid pH. The excretions of salicylates (weak acids) and amphetamines (weak bases) exemplify these principles and underlie the rationale for alkaline diuresis in the treatment of salicylate poisoning. Drugs present in tubular fluid may affect the excretion of other compounds: for example, aspirin and paracetamol reduce the excretion of methotrexate.A low protein diet reduces the acidity of the urine and may thereby lead to increased reabsorption of oxypurinol, a metabolite of allopurinol that is thought to be responsible for some of the adverse side effects of allopurinol[20].

1. Although it is a simplification to disregard the tubular handling of drugs in renal impairment, both filtration and secretion of drugs appear to fall in parallel and in proportion to GFR. The most important aspect of prescribing in renal disease is awareness of the existence of renal impairment and of changes in renal function.

2. **RENAL TUBULAR SECRETION**:
   Not influenced by protein binding
   May be affected by competition with other drugs
   Egs,
   Active drugs: Acids: Penicillin
   Bases:Procaine amide
   Metabolites: Glucuronides, hippurates

3. **REABSORPTION BY NONIONIC DIFFUSION**:
   Affects weak acids and weak bases.
   Only important if excretion of the free drug is major elimination pathway

Egs: Weak acids: Phenobarbitol
Weak bases: Quinidine

4. **ACTIVE REABSORPTION**:
Affects ions, not proved for other drugs
Egs: Halides: Fluoride, bromide
Alkaline metals: Lithium.

Antimicrobials

Many antimicrobial agents are excreted by the kidney. With the exception of aminoglycosides and vancomycin, most have a wide therapeutic index and little or no dose adjustment is usually made until the GFR is less than 20 ml/min.Special consideration should be given to patients with acute changes in renal function, as adverse effects may occur before it is realized that renal function is impaired..

Penicillins: Piperacillin is cited as an example of broad-spectrum injectable penicillin with antipseudomonas activity; azlocillin[21] and ticarcillin[22] require similar dose adjustment. Piperacillin has been combined with tazobactam and ticarcillin with clavulanic acid to confer penicillinase resistance. Tazobactam metabolites accumulate in renal impairment and dose reduction is required; the metabolite is partially cleared by haemodialysis and Peritoneal dialysis[23].

Table 4 - Penicillin dose adjustment

Drug	Dose reduction	Comments
Flucloxacillin	Nil	Dose seldom adjusted
Ampicillin		Dose seldom adjusted
Amoxycillin + Clavulinic acid	GFR < 20 ml/min	Half normal dose posthaemodialysis
Benzylpenicillin	GFR 20-50 ml/min	Daily dose shold not exceed 20 mU
Piperacillin	GFR<20-50 ml/min Half normal dose GFR < 20 ml/min One-third to one-half the normal dose	Half normal dose posthaemodialysis

Cephalosporins

Although there are few absolute indications for this multifarious class of drugs, they are particularly useful as broad-spectrum antibiotics in patients with impaired or changing renal function as less toxic alternatives to aminoglycosides. Cephalexin and cephradine, which are active when given by mouth, can be used in normal dose until the GFR is less than 10 ml/min, at which the daily dose is halved. The combination of loop diuretic and cefuroxime requires caution. In this situation, ceftazidime appears to be a safer alternative[24]. Cefuroxime is often prescribed in excessive doses. Cefotaxime, ceftazidime, and the newer cefoxitin can also be adjusted by increasing the dose interval to once a day if GFR is less than 10 ml/min. Ceftriaxone and cetizosime should be treated like cefuroxime by dose reduction.

Cephalosporin dose adjustment :

Drug	GFR (ml/min)	Dose Reduction
Cefotaxime	20-50	one –fifth to one-half the normal dose
Ceftazidime	20-50	one –fifth to one-half the normal dose
Cefuroxime	20-50	one –tenth to one-half the normal dose
Cefotaxime	<20	one –tenth to one-half the normal dose
Cefuroxime	<20	one –tenth to one-half the normal dose

Aminoglycosides:

Even in mild renal failure an adjustment of dose is needed for the aminoglycosides. Furthermore, they are inherently nephrotoxic, and their use may worsen renal impairment and cause ototoxicity. Several factors make nephrotoxicity more likely: previous or prolonged treatment, hypovolaemia, dehydration, concomitant administration of diuretics, hypokalaemia, and hypomagnesaemia[25], and there may be particular problems in the elderly[26]. Obstructive jaundice also increases the risk[27] .The simplest way to prevent aminoglycoside toxicity is to avoid their use altogether in patients with any suspicion of renal impairment. Of the available aminoglycosides, tobramycin is marginally less nephrotoxic than gentamicin[28] and netilmicin appears to be less ototoxic than tobramycin[29] .

A now favoured method is to give a single daily dose starting with 5 mg/kg [30] with daily measurement, when renal function is changing, of trough drug concentration. The rationale behind this concept is that peak values need to be high to achieve bactericidal activity, particularly in the presence of neutropenia. The nephrotoxic effects will be less because trough concentrations are low[31].

Table 6 - Doses and therapeutic Plasma concentration of aminoglycosides:

Drug	Usual daily dose	Therapeutic concentration	
		Peak (mg/l)	Trough (mg/l)
Gentamycin	2-5 mg/kg	5-10	<25
Tobramycin	2-5 mg/kg	5-10	<25
Netilmycin	2-5 mg/kg	5-10	<25
Amikacin	10-30 mg/kg	20-30	<10
Kanamycin	10-30 mg/kg	20-30	<10

Netilmycin dose can be increase to 7.5 mg/kg/day in severe infections but with careful therapeutic monitoring.. The rationale behind this concept is that peak values need to be high to achieve bactericidal activity, particularly in the presence of neutropenia. The nephrotoxic effects will be less because trough concentrations are low.

Vancomycin:

Vancomycin is used extensively in patients with staphylococcal infections. It is indicated in the treatment of epidemic methicillin-resistant strains and is used in the treatment of peritonitis in CAPD, which is often caused by Staphylococcus epidermidis. It is used for intravenous-line sepsis, particularly in patients in the intensive care unit. The target steady-state plasma concentration is approximately 15 mg/l [32].Vancomycin is excreted by the kidney and the dose interval should be increased in renal impairment. In endstage renal failure a loading dose of 1.5 mg/kg may maintain therapeutic levels for some days. Measurement of plasma drug concentration can be used to determine the timing of subsequent doses.

Teicoplanin

This antibiotic is a glycopeptide related to vancomycin. It is used intravenously but can also be given intraperitoneally and reportedly enters the bloodstream but does not cross back into the peritoneal cavity. In renal failure the half-life is approximately three times that in normal individuals [33].After a loading dose of 400 mg the maintenance dose of 200 mg/day should be reduced after 3 days, even in mild renal impairment.

Linezolid is an oxazolidinone and is also active against MRSA. It should be treated as a monoamine oxidase inhibitor with respect to potential interactions. The dose requires reduction if the GFR falls below 30 ml/min and the drug is cleared by haemodialysis.

Aztreonam

Aztreonam is a monocyclic /Beta-lactam. It has a wide spectrum of activity against Gram-negative organisms. It is usually given in a dose of 1g eight-hourly. However, the dose should be reduced in renal impairment[34,35]. If the GFR is less than 10 ml/min a loading dose of 1g is given, followed by a maintenance dose of 250 mg eight-hourly. Aztreonam is haemodialysed and half the usual dose is given as a supplement after dialysis.

Carbapenems: Imipenem is combined with cilastin to prevent inactivation in the kidney and is more likely to induce seizures[36]. Dosage adjustment is required with renal impairment, with particular accumulation with cilastin, and both are cleared by haemodialysis or filtration[37,38].

Macrolides

Erythromycin, clarithromycin, and azithromycin are often used in upper respiratory-tract infections (including mycoplasma, psittacosis, and legionnaire's disease) and soft tissue infections. They are particularly useful in patients who are allergic to penicillin. They are handled differently in the presence of renal impairment. Erythromycin and azithromycin need no dose adjustment but clarithromycin needs dose reduction if the GFR falls below 30 ml/min. They are not haemodialysed to any significant extent[39] .They will all interfere with cyclosporin by inhibiting its metabolism and may, therefore, cause cyclosporin toxicity in transplant recipients.

Tetracyclines

All the tetracyclines, with the exception of minocycline and doxycycline, are excreted renally. Plasma half-lives are markedly prolonged (up to 100 h) in renal impairment and as they are antianabolic there is a concentration-related increase in blood urea, which itself may cause an osmotic diuresis. This emphasizes the importance of a measure of GFR independent of blood urea (e.g. plasma creatinine) in patients with potential renal impairment before prescribing these drugs. Doxycycline or minocycline can be used cautiously in patients with renal impairment, but the other tetracyclines are contraindicated. Doxycycline does have some renal clearance but hepatic clearance increases with renal impairment, partly because there is a reduction in binding to plasma proteins and red blood cells[40].

Metronidazole : Metronidazole is used against anaerobic bacteria and against protozoa including Trichomonas spp. and Entamoeba histolytica. It is given in usual doses to patients with renal impairment. It is dialysed and a supplemental dose (half the usual dose) is required after dialysis.

Sulfonamides, trimethoprim, and cotrimoxazole :

The use of sulfonamides as single agents has largely been superseded. They are eliminated by acetylation followed by renal excretion, and acetylated metabolites (which have no antibacterial activity) cause crystalluria and tubular damage. Most sulfonamide usage is currently accounted for by cotrimoxazole (sulfamethoxozole 400 mg and trimethoprim 80 mg). However, it is now appreciated that trimethoprim as a single agent alone is effective for most urinary infections that were previously treated with cotrimoxazole, thus avoiding the toxicity of the sulfonamide. Sulfamethoxazole and trimethoprim display similar renal excretion, except at extremes of urinary pH. Alkaline urine promotes sulfamethoxazole excretion, acid urine trimethoprim[41].It is doubtful if this is clinically important. In the presence of renal impairment (GFR < 20 ml/min) one-half the usual dose may be used. A supplement of one-half the normal dose is given after dialysis.

Much greater doses of cotrimoxazole are needed in the treatment of Pneumocystis carinii infection, the risk of adverse effects being balanced against the seriousness of the condition in patients who often have impaired renal function. The dose is trimethoprim 20 mg/sulfa-methoxazole 100 mg/kg body weight per day divided into two or more doses. The plasma concentration should be maintained at approximately 5-8µg/l measured after five doses and can by achieved by lower maintenance doses.

Fluoroquinolones :

Ciprofloxacin is the first and most widely used of this group of drugs and although related to nalidixic acid, differs from it in that it can be prescribed for urinary infections in patients with renal impairment..It can also be used in the treatment of peritonitis in CAPD[42], for which it can be given orally (500 mg six-hourly or 750 mg 12-hourly). Renal excretion exceeds the GFR, and in patients with normal renal function approximately 60 per cent is cleared by the kidneys[43].It is recommended that the dose should be reduced (except as above) in renal impairment (500-750 mg/day maximum); however, the proportion that is eliminated by the kidney is reduced in renal failure[44] as a result of an increase in hepatic clearance and of secretion through the bowel wall[45] .Ciprofloxacin is not significantly removed by haemodialysis but is removed by haemo-filtration[46].Ofloxacin and levofloxacin appear to behave differently when the GFR falls below 35 ml/min they are not removed by dialysis .

Antimicrobials in urinary tract infections :

Nitrofurantoin and nalidixic acid are used in the treatment of cystitis, but are of limited use in pyelonephritis. If there is renal impairment, nalidixic acid will not reach sufficient urinary concentrations. In addition, nitrofurantoin causes peripheral neuropathy in patients with impaired renal function.

Tuberculosis

Tuberculosis can be a difficult therapeutic problem in patients with renal failure. Rifampicin[47] and isoniazid can be given in the usual dosage. Neither is cleared significantly by dialysis.The plasma half-life of ethambutol is, however, prolonged in renal impairment[48] .If the GFR is less than 30 ml/min, the dose should be 10-15 mg/kg per day with a further reduction to 4 mg/kg daily if the GFR is less than 10 ml/min. Although 10 mg/kg daily has been used at these levels of GFR, cases of optic atrophy have been reported . Pyrazinamide should be given at reduced dose (10-15 mg/kg). Capreomycin,[49] a second-line drug, can be used in isoniazid or streptomycin resistance but is itself nephrotoxic and ototoxic but can be given in a single dose of 500 mg. of cyclosporin very substantially as a result of hepatic enzyme induction[50].The necessity to use more than three agents will be dictated by the nature and severity of the infection. Treatment may need to be prolonged to between 9 and 12 months in uraemic or immunosuppressed patients, in contrast to the shorter courses that are preferred in patients with normal renal function.

Antiviral agents

Acyclovir, valacyclovir, and ganciclovir are all eliminated by the kidney and adjustments are needed in patients with renal impairment. Valacyclovir is better absorbed after oral administration. In herpes zoster infections and herpes simplex encephalitis, acyclovir is required in huge doses, which may themselves cause renal impairment particularly if the patient is dehydrated. Adverse effects including cerebral irritation, ataxia, and myoclonus which can be avoided with dose reduction[51]. The intravenous dose should be reduced stepwise from 800 mg daily at a GFR of less than 10 ml/min. In patients on haemodialysis a loading dose of 400 mg followed by 200 mg 12-hourly and a supplemental dose of 400 mg postdialysis achieves therapeutic concentrations[52]; a single daily dose of 800 mg is sufficient in patients on CAPD .Ganciclovir[53] is active against cytomegalovirus. The dose should be reduced from 5 mg/kg 12-hourly to 2.5 mg/kg 24-hourly, if the GFR is less than 25 ml/min. A single dose of 1.25 mg/kg can be given after dialysis .Foscarnet is used to treat cytomegalovirus retinitis in patients with acquired immune deficiency. It cannot be used if the serum creatinine exceeds 250 *u*mol/1. Adequate hydration and adjustment from 200 mg/kg per day in patients with normal renal function to 20 mg/kg per day at a creatinine of 250 πa,mol/l are required.

Zidovudine:

It is a basic substance and undergoes glucuronidation and is eliminated by the kidney by tubular secretion. The dose should be reduced in patients with renal impairment. Probenecid will block the glucuronidation of the drug and will partially block the tubular excretion of this metabolite[54] ,but will not block the tubular excretion of zidovudine itself. The drug is cleared by haemodialysis.

Antifungal agents:

Crystalline amphotericin is nephrotoxic and should be used with great caution in patients with existing renal impairment[55] . Its toxicity may be caused in part by vasoconstriction[56] and its adverse effects may be ameleriorated by sodium supplementation. Amphotericin encapsulated in liposomes (liposomal amphotericin) is thought to be less toxic, although that view has been questioned[57] .Both forms will cause hypokalaemia and hypomagnesaemia. The protein binding of amphotericin is reduced in renal impairment and low plasma concentrations need interpretation accordingly.

Flucytosine

Flucytosine clearance follows the GFR[58] and the dose should be reduced progressively from roughly one-half the usual dose with a GFR of 50 ml/min to one-fourth with a GFR below 20 ml/min with monitoring of the individual plasma concentrations. It is cleared by haemodialysis and half the dose should be given postdialysis. As it is excreted by the kidney it is useful in fungal pyelonephritis and urinary infections. It should be used in conjunction with another antifungal agent to avoid development of resistance.

Imidazoles :

Ketoconazole, miconazole The oral absorption of ketoconazole is reduced in patients with renal impairment . Both miconazole and ketoconazole are extensively metabolized and can be used in the usual dosage despite renal impairment.Neither ketoconazole nor miconazole should be used with cyclosporine as they induce metabolizing enzymes causing plasma concentrations of cyclosporine to decline substantially.

Fluconazole: Fluconazole is used in Candida and cryptococcal infections. It is also used prophylactically in immunocompromised patients.Unlike the other imidazoles, its elimination is dependent upon GFR; thus, it should be reduced to one-half the usual dose—400 mg on the first day followed by 100 mg once daily after the first day of therapy in patients with a GFR of less than 50 ml/min; with normal renal function it achieves a high urine concentration.It should be assumed that Ketoconazole will interfere with both cyclosporine and tacrolimus drug concentrations. **Griseofulvin**:Griseofulvin can be given in usual dosage to patients with renal impairment. It does not interfere with cyclosporine.

Antiprotozoal agents

Malaria

.**Severe and complicated malaria :** Quinine may be given by slow intravenous infusion to patients severely ill with Plasmodium falciparum infection. It should be given in usual dosage[59] to patients with chronic renal impairment. If acute renal failure develops as a complication of the disease, then the dose may need to be reduced after 2-3 days. It is not removed by haemodialysis or PD and can be given every 24 h.

Uncomplicated malaria P. falciparum infection : Is treated with quinine in usual dosage. Tetracycline is often given to patients with normal renal function to enhance the curative effect of quinine, but only doxycycline is appropriate in this regard in patients with renal impairment. Fansider (pyrimethamine with sulfadoxine) is given following quinine, but caution should be exercised, as for any sulfa-containing drug, in renal impairment.

Infection with P. vivax, P. ovale, and P. malariae can be treated with chloroquine. The dose is reduced by one-half if the GFR is less than 50 ml/min and to one-fourth if the GFR is less than 10 ml/min. Primaquine can be given in the usual doses to achieve a radical cure with elimination of hepatic forms.

Prophylaxis: Chloroquine (usual dose 300 mg/week) can be given to patients with renal impairment. Proguanil (usual dose 200 mg daily) should be given at one-half the usual dose if the GFR is below 10 ml/min.

Patients with multisystem failure

Many of the most complex prescribing problems arise in patients with acute renal failure particularly if this occurs as part of multisystem failure perhaps in a patient requiring artificial ventilation and some form of renal replacement therapy.

Neuromuscular blocking agents

Succinylcholine is rapidly hydrolyzed by plasma cholinesterase. No dose adjustment is needed. For more prolonged paralysis use atracurium, which is degraded by non-enzymatic Hofmann elimination independent of renal or hepatic function. It is removed by dialysis and haemofiltration and the dose titrated to produce a therapeutic effect[60].Avoid tubocurarine, gallamine, alcuronium, pancuronium, and vecuronium[61].Aminoglycosides, which accumulate in renal impairment without monitoring and appropriate dose adjustment, are themselves weak, non-polarizing, neuromuscular blocking agents (particularly if there is hypokalaemia) and may interact to produce prolonged paralysis.

Anaesthetic and sedating agents

Inhalation anaesthetics and injectable anaesthetics such as propofol are used in the usual dosage in patients with renal impairment. Fentanyl and alfentanyl require no dose adjustment [62,63], but may have prolonged effects if there is concomitant hepatic dysfunction. The potency of thiopentone , which is cleared by non-renal means, and other barbiturates is increased in uraemia by a direct effect of uraemia upon the central nervous system .The pharmacokinetic effect does not warrant precise dose adjustment. Diazepam has metabolites which accumulate and midazolam is preferable with dosage reduction if the GFR falls below 10 ml/min. Phenothiazines, butyrophenones, and heminevrin are given in usual doses. Despite the minor

changes in patients with renal impairment, it is well recognized that patients may have prolonged periods of sedation and confusion following mechanical ventilation.

Narcotic analgesics

Opiates are affected by renal failure and retention of metabolites can produce adverse effects[64] .Reduced intermittent doses, epidural administration, or low dose continuous infusions reduce the incidence of adverse effects. Diamorphine is metabolized into morphine and then to morphine-3-glucuronide and morphine-6-glucuronide, both of which accumulate to prolong both analgesia and respiratory depression. Morphine and its metabolites are removed somewhat more by haemofiltration than by dialysis. Pethidine (meperidine) is converted to norpethidine (normeperidine), which accumulates and can cause seizures[65]. Papaveretum is a mixture of alkaloids of opium including morphine, codeine, noscapine, and papaverene; its use is not recommended.

Treatment of shock

Cardiac inotropes are used in normal dosage, although renal vasoconstriction may be deleterious so the minimum effective dose of adrenaline, noradrenaline, dobutamine, or dopamine should be used. They are not affected by haemodialysis or filtration. Dopamine in low doses (2.5-5 (ig/kg per min) is a renal vasodilator. Intravenous nitrates are given in normal dosage. Sodium nitroprusside may be used in the management of hypertension or left ventricular failure. It is metabolized to sodium thiocyanate , which is eliminated by the kidney, and so may accumulate in renal failure, causing toxicity. It is removed by haemodialysis or PD. In liver failure the detoxification of cyanide to thiocyanate may be impaired so the use of sodium nitroprusside should be avoided in this circumstance. Plasma concentrations greater than 10 mg/dl produce nausea, anorexia, and fatigue; levels greater than 20 mg/dl may be fatal.

Antiarrhythmics

In patients with abnormal renal function it is advisable to keep treatment simple. Most antiarrhythmic drugs are used without dose modification: for example, lignocaine and verapamil. Digoxin is a notable exception with a lower loading and maintenance dose than usual. Flecainide and disopyramide require dosage reduction. Amiodarone requires a lower maintenance dose (100 mg daily) when the GFR falls below 20 ml/min[66] .

Drugs acting on the central nervous system

Drugs acting on the central nervous system may have a prolonged effect not only because of changes in pharmacokinetics but also because of increased sensitivity as a consequence of uraemia.

Antidepressants

All drugs should be used with caution. Tricyclics are given in usual dosage. Fluoxetine, paroxetine, and other SSRIs have been used widely in patients on dialysis although dosage reductions are advised. It is best to avoid citalopram and venlafaxine.

Lithium

Lithium is used primarily in affective disorders. It is filtered and then reabsorbed, mainly in the proximal tubule. The dose should be reduced in renal impairment with careful monitoring of plasma concentration. In sodium depletion (e.g. with chronic thiazide diuretic use) tubular reabsorption of lithium is increased, leading to higher plasma concentrations and toxicity. The effect of non-steroidal anti-inflammatory drugs (NSAIDs) on renal haemodynamics may also be important. Lithium itself is a cause of chronic tubulointerstitial damage.

Major tranquillizers : No dose change is required when phenothiazines or butyrophenones are used in patients with renal impairment. Newer drugs such as clozapine, rispiridone, and sulpiride should be used with caution.

Minor tranquillizers : Benzodiazepines can be prescribed in usual dosage. Diazepam and chlordiazepoxide have active metabolites which may accumulate. Short acting drugs, such as nitrazepam and temazepam may avoid hangover the morning after use as night sedation.

Anticonvulsants :

Phenytoin and valproic acid are both highly protein-bound. The protein binding of phenytoin declines in proportion to the GFR . The unbound (free or active components) will be proportionately greater for a given plasma concentration as the GFR declines and this will have the effect of lowering the

therapeutic range. Changes in the protein binding of valproic acid are not clinically important .Both drugs are prescribed in usual dosage in renal impairment and neither is dialysed . Carbamazepine is prescribed in usual doses.Newer anticonvulsants include Lamotrigene, which needs no dose adjustment, but both Vigabatrin(reduced from the usual dose 2-3g/day when the GFR is <60ml/min and Gabapentin (1200 mg/day reduced to 300mg on alternate days) need dose reduction.Adverse effects are more common with Vigabatrin in patients with renal impairement, even with appropriate dose adjustment.

LIPID LOWERING AGENTS:

Hyperlipidemia is found in patients with the nephrotic syndrome, in most patients with chronic renal failure, and in many patients functioning renal transplants. Diet should be used to control these abnormalities but drug treatment may be needed. The anion-exchange resins (e.g. colestipol) and 3-hydroxy-3-methylglutaryl coenzyme A-reductase (HMG-CoA reductase) inhibitors (e.g. simvastatin, atorvostatin, and pravastatin) can be given in usual doses, with the exception of fluvastatin[67], for which the dose is reduced in both renal impairment and the nephrotic syndrome . Cerivastatin has been withdrawn because of an increased incidence of myopathy and myositis, which remains an important adverse effect of other statins particularly if given in the presence of renal impairment or with cyclosporin or gem-fibrizol. The fibrates (gemfibrizol, bezafibrate) can be used with dose reduction at GFR less than 20 ml/min. There is no role for the use of clofibrate because of its potential to cause peripheral neuropathy.

Thrombolytics, anticoagulants, and haemostatics:

Streptokinase, anistreplase, and alteplase can all be used in patients with renal impairment with acute myocardial infarction but the potential risks of haemorrhage have to be weighed against the advantages. They can be given to transplant patients. Urokinase and alteplase can be used in usual dosages to declot dialysis catheters.

Anticoagulants and antiplatelet agents:

Warfarin is used in normal dosage and its effect monitored by measuring prothrombin time in the usual way. It is highly protein bound and, therefore, not dialysed. It may be subject to displacement from protein binding sites with consequent reduction in volume of distribution. In nephrotic patients, hypoalbuminaemia leads to increased sensitivity to warfarin. Unfractionated (standard) heparin is administered intravenously by infusion in usual dosage. There is now widespread use of low molecular weight heparins (e.g. enoxaparin, tinzaparin) both as prophylaxis and in treatment of thromboembolic disease. The dose is administered subcutaneously and usually prescribed without monitoring of its effect. A study of subjects with normal renal function and varying degrees of renal impairment that absorption (measured by anti-Xa activity) was unchanged but that the elimination half-life was prolonged significantly in those with a GFR less than 30 ml/min, and that this was more evident with repeated dosing. The anti-Xa exposure was significantly increased. It is, therefore, recommended that the dose should be reduced by half in severe renal impairment. Prophylactic aspirin is given in the usual low dose (75-150 mg daily), but clopidogrel dosage should be reduced.

Prostacyclin is used to prevent platelet aggregation in artificial kidneys and haemofilters. It is also used as a vasodilator with particular effects upon the pulmonary circulation. It is rapidly hydrolyzed and, therefore, not affected by renal impairment.

Transexamic acid completely inhibits the activation of plasminogen to plasmin, but the dose should be reduced and the dose interval prolonged in renal failure.Ureteric obstruction by blood clot has been reported in patients with massive haemorrhage from the upper renal tract.

Diabetes mellitus

Insulin: Insulin requirements fall with declining renal function, probably as a consequence of reduced metabolism of insulin by the kidney in both acute and chronic renal failure. The glucose concentration of dialysate in haemodialysis will determine whether insulin adjustments are needed; in critical care when patients may be fed enterally or parenterally or haemofiltration insulin may be required as a continuous infusion.

Oral hypoglycaemic agents

Gliclazide, gliquidone, and glipizide are the safest drugs to use although dose reduction may be needed if GFR is below 10 ml/min. Other sulfonylureas, particularly chlopropamide with its long half-life, should be avoided. Metformin, a biguanide, should not be used if the GFR falls below 20 ml/min, as there is a high risk of lactic acidosis. Metformin induced lactic acidosis may require haemofiltration with bicarbonate as the buffer; haemodialysis may increase metformin clearance in these circumstances.The thiazolidine-diones, rosiglitazone, and pioglitazone require no dose adjustment. Acarbose should be avoided in renal impairment.

Insulin requirements fall with declining renal function, probably as a consequence of reduced metabolism of insulin by the kidney in both acute and chronic renal failure. In patients on haemodialysis it is often necessary to give supplemental insulin during treatment. The same situation applies in patients on haemofiltration in acute renal failure, particularly if they are being fed parenterally, and in continuous arteriovenous haemodialysis (CAVHD) when the dialysate is a glucose based solution. Non-diabetic patients may require insulin temporarily under these circumstances. Patients on CAPD may need a change in insulin preparation and adjustment in the frequency and route of administration. The intraperitoneal requirement is approximately 50 per cent of intravenous requirements.

Asthma

β-Agonists administered by inhalation, oral, or parenteral routes need no adjustment in patients with renal impairment. Although tobuterol is an exception. Aminophylline and theophylline can be given in usual doses, but metabolites may accumulate and theophylline[68] levels may be falsely raised . The leukotrine antagonist montelukast can be used without dosage reduction, although it is recommended that the dose is reduced in moderate to severe renal impairment, advise that this is not necessary.

Gastrointestinal drugs

H2-antagonists and antiulcer drugs: There is an increased risk of confusional states with cimetidine in patients with impaired renal function. Cimetidine[69] is cleared by the liver, but metabolites accumulate if the GFR is less than 20 ml/min. Ranitidine is preferable in this situation, but it should be noted that it interferes with creatinine secretion and increases plasma creatinine. It is partly cleared by the kidneys and the dose should be halved when the GFR is less than 10 ml/min. It is dialysed, and a supplemental dose is needed after dialysis. Approximately one-third of a 50 mg dose is cleared by a single exchange in CAPD and a 150 mg twice daily dose can be used safely. It is commonly given to patients requiring artificial ventilation to reduce the risk of stress ulceration. In these circumstances, 25 mg twice or thrice daily intravenously is sufficient. No supplemental dose is needed during haemofiltration even though 20 per cent may be removed during 20 1 of exchange. Omeprazole and misoprostol are given in usual doses. Misoprostol may cause reductions in GFR through haemodynamic changes in the kidney.

Hyperuricaemia

Allopurinol

Allopurinol is metabolized to oxypurinol, which is retained in renal impairment and may be responsible for some of the adverse effects including rashes, bone marrow depression, and gastrointestinal upset. The dose should be reduced to 100 mg/day when the GFR is less than 20 ml/min, and in haemodialysis patients the dose is given after treatment. Allopurinol interferes with the metabolism of 6-mercaptopurine (an active metabolite of azathioprine) causing accumulation and toxicity (e.g. leucopenia). Treatment of gout in transplant patients is difficult . Reduction in the dose of azathioprine is one step but occasionally the drug has to be stopped altogether. Unfortunately, cyclosporin increases serum uric acid concentrations and probenecid may have to be used..

Uricosuric agents

Uric acid is excreted most efficiently in alkaline urine. This may be achieved with potassium citrate, with care to avoid hyperkalaemia, but in advanced renal failure the urine is relentiessly acidic in pH.

Probenecid: Probenecid inhibits secretion of acids in the proximal tubule and prevents reabsorption of urate from the tubular lumen. It prolongs the effect of penicillins, cephalosporins, naproxen, indomefhacin,

methotrexate, and sulfonylureas (all of which are weak acids), causing accumulation and the potential for toxicity. It also inhibits tubular secretion (and hence activity) of frusemide and bumetanide. It also inhibits liver uptake and, hence, glucuronidation of several drugs including zidovudine

Colchicine: Colchicine has been partly replaced by NSAIDs for the treatment of acute gout. However, it remains valuable in patients in whom NSAID are undesirable (e.g. peptic ulcer disease, cardiac failure, renal impairment) with no dose adjustments.Losartan has been found to act so as to lower serum uric acid concentrations in renal transplant patients. It acts by increasing urinary excretion of uric acid and xanthine as well as oxypurinol. This may be useful as an adjunct to its other indications.

Anti-inflammatory agents

NSAIDs including aspirin inhibit prostaglandin synthesis by inhibition of cyclo-oxygenase. The principal renal prostaglandins in man are PGE, and PGI, each of which is vasodilator and natriuretic. In addition to effects on renal blood flow prostaglandins also influence tubular ion transport directly. In healthy individuals inhibition of cyclo-oxygenase has no detectable effect on renal function, but in patients with cardiac failure, nephrotic syndrome, liver disease, glomerulonephritis, and other renal disease cyclo-oxygenase inhibitors predictably cause a reversible fall in GFR which can be severe. They also cause fluid retention. They may also cause hyperkalaemia. There is evidence that sulindac causes less inhibition of renal cyclo-oxygenase than a dose of ibuprofen that is equi-effective on extrarenal tissues; sulindac may cause less renal impairment than other NSAIDs. Aspirin may also spare cyclo-oxygenase in the kidney to some extent. The clinical relevance of these observations remains uncertain and caution is needed in severe renal impairment for all of this group of drugs. The newer inhibitors of COX-2 are thought to have less gastrointestinal side-effects than other NSAIDs, but will have the same effects upon renal function . Celecoxib is also heavily protein bound. It is eliminated after metabolism to carboxylic acid and glucuronide metabolites and excreted in the faeces and urine. There are no adjustments required in renal impairment .

Indomethacin, azapropazone, and diflunisal have important renal excretion, whereas most other NSAIDs are eliminated by metabolism. Diflunisal is less protein bound in the presence of renal impairment, although the clinical importance of this is slight. Sulindac has an active sulfide metabolite, but in renal impairment this metabolism is reduced. It has been reported to have fewer side-effects than indomethacin.The NSAIDs are highly protein bound and are not removed by dialysis.

Corticosteroids and immunosuppressive agents

Prednisone and prednisolone[70] are not eliminated by the kidney. However, in theory, the dose should be reduced when patients have advanced uraemia . Hepatic clearance is reduced . Bergrem confirms that usual doses of prednisolone can be used in patients with the nephritic syndrome. Hypoalbuminaemia reduces the number of binding sites on plasma protein, but the increase in steroid side-effects failed to account for other factors such as underlying disease and renal dysfunction. Methyl-prednisolone[71] is cleared by haemodialysis, and should be given after dialysis .

Azathioprine accumulates in renal impairment and the dose should be reduced from a maximum of 3 to 1 mg/kg/day if the GFR falls below 10 ml/min . Allopurinol prevents the metabolism of 6-mercaptopurine; the active metabolite of azathioprine, and the combination should be avoided. The metabolism of azathioprine has a genetic variability. Hypoxanthine guanine phos-phororibosyl transferase (HPRT) oxidation by xanthine oxidase shows little variability, but inactivation via methylation by thiopurine methyl transferase (TPMT) is variable. Estimates show that 11 per cent of the population has low TPMT activity with one in 300 with a very low level.[72] This appears to have aroused less interest in renal physicians than in other specialities .Monitoring of white blood count concentration may not always predict toxicity.

Cyclophosphamide[73] is used in a variety of vasculitic conditions often intravenously. The dosing schedules vary, but up to 1 g every 2 weeks may be given as induction therapy. The dose should be reduced stepwise according to estimations of the GFR with half the usual dose administered in severe renal failure. As it is removed by haemodialysis it should be administered postdialysis .Methotrexate is used frequently in rheumatological disorders (rheumatoid arthritis, psoriatic arthropathy, systemic lupus erythematosus), usually as a small weekly dose. It should be noted that the drug is a weak acid and eliminated by proximal tubular secretion, which jjan be blocked by salicylates or NSAID. There are also reports of interaction,

causing increased serum levels, when higher doses are used in conjunction with amoxicillin , and vancomycin although the mechanism was less clear .

Cyclosporin is a highly lipid soluble drug, which is exclusively bound to plasma proteins and has a large volume of distribution. It is metabolized by the liver via the cytochrome P-450 system by mono-and di-hydroxylation as well as N-demethylation. Only minor amounts are excreted in the urine as parent drug or metabolites. Renal impairment does not affect the metabolism. However, since many other drugs may be prescribed to patients taking cyclosporin therapy several important interactions may occur. These will both increase plasma concentration and, therefore, increase the risk of nephrotoxicity or reduce plasma concentrations and increase the risk of transplant organ rejection. Aminoglycosides may have an additive effect upon the nephrotoxicity itself. Tacrolimus and sirolimus can be regarded as behaving in a similar fashion to cyclosporin.MMF converted to its active metabolite MPA has been discussed in the section on pharmacokinetics. Careful monitoring of plasma concentrations and therapeutic effects are needed particularly in renal impairment .

Conclusion

When a drug with clinically important renal excretion is prescribed in the presence of renal impairment, the dose can be adjusted in two main ways. Either the size of each dose or the frequency of administration can. be reduced. Plasma drug concentrations can be used to confirm that the initial adjustment of dosage is correct in that particular individual. Steady-state concentrations of anticonvulsants, digoxin, and the theophylline can be measured after the equivalent of five half-lives of the drug. For antibiotics such as gentamycin, the peak and trough concentrations taken after the first day's administration is essential and continued monitoring is required if renal function is impaired or changing.

Significant reduction in dosage is more likely to lead to subtherapeutic plasma concentrations. A combination of modest reduction in dosage with less frequent administration is suitable for most drugs. Dose adjustments must be kept simple and clear since unfamiliar dosages and the administration of drugs at odd times may result in error.

In summary, the physician should be able to answer the following basic questions about the pharmacokinetics of a prospective drug.

1. Is the drug readily absorbed?
2. Is the drug excreted unchanged in urine or is there significant metabolism?
3. What is the major route of elimination?
4. What are the characteristics of metabolism?

a) Are they active or toxic?
b) Are they rapidly excreted or do they accumulate?

5. What is the onset and duration of pharmacologic action?
6. Does the dose response curve reflect on the pharmacokinetic profile?

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