Appendix 4: Renal impairment

Reduced renal function may cause problems with drug therapy for the following reasons:

1. The failure to excrete a drug or its metabolites may produce toxicity.
2. The sensitivity to some drugs is increased even if the renal elimination is unimpaired.
3. The tolerance to adverse effects may be impaired.
4. The efficacy of some drugs may diminish.

The dosage of many drugs must be adjusted in patients with renal impairment to avoid adverse reactions and to ensure efficacy. The level of renal function below which the dose of a drug must be reduced depends on how toxic it is and whether it is eliminated entirely by renal excretion or is partly metabolized to inactive metabolites.

In general, all patients with renal impairment are given a *loading dose* which is the same as the usual dose for a patient with normal renal function. *Maintenance doses* are adjusted to the clinical situation. The maintenance dose of a drug can be reduced either by reducing the individual dose leaving the normal interval between doses unchanged or by increasing the interval between doses without changing the dose. The interval extension method may provide the benefits of convenience and decreased cost, while the dose reduction method provides more constant plasma concentration.

In the following table drugs are listed in alphabetical order. The table includes only drugs for which specific information is available. Many drugs should be used with caution in renal impairment but no specific advice on dose adjustment is available; it is therefore important to also refer to the individual drug entries. The recommendations are given for various levels of renal function as estimated by the glomerular filtration rate (GFR), usually measured by the creatinine clearance. The serum-creatinine concentration can be used instead as a measure of renal function but it is only a rough guide unless corrected for age, sex and weight by special nomograms.

Renal impairment is usually divided into three grades:

mild —GFR 20–50 ml/minute *or* approximate serum creatinine 150–300 micromol/litre

moderate —GFR 10–20 ml/minute *or* serum creatinine 300–700 micromol/litre

severe —GFR *or* serum creatinine >700 micromol/litre

When using the dosage guidelines the following must be considered:

- Drug prescribing should be kept to a minimum.
- Nephrotoxic drugs should, if possible, be avoided in all patients with renal disease because the nephrotoxicity is more likely to be serious.

- It is advisable to determine renal function not only before but also during the period of treatment and adjust the maintenance dose as necessary.
- Renal function (GFR, creatinine clearance) declines with age so that by the age of 80 it is half that in healthy young subjects. When prescribing for the elderly, assume at least a mild degree of renal impairment.
- Uraemic patients should be observed carefully for unexpected drug toxicity. In these patients the complexity of clinical status as well as other variables for example altered absorption, protein binding or metabolism, or liver function, and other drug therapy precludes use of fixed drug dosage and an individualized approach is required.

Table of drugs to be avoided or used with caution in renal impairment

Drug	Degree of Impairment	Comment
Abacavir	Severe	Avoid
Acetazolamide	Mild	Avoid; metabolic acidosis
Acetylsalicylic acid	Severe	Avoid; sodium and water retention; deterioration in renal function; increased risk of gastrointestinal bleeding
Aciclovir	Mild	Reduce intravenous dose
	Moderate to severe	Reduce dose
Alcuronium	Severe	Prolonged duration of block
Allopurinol	Moderate	100–200 mg daily; increased toxicity; rashes
	Severe	100 mg on alternate days (maximum 100 mg daily)
Aluminium hydroxide	Severe	Aluminium is absorbed and may accumulate NOTE. Absorption of aluminium from aluminium salts is increased by citrates which are contained in many effervescent preparations (such as effervescent analgesics)
Amidotrizoates	Mild	Reduce dose and avoid dehydration; nephrotoxic
Amiloride	Mild	Monitor plasma potassium; high risk of hyperkalaemia in renal impairment; amiloride excreted by kidney unchanged
	Moderate	Avoid
Amoxicillin	Severe	Reduce dose; rashes more common
Amoxicillin + Clavulanic acid	Moderate to severe	Reduce dose
Amphotericin B	Mild	Use only if no alternative; nephrotoxicity may be reduced with use of complexes
Ampicillin	Severe	Reduce dose; rashes more common
Artemether + Lumefantrine	Severe	Caution; monitor ECG and plasma potassium
Atenolol	Moderate	Reduce dose (excreted unchanged)
	Severe	Start with small dose; higher plasma

		concentrations after oral administration; may reduce renal blood flow and adversely affect renal function
Azathioprine	Severe	Reduce dose
Azithromycin	Moderate to severe	Use with caution —no information available
Benzathine benzylpenicillin	Severe	Neurotoxicity—high doses may cause convulsions
Benzylpenicillin	Severe	Maximum 6 g daily; neurotoxicity—high doses may cause convulsions
Bleomycin	Moderate	Reduce dose
Carbamazepine		Manufacturer advises caution
Ceftazidime	Mild	Reduce dose
Ceftriaxone	Severe	Maximum 2 g daily; also monitor plasma concentration if both severe renal impairment and hepatic impairment
Chlorambucil	Moderate	Use with caution and monitor response; increased risk of myelosuppression
Chloramphenicol	Severe	Avoid unless no alternative; dose-related depression of haematopoiesis
Chloroquine	Mild to moderate	Reduce dose in rheumatic disease
	Severe	Reduce dose for malaria prophylaxis; avoid in rheumatic disease
Chlorphenamine	Severe	Dose reduction may be required
Chlorpromazine	Severe	Start with small doses; increased cerebral sensitivity
Ciclosporin		Monitor kidney function—dose dependent increase in serum creatinine and urea during first few weeks may necessitate dose reduction (exclude rejection if kidney transplant)
Ciprofloxacin	Moderate	Use half normal dose
Cisplatin	Mild	Avoid if possible; nephrotoxic and neurotoxic
Clindamycin		Plasma half-life prolonged—may need dose reduction
Clonazepam	Severe	Start with small doses; increased cerebral sensitivity
Cloxacillin	Severe	Reduce dose
Codeine	Moderate to severe	Reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity
Colchicine	Moderate	Reduce dose
	Severe	Avoid or reduce dose if no alternative
Cyclophosphamide		Reduce dose
Dacarbazine	Mild to	Dose reduction may be required

	moderate	
	Severe	Avoid
Daunorubicin	Mild to moderate	Reduce dose
Deferoxamine		Metal complexes excreted by kidneys (in severe renal impairment dialysis increases rate of elimination)
Diazepam	Severe	Start with small doses; increased cerebral sensitivity
Didanosine	Mild	Reduce dose; consult manufacturer's literature
Diethylcarbamazine	Moderate to severe	Reduce dose; plasma half life prolonged and urinary excretion considerably reduced
Digoxin	Mild	Reduce dose; toxicity increased by electrolyte disturbances
Dimercaprol		Discontinue or use with extreme caution if impairment develops during treatment
Doxycycline	Mild	Use with caution; avoid excessive doses
Efavirenz	Severe	No information available—caution advised
Eflornithine		Reduce dose
Enalapril	Mild to moderate	Use with caution and monitor response; initial dose 2.5 mg once daily. Hyperkalaemia and other adverse effects more common
Ephedrine	Severe	Avoid; increased CNS toxicity
Ergometrine	Severe	Manufacturer advises avoid
Ergotamine	Moderate	Avoid; nausea and vomiting; risk of renal vasoconstriction
Erythromycin	Severe	Maximum 1.5 g daily (ototoxicity)
Ethambutol	Mild	Reduce dose; if creatinine clearance less than 30 ml/minute monitor plasma-ethambutol concentration; optic nerve damage
Fluconazole	Mild to moderate	Usual initial dose then halve subsequent doses
Flucytosine		Reduce dose and monitor plasma-flucytosine concentration—consult manufacturer’s literature
Fluphenazine	Severe	Start with small doses; increased cerebral sensitivity
Furosemide	Moderate	May need high doses; deafness may follow rapid i/v injection
Gentamicin	Mild	Reduce dose; monitor plasma concentrations; *see also* section 6.2.2.5
Glibenclamide	Severe	Avoid
Haloperidol	Severe	Start with small doses; increased cerebral sensitivity
Heparin	Severe	Risk of bleeding increased

Hydralazine	Mild	Reduce dose if creatinine clearance less than 30 ml/minute
Hydrochlorothiazide	Moderate	Avoid; ineffective
Ibuprofen	Mild	Use lowest effective dose and monitor renal function; sodium and water retention; deterioration in renal function possibly leading to renal failure
	Moderate to severe	Avoid
Imipenem + Cilastatin	Mild	Reduce dose
Insulin	Severe	May need dose reduction; insulin requirements fall; compensatory response to hypoglycaemia is impaired
Iohexol	Moderate to severe	Increased risk of nephrotoxicity; avoid dehydration
Iopanoic acid	Mild to moderate	Maximum 3 g
	Severe	Avoid
Isoniazid	Severe	Maximum 200 mg daily; peripheral neuropathy
Lamivudine	Mild	Reduce dose; consult manufacturer's literature
Lithium	Mild	Avoid if possible or reduce dose and monitor plasma concentration carefully
	Moderate	Avoid
Lopinavir + Ritonavir		Avoid oral solution due to propylene glycol content; use capsules with caution in severe impairment
Magnesium hydroxide	Moderate	Avoid or reduce dose; increased risk of toxicity
Magnesium sulfate	Moderate	Avoid or reduce dose; increased risk of toxicity
Mannitol		Avoid unless test dose produces diuretic response
Meglumine antimoniate	*see* Pentavalent antimony compounds	
Meglumine iotroxate	Moderate to severe	Increased risk of nephrotoxicity; avoid dehydration
Mercaptopurine	Moderate	Reduce dose
Metformin	Mild	Avoid; increased risk of lactic acidosis
Methotrexate	Mild	Reduce dose; accumulates; nephrotoxic
	Moderate	Avoid
Methyldopa	Moderate	Start with small dose; increased sensitivity to hypotensive and sedative effect
Metoclopramide	Severe	Avoid or use small dose; increased risk of extrapyramidal reactions

Morphine	Moderate to severe	Reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity
Nalidixic acid	Moderate to severe	Use half normal dose; ineffective in renal failure because concentration in urine is inadequate
Nelfinavir		No information available—manufacturer advises caution
Neostigmine	Moderate	May need dose reduction
Nitrofurantoin	Mild	Avoid; peripheral neuropathy; ineffective because of inadequate urine concentrations
Penicillamine	Mild	Avoid if possible or reduce dose; nephrotoxic
Pentamidine isetionate	Mild	Reduce dose; consult manufacturer's literature
Pentavalent antimony compounds	Moderate	Increased adverse effects
	Severe	Avoid
Phenobarbital	Severe	Avoid large doses
Polyvidone–iodine	Severe	Avoid regular application to inflamed or broken mucosa
Potassium chloride	Moderate	Avoid routine use; high risk of hyperkalaemia
Procainamide	Mild	Avoid or reduce dose
Procaine benzylpenicillin	Severe	Neurotoxicity—high doses may cause convulsions
Procarbazine	Severe	Avoid
Proguanil	Mild	100 mg once daily
	Moderate	50 mg on alternate days
	Severe	50 mg once weekly; increased risk of haematological toxicity
Propranolol	Severe	Start with small dose; higher plasma concentrations after oral administration; may reduce renal blood flow and adversely affect renal function
Propylthiouracil	Mild to moderate	Use three-quarters normal dose
	Severe	Use half normal dose
Pyridostigmine	Moderate	Reduce dose; excreted by kidney
Quinine		Reduce parenteral maintenance dose for malaria treatment
Ranitidine	Severe	Use half normal dose; occasional risk of confusion
Ritonavir	*See* Lopinavir with Ritonavir	
Saquinavir	Severe	Dose adjustment possibly required
Sodium chloride	Severe	Avoid
Sodium hydrogen	Severe	Avoid; specialized role in some forms of

carbonate		renal disease
Sodium nitroprusside	Moderate	Avoid prolonged use
Sodium valproate	*see* Valproic acid	
Spironolactone	Mild	Monitor plasma K^+ ; high risk of hyperkalaemia in renal impairment
	Moderate	Avoid
Stavudine	Mild	20 mg twice daily (15 mg if body weight less than 60 kg)
	Moderate to severe	20 mg once daily (15 mg if body weight less than 60 kg)
Streptomycin	Mild	Reduce dose; monitor plasma concentrations
Sulfadiazine	Severe	Avoid; high risk of crystalluria
Sulfamethoxazole + Trimethoprim	Mild	Use half normal dose if creatinine clearance 15–30 ml/minute; avoid if creatinine clearance less than 15 ml/minute and if plasma-sulfamethoxazole concentration cannot be monitored
Sulfasalazine	Moderate	Risk of toxicity including crystalluria—ensure high fluid intake
	Severe	Avoid
Trimethoprim	Mild	Use half normal dose after 3 days if creatinine clearance 15–30 ml/minute
	Moderate to severe	Use half normal dose if creatinine clearance less than 15 ml/minute; avoid if creatinine clearance less than 10 ml/minute (unless plasma-trimethoprim concentration monitored)
Valproic acid	Mild to moderate	Reduce dose
	Severe	Alter dosage according to free serum valproic acid concentration
Vancomycin	Mild	Reduce dose—monitor plasma-vancomycin concentration and renal function regularly
Vecuronium	Severe	Reduce dose; duration of block possibly prolonged
Warfarin	Severe	Avoid
Zidovudine	Severe	Reduce dose; manufacturer advises oral dose of 300–400 mg daily in divided doses or intravenous dose of 1 mg/kg 3–4 times daily