Bradford Districts & Craven Palliative Care Managed Clinical Network

A GUIDE TO USE OF COMMON PALLIATIVE CARE DRUGS IN RENAL IMPAIRMENT

These guidelines bring together information and recommendations from the Palliative Care formulary (PCF6)

BACKGROUND

Measuring renal function:

• eGFR is reported in routine laboratory results using the MDRD formula, it is less accurate at values of > 60ml/ min.
(90%of estimates <60mL/min/1.73m will be within 30% of the true value)

Changes in MDRD eGFR are more reliable than single estimates, with a decrease of ≥15% likely to represent a true change in renal function.

• Cockcroft-Gault formula is used in drug manufacturer's information so drug dosing is based on renal function derived using this formula. For the majority of patients, the difference in eGFR using either equation will not lead to a difference in drug dosages, except in patients whose body size is very different than average, when Cockcroft Gault is more accurate.

In palliative care patients who are elderly, malnourished, cachectic and/or oedematous, renal impairment may exist even when the serum creatinine or the lab eGFR are within normal limits, and it may be prudent to assume that there is at least mild renal impairment in such patients. Even when abnormal, the serum creatinine or the lab eGFR may both underestimate the actual degree of renal impairment.

A baseline serum creatinine and lab eGFR can help to indicate the need for dose modification and serial measurements can be used to monitor the effect of the drug on renal function.

Hospital pathology labs give eGFR based on MDRD and the BNF gives its drug dose adjustments based on this but other dose adjustment calculations (e.g. manufacturers and renal handbook and PCF) are based on Cockcroft Gault calculation

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STAGES OF RENAL DISEASE

Table 1: Five stages of chronic kidney disease (CKD) are categorized according to eGFR

CKD stage 1	Normal renal function	
CKD stage 2	Mild impairment (eGFR 60-89 ml/min)	Asymptomatic
CKD stage 3a	Moderate impairment (eGFR 45-59 ml/min)	Asymptomatic
CKD stage 3b	Moderate impairment (eGFR 30-44 ml/min)	Anaemia, fatigue, muscle cramps
CKD stage 4	Severe impairment (eGFR 15-29 ml/min)	In addition: anorexia, nausea, insomnia, neuropathy, gout
CKD stage 5	End stage renal disease (eGFR < 15 ml/min)	In addition: itch, headache, cognitive impairment; death

Management of Complications in CKD:

Hypertension:
Aim to control hypertension and optimise BP. To avoid ACE – inhibitors and Angiotension 2 receptor blockers in advanced nephropathy.

Fluid retention:
To trial small doses diuretics but beware risk of rise in creatinine and potential electrolyte imbalance. If severe fluid retention / generalised swelling then may need to consider admission for intravenous diuretics.

Exposure to renal insults:
Advise patients to keep a record of previous events including what happened, when and how to avoid. To advise patients to avoid dehydration, treat infections promptly and relieve urinary retention.

Increased Phosphate levels:
To ensure full bone profile is checked. Consider phosphate binders and referral to dietician services.
Of note: high phosphate, low/normal calcium and high parathyroid hormone levels are expected in patients with stages 3 to 5 CKD.

Glycaemic Control:
To optimise glycaemic control but to be aware of potential hypoglycaemia risk which is common in Chronic Kidney Disease. May need to consider reducing doses of diabetic medication.

Table 2: Hypoglycaemic Drugs in CKD

Drug	Excretion	Risk	Recommendation	Caution
Metformin	Renally	Lactic acidosis	NICE guidelines Reduce dose if eGFR between 30-60mls/min Avoid if eGFR <30mls/min	Co-treatment with NSAIDs, Diuretics, Contrast, ACEi's, fluctuating UCE's
Sulphonylureas	Active metabolite excreted through kidney	Severe Hypos	Gliclazide can be used (intermediate acting sulphonylurea) Avoid if <45mls/min	Not eliminated in Dialysis patients. Some drugs (including B-Blockers and warfarin) can increase their free levels
Glinides	Liver	Less hypos	Can be used for CKD/Dialysis pts	
Glitazones	Liver	No dose adjustment	Caution if eGFR <60mls/min Avoid if eGFR <30mls/min	CCF present alongside CKD (as can cause fluid retention)
Gliptins	Linagliptin excreted by liver. All other Gliptins renally excreted	Low risk of hypo	Dose adjustment/reduction advised (With exception of Linagliptin)	Experience is still limited for CKD and Dialysis patients
Insulin	Decrease in renal insulin catabolism		Therapeutic education Adjust if eGFR falls below 60 by 25% Below 20 by 50%	Haemodialysis and Peritoneal Dialysis patients

Metabolic acidosis:

If bicarbonate levels <21 mmol/l consider adding oral sodium bicarbonate 500mg – 1g b.d. / t.d.s. (for cautious introduction and titration if calcium is low and fluid retention present). There is also option to consider IV Sodium Bicarbonate – please discuss with renal team for further advice.

Anaemia:
Ensure full haematinic screen is sent including ferritin levels. Try to correct iron levels first by administering either oral or intravenous iron and / or Erythropoietin (EPO). Please consult with your local / regional renal team to clarify doses and frequency.

Hyperkalaemia:
Review medications and if need to stop or reduce doses. Aim to correct any metabolic acidosis present and optimise hyperglycaemia. Consider referral to Dietician services and avoid calcium resins long term. In oncology patients, to consider the possibility of tumour lysis syndrome.
Can also consider use of Veltassa (Patiromer). This is a non-absorbed cation exchange polymer which contains a calcium – sorbitol complex. Veltassa increases faecal potassium excretion through binding of potassium in the gastro-intestinal tract. Binding of potassium reduced the concentration of free potassium in the gastro-intestinal tract, resulting in a reduction of potassium levels.

If any further advice is required then please contact the Renal team at Bradford Teaching Hospitals Foundation Trust (via main switchboard 01274 542200) for further discussion.

Alternatively your local Specialist Palliative Care Services can also be contacted for further advice/support.

PRESCRIBING GUIDELINES

- Many drugs need dose alteration in renal impairment especially if severe. This includes most analgesics, some antibiotics and antiemetic amongst others.

- If you are starting a new drug in someone with renal impairment you should check if it needs dose alteration by either using a reliable reference source such as the BNF, PCF6 or the Renal Drug Handbook, or speaking to a pharmacist

- When a drug dose modification has been necessary, or for drugs known to cause renal impairment, a clinical review and evaluation of renal function should be carried out within 2 weeks, or at any time if drug-induced nephrotoxicity is suspected, e.g. symptoms such as rash, arthralgia, oedema.

- Table 3 gives some guidance on common analgesics and antiemetics used in palliative care and these are based on recommendations in the palliative care formulary

OPIOIDS AND RENAL IMPAIRMENT

In renal impairment and end-stage renal failure, regardless of the opioid used, extra caution is *always* required whether or not the patient is on dialysis. This is particularly necessary in patients with rapidly deteriorating renal function or when acutely unwell, e.g. because of sepsis.

Clear written instructions regarding analgesic drug regimens should routinely be provided together with close monitoring. Patients and their carers should be educated about the early symptoms of opioid toxicity and the actions required should they occur.

Opioids differ in their potential to cause toxicity when renal function is impaired. However, the evidence base from clinical studies is limited, and stratification of risk is based on the presence of active metabolites, risk of accumulation, and expert opinion.

The pharmacokinetics and pharmacodynamics of opioids are altered by renal impairment. Accumulation of an opioid or active metabolite will lead to a prolonged duration of action and increased toxicity. Changes in plasma protein concentrations or alterations in the blood-brain barrier also increase the potential for toxicity with **any opioid**. If an opioid is necessary, it is important to:

- start at lower than usual doses
- consider increasing the intervals between doses
- monitor closely for toxicity, both immediate and delayed.

If eGFR is less than 50 ml/min and/or rapidly deteriorating, there should be a review of the opioid prescribed and consideration of conversion from morphine to oxycodone preparations (if applicable).

At the end of life, UK guidelines suggest it may be appropriate to consider either **fentanyl** or **alfentanil** as the preferred strong opioid of choice for patients with severe renal impairment or failure. Experience with this approach is increasing. However, in some settings, the cautious use of a familiar opioid may still be preferred over switching to an unfamiliar (albeit 'renally safer') one.
Please seek specialist palliative care advice if needing further guidance in prescribing fentanyl or alfentanil.

Table 3: Prescribing advice for palliative care patients with chronic kidney disease/renal impairment
For further information see: Palliative Care Formulary

Drug	Renal Impairment			Dialysis Clearance		Comments
	Mild: GFR 60-89 ml/min	Moderate: GFR 30-59 ml/min	Severe: GFR <30 ml/min	HD	PD	
ANALGESICS						
Paracetamol (oral)	Normal starting dose	6 hourly dosing	May require 50% reduction of normal dose; 6-8 hourly dosing	Cleared	No	Safe non-opioid
NSAIDs	CAUTION Consider 50-75% dose reduction	AVOID	AVOID	No	No	Nephrotoxic, ↑ risk of GI bleed (platelet dysfunction).
Codeine/ dihydrocodeine	Normal starting dose (monitor closely)	AVOID or use small dose and titrate slowly	AVOID codeine: Dihydrocodeine:	Unknown	Unknown	Metabolites accumulate. Reports of severe toxicity in CKD stage 4/5.
Tramadol	Normal starting dose	50mg oral immediate release preparation, 12 hourly (Max 200 mg / 24 hrs)	CAUTION	Yes	Unknown	Use 50mg oral immediate release preparation, 12 hourly for dialysis patients. Risk of confusion/delirium. Drug interactions. Check BNF.
Morphine/diamorphine	75% normal dose	50% normal dose, 6 hourly or consider safer alternative	AVOID or use very small doses – seek advice	Yes Occasionally - post dialysis dosing.	No	CNS depot clears slowly in HD. Metabolites accumulate in PD. Single dose post HD can be used. Monitor closely.
Oxycodone	Normal starting dose	Normal starting dose usually safe but monitor carefully for toxicity , may require dose reduction	AVOID or use very low dose & monitor closely	Unknown	Unknown	↑ half life, and ↓ excretion of metabolites.
Fentanyl	Normal starting dose	Normal starting dose usually safe but monitor carefully for toxicity , may require dose reduction	May require 50% normal dose	No	No	Can accumulate after longer term use; monitor and adjust dose.
Buprenorphine	Normal starting dose	May require 75% normal dose	May require 50% normal dose	No	No	Has an active metabolite which may accumulate, clinical relevance uncertain
Alfentanil (see: guideline)	Normal starting dose	Normal starting dose	Normal starting dose	No	No	Short acting

Methadone	Normal starting dose	Normal starting dose	50% normal dose	No	No	Seek specialist advice re dose and titration
ANTI-EMETICS						
Metoclopramide	Normal starting dose (10mg, 8 hourly)	50% dose, 8 hourly	50% dose, 8 hourly	Yes	No	Reduced clearance; more risk of arrhythmias and extrapyramidal side effects.
Domperidone	Normal starting dose (10mg, 6-8 hourly)	Normal starting dose (10mg, 6-8 hourly)	Reduce dose frequency to 12hrly	Unknown	Unknown	
Cyclizine	Normal starting dose (50mg, 8 hourly)	Normal starting dose (50mg, 8 - 12 hourly)	Normal starting dose (50mg, 8 - 12 hourly)	Unknown	Unknown	Dry mouth. More CNS side effects. Hypotension, tachyarrhythmias reported.
Haloperidol	Normal starting dose (1.5mg, nocte)	Normal starting dose (1.5mg, nocte)	50% normal dose	No	No	Lowers seizure threshold, ↑ risk cardiac arrhythmias, may accumulate.
Levomepromazine	Normal starting dose (2.5mg-6.25mg, nocte)	Start low & titrate	Start low & titrate	Unknown	Unknown	Sedation at higher doses. Causes hypotension. Lowers seizure threshold.
Ondansetron/ Granisetron	Normal starting dose	Normal starting dose	Normal starting dose	No	Unknown	May help itch, constipating.
BENZODIAZEPINES						
Diazepam	Normal starting dose	Start lower	Start lower & titrate	No	No	Used for insomnia, anxiety and muscle spasm/ myoclonus.
Lorazepam	0.5mg, oral, 6 hourly	0.5mg, cautious titration May need to increase dosing interval	0.5mg, cautious titration May need to increase dosing interval	No	Unlikely	Start lower and titrate dose for all benzodiazepines. Metabolites excreted renally and protein binding is reduced.
Midazolam SC	2.5mg 1-2 hourly	Start lower	Start lower & titrate	No	Unlikely	
Temazepam	Normal starting dose	Max dose 20mg, oral	Max dose 10mg, oral	No	Unknown	
Clonazepam	0.5mg, oral, nocte	Start low dose & titrate	Lower dose & titrate	No	Unknown	

ANTI-EPILEPTICS						
Gabapentin	Starting dose 200mg tds Max dose 600mg tds	Starting dose 100mg tds Max dose 300mg tds	eGFR 15-29: Starting dose 100mg nocte, titrate slowly Max dose 300mg bd eGFR <15(non-dialysis/peritoneal dialysis only): Starting dose 100mg on alternate nights, max	Yes	Probable	Parent drug accumulates. Withdraw gradually, over several weeks. HD patients with urine output >100ml/24h: start with 100mg nocte. Consider either supplementary dose after each HD session or time daily dose post-HD. For anuric HD patients: start with 100mg stat dose and 100mg after each HD session

			dose 300mg nocte			
Pregabalin	Starting dose 25-50mg bd Max dose 300mg bd	Starting dose 25mg bd Max dose 150mg bd	eGFR 15-29: Starting dose 25-50mg od, max dose 150mg od eGFR <15: Starting dose 25mg od, max dose 75mg od	Yes will need a post dialysis dose	Probable	Withdraw gradually , over several weeks HD patients: dose adjust according to creatinine clearance and to give a supplementary single dose after each dialysis session (see PCF 7 for more details)
Sodium valproate	Oral starting dose 150-200mg, 12 hourly	Normal starting dose	Normal starting dose	No	Unknown	Well tolerated, avoid if liver disease. Titrate slowly.
Carbamazepine	Oral starting dose 50-100mg, 12 hourly	Normal starting dose	Normal starting dose	No	No	Drug interactions. Check BNF.
Amitriptyline	Oral starting dose 10mg, nocte	Normal starting dose	Normal starting dose	No	No	Drug interactions, side effects, and contraindications can limit use. Titrate slowly.
ANTI-DEPRESSANTS Citalopram Sertraline Mirtazapine	 Normal starting dose Normal starting dose Normal starting dose	 Normal starting dose Normal starting dose Normal starting dose	 Use with caution Normal starting dose Start at low dose and monitor closely Max dose 30mg po nocte	 No	 No	 Check BNF for drug interactions (e.g. with Tramadol). Start at lowest dose and titrate carefully in CKD stages 4/5.
OTHERS						
Baclofen	Max 5mg, oral, 8 hourly	Max 5mg, oral, 12 hourly	AVOID	Unknown	Unknown	See PCF for further details Withdraw gradually.
Ketamine oral or SC	Oral starting dose 5-10mg, 6 hourly	Normal starting dose	May be tolerated in standard doses but start at low dose and monitor closely	No	Unknown	Little information available. Less than 2-3% of ketamine is excreted unchanged. Can accumulate. Seek specialist advice.
Ranitidine	Normal starting dose	Normal starting dose	50-100% normal dose	Yes	Unknown	Accumulates.
PPIs	Normal starting dose	Normal starting dose	Normal starting dose	Unknown	Unknown	Also use reduced dose in hepatic failure
Fluconazole	Normal starting dose	50% dose	50% normal dose	Yes	Yes	Drug interactions. Check PCF or BNF.
Hyoscine butylbromide (Buscopan) SC	20mg SC, oral, 1-2 hourly	Normal starting dose	Normal starting dose	Unknown	Unknown	Peripheral antimuscarinic side effects Use for respiratory secretions, bowel colic, bladder spasms.

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References:

Palliative Care Formulary 7th Edition (2020)

The Renal Drug Handbook 5th Edition (2019)

Renal Drug Database: http://renaldrugdatabase.com/