

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

*These guidelines bring together information and recommendations from the Palliative Care formulary (PCF5)*

### **BACKGROUND**

#### **Measuring renal function :**

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

*Changes in MDRD eGFR are more reliable than single estimates, with a decrease of  $\geq 15\%$  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 GFR 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 (eg manufacturers and renal handbook and PCF) are based on Cockcroft Gault calculation

## STAGES OF RENAL DISEASE

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

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

## 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, PCF5 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.

At the end of life, UK guidelines for analgesia in patients with severe renal impairment or failure (GFR <30mL/min) opt for **fentanyl** or **alfentanil** as the preferred strong opioid. 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.

## 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	
Paracetamol (oral)	Normal starting dose	6 hourly dosing	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	50-100mg, oral, 12 hourly (Max 200 mg / 24 hrs)	CAUTION	Yes	Unknown	Use 50mg orally, 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
Metoclopramide	Oral starting dose	50% dose, 8 hourly	50% dose, 8 hourly	Yes	No	Reduced clearance; more risk of arrhythmias and

Domperidone	(10mg, 8 hourly) Oral starting dose (10mg, 6-8 hourly)	Normal starting dose	Reduce dose frequency to 12hrly	Unknown	Unknown	extrapyramidal side effects.
Cyclizine	Oral starting dose (25mg-50mg, 8 hourly)	Normal starting dose	Normal starting dose	Unknown	Unknown	Dry mouth. More CNS side effects. Hypotension, tachyarrhythmias reported.
Haloperidol	Oral starting dose (1.5mg, nocte)	Normal starting dose	50% normal dose	No	No	Lowers seizure threshold, ↑ risk cardiac arrhythmias, may accumulate.
Levomepromazine	Oral 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.

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	Mild: GFR 60-89 ml/min	Moderate: GFR 30-59 ml/min	Severe: GFR 15-29 ml/min	HD	PD	
Diazepam	Normal starting dose	Start lower	Start lower & titrate	No	No	Used for insomnia, anxiety and muscle spasm/ myoclonus.  Start lower and titrate dose for all benzodiazepins. Metabolites excreted renally and protein binding is reduced.
Lorazepam	0.5mg, oral, 6 hourly	Start lower	Start lower & titrate	No	Unlikely	
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	
Gabapentin	Starting dose 200mg tds Max dose 600mg tds	Starting dose 100mg tds Max dose 300mg tds	300mg, oral, alternate days	Yes; 300mg post HD	Probable	Parent drug accumulates. Withdraw gradually, over a week.
Pregabalin	Starting dose 75mg bd Max dose 300mg bd	Starting dose 25mg tds Max dose 150mg bd	Starting dose 25-50mg od Max dose 150mg od	Yes will need a post dialysis dose	Probable	Withdraw gradually, over several weeks
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 100-200mg, 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.
Citalopram	Normal starting dose	Normal starting dose	Use with caution	No	No	Check BNF for drug interactions (eg. with Tramadol). Start at lowest dose and titrate carefully in CKD stages 4/5.
Sertraline	Normal starting dose	Normal starting dose	Normal starting dose			
Mirtazapine	Normal starting dose	Normal starting dose	Start at low dose and monitor closely			
Baclofen	Max 5mg, oral, 8 hourly	Max 5mg, oral, 12 hourly	AVOID		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% dose	Yes	Unknown	Accumulates.
PPIs	Normal starting dose	Normal starting dose				
Fluconazole	Normal starting dose	50% dose	50% 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.