

# Use of opioids in Patients with Impaired Renal Function

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Great care is required when prescribing opioids to patients with impaired renal function. Many opioids (and/or their active/toxic metabolites) are renally excreted e.g. morphine. Accumulation occurs in renal failure potentially leading to extreme opioid sensitivity.

## Introduction

There are many potential pharmacokinetic and pharmacodynamic problems in renal failure<sup>1</sup>:

- Active/toxic metabolites may accumulate
- Altered drug distribution -affected by changes in hydration
- Hypoproteinaemia/altered drug binding in uraemia
- Increased permeability of blood brain barrier
- Increased sensitivity to CNS side effects of opioids e.g. drowsiness

Decreased renal clearance of any drug/metabolite closely follows renal function as measured by creatinine clearance. In consequence, drug toxicity in renal disease depends on the extent to which renal clearance contributes to total drug/metabolite clearance and how critical a drug/metabolite concentration is.

The K-DOQI classification of chronic kidney disease (CKD) stages 1-5 has recently been adopted in the UK. Allied to this is the reporting of the estimated GFR (eGFR) from most UK labs, which enables the clinician to accurately establish a patient's degree of renal impairment.

- Stage 1 - Normal GFR; GFR >90 mL/min/1.73 m<sup>2</sup> (+ \*)
- Stage 2 - Mild impairment; GFR 60-89 mL/min/1.73 m<sup>2</sup> (+ \*)
- Stage 3 - Moderate impairment; GFR 30-59 mL/min/1.73 m<sup>2</sup>
- Stage 4 - Severe impairment: GFR 15-29 mL/min/1.73 m<sup>2</sup>
- Stage 5 - Established renal failure (ERF): GFR <15 mL/min/1.73 m<sup>2</sup> or on dialysis

### **Other evidence of chronic kidney damage ( \* )**

- Persistent microalbuminuria
- Persistent proteinuria
- Persistent haematuria (after exclusion of other causes, e.g. urological disease)
- Structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests, e.g. polycystic kidney disease, reflux nephropathy
- Biopsy-proven chronic glomerulonephritis (most of these patients will have microalbuminuria or proteinuria, and/or haematuria)

However, when considering drug dosage amendments, it is worth noting that in practice, doses rarely need to be altered before the GFR drops below 50 ml/min. Hence, when prescribing for patients with renal impairment, the old classification, as given below, is still relevant.

Definitions of Degrees of Renal Impairment (Renal Drug Handbook<sup>2</sup>)

	GFR (ml/min)	Creatinine
Mild renal impairment	20-50	150-300*
Moderate renal impairment	10-20	300-700
Severe renal impairment	<10	>700

\* Creatinine is not a reliable estimate of renal function but in the hospice setting may suffice

## Standards

1. Improve symptom control within 48h
2. Prescribe appropriate analgesic
3. Medication prescribed by appropriate route
4. Prescribe appropriate breakthrough dose
5. Give information/advice on management of side effects
6. Prescribe regular laxatives
7. Prescribe PRN antiemetic
8. Monitor at least every 24h while titrating to steady state

## Recommendations for Mild to Moderate Chronic Pain

### **Paracetamol**

Safe in moderate renal failure. Use up to 1g QDS. Care in severe renal failure max 1g tds. If pain is not adequately controlled add or switch to a moderate strength analgesic, tramadol.

### **Tramadol**

Modification of dose/timing required as is removed during haemodialysis. Main side effects: confusion, drowsiness. The modified release preparation is best avoided.

Tramadol	% Normal Dose	Dose (mg)	Dose Interval (hrly)
Mild renal failure	100	50-100	6
Moderate renal failure	50	50-100	6-8 (modify as needed)
Severe renal failure	50	50	6-8 (modify as needed)

If pain is not controlled after 48hrs, increase the daily dose by approximately 30-50% either by increasing the regular dose or reducing the dosing interval, if permitted (see charts below). Allow at least 48 hr between dose or interval adjustments to allow time to achieve steady state. If necessary, and only if tolerated, increase dose/reduce intervals to achieve maximum permitted 24hr dose.

- Avoid codeine and dihydrocodeine. There are also reports of serious side effects following codeine use in patients with advanced renal failure, in particular severe hypotension, respiratory arrest, and profound narcolepsy.
- Avoid co-proxamol which contains dextropropoxyphene -long half life and toxic metabolite accumulates.

If there is inadequate response to maximum doses of moderate opioids then stop and move to strong opioids. It may be appropriate to continue with paracetamol

## Recommendations for Severe Chronic Pain

### **Oxycodone**

Mainly metabolised in the liver although 19% is excreted unchanged in the urine. Use immediate release preparation only (Oxynorm liquid 1mg/ml)

Oxynorm	% normal dose	Dose (mg)	Dose interval (hrly)
Mild renal failure	50	2.5 - 5	6
Moderate renal failure	25-50	2.5 - 5	6-8 (modify as needed)
Severe renal failure	25-50*	2.5 - 5	8-12 (modify as needed)

\*Manufacturer's guidance: Contraindicated in severe renal failure with dose reduction advised in mild to moderate renal failure<sup>6</sup>. There are a few papers supporting its use in patients with little or no renal function (ref awaited). Both oxycodone and its metabolites are partially removed by Haemodialysis. Oxycodone is used extensively in dialysis-dependent patients at the Royal Free, and it is well-tolerated.

**Starting Dose:** if opioid naïve use oxynorm at the lowest dose as per chart above. 2.5-5mg oxynorm is equivalent to 5-10mg oramorph. If patient has been on moderate opioids without toxicity start at next dose up (as per chart).

**Dosing frequency:** As per chart. Patients need to be monitored closely for signs/symptoms of toxicity. If pain is not controlled after 48-72hr the dosing interval can be decreased provided the patient is not opioid toxic.

**Breakthrough pain:** PRN doses equal to the regular doses may be needed for breakthrough pain that occurs before the next regular dose of analgesia is due. Limit breakthroughs to 4/24 hours. If more are needed seek consultant advice.

**Incident pain:** pain, which occurs with movement/activity, may need to be covered by an additional dose (the same amount as the regular dose) 30mins before the anticipated incident.

### **Dose Modifications**

**Increases:** Check that the pain is responding to the medication. If not consider other approaches. Usually wait 72h before considering a dose increase or dose interval reduction to allow time to achieve steady state (unless the patient is in a pain crisis). Titrate up the regular dose in line with the total PRN doses used in the preceding 24hr. If the patient is still in pain but has not accessed PRN doses, increase total 24hr dose by 30-50% by either increasing the regular dose or (if permitted) decreasing the dosing interval. Monitor response and modify 24hrly dose every 72 hr until the patient remains pain free between regular doses.

**Decreases:** If toxicity develops stop the drug, wait until toxicity subsides and resume at half previous dose and/ or extended dosing interval. Monitor pain control and side effects regularly

### **Other Strong Opioids**

**Fentanyl:** mainly metabolised in liver to inactive metabolites, is a useful strong opioid for patients with impaired renal function who have stable pain.

Transdermal fentanyl: Takes 3 days to reach steady state. Patients require access to regular doses of immediate release opioid during first 12-24h and for breakthrough medication. Smallest patch is 12mcg/hour patch, equivalent to 70mg morphine/24 hours, therefore do not use in opiate naïve patients.

Fentanyl can be given transmucosally or sublingually for incident pain. It is rapidly absorbed and has a short half-life by these routes. Fentanyl is not dialysable due to high protein binding and a high volume of distribution.

## Transdermal Buprenorphine

Thought to be safe in renal failure (limited evidence). Transtec 35mcg/hr is approximately equal to Fentanyl 25mcg/hr. 7 day patches in much lower doses (Butrans) are also available (5, 10 and 20mcg/hour). Buprenorphine plasma concentrations and pain relief is not affected by haemodialysis.<sup>8</sup>

## Methadone

Discuss with consultant if considering using methadone.  
Useful drug in renal failure especially if pain is neuropathic as it is metabolised in liver and predominantly excreted in faeces. Not removed by haemodialysis. In severe renal impairment a dose reduction of 50 to 75% is recommended, and then adjusted upwards according to patient tolerability. See methadone guidelines.

## Morphine

Active metabolites accumulate in renal failure - long term use is contraindicated in moderate/severe renal failure. Use only if no other opioid is available.

Morphine	% normal dose	Dose (mg)	Dose interval (hrly)
Mild renal impairment	75	2.5-5	6
Moderate renal impairment	50	2.5-5	6-8
Severe renal impairment	Use small doses	1.25-2.5	8-12

Titrate doses upwards as tolerated by the patient.

## Subcutaneous Opioids:

### Alfentanil

Not renally excreted and is the drug of choice in a CSCI. It is not ideal for 'as required' parenteral use because of its short duration of action. 1mg s/c alfentanil is equipotent to 10mg s/c diamorphine.

### Oxycodone

Can be converted to the subcutaneous route. Oral:subcutaneous ratio 3-2:1

### Diamorphine

If the patient is imminently dying, diamorphine can be used in CSCI or for breakthrough analgesia even though its metabolites accumulate in renal failure. Prescribe in reduced doses e.g. 25-50% of dose used in normal renal function.

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