

Prescribing analgesia for patients with impaired renal function

Prescribing analgesia is a fundamental skill for all junior doctors. Effective pain management dramatically improves patient experience, as well as affecting recovery and length of hospital stay. For patients with impaired renal function this can be challenging as many drugs require dose adjustment or avoidance. Wariness of possible drug complications can lead to the under-treatment of pain or, conversely, the failure to dose adjust can lead to incidents of toxicity, as shown in the *Case study*. This article outlines the relevant pharmacology of common analgesics and provides guidance to enable junior doctors to confidently prescribe analgesia for patients with renal impairment.

General considerations for prescribing analgesia in patients with renal impairment

The World Health Organization analgesic ladder for pain management is effective and adaptable for patients with impaired renal function (Launay-Vacher et al, 2005; Barakzoy and Moss, 2006), although special consideration is needed to safely prescribe

CASE STUDY

A 56-year-old man was admitted for elective total hip replacement. He had a background history of end-stage renal failure secondary to reflux nephropathy. The surgery was successful with no surgical complications. Postoperatively he had an acute kidney injury on the background of his chronic kidney disease (creatinine level 412 umol/litre from baseline 270 umol/litre, estimated glomerular filtration rate 40 ml/min/1.73 m²).

Two days postoperatively the patient became drowsy and the orthopaedic F2 doctor was alerted. It was noted that tramadol 50 mg four

times a day had been prescribed regularly as well as oral morphine 5–10 mg 2-hourly as required. In total the patient received 100 mg tramadol and 80 mg oral morphine over 24 hours. The patient's drowsiness was felt to be secondary to opiate toxicity in the context of his renal impairment.

Despite an initial response to naloxone he continued to deteriorate. He became hypercapnic, profoundly acidotic and hyperkalaemic. His renal function had worsened further since admission. The patient was transferred to the intensive care unit for emergency haemofiltration.

analgesics in this population. Assessment of renal function should be carried out before any prescription. Ideally this should be a calculation of creatinine clearance using the Cockcroft–Gault equation below (Cockcroft and Gault, 1976), adjusted to ideal body weight.

$$eCrCl = \frac{(140 - \text{age}) \times \text{weight (kg)} \times 0.85 \text{ if female}}{72 \times \text{creatinine serum (mg/dl)}}$$

In addition to the degree of renal impairment the necessary alteration of analgesic regimens in patients with renal impairment largely depends on the extent of renal excretion and whether the drug has active or toxic metabolites. In patients who are dialysed, further consideration of the ability of dialysis to clear drugs and their metabolites is essential. Morphine is an example of a drug which is readily dialysed whereas fentanyl and codeine are not (Ashley and Currie, 2011). In general, molecules with a low molecular weight, high water solubility, small volume of distribution and limited protein binding are more likely to be removed by dialysis (Trainor et al, 2011).

Non-opioid analgesics

Paracetamol

Paracetamol is generally safe but the elimination of paracetamol is slightly delayed and metabolites may accumulate in patients with severe renal impairment

(creatinine clearance <10 ml/minute) where a dose reduction to 1 g 8-hourly should be considered (Prescott et al, 1989; Ashley and Currie, 2011).

Non-steroidal anti-inflammatory drugs

The effects of non-steroidal anti-inflammatory drugs on renal haemodynamics can cause a significant deterioration in renal function and these should be avoided in patients with renal impairment. Renal patients are also at increased risk of gastrointestinal adverse effects, and haematological complications may be exacerbated as a result of uraemic-induced platelet dysfunction (Jankovic et al, 2009). Use of non-steroidal anti-inflammatory drugs with gastro-protection may be considered in anuric haemodialysis patients but should be discussed with their nephrologist.

Opioid analgesics

Most opioids are metabolized in the liver, with both the drug and its metabolites excreted renally. Opioid toxicity can result from accumulation of the active compound and its metabolites in patients with renal impairment. Potential adverse effects include hypotension, respiratory depression and narcolepsy. The pharmacokinetics of different opioids are complex, and dose adjustment recommendations are based on individual drug types and degree of renal impairment (*Tables 1 and 2*).

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Table 1. Conversions between commonly used oral opioids

Drug	Equivalent opioid dose															
Oral morphine (mg/24 hours)	10	15	30	45	60	90	120	150	180	210	240	270	360			
Oral oxycodone (mg/24 hours)	5	7.5	15	22.5	30	45	60	75	90	105	120	135	180			
Transdermal fentanyl (µg/hour)				12				25				50			75	100
Transdermal buprenorphine (µg/hour)	5	10	20			35	52.5	70								

Adapted from Faculty of Pain Medicine (2018)

Codeine phosphate

Codeine is extensively metabolized in the liver. It is a prodrug and morphine is one of its major metabolites (5–15%) (Smith et al, 2016). Owing to genetic variations in the cytochrome P450 enzyme CYP2D6 which is responsible for this conversion, some people who are ‘fast’ metabolizers will convert more codeine to morphine. Morphine and its active metabolite accumulate in patients with renal impairment (see below) which may lead to opiate toxicity (Guay et al, 1988). Codeine doses should therefore be adjusted according to the patient’s creatinine clearance (Table 2).

Tramadol

Tramadol is a synthetic opioid. In addition to its opioid receptor-mediated mechanism of action, tramadol also exerts its analgesic effect via inhibition of neuronal reuptake of noradrenaline and enhancing serotonin release (Smith et al, 2016). It is 85% metabolized in the liver and has one active metabolite (O-desmethyltramadol). Excretion is almost entirely renal so dose modification is required (Table 2) (Accord-UK Ltd, 2016). It should also be noted that uraemia lowers the seizure threshold so there is an increased risk of tramadol precipitating seizures in renal patients.

Morphine

Morphine is metabolized by the liver into three metabolites: morphine-3-glucuronide (M3G), morphine-6-glucuronide (M6G) and normorphine. These metabolites are excreted by the kidneys and accumulate in patients with renal failure (Hasselström and Säwe, 1993). M6G is an analgesic, crossing the blood–brain barrier to act as a CNS depressant. This process is slow and therefore re-equilibrium with the systemic circulation is prolonged and can lead to persistent CNS side effects long after stopping the drug or

Table 2. Dose adjustment of analgesia in patients with renal impairment

Impairment	Drug	Dose	Dosing interval
Mild renal impairment (creatinine clearance 20–50 ml/min)	Paracetamol	1 g	6-hourly
	Codeine (PO)	30–60 mg	6-hourly
	Tramadol (PO/IM/IV)	50–100 mg	6-hourly
	Oxycodone (PO)	2.5–5 mg	6-hourly
Moderate renal impairment (creatinine clearance 10–20 ml/min)	Paracetamol	1 g	6-hourly
	Codeine (PO)	30 mg	4-hourly (increase as tolerated)
	Tramadol (PO/IM/IV)	50–100 mg	6–8-hourly (increase as tolerated)
	Oxycodone (PO)	1.25–2.5 mg	6–8-hourly (increase as tolerated)
Severe renal impairment (creatinine clearance <10 ml/min)	Paracetamol (PO/IV)	1 g	6–8-hourly
	Codeine (PO)	30 mg	6-hourly (increase as tolerated)
	Tramadol (PO/IM/IV)	50 mg	8–12-hourly (increase as tolerated)
	Oxycodone (PO)	1.25–2.5 mg	8–12-hourly (increase as tolerated)
Dialysis	Paracetamol (PO/IV)	As for creatinine clearance <10 ml/min	
	Codeine (PO)	As for creatinine clearance <10 ml/min, but care in peritoneal dialysis because of the increased risk of constipation	
	Tramadol (PO/IM/IV)	As for creatinine clearance <10 ml/min, but modification of dose or timing may be required as tramadol is removed by haemodialysis	
	Oxycodone (PO)	As for creatinine clearance <10 ml/min, but modification of dose or timing may be required as oxycodone is at least partially removed by haemodialysis	

**Please note that in patients whose weight is less than 50 kg, the dose of paracetamol may need to be reduced accordingly, take particular care with intravenous use. IM = intramuscular; IV = intravenous; PO = per oral.*

post dialysis (Mercadante and Arcuri, 2004). Morphine should be used with extreme caution in patients with renal failure, with reduced doses and longer intervals (Table 1) titrated to response (Dean, 2004). If morphine cannot be avoided, the authors would recommend dose adjustments according to creatinine clearance (Table 3). Alternative opioids such as oxycodone or

fentanyl are generally preferred, although there is only limited evidence to support this practice which is based on clinical experience and pharmacokinetic principles.

Oxycodone

Oxycodone is a semisynthetic opium derivative which is often used as an alternative to morphine in patients with renal

Table 3. Recommended doses of morphine for different levels of renal function

Morphine	Renal function (creatinine clearance)	Dose (per oral)	Dosing interval
Mild	20–50 ml/min	2.5–5 mg	6-hourly
Moderate	10–20 ml/min	2.5–5 mg	6–8-hourly
Severe	<10 ml/min	1.25–2.5 mg	8–12-hourly
Dialysis	As for creatinine clearance <10 ml/min but modification of dose and/or timing may be required as morphine and its metabolites are removed by haemodialysis		

Table 4. Recommended doses of gabapentin for different levels of renal function

Gabapentin	Renal function (creatinine clearance)	Dose (per oral)	Dosing interval
Mild	30–60 ml/min	300 mg	Daily (increase according to response)
Moderate	15–30 ml/min	100 mg	Daily (increase according to response)
Severe	<15 ml/min	100 mg	Daily (increase according to tolerability)
Dialysis	As for creatinine clearance <10 ml/min but ensure dose is given post dialysis		

impairment and moderate to severe pain. It undergoes extensive hepatic metabolism and has one active metabolite (oxymorphone) but plasma levels are negligible in patients with normal renal function (Dean, 2004). Higher concentrations have been demonstrated in patients with moderate to severe renal impairment with a significantly prolonged elimination half-life but this does not necessarily equate to toxicity and there is no evidence to support a particular regimen of dose reduction (Pham et al, 2017). Nevertheless the authors recommend a reduced dose in patients with moderate and severe renal impairment (as per the Cockcroft–Gault equation). This should be titrated to effect and clinical signs of opioid toxicity.

Oxycodone can be administered orally, subcutaneously or intravenously. Oral oxycodone 10 mg is equivalent to oral morphine 20 mg and the oral to parenteral dose ratio is approximately 2:1 (Smith et al, 2016). Oxycodone is available as a modified-release preparation but this should generally be avoided in patients with renal impairment.

Fentanyl

Fentanyl is a potent synthetic opioid which is metabolized primarily in the liver to inactive, non-toxic metabolites (Guay et al, 1988), making it an ideal drug in patients with renal

impairment. It cannot be given orally. When administered intravenously it has a rapid onset and short (dose-dependent) duration of action (Peck and Hill, 2014). This mostly limits its use to intraoperative and procedural analgesia but it may also be used effectively in patient-controlled analgesia pumps for patients with acute severe pain (Woodhouse et al, 1999).

For longer term pain fentanyl can be administered via a transdermal patch. Plasma levels take at least 12 hours to reach equilibrium and the dose should not be titrated in the first 3 days (Peck and Hill, 2014). Sublingual fentanyl tablets and oromucosal lozenges are available and licensed for breakthrough pain in cancer patients who have already been receiving regular opioids for over a week. The products are not interchangeable and dose titration is complex.

Transdermal buprenorphine

Buprenorphine is metabolized in the liver and primarily excreted in the bile (Hand et al, 1990). Transdermal buprenorphine can therefore be used at conventional doses in patients with impaired renal function. Plasma levels take 3 days to reach steady state so breakthrough analgesia should be prescribed for the first 12–24 hours and the dose should not be titrated during the first 3 days.

TOP TIPS

- Always think about a patient's renal function when prescribing analgesia.
- In patients with acute renal impairment always review the existing medication and consider dose adjustments if necessary.
- If in doubt make use of valuable resources such as *The Renal Drug Handbook* and the prescribing section of www.renalmed.co.uk
- Alternatively contact the renal team, acute pain team or your hospital's renal pharmacists.
- Remember that pain has a negative impact on patient experience, impairs recovery and leads to prolonged hospital stay.

Opioid antagonism in patients with renal impairment

Patients with renal impairment displaying signs of opioid toxicity can safely be treated with naloxone. Naloxone is a pure opioid antagonist and will reverse opioid effects at μ -, κ - and δ -receptors. However, its duration of action is 30–40 minutes which is shorter than that of many opioids (Peck and Hill, 2014). This is particularly true in patients with renal impairment where clearance of active opioids and their metabolites is reduced. For this reason a naloxone infusion may be required in such circumstances.

Adjuvant agents for neuropathic pain

Amitriptyline can be used at conventional doses as its elimination half-life is unchanged in patients with renal impairment (Ashley and Currie, 2011). Gabapentin is excreted entirely unchanged in the urine and therefore clearance is directly proportional to creatinine clearance (Smith et al, 2016). Start with the lowest dose and increase based on response and tolerability, while monitoring for drowsiness and confusion (Ashley and Currie, 2011). *Table 4* lists recommended doses for different levels of renal function.

Do junior doctors understand how to prescribe analgesia in renal impairment?

The authors surveyed junior doctors within their trust to assess both knowledge and confidence in analgesia prescribing in

patients with renal impairment. They analysed 30 responses from a range of specialities including medicine and surgical specialities.

Only 43% of doctors surveyed felt confident in prescribing analgesia for patients with known renal impairment. One fifth of junior doctors thought morphine could be prescribed for long-term use (>3 days) in patients with chronic kidney disease stages 4 or 5. This highlights the lack of knowledge and confidence among juniors doctors in prescribing analgesia for patients with renal impairment.

These results appear to align with existing literature. The graduate cohort questionnaire reported by Illing et al (2008) demonstrated low-preparedness for prescribing from responders. Dornan et al (2009) examined prescribing errors among doctors in the UK and reported a prescribing error rate of 10.3% in all grades of doctors. The classes of drugs most commonly involved included analgesics. They also highlighted a large variation in undergraduate prescribing and pharmacology training.

Conclusions

Failure to dose adjust analgesia for patients with impaired renal function can cause harm. Untreated pain can reduce quality of life and the accumulation of certain opioids can cause life-threatening adverse effects. Confidence levels with regard to prescribing vary among junior doctors, highlighting a need for education among junior doctors. Opioid analgesics such as morphine and codeine should be avoided as they are excreted by the kidneys and can accumulate in patients with renal impairment, leading to toxicity. Oxycodone and fentanyl should be considered as they are less likely to cause toxicity. Nevertheless, dose adjustments are still needed and junior doctors are should seek guidance from the renal team if unsure. **BJHM**

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KEY POINTS

- Patients with chronic diseases including those with renal impairment often suffer from pain.
- Prescribing analgesia for patients with impaired renal function requires care and consideration.
- Opioids such as codeine and morphine are metabolized by the liver and excreted by the kidneys so can cause toxicity in those with renal impairment.
- Opioids such as oxycodone, fentanyl and buprenorphine are safer in patients with renal impairment but should still be used with caution.
- Resources such as *The Renal Drug Handbook* provide a comprehensive prescribing guide as well as recommendations for dose adjustments.

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