Q&A 402.1

Which opioids can be used in renal impairment?

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Background

Opioids are used in a wide variety of clinical settings and are well established for the treatment of both acute and chronic pain (1). The presence of renal impairment (RI) not only alters the clearance of the parent compound but also affects the accumulation of its metabolites (2,3). This varies for individual opioids therefore it is important to understand the pharmacokinetics of each drug to minimise the risk of toxicity (2). Absolute recommendations on the appropriate reduction of opioid doses are difficult, as a clear relationship between renal function and clearance of opioid metabolites has yet to be identified. Recommendations are based on pharmacokinetics and clinical experience (4). This Q&A will review the pharmacokinetics of individual opioids and the recommendations on which opioids are preferred in RI, including those that require dose adjustments and those that should be avoided.

Answer

Opioids that should be avoided in renal impairment

Codeine is metabolised to many pharmacologically active metabolites. Codeine-6-glucuronide is the main metabolite, which is pharmacologically active and is excreted renally. Approximately 10% of codeine is metabolised to morphine which accounts for most of codeine's analgesic properties (2,5). The renal clearance of codeine and its metabolites is significantly reduced in patients with moderate to severe RI. There have been reports of severe hypotension, respiratory arrest and profound narcolepsy in patients with advanced RI therefore it is best avoided (6). However, codeine is used in practice in some renal units.

Dihydrocodeine is a semi-synthetic derivative of codeine and is thought to have similar metabolism and elimination (2,6). There have been reports of prolonged sedation in patients with RI (2). Dihydrocodeine has not been intensively studied in RI therefore should be avoided (2).

Pethidine is primarily metabolised by hepatic demethylation to the active metabolite norpethidine. The half life increases from 14-21 hours in normal renal function to 35 hours in RI (2). Norpethidine is excreted unchanged in the urine and accumulation can result in seizures and death (2,3). Naloxone does not reverse, and may increase, symptoms of norpethidine toxicity (5). For example, in patients with normal renal function, receiving pethidine via IV patient –controlled analgesia (PCA), toxicity occurred in 19% of cases where doses exceeded 10mg/kg/day. Therefore toxicity can be expected even with lower doses when used in RI (2). As safer alternatives are available, pethidine is best avoided in the presence of RI.

Opioids that should be used with caution in renal impairment

Tramadol is metabolised in the liver to the active metabolite, O-desmethyltramadol (M1) which contributes to its analgesic effect. Both parent drug and metabolite undergo renal excretion, with approximately 90% of the oral dose excreted by the kidneys, therefore it can accumulate in RI (2,6,7).

The adverse effect profile of tramadol differs slightly from that of other opioids, causing less constipation compared to morphine and a reduced risk of respiratory depression at equianalgesic doses. Significant respiratory depression has been reported in patients with severe RI which could be explained by accumulation of the metabolite M1, which has a high affinity for opioid receptors (5).

According to the manufacturer the elimination half-life of M1 (in 6 healthy volunteers) is 7.9 hours (range 5.4 – 9.6 hours) and is approximately that of tramadol. In patients with severe RI (CrCl < 5ml/min) the half-life of tramadol and M1 increased to 11 $\pm$ 3.2 hours and 16.9 $\pm$ 3 hours respectively, although extreme values have been observed for tramadol (19.5 hours) and M1 (43.2 hours) (7).

The manufacturer recommends that the dosage interval should be increased to 12 hours if CrCl is less than 30ml/min (7). Modified release preparations should be avoided (6). In severe RI (CrCl <10ml/min), tramadol is not recommended due to prolonged elimination (7).

Diamorphine and Morphine Morphine is the most widely used opioid for pain management and is the standard against which other opioids are compared (5). Diamorphine is di-acetylated morphine which is rapidly metabolised to morphine and 6-monoacetyl-morphine. Subsequently it behaves in a similar way to morphine (6). Morphine is metabolised in the liver to two main metabolites; morphine-3-glucuronide (M3G) (55%) and morphine-6-glucuronide (M6G) (10%) which are excreted renally along with 10% of the parent drug (5,6,8).

M6G is a more potent mu opioid agonist than morphine. It is a potent analgesic and CNS depressant (8). It is highly dependent on renal excretion and may cause prolonged clinical effects as the half-life increases from 2.1 hours in normal renal function to up to 27 hours in end stage renal failure (ESRF) (2). Moreover, M6G slowly crosses the blood brain barrier and slowly re-equilibrates back into the systemic circulation thereby explaining the prolonged effects on the CNS after morphine has been discontinued (3, 8). M3G accumulates in RI but the effects are less well understood. It has a low affinity for opioid receptors and no analgesic properties. M3G has been shown to be neurotoxic in animal studies (5,6).

In a case control study, 6 patients with ESRF on haemodialysis and 8 with normal renal function who were to undergo surgery under spinal anaesthesia were given 30mg of morphine preoperatively as a modified-release tablet. The peak morphine cerebrospinal fluid levels were similar between the two groups but M6G levels peaked at 12 hours in the group with normal renal function whilst it continued to rise to a peak at 24 hours in the ESRF group. The peak was found to be at least 15 times higher than in the group with normal renal function, with the consequent risk of delayed sedation (9). There have also been reports of significant narcosis, toxic agitation, profound respiratory depression in patients with severe RI following the use of morphine (8). There is one case report of delayed and prolonged unconsciousness of 45 hours duration with an onset time of 31 hours post surgery after postoperative patient controlled analgesia (PCA) with morphine. Unconsciousness started at a time when morphine was no longer detectable in plasma, and M6G concentrations had been at their peak for 26 hours (10).

There are varying opinions regarding the use of morphine in RI. Morphine appears relatively safe if carefully titrated in small doses and if it is not used where larger doses of opioids are required (2,6). The dosage should be reduced in moderate to severe RI (11), with some sources suggesting completely avoiding morphine if the eGFR is < 30ml/min) (8). If larger doses are required or for on-going analgesia (e.g. continuous subcutaneous infusions), switching to an alternative shorter acting drug such as fentanyl or oxycodone is preferred (2). Modified release morphine should be avoided as adverse effects may be prolonged (4).

Hydromorphone is a semi synthetic derivative of morphine with a shorter duration of action. It is metabolised to hydromorphone-3-glucuronide (H3G) which accumulates in RI, reaching levels up to 4 times higher than in normal renal function (2, 3). Accumulation can result in neuro-excitation and cognitive impairment (2). A retrospective study looked at patients switched from other opioids (mostly morphine) to hydromorphone. The study included 29 patients with RI of varying severity and found that 80% had an improved side effect profile after switching opioid. But the median serum creatinine concentration for these patients was 127micromol/L which suggests most of the patients only had mild RI (12). Currently the evidence for the use of hydromorphone in RI is extremely limited therefore doses should be slowly titrated upwards and patients may require a lower dosage for adequate pain relief (6,13,14)

Methadone has a long half life therefore is not appropriate for the initial management of acute pain (2). Approximately 20% of the dose is renally excreted unchanged, whilst the majority is metabolised by the liver and excreted as inactive pyrrolidine metabolites in the GI tract (2,6).

Methadone pharmacokinetics were studied in 3 patients on chronic methadone treatment: one oliguric patient on peritoneal dialysis, one anuric patient on haemodialysis and one renal transplant patient with a serum creatinine of 133-177 micromol/L. Serum methadone levels were within the expected range; i.e. similar to those in patients with normal renal function receiving comparable doses. The faecal route accounted for almost all of the excretion of methadone and its metabolites in the anuric patient, whilst less than 1% of the daily dose was removed by peritoneal dialysis or haemodialysis. There was no clinical evidence for accumulation of methadone therefore the author concluded that methadone is safe to use in patients with renal disease (15).

Despite this data, methadone should be used with caution, under specialist supervision as accumulation and toxicity have been reported in patients with normal renal function. Moreover, there is wide pharmacodynamic and pharmacokinetic interindividual variation therefore close monitoring is required (6). The manufacturer states that the dose interval should be prolonged to a minimum of 32 hours if the CrCl is between 10-50mL/min and a minimum of 36 hours if the CrCl is less than 10ml/min (16).

Oxycodone mainly undergoes hepatic metabolism to noroxycodone and oxymorphone. Of these metabolites only oxymorphone has been shown to have significant pharmacological activity (6,8).

One controlled study compared 10 patients with normal renal function with 10 uremic patients who underwent cadaver renal transplantation with no immediate graft function. The half-life of oxycodone was significantly prolonged in the uremic patients, although there was significant interindividual variation within this group. This was accounted for by an increased volume of distribution and reduced clearance of oxycodone and noroxycodone resulting in a longer half life. Smaller quantities of both free oxycodone and noroxycodone and both free and conjugated oxymorphone were excreted in the urine of the uremic group compared with the controls. The authors concluded that elimination of oxycodone is impaired in ESRF (17).

There is limited evidence for the use of oxycodone in RI. There is a single case report of a patient on chronic haemodialysis who received multiple doses of oxycodone as oxycodone/paracetamol tablets. The patient developed lethargy, hypotension and respiratory depression due to accumulation of oxycodone and needed 45 hours of continuous naloxone infusion (18). The manufacturer reports that preliminary data on patients with mild to moderate RI (not defined) showed peak plasma concentrations of oxycodone and noroxycodone to be 50% and 20% higher and AUC values for oxycodone , noroxycodone and oxymorphone to be 60%, 60% and 40% higher than in normal subjects (19).

Oxycodone should therefore be started at low doses and increased carefully (2,8,19). The manufacturer contraindicates its use in severe RI (CrCl <10ml/min) (19,20).

Opioids that can be used in renal failure

Fentanyl is a short acting synthetic opioid with a half-life of 1.5 - 6 hours which is metabolised in the liver primarily to norfentanyl and other inactive and non-toxic metabolites (3,8)**.** Approximately 10% of fentanyl is excreted unchanged by the kidneys (8,21).

There is contradictory evidence regarding the pharmacokinetics of fentanyl in RI. Fentanyl clearance was reduced in eight patients with ESRF undergoing renal transplantation, who were given an IV loading dose of 25micrograms/kg. The authors concluded that the reduction in clearance was strongly correlated to increased levels of urea, particularly when urea was twice the normal level (22). Moreover, an increased half-life (up to 25 hours) and volume of distribution have been reported in critically ill patients receiving fentanyl by continuous intravenous infusion (2,8).

In another study, fentanyl was given as single bolus injection to surgical patients with severe RI and the clearance and distribution were found to be similar to those in patients with normal renal function. This suggests no dose alterations are required for single doses of fentanyl although it is known that there is wide inter patient variability in the pharmacokinetics of fentanyl (8).

There have been anecdotal reports of respiratory depression caused by the use of 25microgram fentanyl patches in ESRF, particularly in patients who are opioid naïve. As with patches used in patients with normal renal function, the patches are best introduced when pain is already controlled by an alternative route of analgesia (6) (refer to Q&A 302.2 How should conversion of morphine to fentanyl be carried out?).

Despite the limited evidence and concerns regarding drug accumulation, fentanyl is the preferred opioid in RI due to its inactive and non-toxic metabolites (2,6). It is nevertheless advisable to monitor for signs of opioid toxicity due to wide inter-patient variability in fentanyl pharmacokinetics (8).

Alfentanil is chemically related to fentanyl but has a faster onset and shorter duration of action which lasts between 5 and 10 minutes. This is because of its small volume of distribution and a short half-life of 1.5 - 3 hours. Alfentanil is metabolised by the liver to inactive, non-toxic metabolites which are renally cleared (6,8). Pharmacokinetic studies have shown no changes in the volume of distribution or half life of alfentanil in patients with RI (8), although there have been reports of an increase in unbound plasma fraction which did not affect drug clearance. The manufacturer therefore suggests that it should be used with caution in RI (23, 24). There have been no reports of adverse effects in patients with severe RI suggesting its safety in patients with RI. Nevertheless it is advisable to start with low doses and increase carefully, as for all opiates. For most patients fentanyl is preferred due to its longer duration of action, familiarity in use and lower cost (6,8).However if high doses of opioid are needed, alfentanil is a better choice as it can be given in small volumes of injection fluid when given by continuous subcutaneous infusion.

Buprenorphine is metabolised by the liver to norbuprenorphine-3-glucuronide (B-3-G) and norbuprenorphine. These metabolites are excreted renally, whilst the unchanged parent drug primarily undergoes biliary excretion (2,6). There have been limited studies on the use of buprenorphine in RI (6).

One study in 5 patients with ESRF showed no changes in the pharmacokinetics of buprenorphine compared to healthy subjects, although metabolite levels were not measured (6). Another study showed a fourfold increase in norbuprenorphine and fifteen fold increase in B-3-G in patients with severe RI (CrCl <9ml/min) compared to healthy individuals, during a buprenorphine infusion (25). Norburprenorphine is 40 times less potent as an analgesic than buprenorphine, whilst B-3-G is inactive as an analgesic. It is not known if these metabolites cause adverse effects, but both studies reported no adverse effects. (6).

There is a lack of evidence for the use of buprenorphine in RI. Theoretically, on the basis of its pharmacokinetics, it should be relatively safe (6). The manufacturers of the buprenorphine patch suggest no dose changes are required (26) whereas RI is listed as a precaution for the 2mg sublingual tablets (27).

Summary

- Opioids are used in a wide variety of clinical settings and are well established for the treatment of both acute and chronic pain. Renal impairment (RI) not only alters the clearance of the parent compound but also affects the accumulation of its metabolites. Elimination may be prolonged.
- Absolute recommendations on reductions of opioid doses are difficult as a clear relationship between renal function and removal of opioid metabolites has yet to be identified.
- Recommendations for adjustment of doses are based on pharmacokinetic studies and clinical experience
- Codeine, dihydrocodeine and pethidine should be avoided in RI, although codeine is used in practice in some renal units
- Tramadol, diamorphine, morphine, hydromorphone, methadone and oxycodone should be used with caution in RI. Patients should be started on low doses and/or with extended dosage intervals. The dose should be slowly titrated upwards depending on response and any observed adverse effects.

- Fentanyl, alfentanil and buprenorphine are the safest opioids for use in RI. Fentanyl and alfentanil are metabolised to inactive, non-toxic metabolites whilst buprenorphine is primarily excreted in the bile. There is limited evidence for the use of these drugs in RI but on the basis of their pharmacokinetics they can be used in RI; monitoring for signs of toxicity is still required.

Table 1. Dosage recommendations for opioids in renal impairment

Opioid	Renal Drug Handbook (28)	Summary of Product Characteristics	Other guidance, adapted from Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (2010) (43)
Alfentanil	• <10-50ml/min: Dose as in normal renal function	Present data suggests that clearance of alfentanil is unaltered in RI. There is an increased free fraction hence dosage requirements may be less than in patients with normal renal function (23,24)	No dosage adjustment required unless severe RI
Buprenorphine	• 20-50ml/min: Dose as in normal renal function • 10-20ml/min : Dose as in normal renal function but avoid very large doses • < 10ml/min Reduce dose by 25-50% and increase as tolerated. Avoid very large single doses • Transdermal: Dose as in normal renal function	**Patch:** No dose adjustment required (26) **Sublingual Tablet:** Subutex 2mg (licensed for opioid dependence): Elimination may be prolonged (27) Temgesic 200mcg, 400mcg (licensed for pain): no dosage adjustment guidance given by (29,30) **Injection:** No information given by manufacturer (31)	No dosage adjustment required
Codeine	• 20-50ml/min: dose as in normal renal function • 10-20ml/min: 30mg up to every 4 hours. Increase if tolerated • < 10ml/min: 30mg up to every 6 hours. Increase if tolerated	Use with caution in RI (32) Dosage should be reduced in elderly where there is RI (33)	Dose adjustment recommended or use an alternative if possible
Diamorphine	• 20-50 ml/min dose as in normal renal function • 10-20 ml/min use small doses eg.2.5mg SC/IM approx. 6 hourly and titrate to response • <10 Use small doses, eg. 2.5mg SC/IM approx. 8 hourly and titrate to response	Start at low doses and titrate to therapeutic effect in RI The dosage should be reduced in moderate to severe RI (34, 35)	No information on dose adjustment in RI
Dihydrocodeine	• 20-50ml/min: Dose as in normal renal function • <10 – 20ml/min: Use small doses and titrate to response	Dihydrocodeine should be avoided or reduced in RI (36)	Insufficient evidence: use not recommended
Fentanyl	• 20-50ml/min: Dose as in normal renal function • 10-20ml/min: 75% of normal dose. Titrate according to response • <10ml/min: 50% of normal dose. Titrate according to response	**Patch:** Observe carefully for signs of toxicity and reduce dose if necessary (21) **Lozenge:** Use with caution. The influence of renal impairment on the pharmacokinetics has not been evaluated (37) **Injection:** Monitor closely and titrate carefully (38)	No dose adjustment required

Opioid	Renal Drug Handbook (28)	Summary of Product Characteristics	Other guidance, adapted from Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (2010)(43)
Hydromorphone	• 20-50ml/min: Dose as in normal renal function • <10-20ml/min: Reduce dose – start with lowest dose and titrate according to response	Dose should be titrated to reach adequate analgesia. Patients may require a lower dosage to achieve adequate analgesia (13,14)	Dose adjustment recommended or use alternative opioid
Methadone	• 10-50ml/ml: Dose as in normal renal function • <10ml/min: 50% of normal dose, and titrate according to response	Caution should be exercised in RI. The dose interval should be lengthened to a minimum of 32 hours if GFR is 10-50ml/min and to a minimum of 36 hours if GFR less than 10ml/min (16)	Dose adjustments may be required in severe RI
Morphine	• 20-50ml/min: 75% of normal dose • 10-20ml/min: Use small doses, eg. 2.5-5mg and extended dosing intervals. Titrate according to response • <10ml/min: Use small doses. Eg.1.25-2.5mg and extended dosing intervals. Titrate according to the response • Avoid slow release oral preparations as any side effects may be prolonged	**Oral:** May require a reduction in dosage (39,40) **Injection:** The dosage should be reduced in moderate to severe renal impairment (11)	Dose adjustment recommended or use an alternative
Oxycodone	• 10-50ml/min: Dose as in normal renal function • <10 ml/min: Start with small doses • Has been used in CKD 5 patients; start with lowest dose and gradually increase dose according to response	**Oral:** Plasma concentration may be increased in mild to moderate RI. Patients should be started on Oxycontin (modified release) 5mg 12-hourly or Oxynorm liquid 2.5mg 6 hourly and titrated to pain relief (19) Contraindicated in severe RI (20) **Injection:** use with caution in mild to moderate RI. Contraindicated in severe RI (41)	No dose adjustment required
Pethidine	• 20-50ml/min: Dose as in normal renal function • 10-20ml/min: Use small doses – increase dosing interval to 6 hours and decrease dose by 25% • <10 Avoid if possible. If not use small doses: increase dosing interval to 8 hours and decrease dose by 50%	Use with caution and with reduced dosage in RI (42)	Use of an alternative is recommended
Tramadol	• 20-50ml/min: Dose as in normal renal function • 10-20ml/min: 50-100mg every 8 hours initially and titrate dose as tolerated • <10ml/min: 50mg every 8 hours initially and titrate dose as tolerated	The elimination of tramadol may be prolonged. The usual initial dosage should be used in RI. For patients with CrCl <30ml/min, the dosage interval should be increased to 12 hours. Tramadol is not recommended in patients with severe renal impairment (CrCl <10ml/min) (7).	Dose adjustment recommended. Use alternative in severe RI

Limitations

This Q&A is intended for use in dosing of adult patients only. It is not intended as a comprehensive prescribing guide and provides advice on dosing in renal impairment of selected opioids only. The use of opioids in renal replacement therapies is not discussed.

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Search strategy
- Embase (EXP opiates) and (EXP kidney dysfunction OR EXP kidney failure OR EXP Kidney disease).
- Medline (EXP Analgesics, Opioid) and (EXP kidney dysfunction OR EXP kidney failure OR EXP Kidney disease).
- In-house renal databases and resources
- Micromedex
- The Renal Association: http://www.renal.org/home.aspx
- NICE guidelines www.nice.org.uk
- www.medicinescomplete.com
- The British Pain Society http://www.britishpainsociety.org/pub_professional.htm
- Internet search (Google, Cochrane library)
- Clinical expert: Aileen Dunleavy. Editor, Renal Drug Handbook