Review

PALLIATIVE MEDICINE

Palliative Medicine
25(5) 525–552

DOI: 10.1177/0269216311406313
pmj.sagepub.com
SAGE

A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: A European Palliative Care Research Collaborative opioid guidelines project

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Abstract

Background: Opioid use in patients with renal impairment can lead to increased adverse effects. Opioids differ in their effect in renal impairment in both efficacy and tolerability. This systematic literature review forms the basis of guidelines for opioid use in renal impairment and cancer pain as part of the European Palliative Care Research Collaborative's opioid guidelines project.

Objective: The objective of this study was to identify and assess the quality of evidence for the safe and effective use of opioids for the relief of cancer pain in patients with renal impairment and to produce guidelines.

Search strategy: The Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, MedLine, EMBASE and CINAHL were systematically searched in addition to hand searching of relevant journals.

Selection criteria: Studies were included if they reported a clinical outcome relevant to the use of selected opioids in cancer-related pain and renal impairment. The selected opioids were morphine, diamorphine, codeine, dextropropoxyphene, dihydrocodeine, oxycodone, hydromorphone, buprenorphine, tramadol, alfentanil, fentanyl, sufentanil, remifentanil, pethidine and methadone. No direct comparator was required for inclusion. Studies assessing the long-term efficacy of opioids during dialysis were excluded.

Data collection and analysis: This is a narrative systematic review and no meta-analysis was performed. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the quality of the studies and to formulate guidelines.

Main results: Fifteen original articles were identified. Eight prospective and seven retrospective clinical studies were identified but no randomized controlled trials. No results were found for diamorphine, codeine, dihydrocodeine, buprenorphine, tramadol, dextropropoxyphene, methadone or remifentanil.

Conclusions: All of the studies identified have a significant risk of bias inherent in the study methodology and there is additional significant risk of publication bias. Overall evidence is of very low quality. The direct clinical evidence in cancer-related pain and renal impairment is insufficient to allow formulation of guidelines but is suggestive of significant differences in risk between opioids.

Recommendations: Recommendations regarding opioid use in renal impairment and cancer pain are made on the basis of pharmacokinetic data, extrapolation from non-cancer pain studies and from clinical experience. The risk of opioid use in renal impairment is stratified according to the activity of opioid metabolites, potential for accumulation and reports of successful or harmful use. Fentanyl, alfentanil and methadone are identified, with caveats, as the least likely to cause harm when used appropriately. Morphine may be associated with toxicity in patients with renal impairment.

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Unwanted side effects with morphine may be satisfactorily dealt with by either increasing the dosing interval or reducing the 24 hour dose or by switching to an alternative opioid.

Keyword
kidney failure, neoplasms, opioids, pain

Background

Approximately 60% of cancer patients have a creatinine clearance (CrCl) of less than 90 ml/min but less than 10% will have a raised serum creatinine.[1] A study has indicated that approximately 20% of cancer patients (excluding patients with myeloma) have a CrCl of less than 60 ml/min, four times the prevalence in the general population.[1,2]

Renal function is increasingly stratified according to internationally accepted criteria for chronic kidney disease (CKD), which classifies the degree of function according to estimated glomerular filtration rate (eGFR) (see Table 1).[3,4] This classification system was not specifically designed for cancer patients, or for acute renal impairment, but it is widely used. GFR or CrCl measurements are superior to serum creatinine alone in assessing the degree of renal impairment. The accuracy of formulae to derive eGFR or CrCl measurements is less in the presence of oedema, cachexia, low protein states and for acute renal failure, all seen frequently in cancer patients. Adverse effects secondary to opioids can have a significant impact on patients and families and there have also been concerns that opioid toxicity can be mistaken for an irreversible terminal decline.

Over recent decades there has been a significant change in understanding of the impact of renal function on opioid use with increasing recognition that metabolites, or parent drugs, can accumulate and cause toxicity. However, not all opioids behave in the same way. The literature on prescribers' awareness of renal function in relation to drug prescription is minimal, but there are reports of inadequate awareness of a patient's renal function, poor awareness of its importance in relation to opioid prescription and variability in choice of opioids for the renally impaired and in recommendations for doses of opioid in renal impairment.[5–7] A survey of renal and palliative care physicians showed great variation in the choice of opioid, dose and method of assessment of renal function.[5] Palliative care physicians were more likely to use creatinine than the eGFR in their assessment. Knowledge of which opioids, at what dose, to use in different levels of renal impairment could contribute significantly to effective and safe pain control in those with cancer.

The opioids included in this review are morphine, diamorphine, codeine, dextropropoxyphene, dihydrocodeine, oxycodone, hydromorphone, buprenorphine, tramadol, alfentanil, fentanyl, sufentanil, remifentanil, pethidine and methadone. Drugs were included if they were commonly used, if they had been advocated for use in patients with renal impairment or if there was any suggestion that they were more likely to cause problems than other opioids in renal impairment.

The objectives of this systematic review are to identify and critically appraise the literature relevant to opioid use in renal failure and cancer-related pain and formulate guidelines for their use.

Table 1. Stratification of glomerular filtration rate (GFR; stage of chronic kidney disease)

Stage	GFR	Notes and description
1	>90 ml/min	Normal renal function
2	60–89 ml/min	Mild renal impairment (if other evidence of chronic kidney damage)
3	30–59 ml/min	Moderate renal impairment
4	15–29 ml/min	Severe renal impairment
5	<15 ml/min	End-stage renal failure

Methods

The systematic review was conducted according to a predefined, unregistered protocol. A deliberately inclusive approach was taken due to the perceived paucity of literature available on the subject and the variability in the way in which it is reported, making a very specific database search insensitive for relevant studies.

Eligibility

We included studies that reported a clinical outcome related to renal impairment in adult patients with cancer-related pain. A proportion of the participants

Table 2. MedLine search strategy (MESH and text search)

1. Opioid*.mp	30. Sufentanil.mp
2. Opiate*.mp	31. Meperidine/
3. Opiate alkaloids/	32. Meperidine.mp
4. Analgesics opioid/	33. Pethidine.mp
5. Narcotics/	34. 1 or 2 or 3. 33
6. Morphine/	35. Renal insufficiency/
7. Morphine.mp	36. Renal impairment.mp
8. Oxycodone/	37. Renal failure.mp
9. Oxycodone.mp	38. Renal disease.mp
10. Methadone/	39. Acute renal impairment.mp
11. Methadone.mp	40. Chronic Kidney disease.mp
12. Hydromorphone/	41. Kidney failure, Chronic/
13. Hydromorphone.mp	42. 35 or 36 or. . .41
14. Heroin/	43. Cancer*
15. Heroin.mp	44. Tumor* or tumour*
16. Diamorphine.mp	45. Malignancy.mp
17. Fentanyl/	46. Neoplasms/
18. Fentanyl.mp	47. Carcinoma/
19. Buprenorphine/	48. Neoplasm*.mp
20. Buprenorphine.mp	49. 43 or 44 or. . ..48
21. Tramadol/	50. Pain/
22. Tramadol.mp	51. Pain.mp
23. Alfentanil/	52. 50 or 51
24. Alfentanil.mp	53. 34 and 42 (opioids and renal disease)
25. Codeine/	54. 34 and 42 and 49 (opioids and renal and cancer)
26. Codeine.mp	55. 34 and 42 and 49 and 53 (opioids and renal and cancer pain)
27. Dihydrocodeine.mp	
28. Remifentanil.mp	
29. Sufentanil/	

within the trials had to have renal impairment defined as a serum creatinine above the normal range for the study, CrCl or GFR measurements less than 90 ml/min, or as per the study definition.

We excluded studies assessing the longer-term efficacy of opioids during dialysis and trials not reported in English.

Search strategy

The following databases were systematically searched from databases set up to 31 July 2009: Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, MedLine, EMBASE and CINAHL. The reference lists of relevant screened full text articles were searched in addition to hand searching of Palliative Medicine, Journal of Pain and Symptom Management, Journal of Palliative Medicine, Supportive Care in Cancer, American Journal of Hospice and Palliative Medicine and the European Journal of Palliative Care (from 2002 to July 2009). Grey literature was sought from 'opensigle.-insist.fr.', ProQuest Dissertations and Thesis Database and a hand search of international conference proceedings in the hand-searched journals.

The search strategy for Medline is shown in Table 2 and adapted appropriately for other databases. The strategy combines free text and MESH terms.

Data collection and analysis

The titles and abstracts of identified papers were screened and if it was unclear whether they met the inclusion criteria then full text articles were obtained and reviewed. Duplicate publications were identified from reviewing the study details.

All included studies were independently assessed for quality and predefined data collection forms were used for data extraction. The form recorded publication details, interventions, duration of study, outcome measures used and information relevant to trial quality, such as allocation concealment and blinding. If there was disagreement on whether to include studies then inclusion was discussed between SK, KF and GH. Results from the systematic review were presented as a narrative analysis, since meta-analysis was not possible from the published data.

Quality assessment. The assessment of the quality of included papers and subsequent guideline formation was undertaken using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[8,9] This method balances the intrinsic strengths and weaknesses of the study methodology with any study limitations, and the directness, precision, consistency and any strengthening factors across all of the studies and within each study. The quality of the available evidence and judgements made in the guideline formation process are clearly stated, with an explanation of how the strength of the guidelines is determined.

Results

Searches of electronic databases obtained 1780 references with 187 additional references from searching of reference lists, hand searching of journals and grey literature searching. There were 292 full text articles obtained for detailed analysis, of which 15 met the inclusion criteria. The included studies were eight prospective observational studies and seven retrospective studies. No randomized, controlled trials were

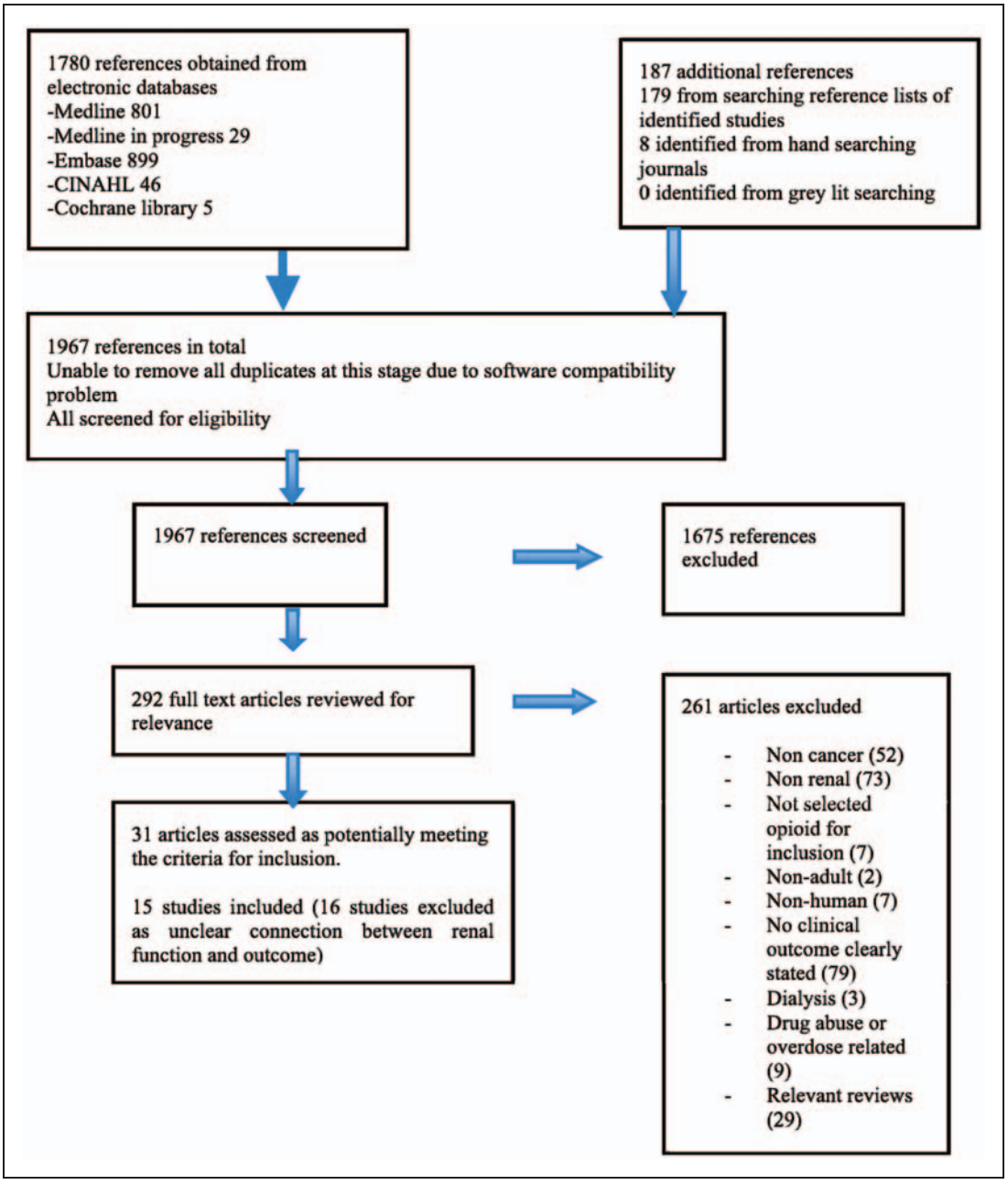

Figure 1. PRISMA flowchart.

identified. Details of the study screening and identification process are shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[10] flowchart in Figure 1.

There were 16 studies excluded due to difficulties linking the outcome described directly with renal impairment.[11–26] The studies were predominantly case reports. Exclusion of these studies does not change the final conclusions of the systematic review.

The included studies are described in Table 3.

Narrative summary of the evidence for each opioid. In the following, mg/dl units are converted to μmol/l by multiplying by 88.4 throughout.

Morphine. Five prospective studies and two retrospective reviews were identified with relevance to morphine.

Eighteen non-consecutive hospice cancer patients, who were receiving morphine for pain, were recruited by Wood et al.[27] Seven of the patients experienced nausea and vomiting believed to be caused by

Table 3. Included studies

Study and design	Objectives/intervention	Patients	Outcome measure	Results	Notes
Wood et al.[27] (Prospective study)	Assessment of the pharmacokinetics and neuropsychological effects of morphine in hospice inpatients. Average morphine dose for all patients was 100 mg/24 hours (range 15–600 mg) Oral (9) or subcutaneous (9)	18 patients, 9 had oral morphine and 9 had subcutaneous morphine All receiving morphine on regular basis for more than 3 days Hospice patients, all with advanced incurable cancer Also receiving other drugs No withdrawals	National Audit Reading Test, Williams Delayed Recall Test, Immediate memory for Digits, Training Making Test, Recall of the Williams Delayed Recall Test and Digit Symbol Substitution Test Also standard reporting of adverse events	7 patients with nausea and vomiting likely to be due to morphine The group with nausea had a statistically significant, higher serum creatinine concentration (80 ± 30 μmol/l compared with 100 ± 20 μmol/l) The group with nausea also had worse neuropsychological performance ($p < 0.05$) Serum creatinine did not differ between the two routes Seven patients with nausea and vomiting who had renal impairment also had elevated M3G concentrations	Funded by Mary Potter Foundation and University of Adelaide Same research group as Ashby study below No clear assessment of extent of disease in patients with and without renal impairment
Ashby et al.[28] (Prospective study)	Assessment of morphine and metabolite levels in hospice inpatients 17 patients received morphine orally every 4 hours (median dose 110 mg, range 20–600 mg), 19 received morphine by CSCI (median dose 50 mg (range 20–830 mg)	36 patients (7 had biochemical evidence of renal impairment). Mean creatinine 120 μmol/l (range 40–620 μmol/l) Hospice inpatients, all with advanced incurable cancer Patients with severe renal failure of multi-organ failure were excluded	No formal outcome measures. Reported side effects	Serum creatinine concentration significantly higher in the group with side effects $p = 0.031$ (as was dose corrected M3G and M6G levels, $p = 0.029$ and 0.042) All patients with raised creatinine had symptoms of nausea/vomiting or organic brain dysfunction No difference in age between normal and abnormal creatinine group Mean creatinine in no symptoms group 80 ± 20 μmol/l, $N = 17$ Mean creatinine in symptomatic group 160 ± 140 mmol/l, $N = 19$	Hepatic and renal failure did not coexist in any patient No clear assessment of extent of disease in patients with and without renal impairment

(continued)

Table 3. Continued

Study and design	Objectives/intervention	Patients	Outcome measure	Results	Notes
Tiseo et al.[29] (Prospective study)	Assessment of the relationship between morphine-6-glucuronide concentrations and opioid side effects in cancer patients 48 hr total morphine dose 486 mg (40–4800 mg) in oral group and 931 mg (10–9062 mg) in parenteral group	Convenience sample 109 patients. Referrals to a New York pain service Patients with severe renal failure of multi-organ failure were excluded	Myoclonus present or absent Cognitive impairment present or absent	Renal function was not associated with severe toxicity(but only 9 episodes of severe side effects No statistically significant difference between the creatinine of the group with symptoms and those without despite mean creatinine being 114 and 164 μmol/l in the non-symptomatic and symptomatic groups, respectively. Moderate but significant correlation between M6G:M ratio and serum creatinine. Very large variation in M6G:M ratio. Trend towards a higher morphine and M6G values in the side effect group	National institute of Health Grant (USA)
Somogyi et al.[30] (Prospective study)	Assessment of any relationship between plasma concentrations of morphine and its metabolites and pain scores Dose range of 10–100 mg every 4 hours	11 patients (CrCl 52–180 ml/min) Receiving oral morphine on a regular basis 4 hourly for 3 days All cancer patients, location not directly stated, ethical approval from Royal Adelaide Hospital, Australia	101-point numerical rating scale	No statistically significant relationship between plasma concentrations of morphine and its metabolites (M3G and M6G) to creatinine clearance. No apparent relationship between drug concentrations and pain scores (but from visual inspection of the data only) Side effects were not specifically assessed or reported	The study excludes patients with significant renal impairment Funded by the Anticancer Foundation of the Universities of South Australia and the Royal Adelaide Hospitals Research Fund
Klepstad et al.[31] (Prospective study)	An assessment of whether routine monitoring for morphine and morphine metabolite concentrations	300 patients. 12 patients (3.7%) had a creatinine of greater than 15 μmol/l All patients admitted	European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire	No correlation between morphine or metabolite levels and pain intensity. No correlation between	Funding from the Norwegian Research Council

(continued)

Table 3. Continued

Study and design	Objectives/intervention	Patients	Outcome measure	Results	Notes
	helped predict clinical observations in cancer patients Median time from start of morphine therapy was 1 month	to Trondheim University Hospital due to malignant disease and who received chronic treatment with morphine (stable dose for at least 3 days pre admission) Median time from establishing diagnosis of cancer was 19 months Median creatinine 77 (39–485) μmol/l	(EORTC QLQ-C30) Brief Pain Inventory (BPI) Mini-mental State examination Karnofsky perfor mance score	serum concentrations of morphine and its metabolites No specific assessment of correlation between renal function and clinical state.	
Riley et al. 2004[32] (Retrospective study)	Assessment of biochemical and haematological factors that might influence the need to switch from morphine due to intolerable side effects	77 opioid switchers and 100 controls Non-responders to morphine were either those with morphine-related side effects not responsive to adjuvant medication or poor pain control. This was a subjective assessment by a clinician Controls had been taking morphine for at least 3 consecutive months with no problems 1 patient had end-stage renal failure with a creatinine of 849 μmol/l who was removed from the analysis	Need to switch from morphine due to uncontrolled pain with side effects	Serum creatinine was found not to differ significantly between the groups of responders and non-responders Switchers creatinine concentration mean 79.5 (37–816) μmol/l Controls creatinine concentration mean 81 (49–246) μmol/l	For switchers, blood results within 2 weeks of the need to switch could be used thus potentially missing resolved renal impairment as the precipitant for switching
Riley et al.[33] (Prospective study)	Assessment of biochemical and haematological factors that might influence the need to switch from morphine due to intolerable side effects Non-responders switched to oxycodone as first line, second line switch fentanyl or methadone	186 patients taking morphine Responders had been taking morphine for at least 4 weeks with clear benefit. Non-responders to morphine were either those with morphine-related side effects not responsive to adjuvant medication or	Brief pain inventory, need to switch, toxicity scores	Serum creatinine was found not to differ significantly between the groups of responders and non-responders. Note that excluded if creatinine greater than 1.5 times normal range	Excluded patients with a creatinine of greater than 1.5 × normal

(continued)

Table 3. Continued

Study and design	Objectives/intervention	Patients	Outcome measure	Results	Notes
		poor pain control. This was a subjective assessment by a clinician Excluded if creatinine concentration greater than 1.5 times the normal range Mean creatinine in responders 69 μmol/l (40–170) and in non-responders 71 μmol/l (44–152)			
Kirkham and Pugh[34] (Retrospective study)	Retrospective assessment of the use of alfentanil	4 patients intolerant of diamorphine. Described as having renal impairment but extent of impairment not stated	No formal outcome measures	Agitation improved on a change to alfentanil	Published as letter
Urch et al.[35] (Retrospective study)	A retrospective assessment of the use of alfentanil	48 (51% reported to have renal impairment) inpatients in Royal Marsden Hospital, UK	No formal scoring for efficacy or side effects	Most patients converted to alfentanil because of opioid toxicity. Six of 16 patients converted back to oral opioids developed toxicity	Audit of guidelines on the use of alfentanil No direct statement of number of patients with cancer (presumed on basis of high chance of involving predominantly cancer patients)
Kaiko et al.[36] (Prospective study)	Assessment of factors associated with pethidine toxicity in patients referred due to neurological symptoms	67 patients, 19 of whom had cancer Referrals to cancer pain centre in New York All patients received pethidine Mean dose per day of pethidine was 170 (75–380) mg in asymptomatic patients, 350 (59–1080) mg in patients with shaky feelings, 370 (46–1100) mg in patients with tremor/twitch and 420 (260–540) mg in patients with myoclonus or tonic clonic seizures	No formal outcome measures were described other than reported side effects	Those with CNS symptoms had a higher norpethidine plasma level and a higher norpethidine to pethidine plasma ratio ($p < 0.001$). 14 out 48 symptomatic patients had elevated blood urea nitrogen	Funded in part by US Public Health Service

(continued)

Table 3. Continued

Study and design	Objectives/intervention	Patients	Outcome measure	Results	Notes
		Mean blood urea nitrogen 12 mg/dl in 12 of 19 asymptomatic patients Mean blood urea nitrogen 27 mg/dl in 41 of 48 symptomatic patients (14 had level greater the 20 mg/dl)			
Mazzacato et al.[37] (Retrospective study)	Retrospective assessment of the use of fentanyl in severely ill patients and renal failure	53 patients with a GFR of less than 60 ml/min. Median GFR was 25 ml/min. 62% had cancer Tertiary Hospital Palliative Care patients, Switzerland	No formal outcome measures	Pain control was complete in 59% and partial in 26%. Of those with neurotoxicity prior to a change to fentanyl, 31% completely improved, 26% partially improved	Myoclonus still occurred in three patients. Published as conference abstract
White et al.[38] (Retrospective study)	Retrospective assessment of the use of sufentanil due xto difficulties in using other opioids Median final dose 130 μgrams per 24 hours Median duration of sufentanil infusion was 4 days (1–14 days range)	48 participants with the majority described as having some degree of renal impairment All patients with advanced malignancy in hospital palliative care setting	No formal outcome measures	Informal description of a 'generally favourable result'	Published as letter
Narabayashi et al.[39] (Prospective study)	Assessment of the effect of rotation from oral morphine to oxycodone in patients with intolerable side effects. Primarily designed to assess pharmacokinetic parameters	9 with renal impairment (CrCl $<$ 60 ml/min) 18 cancer patients with no renal impairment Serum creatinine 62 ± 18 μmol/l compared to 114 ± 62 μmol/l Patients from 14 medical institutions across Japan	Adequate pain control rate using categorical scale and no formal measure for side effects	Report of 'high adequate pain control' in both groups ('normal' and abnormal renal function). Data presented as 84% with adequate pain control across all groups. Informal report of improved side effects in all but one patient but did not define the group of this patient	Funding by Shionogi & Co, Japan Pre-selects a group that are intolerant to morphine
Lee et al.[40] (Retrospective study)	Retrospective assessment of the use of hydromorphone in	29 patients with impaired renal function compared with 26 with normal	No formal outcome measures used	No statistically significant difference between patients with and without renal	Pre-selects a group that are intolerant to morphine

(continued)

Table 3. Continued

Study and design	Objectives/intervention	Patients	Outcome measure	Results	Notes
	patients with normal and abnormal creatinine	renal function mean creatinine concentrations were 127.5 μmol/l (90–756) and 81.5 μmol/l (53–96) The reason for a switch to hydromorphone was cognitive impairment, drowsiness or nausea Previous treatment was morphine (46), coproxamol (3), fentanyl (2) and diamorphine (1).		impairment for drowsiness or hallucinations Improvement in side effect profile for >80% of patients. Following a change to hydromorphone, confusion improved in 77% (10/13) of the renal group compared with 90% of the non-renal group Hallucinations improved in 100%	
Twomey et al.[41] (Retrospective study)	Retrospective assessment of the occurrence of toxicity in hospice inpatients with CKD	40 patients with CKD identified. 34 patients prescribed opioids. 11 had CKD stage 3, 22 had CKD stage 4 and 7 CKD stage 5. 53% received codeine, morphine or diamorphine, 26% oxycodone and 21% a combination of opioids. All patients had cancer with 82.5% having metastatic disease	No formal outcome measures. Assessment of reported toxicity from case notes only	13 of 40 patients (33%) developed toxicity	Conference abstract

M3G: morphine-3-glucuronide, M6G: morphine-6-glucuronide, CSCI: continuous subcutaneous infusion, CrCl: creatinine clearance, BPI: brief pain inventory, CNS: central nervous system, GFR: glomerular filtration rate, CKD: chronic kidney disease

Note: The units for serum creatinine concentration have been converted to μmol/l when expressed in studies as mg/dl (mg/dl multiplied by 88.4). Units were changed for Narabayashi et al.[39] and Tiseo et al.[29]

morphine. This symptomatic group was found to have a higher creatinine concentration than the asymptomatic patients (100 +/− 20 μmol/l and 80 +/− 20 μmol/l, $p < 0.05$) and elevated morphine-3-glucuronide (M3G) but not morphine-6-glucuronide (M6G). There was also a significant difference in neuropsychological performance as assessed by a variety of formal measures, for example, Williams Delayed Recall Test and a Digit Symbol Substitution Test. The same authors (as Ashby et al.[28]) had previously published a similar study of 36 hospice inpatients on morphine in which serum creatinine levels were significantly higher in the group with side effects, as were M3G and M6G levels. All of the patients with elevated serum creatinine levels had nausea and vomiting or delirium (160 μmol/l compared to 80 μmol/l).

A further prospective study by Tiseo et al.[29] did not show any significant association between renal function and toxicity. It should be noted, however, that there was a trend towards an association with creatinine, with the mean creatinine concentration in the group with no side effects being 114 μmol/l compared to 164 μmol/l for the group with side effects. This was, however, in just nine episodes of critical adverse events. There was no significant difference between those with and without side effects and any morphine related variable, such as M6G concentration (M3G levels were not measured). Tiseo et al. studied patients in a cancer centre, whilst Ashby et al. studied patients in a hospice who were likely to be more unwell.

Somogyi et al.[30] found no significant relationship between metabolite (M3G and M6G) to morphine ratios and serum creatinine concentration in 11 cancer patients receiving morphine. All patients had a CrCl measurement between 52 and 180 ml/min. There was also no evidence of a relationship between morphine, metabolite levels and pain scores. No statistical analysis was performed for a relationship between the pain scores and renal function; the authors merely comment on no apparent relationship from visual inspection. Klepstad et al.[31] describe a prospective observational study of 300 cancer patients aimed at determining if routine measurement of serum concentration of morphine and its metabolites could predict clinical outcomes. Only 3.7% of the patients had a serum creatinine concentration of greater than 150 μmol/l and no specific analysis was reported for those with impaired renal function. No clear correlation was detected between morphine, M3G and M6G concentrations and pain intensity or treatment failure.

Two studies by Riley et al.[32,33] investigating possible factors that might predict a need to switch opioids did not show any evidence of renal function as a risk factor. The prospective study deliberately excluded patients with a serum creatinine concentration over 1.5 times the normal range and the statistical significance of a connection between creatinine and risk of needing to switch was lost with the removal of one patient with end-stage renal failure in the retrospective study. Although excluding patients with a creatinine concentration of 1.5 times normal is likely to remove most with severe renal impairment, it is useful to include such studies in this review. A serum creatinine concentration of 1.5 times the normal range may still reflect a significantly reduced GFR. Any information on what level of GFR relates to an increased risk of toxicity or side effects are useful data. The absence of an apparent effect at mildly or moderately reduced GFR has potential significance.

Alfentanil. Kirkham and Pugh[34] described a retrospective series of four patients with impaired renal function who were agitated on a continuous subcutaneous infusion (CSCI) of diamorphine. All four cases settled on changing to alfentanil. Urch et al.,[35] in a retrospective review of alfentanil use in a hospital palliative care setting, described 41 patients with renal impairment (out of 81 using alfentanil). Alfentanil was routinely used as an alternative to morphine if serum creatinine was over 105 μmol/l. Approximately half of the patients who were subsequently converted back to oral opioids developed opioid toxicity within 48 hours.

Pethidine. Kaiko et al.[36] reported 67 patients within a prospective study who were referred to a neurological service for shaky feelings, tremors and myoclonus whilst on pethidine. Nineteen of the patients had cancer and at the time of study all the cancer patients were symptomatic. Fourteen of the 48 symptomatic patients had elevated blood urea nitrogen. Ten patients with myoclonus and seizures improved on stopping pethidine. It was unclear, however, how many of the cancer patients had renal impairment. There was a higher norpethidine level in symptomatic patients, which was statistically significant.

Fentanyl. A retrospective review by Mazzacato et al.[37] described 53 patients in a palliative care unit, all of whom had a CrCl measurement of less than 60 ml/min (median 25) and were all treated with subcutaneous fentanyl. Pain control was complete or partial in 85% and, of those with opioid-related neurotoxicity (26) as the reason for using fentanyl, an improvement was seen in 57%. Myoclonus occurred in three of these patients.

Sufentanil. White et al.[38] outlined a retrospective study of 48 patients in a hospice setting who were treated with sufentanil for pain. The majority of the patients had some degree of renal impairment, although this was

not made explicit. The overall outcome was described as favourable but with no formal outcome measure.

Oxycodone. A prospective observational study by Narabayashi et al.[39] showed that in nine patients, with renal impairment (CrCl < 60 ml/min) who had difficulty using morphine, a switch to oxycodone resulted in 'high adequate pain control' (authors' description with no additional information).

Hydromorphone. Lee et al.[40] retrospectively assessed groups of patients with and without renal impairment using hydromorphone. For those with renal impairment, 26/29 were on morphine prior to being switched to hydromorphone because of cognitive impairment, drowsiness or nausea. There was no statistically significant difference between the groups for drowsiness or hallucinations. The mean serum creatinine concentration in the group with renal impairment was 127.5 μmol/l (range 90–756).

A conference abstract by Twomey et al.[41] reported that 13 out of 40 patients with stage 3, 4 or 5 CKD prescribed opioids for cancer-related pain developed toxicity. The patients were given a variety of opioids and detailed results were not presented for each individual medication. Little can be concluded directly from this study other than renal failure may be a risk factor for toxicity when prescribing opioids.

No studies were identified that met the inclusion criteria for diamorphine, codeine, dihydrocodeine, buprenorphine, tramadol, dextropropoxyphene, methadone or remifentanil.

Quality assessment

There is a significant risk of bias within all the studies identified for this review because of the design methodologies used (uncontrolled prospective and retrospective studies only). There are also many potential confounding factors within the studies, such as the possible effect of renal failure in causing symptoms or renal failure being a marker for greater disease burden. There were no factors in any of the studies identified that would increase the quality of the evidence according to the GRADE criteria. The populations chosen for study were relevant to palliative cancer care, although the heterogeneous nature of these populations may present some difficulty in comparing results. Many of the studies were very small in scale.

Using the GRADE criteria to assess the quality of the studies, and the evidence across all the identified literature, results in a grading of very low quality relating to the use of morphine, alfentanil, pethidine, fentanyl, sufentanil, oxycodone and hydromorphone. This grade is determined because of the nature of the study types, sparseness of data and a high chance of publication bias. Although the grade of evidence is the same for each opioid listed, there is clearly more evidence available on morphine use compared with other opioids. This evidence is suggestive of an increased chance of toxicity when morphine is used in patients with renal impairment.

Discussion and guideline development

The overall level of direct clinical evidence for opioid use in renal failure is very poor or absent for the opioids chosen for this review. There were no studies identified to clearly indicate the relative risk of toxicity of opioids in patients with renal impairment compared to those with normal renal function or to compare different opioids.

Within any systematic review there is potential for bias in the retrieval of appropriate studies. Although an inclusive approach was chosen, not all studies may have been retrieved. This is in part because of language limitations in the search for papers and not directly approaching known investigators and drug companies for additional data. A number of studies were excluded from the review at the final discussion stage because of difficulties in linking renal failure with a direct clinical outcome. They were predominantly case studies in which there were many reported or potential confounding factors that could have explained the clinical outcome. Whilst there was some degree of subjectivity in whether to include these reviews or not, inclusion of any of these papers into the formal review would not have influenced the final conclusion as to the evidence base available on this subject.

The addition of studies on non-cancer pain is unlikely to have changed the results of this review dramatically, as assessed by an informal evaluation of the literature during the literature search.

Progressing from the evidence to guidelines requires judgements about the evidence and other factors that might influence any recommendation. This is clearly described within the GRADE guideline development process. There were a number of important judgements made during the development of the guideline.

It is important to be clear about the level of evidence used to make any recommendations and to show consistency in approach to all of the opioids. In the guideline development process consideration was given to making weak recommendations against the use of morphine on the basis of this presented evidence. It was felt, however, that there is significant potential bias across all of the evidence and that the evidence was so limited in quality and quantity that it was more appropriate to make no recommendation on this evidence alone. Given the very low quality of clinical evidence we do

not feel there is sufficient evidence to make a formal guideline for any one opioid from the research presented. There is, however, a danger in producing no recommendations at all. Anecdotally there is significant variation in practice and variable awareness of the relevance of renal function to opioid use and to appropriate ways of improving analgesic efficacy and tolerability by taking this into consideration. We therefore propose making recommendations for opioid use in renal impairment based on clinical experience and pharmacological data, congruent with the foundations of evidence-based medicine, which recognize the importance of integrating clinical expertise with the best available research evidence, pending further investigations.[42]

A systematic review of the pharmacological data about opioid use in renal impairment would be useful because there are inconsistencies and controversies that still exist. Although every effort has been made to include and discuss conflicting results this is not a systematic review of the pharmacology and there is potential for bias.

Currently available guidance

During the course of this systematic review guidance and a number of guidelines were identified on the issue of opioid use in renal impairment. The articles varied from formal guidelines from national or international bodies[43–45] to reviews and guidance from experts and interested professionals.[5,46–69]

Formal guidelines on the use of opioids differ in their inclusion of renal failure as a topic of specific importance. The World Health Organization (WHO) cancer pain guidelines of 1996 make no clear reference to the use of opioids in renal impairment.[70] The European Association for Palliative Care (EAPC) guidelines of 2001 make brief reference to the potential of morphine metabolites to accumulate in renal impairment, whereas there is a section devoted to this topic in the Scottish Intercollegiate Guidelines Network (SIGN) guidelines of 2008.[43,44] Consensus-based guidelines for the adult patient dying with advanced CKD and the Laboratory of Cancer Prevention (LCP) renal pathway are examples of guidance specifically designed for those dying with advanced renal disease and make specific recommendations for opioid use in end-stage renal impairment.[55,71] This guidance partly reflects an increasing awareness of the issue over time and an increased number of alternative drugs from which to choose. There have also been many pharmacological reviews on the topic with or without recommendations made for clinical practice.[53,72–78]

There is significant variation between these publications with regard to the assessment of renal impairment, the degree of caution needed with varying levels of renal impairment, drug recommendations and recommendations on dose and frequency of particular drugs. However, some of these differences are accounted for by changing attitudes over time. The target patient population for the guidance is also variable, with some aimed at dialysis patients, some for dying patients and some for cancer patients specifically, but the majority are general guidelines for opioid use in renal impairment. There are also varying degrees of clarity as to how the recommendations were derived from the available literature. This is particularly true for dose recommendations and why one opioid was chosen over another. This is emphasized by a systematic review of recommendations about drug dosage in renal impairment in which there was significant variation in recommendations and methods for stratifying renal impairment. In none of the reference sources was the evidence base for the dose recommendations described.[6]

Attempts to test recommendations

The WHO analgesic ladder has been adapted for use in patients with renal impairment by a number of groups.[50,61,79] Two studies have investigated the efficacy of such guidance in haemodialysis patients over two- and four-week periods.[50,79] Both indicated an improvement in pain ratings, one from baseline in a single cohort of patients and another in two separate cohorts, pre and post implementation of the guidance. No opioid toxicity was noted in either study and there were only three adverse events reported. However, it is difficult to extrapolate from these studies to non-dialysis patients and the studies differed in their recommendations for suitable opioids.

Pharmacokinetics of opioids

Minor structural differences between opioids appear to result in significant differences in many pharmacokinetic parameters and may influence their pharmacodynamic effects in renal failure.

In renal failure, alterations in the response to a given dose of opioid may result from impaired elimination and accumulation of the parent drug or metabolites, acid base changes, changes in protein levels, volume of distribution and changes in absorption.

Processes involved in opioid metabolism include glucuronidation, N-demethylation and 0-demethylation. These occur mainly via the action of uridine diphosphate-glucuronosyltransferase (UGT) enzymes CYP3A4 and CYP2D6, although many other enzymes from the same groups can be involved to a lesser extent. Non-specific tissue esterases are also involved in the metabolism of some opioids.

Morphine

Morphine is almost completely absorbed in the upper small bowel and is also well absorbed across the rectal mucosa.[80,81] Extensive presystemic elimination of the drug occurs during its passage across the small bowel wall and liver.[80] About 90% is converted to metabolites, principally M3G, M6G and minor metabolites, including normorphine and morphine ethereal sulphate.[73,82] In man the liver appears to be the predominant site for metabolism, although extra hepatic metabolism has been demonstrated.[83–85]

In recent years there has been speculation about the role of M6G in the pharmacodynamics of oral morphine, both in its therapeutic effects and in toxicity associated with renal impairment.[28,73,86,87]

Investigation of morphine kinetics prior to the mid 1980 s was confounded by cross-reacting antibodies used in 'standard' radio-immuno-assay (RIA) antisera. In one study, 15 patients with end-stage renal failure were given a single dose of morphine sulphate after renal transplantation and it appeared that morphine elimination was affected by renal function.[88] There were many conflicting results around this time.[89–91] Subsequently, RIAs were developed that could reliably differentiate between morphine and its main metabolites and new studies did not suggest a role for the kidney in morphine metabolism. There is, however, accumulation of the major metabolites of morphine in renal impairment and this has been confirmed in a wide variety of studies and patient groups.[27–29,86,90,92–107] These studies represent a wide range of creatinine values for which accumulation has been demonstrated, not just end-stage renal failure. Somogyi et al.[30] did not identify any relationship between metabolite levels and renal function in a group of patients with a CrCl measurement between 52 and 180 ml/min, but suggested possible confounding from concomitant medications. Despite M6G being slow to cross the blood brain barrier, a number of studies have confirmed cerebrospinal fluid (CSF) accumulation of M6G in renal impairment that persists longer than plasma and CSF morphine concentrations.[86,87,94]

Several of the metabolites of morphine have been demonstrated in animal models to have analgesic activity, in particular M6G and normorphine.[108,109] There has been some speculation that M3G has an anti-analgesic effect and blocks the analgesic action of morphine and M6G.[110,111] M3G had always been assumed to be inert on the basis of animal studies and opioid receptor binding studies.[112–115] Recent evidence suggests that it does not have a role in the pharmacodynamics of morphine.[116,117] There is some evidence of neuro-excitatory effects associated with subarachnoid or intrathecal administration of M3G in rodents,[111,118,119] but no evidence of significant toxicity attributable to M3G in man.[116,117]

M6G has confirmed affinity at opioid receptors.[112,113,115] It has been shown to have analgesic activity in healthy volunteers and peri-operative patients with randomized controlled trial evidence to support similar efficacy to morphine.[116,120–125]

Normorphine is produced in relatively small quantities in patients with normal renal function. There is evidence of analgesic activity when given parenterally in man but there are very few data.[108] Case reports of elevated levels in association with renal impairment and myoclonus have been reported.[15]

The evidence relating morphine metabolite concentrations to clinical effects in patients with renal impairment is conflicting. There are numerous small series and case reports showing elevated plasma metabolite levels in patients with side effects attributable to morphine. Sjogren et al.[126] and Osborne et al.[101] describe cases where significant levels of metabolites and low levels of morphine are associated with adverse reactions. Other studies in renal impairment have shown elevated levels of M3G, M6G and normorphine associated with myoclonus, sedation and respiratory depression.[15,18,93,94,127] There is also some indication of a time lag between onset of symptoms post dose and a delay in resolution of symptoms that parallels metabolite levels, despite clearance of the parent drug.[93]

Larger prospective studies vary in the detection of any relationship between morphine, metabolite levels and clinical effects.[27–31,128–131] It seems unlikely that the levels of renal impairment described in these studies should cause nausea and other symptoms directly, but one difficulty in interpreting these data is distinguishing between opioid-related side effects and symptoms directly due to renal failure.

In spite of much conflicting data it is possible to draw some broad conclusions to guide current practice. Morphine is associated with an increased risk of adverse effects in patients with renal impairment. Several of the metabolites of morphine are active and the most likely candidate to cause problems in patients with renal impairment is M6G. M6G in rodents has analgesic activity 20%–45% greater than morphine when injected directly into the central nervous system (CNS) and there is some evidence of analgesic activity in man. M6G accumulates in patients with renal impairment and anecdotal experience suggests that reducing the frequency of administration or the dose will ameliorate adverse effects in a substantial proportion of patients.

Codeine

Codeine (methylmorphine) produces its analgesic effects partly through biotransformation to morphine

by cytochrome E450CYP2D6. Codeine phosphate is absorbed well from the gastrointestinal tract and the main metabolites are codeine-6-glucuronide with greater amounts of norcodeine, morphine and M3G also produced.[132,133]

The 0-demthylation of codeine to morphine is catalysed by CYP2D6 and is influenced by relatively common genetic polymorphisms. Approximately 8% of the European population are poor metabolizers, producing minimal morphine, with resulting diminished analgesic efficacy[134] There appears, however, to be great interindividual variation in the amount and ratios of metabolite production that are not all accounted for by known polymorphisms. CNS adverse effects have been shown to occur even in the absence of significant CYP2D6 activity, suggesting a potential role for metabolites other than morphine in toxicity.[135–137] Morphine and its metabolites are discussed earlier and have been shown to be active.

Codeine is not generally given as a single agent when used orally as an analgesic; it is usually combined with a non-opioid, typically paracetamol.

Dihydrocodeine

The metabolism of dihydrocodeine is similar to that of morphine (glucuronidation, 0-demethylation and N-demethylation), producing nordihydrocodeine, dihydrocodeine-6-glucuronide, dihydromorphine, dihydromorphine-3-glucuronide and dihydromorphine-6-glucuronide.[73,138] Many of these metabolites are active at opioid receptors and excreted by renal mechanisms.[138] Dihydromorphine has a μ receptor affinity of close to 100 times greater than dihydrocodeine. The relative contribution to analgesia and potential side effects from each metabolite are not clear. Investigations have suggested that dihydrocodeine levels are sustained in renal dialysis patients for over 24 hours after a single dose, longer than in controls.[139–141] There are also case reports of respiratory depression and decreased consciousness associated with dihydrocodeine use and renal impairment.[142,143]

Diamorphine

After intravenous (IV) injection, 70% of a diamorphine dose is found in the urine in the form of metabolites, including morphine, M3G, M6G, normorphine glucuronide, codeine, morphine-3-6-diglucuronide and morphine-3-ethereal sulphate. Diamorphine is rapidly hydrolysed to 6-monacetylmorphine following injection and thereafter to morphine and other metabolites. The process is catalysed by abundant tissue esterases and appears to occur rapidly after injection.[144] As conversion to morphine occurs rapidly, this does not appear to be a rate-limiting step in the elimination of diamorphine. Data on the accumulation of metabolites and toxic effects in renal impairment are limited but can be presumed to be similar to that of morphine.

Dextropropoxyphene

Dextropropoxyphene is eliminated by transformation to norpropoxyphene, the major metabolite, by a CYP3A4 catalysed reaction. Norpropoxyphene is physiologically active, excreted by renal mechanisms and elevated levels are closely associated with toxic effects in the CNS and heart.[145–148] In one study seven healthy and seven dialysis patients were compared with regard to dextropropoxyphene plasma concentrations.[149] This study showed elevated levels of both dextropropoxyphene and norpropoxyphene in the dialysis patients that were statistically significant and showed a prolonged elimination half life for norpropoxyphene. This accumulation is further supported by another study in dialysis patients.[150] Dextropropoxyphene has been withdrawn from use by the European Medicines Evaluation Agency due to concerns over toxicity, particularly in overdose.

Pethidine (meperidine)

Pethidine is metabolized to pethidinic acid, norpethidine and norpethidinic acid. Norpethidine has been shown to have analgesic and convulsant effects.[151–154]

Pethidine elimination does not appear to be unduly affected by renal impairment, but norpethidine is renally excreted and accumulates in renal impairment.[154–157] Many case reports have been published of CNS toxicity in association with elevated norpethidine concentrations in patients with renal failure.[154,158–160] The adverse effects included myoclonic jerks, confusion, seizures and death. In one study a high proportion of patients noted to have CNS adverse effects with pethidine had renal impairment and the severity of CNS toxicity was significantly related to the plasma concentration of norpethidine.[36] Other reports of toxicity in renal failure, without direct evidence of elevated metabolites, include those of Hochman[152] and Stock et al.[161] Toxicity associated with elevated norpethidine has also occurred in the absence of renal impairment.[162] Cases of norpethidine-associated toxicity have been treated successfully with haemodialysis with a decrease in norpethidine levels accompanying a clinical improvement.[155] The CNS toxicity of pethidine/norpethidine is relatively resistant to reversal by naloxone.[36]

Tramadol

Tramadol inhibits noradrenaline and serotonin uptake in addition to its weak opioid receptor activity.

This highlights the potential for serotonin-type side effects in addition to opioid adverse effects, both with and without renal impairment. There is a case report of seizures, confusion and a possible serotonin syndrome in a subject who took an overdose of tramadol.[163]

Unchanged tramadol and its metabolites are predominantly excreted in the urine.[164] In renal impairment there are reports of decreased clearance and a two-fold increase in half life for both tramadol and the main metabolite O-desmethyl-tramadol.[165] However, a single patient undergoing dialysis was shown to have a terminal elimination half life for tramadol that was similar to that expected in normal subjects, but decreased volume of distribution led to decreased total body clearance and elevated plasma levels.[166] No side effects were noted in this patient. As 0-demethylation occurs via CYP2D6, genetic polymorphisms can lead to alterations in response to tramadol in a similar way to codeine.[167] O-desmethyltramadol is active and has a higher affinity at the μ-opioid receptor than the parent drug.[168] Despite an active metabolite that accumulates, in vivo, production seems to be slow with minimal clinically relevant accumulation.[164,169]

There are some case reports of toxicity with tramadol associated with renal impairment.[167,170] Conversely, the cautious use of tramadol in patients with renal impairment has been advocated by a number of authors who report successful use of tramadol in modified doses in these circumstances.[57,64,171]

Oxycodone

Oxycodone can be excreted in conjugated and unconjugated (8%–14%) form with the main metabolites noroxycodone and oxymorphone also found in urine.[172] The production of noroxycodone, the most abundant metabolite, is catalysed by CYP3A4, whilst oxymorphone results from the action of CYP2D6. Oxycodone itself exhibits a prolongation of its elimination half life when used in renal failure[173] and the metabolites may also have delayed elimination and increased blood levels.[173,174]

Oxymorphone is active as an opioid receptor agonist and as an analgesic in humans.[175–177] Noroxycodone has some analgesic properties in animal models but is thought to have minimal clinical effect in humans under normal conditions.[178] The role of active metabolites in mediating either the therapeutic or toxic effects of oxycodone is unclear.

There are case reports of toxicity in association with oxycodone use in renal impairment, and increased sedation and accumulation of oxycodone and its metabolites in renal failure has been reported.[174,179,180]

Hydromorphone

The metabolites of hydromorphone include hydromorphone-3-glucuronide (H3G), dihydromorphone, dihydroisomorphine, norhydroisomorphone, hydromorphone-3-sulfate and norhydromorphone.[181–183] H3G is the most abundant metabolite and in contrast to morphine there is negligible production of the 6- glucuronide, H6G.[181–183]

Dihydromorphone and dihydroisomorphone are active but produced in very small amounts and there is no evidence that they accumulate in renal failure.[184] H3G accumulates in renal impairment and is active in rats.[11,185,186]

Toxicity in association with hydromorphone use and renal impairment has been reported in a number of cases.[11,13] However, hydromorphone is used in many units that deal with renal impairment frequently and there are many reports of its successful use in such patients when titrated carefully.[40,57,187] A retrospective study in cancer patients with mild renal impairment (mean creatinine 127.5 μmol/l) has reported safe use in 29 people.[40] A further study of 140 patients with renal failure (mean creatinine measurement 424.3 μmol/l), the majority of whom were on morphine, suggested that a change to hydromorphone resulted in greater analgesia and reduced adverse effects.[187]

Buprenorphine

Studies using radio-labelled buprenorphine indicate that the majority of the dose, approximately 70%, is excreted in the faeces as unchanged buprenorphine. Metabolism occurs via N-dealkylation (catalysed by CYP3A4) to norbuprenorphine and, to a minor extent, glucuronidation to B3G.[188] Some urinary excretion of metabolites occurs, predominantly as norbuprenorphine and B3G.[189,190]

Norbuprenorphine is known to have a weak analgesic effect.[191,192] The metabolite can produce dose-related respiratory depression in rats but is less potent than the parent drug with limited ability to cross the blood brain barrier (although the blood brain barrier may be impaired in uraemia).[193] It has been suggested, however, that buprenorphine can be protective against the respiratory depressant effects of norbuprenorphine, again in rats.[194] B3G appears to be inactive.[191]

Hand et al.[191] showed that buprenorphine does not accumulate in renal failure in surgical patients compared with controls with normal kidney function. Summerfield et al.[195] showed that there was no statistically significant difference between postoperative patients in buprenorphine disposition compared to patients with and without altered renal function. The study period was only 3 hours, however, and

metabolites were not measured. No clinical adverse effects were noted. A study by Filitz et al.[196] of 10 patients showed levels of buprenorphine and norbuprenorphine in patients pre dialysis were not elevated after titration to pain with a transdermal patch. Three patients experienced either nausea or sweating. Any patient who could not tolerate buprenorphine had, however, been excluded from the study. In contrast, in the study by Hand et al.,[191] eight patients with renal impairment had dose-corrected levels for norbuprenorphine and buprenorphine-3-glucuronide that were increased compared to the group without renal failure. This statistically significant difference was four fold for norbuprenorphine and 15 fold for B3G. This did not correlate with any symptoms. The apparent differences may relate to higher doses and IV administration by Hand et al.[191] compared with transdermal buprenorphine at roughly half the dose.

A number of reviews have recommended buprenorphine as safe in renal impairment. However, there is relatively little experience with this drug in cancer pain, which limits its potential in this specific indication.[188,197]

Fentanyl

Elimination of fentanyl occurs by initial rapid redistribution followed by biotransformation to metabolites and subsequent renal excretion. Metabolites include norfentanyl (major metabolite via CYP3A4), despropionylfentanyl, hydroxyfentanyl and hydroxynorfentanyl.[198] Both fentanyl and norfentanyl can be found in human urine after IV administration and represent 0.3%–4% and 26%–55% of the dose, respectively.[199] None of the metabolites of fentanyl appear to have significant pharmacological activity.

There are case reports of the successful use of fentanyl in patients with renal failure and it is used as the opioid of first choice in renal failure by many centres.[21,37,57] Subcutaneous fentanyl has been used successfully by many centres in cancer patients intolerant to morphine. However, there are reports of substantial inter-patient variability in the pharmacokinetics of fentanyl when given subcutaneously in palliative care patients and normal volunteers.[200] When converting from sc morphine to sc fentanyl a widely used conversion ratio is 25 μg fentanyl to 2 mg of sc morphine.[71] Newer intranasal, buccal or sublingual preparations of fentanyl may offer more patient-friendly alternatives to subcutaneous fentanyl for pro re nata (PRN) use, although there is limited direct evidence for their efficacy in renal failure.

The duration of the action of fentanyl is an important consideration as PRN doses may need to be given in addition to continuous subcutaneous or transdermal administration. Although at lower doses there is rapid distribution, at higher doses and in chronic use, redistribution is limited by saturation of other tissues. Hence the duration of action may be prolonged at high doses.

Alfentanil

Alfentanil has a rapid onset of action and a relatively short half life. It is metabolized to a large number of metabolites, with noralfentanil and N-(4-hydroxyphenyl) propanamide being the most abundant in humans. Unchanged alfentanil in the urine over the first 24 hours accounts for less than 0.5% of the total dose.[201]

The metabolites of alfentanil are widely reported as inactive, but evidence for this is very limited, as is evidence for any accumulation of alfentanil metabolites in patients with impaired renal function. Published evidence for safe use in renal impairment is limited to retrospective reports of adequate analgesia and improved symptoms in patients with renal impairment switched from other opioids due to poor tolerability.[34,35] It is used as an opioid of second choice for renal patients in some centres.[57] There is some controversy as to whether tolerance to the analgesic effects of alfentanil occurs more rapidly than with other opioids, although this has not been demonstrated in a palliative care population.[34,35,202,203]

Because of its shorter duration of action, its use as an as required opioid is best limited to breakthrough pain or for procedures. Titration of dose or rescue doses requires an alternative opioid to avoid multiple doses and poorly controlled pain. Alfentanil can be useful as an alternative continuous infusion when high doses and therefore volumes of fentanyl create practical difficulties in giving it via a syringe driver. This is because higher concentrations of alfentanil are available.

Methadone

Methadone is primarily excreted in the faeces and although a proportion (20% of unchanged drug) is excreted in the urine it does not seem to be dependent on the kidney for its elimination or that of its metabolites. Renal excretion is known to be influenced by urinary pH, but the significance of this for excretion when renal function is impaired is unclear.[204,205] The main metabolites are 1,5,-dimethyl-2-ethyl3,3-diphenyl-1-pyrroline (EDDP), methadol and 2-ethyl-5-methyl-3,3-dipenylpyrrolidine (EMDP). EDDP is the primary metabolite, produced by N-dealklation catalysed by CYP3A4 and is inactive.[204,206,207] Other metabolites have also been shown to have minimal affinity for recombinant human μ opioid receptors.[208] Although

there is some evidence of activity of minor metabolites they are felt to be produced in such small quantities that they are unlikely to be clinically significant.[73]

Methadone tends to accumulate in tissues with chronic use, has a long half life and is highly protein bound. These factors make methadone use for analgesia potentially complex even in the absence of renal failure. It has been recommended that methadone should only be used under experienced specialist supervision because of the risks of accumulation and toxicity. There seems to be a disparity between the successful, confident use of methadone in some European countries and the concern and mistrust over its use in other countries. Advantages of methadone do include a relatively low cost and it being synthetically derived.

Remifentanil

Remifentanil has been used for analgesia during induction of anaesthesia for a number of years and has been approved for analgesia in ventilated intensive treatment unit (ITU) patients by the European Medicines Agency since 2002. Its short half life and mechanism of metabolism have led to speculation about its potential use in patients with renal failure. It has a terminal half life of 10–20 minutes. Remifentanil is metabolized to remifentanil acid (RA) by non-specific esterases in blood and tissues. This main metabolite is excreted by renal mechanisms.[209]

No increased incidence of respiratory depression has been shown in association with elevated RA levels.[210–212] RA has been shown to be 4600 times less potent than remifentanil in dogs.[213] Prior estimates using the motility of guinea pig ileum had suggested a potency of 1/300–1/1000.[214] If used for analgesia in cancer patients, the short half life could present problems for as-required use.

Sufentanil

Sufentanil is an analogue of fentanyl. There are limited published data on the metabolism of sufentanil, but in animal models (dogs) metabolism is by N-dealkylation and 0-demethylation. Approximately 1% of a dose is excreted unchanged in the urine. The exact role of the kidney in sufentanil elimination is unclear. Desmethyl sufentanil has 10% of the activity of sufentanil.[215]

Sufentanil has been used successfully for cancer-related breakthrough pain in an intranasal preparation and in palliative care as a CSCI.[38,216] The majority of the patients receiving sufentanil as a CSCI had some degree of renal impairment, although the level was not specified.[38]

Naloxone

Naloxone is a potent opioid antagonist with a relatively short half life. Multiple doses or prolonged infusion may be required to counter respiratory depression after overdose of many opioids and this may be more prolonged in cases of renal impairment. It is important to use or titrate naloxone to the degree of respiratory depression rather than conscious level alone. Care is needed to avoid precipitating withdrawal or a return of pain. Toxic effects of opioids and their metabolites are not always mediated by opioid receptors and hence naloxone will not necessarily resolve all side effects. Incomplete reversal may also occur with tramadol, buprenorphine and methadone at conventional doses. A case study has shown that the effects of naloxone may be prolonged in renal impairment, but due to the potentially prolonged effect of opioids in this situation repeat doses or infusions may still be required.[217]

Summary of evidence

Overall there are gaps in the pharmacokinetic data for many of the opioids and some inconsistencies. There are few randomized trials, no long-term studies and many confounding factors in the studies, such as the effects of renal impairment itself. There is no clear, prospective evidence for the safe use of any opioid in renal impairment so all should be used with a degree of caution. There are no studies giving a clear relative risk for one opioid compared to another. It also remains unclear from direct evidence at what level of renal impairment caution is needed. Given the lack of relevant clinical data, stratification of risk needs to be based largely on the activity of metabolites and the potential of the metabolite to accumulate. There is clear evidence for the activity of morphine metabolites and their accumulation in renal impairment. Whilst the direct clinical evidence for the association of adverse effects and renal impairment for morphine is rated as very low quality, the association is significantly strengthened by consistent pharmacological data and clinical experience. Assumptions are made for a similar potential for toxicity with diamorphine and codeine, because the same metabolic pathways are involved. Whilst there is still a relative paucity of published data on dextropropoxyphene and pethidine, there are sufficient data on the toxicity of the metabolites to give great cause for concern. Active metabolites of dihydrocodeine and their dependence on renal mechanisms for elimination put the drug in a similar category to codeine. There is evidence that oxycodone, tramadol and hydromorphone all have active metabolites, but there is inconsistency on the significance of any accumulation. There is clinical experience and some

published retrospective data suggesting that hydromorphone and tramadol may be safer than morphine in renal impairment.

Opioids for which there are thought to be no clinically significant metabolites include fentanyl, alfentanil and methadone. For fentanyl and alfentanil the assumption of no relevant activity is largely based on animal experiments or the absence of opioid receptor mediated effects. The absence of opioid activity does not mean there is no physiological activity. However, the absence of clinically significant metabolites is congruent with clinical experience and significant toxic effects are unlikely.

For buprenorphine, remifentanil and sufentanil there are either inconsistencies or insufficient evidence or experience to make a firm conclusion as to their safety, but further research may help clarify their role.

Stratifying risk

The opioids considered here have been divided into three broad groups on the basis of their potential risk in renal failure. These groups are indicated in Table 4 and are divided on the basis of those with no active metabolites (at least in clinically significant quantities), those with active metabolites and those for whom there is insufficient experience to make a recommendation. The group with active metabolites can be further divided according to potential risk. This is on the basis of the degree of toxicity of the metabolite and its potential for accumulation. There is no direct clinical or pharmacological evidence for this comparison and this is largely based on clinical experience. Toxicity in this review has been defined broadly, but it appears that the metabolites of pethidine and dextropropoxyphene have toxic effects that are not limited to typical opioid toxicity.

Other important considerations

The use of CrCl or eGFR rather than creatinine concentration is more likely to identify those with renal impairment and allow stratification of risk. Many guidelines and clinicians use an eGFR of 15 ml/min as the point at which most caution should be exercised with opioid use. This is partly pragmatic, but also identifies the point at which excretory function is most likely to affect drug elimination. There is minimal evidence to quantify the risk of toxicity from opioids at this or higher levels of GFR. There are potential difficulties in assessing or estimating GFR in patients with cachexia, oedema, low protein states and with acute renal failure. These are frequently associated with cancer, and more advanced disease. Given these problems are likely to occur frequently in a cancer population, a pragmatic decision to use 30 ml/min has been taken to allow for errors in eGFR, as well as the progressive nature of many cancers. Some clinicians will also use additional caution at a CrCl concentration of less than 59 ml/min.

Adjuvant analgesic medications, appropriately adjusted for renal impairment as needed, should still be used to maximize the control of cancer pain.

Opioids remain the key to relieving cancer pain and the presence of renal failure should not be allowed to delay the appropriate use of an opioid analgesic.

Table 4. Metabolite activity and risk stratification

Group 1 (No clinically significant active metabolites)
Fentanyl, alfentanil and methadone
Group 2 (Active or probably active metabolites-stratified according to degree of toxicity or risk of accumulation)
a) Tramadol and hydromorphone (possible reduced risk of toxicity)
b) Morphine, diamorphine, codeine, dihydrocodeine and oxycodone
c) Pethidine and dextropropoxyphene (high risk of toxicity recommend against use)
Group 3 (Insufficient evidence or experience to make a recommendation for chronic use)
Buprenorphine and sufentanil (active metabolites). Remifentanil (inactive metabolites)

Table 5. Mild to moderate renal impairment

Recommendations for the use of opioids in cancer related pain:
Estimated glomerular filtration rate (GFR)
30–89 ml/min (mild to moderate renal impairment)
The presence of renal failure should not be a reason to delay the use of an opioid for those with cancer pain when needed
• All opioids that are appropriate for cancer pain can be used with consideration of reduced dose or frequency at a lower eGFR
• Monitor for changes in renal function and consider a pre-emptive change of opioid in rapidly deteriorating renal function
• Assess for any reversible factors
• Be aware that estimations of GFR may be less accurate in the presence of cachexia, low protein states, oedema and with acute renal failure. An estimated GFR at the lower end of the moderate renal impairment range should therefore prompt consideration of a change of opioid to one considered safer in renal impairment.

Recommendations

These recommendations are based on clinical experience guided by relevant pharmacological studies and clinical data where available. The use of clinical data alone is not sufficient to formulate comprehensive

Table 6. Severe and end stage renal impairment

Recommendations for the use of opioids in cancer related pain: **Estimated glomerular filtration rate (GFR) <30 ml/min (end-stage renal failure and severe renal impairment)** The presence of renal failure should not be a reason to delay the use of an opioid for those with cancer pain when needed			
Drug		Dose and route	Notes
Fentanyl	1st Line	Opioid naïve patient 25 μg subcutaneously (SC) is equivalent to morphine 2 mg SC (at lower doses) • 12.5–25 μg SC PRN • 100–300 μg/24 hours as SC infusion	-If using more than 2 ml for PRN dose, injection may be painful. -If the volume of fentanyl required is too great for a syringe driver then convert to alfentanil
		If converting from another opioid Standard conversion tables can be used but a reduction of 20% is suggested	-Buccal/sublingual or intranasal fentanyl may be used but are not appropriate for titration of dose -Monitor closely for toxicity
Alfentanil	2nd Line	Used subcutaneously. ¼ as potent as fentanyl (i.e. 100 μg alfentanil is approximately equivalent to 25 μg fentanyl) Short duration of action can limit its effectiveness as PRN medication	Due to the shorter duration of analgesia with alfentanil, fentanyl is recommended unless the volume required is prohibitive
Tramadol	Use with care	50 mg, 12 hourly	
Hydromorphone	Use with care	In opioid naive 0.5–1.3 mg 6 hourly and PRN If tolerated increase to 4 hourly as needed. If higher doses required convert to an alfentanil syringe driver as appropriate and titrate to pain/side effects	The range of 0.5–1.3 mg is given to reflect variation in the availability of different doses across countries.

• Due to the delay in the onset and offset of action, the transdermal route should be avoided if stable pain control has not been achieved. Even with stable pain control careful consideration is needed due to potential for delayed toxicity.

• Methadone may be useful if used by those experienced in its use for pain management, but due to the risk of accumulation, even in the absence of renal impairment, it is not otherwise recommended.

• Buprenorphine, remifentanil and sufentanil need further assessment as to their suitability for use in cancer pain and renal impairment but may be of use following further investigation.

• If fentanyl or alfentanil is not available alternative opioids may be used at reduced doses and frequency and with careful monitoring. If it is not appropriate or practical to use injectable, buccal, sublingual or nasal preparations for PRNs then alternative opioids may need to be used (at reduced doses and frequencies). However this is likely to represent a risk of toxicity.

PRN: pro re nata

guidelines. The recommendations are detailed according to the degree of renal impairment in Tables 5 and 6. Although not the main focus of this review, information relevant to the use of opioids in dialysis patients is described in Table 7.

The key points are as follows.

- Recognition that all opioids have a risk of toxicity in renal failure, but some may cause fewer problems than others.
- Assessment of renal function should use eGFR or CrCl, not serum creatinine concentration.
- Renal impairment should not delay the use of opioids for cancer pain.
- Close monitoring of pain severity and for signs of toxicity is needed.
- Titration from low dose and decreasing frequency for some drugs.
- Choice of appropriate opioid, route and preparation (based on pharmacological and clinical evidence). Opioids thought to have no clinically significant active metabolites should be used as first line (see Table 4).
- Other opioids should only be used if those with no significant metabolites are not available or appropriate.
- Use of regular medication, not just as required.
- Inform the patient and/or family to be observant for signs of toxicity and what these are.

Scope of recommendations

The target audience for these recommendations is all physicians and health professionals in hospital, hospice and community settings, whether or not experienced in palliative medicine or cancer care. The aim is that they

Table 7. Opioid use in dialysis patients

Based on clinical experience and a non-formalized review of available evidence		
Drug	Dialysable?[a]	Safe and effective use in dialysis patients?[b,c]
Fentanyl	No[d]	Yes (with caution)
Alfentanil	No	Limited evidence
Methadone	No	Yes (with caution, only by clinicians experienced in its use for pain relief)
Tramadol	Yes	Yes (with caution, max 200 mg/24 hours)
Hydromorphone	Yes (metabolite but not parent drug)	Yes (with caution)
Morphine	Yes	Avoid if possible
Codeine	Yes	Avoid if possible
Oxycodone	Conflicting evidence	Limited evidence
Buprenorphine	No	Yes (with caution)
Remifentanil	Limited evidence	Limited evidence
Sufentanil	Limited evidence	Limited evidence

[a]Whether an opioid is dialysable is a more complex issue that the yes/no answer implies and needs to take into account whether metabolites are also removed (amongst other factors). The term is used here to indicate if potentially significant amounts of the drug or its metabolites can be removed by dialysis. The indication given here of whether an opioid can be dialysed is a generalization that may vary with patient and dialysis related factors.
[b]Caution should be used with all opioids in renal impairment and consideration given to reducing dose and frequency of administration
[c]The evidence base consists largely of case reports and clinical experience and has not been systematically reviewed in this publication. Clinical practice varies amongst nephrologists.
[d]Some dialysis membranes may partially remove fentanyl.
General notes.

- Additional analgesia may be needed around the time of dialysis. Dosing schedules do not automatically need adjustment but breakthrough doses may be needed around the time of dialysis
- Any dose changes need regular and close monitoring for efficacy and tolerability
- Pethidine and dextropropoxyphene are not recommended for use in chronic cancer pain irrespective of renal function

should be relevant in any country regardless of resources or opioid availability. There are potential cost implications of these recommendations and limitations in some areas due to lack of availability of opioids.

Unanswered questions: The future

There are many potential difficulties with research into opioid use in patients with renal failure. These include distinguishing symptoms due to renal failure, co-morbidities and opioid use from each other, attrition in an un-well population, and wide interindividual variability in pharmacological parameters.

Large-scale randomized controlled trials are possible but potentially complex. Not only are there practical design difficulties, but also ethical considerations, concerning which opioid should be tested at what level of renal impairment. Patients with GFR levels of between 15 and 59 ml may be the most feasible to take part in such research. Other options to gain more data are encouraging researchers not to exclude patients with renal impairment from trials of opioids in general. Given the difficulties of conducting research in many areas of palliative medicine, an attractive option is the use of shared, multi-centre databases to collect information on opioid use in renal impairment and associated clinical parameters. Qualitative data on patients' views, concerns or perceptions of toxicity and opioid use may also be useful.

Funding

SK was funded by the European Palliative Care Research Collaboration (EPCRC) within the EC 6th Framework Programme and by the Department of Palliative Medicine of the University of Bristol, UK

Conflicts of interest

None declared.

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