Review Article

Opioids in Renal Failure and Dialysis Patients

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Abstract
This article reviews the literature pertaining to the metabolism of several of the commonly used opioids, and the known activity of their metabolites. The effect of renal failure on the pharmacokinetics of these drugs and metabolites is then reviewed. Finally, the effect of renal dialysis on opioid drugs and metabolites is reviewed. Based on the review, it is recommended that morphine and codeine are avoided in renal failure/dialysis patients; hydromorphone or oxycodone are used with caution and close monitoring; and that methadone and fentanyl/sufentanil appear to be safe to use. Note is made that the "safe" drugs in renal failure are also the least dialyzable. J Pain Symptom Manage 2004;28:497–504.

Key Words
Opioids, metabolism, renal failure, renal dialysis, peritoneal dialysis

Introduction

The presence of renal failure affects the pharmacokinetics of many drugs, and the opioids are no exception. The effect of renal failure on individual opioids varies, and for many, one must consider the effect of renal failure on the drug's metabolites, as much as upon the parent compound. If the renal failure patient is receiving dialysis, other factors related to the mechanics of the dialysis procedure come into play. This article is a brief literature review of opioid metabolism, and the influence of renal failure and/or dialysis upon the clinical effects of both the parent drug and its metabolites. A database search was carried out using the terms *opioids, kidney failure, dialysis, oxycodone, codeine, morphine, hydromorphone, fentanyl, and methadone.* Not all of the opioids have been well studied.

In the absence of tubular secretion or reabsorption, the rate of elimination of any drug is, in theory, proportional to the glomerular filtration rate (GFR). However, the opioids are weak organic bases, and changes in the urine pH can alter tubular handling and affect the relationship between GFR and renal elimination. Formulas for calculating GFR can be used to predict drug pharmacokinetics, but the ability of such formulas to predict pharmacokinetic profiles has not been determined for the majority of drugs.[1] Nevertheless, the GFR approximates the renal excretion of many drugs, and some authors have made recommendations for adjustment of opioid dosage based on the GFR[2] (see Table 1), although the basis for the calculation of the dose reduction is not always clear. If more than one drug is competing for the same renal pathway, then elimination may be compromised.

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Opioid Metabolism and Renal Failure

Morphine

Morphine is by far the most-studied opioid. It is metabolized in the liver to morphine-3-glucuronide (M3G) (55%), morphine-6-glucuronide (M6G) (10%), and normorphine (4%), all of which are excreted renally, along with about 10% of the parent compound, in subjects with normal renal function.[3,4] Hasselström and Sawe found that renal clearance of morphine and M6G exceeded creatinine clearance, suggesting an active secretion process by the kidney.[3] M6G is analgesic, and depresses the central nervous system (CNS), but its effect on respiration is uncertain. In a recent review, Andersen et al. summarized the literature and confirmed the analgesic activity of M6G, but noted that its potency is not yet established. The reduced binding of M6G at the mu-2 receptor (main mediator of respiratory depression) may be one reason why the respiratory effect of this metabolite is variable.[5,6] M6G has been reported to mediate respiratory depression when it accumulates in renal failure.[7] Morphine clearance in renal failure is not significantly different from clearance in non-renally compromised subjects, but the glucuronide metabolites are excreted renally,[3] and in renal failure, these metabolites accumulate.[8–11]

M6G achieves high serum levels in patients with reduced renal function, and although it crosses the blood–brain barrier slowly, once in the CNS its effects can be prolonged.[12] There may be two forms of M6G—one that is extended and hydrophilic, and the second, occurring in water-poor tissue, that is folded and more lipophilic.[13] For this reason, after discontinuing morphine or dialyzing to remove the M6G, the CNS effects may persist for some time as the M6G slowly re-equilibrates across the blood-brain barrier back into the systemic circulation.[12]

Table 1
Dosage Reductions for Reduced Glomerular Filtration Rate, As Recommended by Bunn and Ashley

GFR (mL/min)	Morphine Dosage (% of normal)	Methadone Dosage (% of normal)
20–50	75	100
10–20	50	100
<10	25	50

GFR = Glomerular filtration rate.
Developed from Bunn and Ashley.[2]

The role of M3G is less clear, but has been summarized in reviews by Christrup[14] and Mercadante.[15] It has a low affinity for opioid receptors, and has no analgesic activity. Some authors have shown that M3G antagonizes the analgesic effects of both morphine and M6G when given intra-cerebroventricularly,[16,17] but others show no effect at the spinal level[18,19] or prolongation of the analgesic effect.[20] M3G has been shown to stimulate respiration,[21] but whether this is due to direct stimulation, or antagonism of the morphine and M6G effects is not clear. It can cause behavioral excitation in rats and mice,[22] as well as hyperesthesia and allodynia.[23] Opinions are divided as to whether an opioid antagonist such as naloxone reverses the excitatory behavior.[24,25]

Hydromorphone

Hydromorphone is metabolized in the liver to hydromorphone-3-glucuronide (36.8%), dihydromorphine (0.1%) and dihydroisomorphine (1.0%), as well as small amounts of hydromorphone-3-sulfate, norhydromorphone, and nordihydroisomorphone.[26] All metabolites are excreted renally, along with a small amount of free hydromorphone. Although further metabolism of the dihydro- forms to hydromorphone-6-glucuronide has been suggested,[27] Zheng et al. found no evidence of such a compound excreted in urine.[26] Durnin et al. studied hydromorphone pharmacokinetics in volunteers with normal renal function and with varying degrees of renal failure. They found that the area under the curve for the plasma concentration/time plot increased in a ratio of 1:2:4 for patients with normal renal function, moderate renal failure (creatinine clearance (Ccl) 40–60mL/min), and severe renal failure (Ccl <30mL/min), respectively. Although a single-dose study, they recommended lower starting doses for moderate renal failure, as well as an increased dosing interval for severe renal failure, and close monitoring for both groups.[28]

The 3-glucuronide is reported to have no analgesic activity, but is neuro-excitatory in rats,[29] and possibly in humans.[30–32] Babul and colleagues showed that hydromorphone-3-glucuronide does accumulate in renal failure, its ratio to hydromorphone increasing from 27:1 in patients with normal renal function to around 100:1 in a patient with impaired renal function.[31] They suggested that it is responsible for neuroexcitation, although the patient they

studied showed no signs of neuroexcitation. Fainsinger et al. reported agitation, confusion, and hallucinations, progressing to coma, in a patient with renal failure (probably due to captopril) who was taking hydromorphone.[32] However, in a retrospective study, Lee et al. found no significant differences in dose requirements between patients with normal renal function and those with end-stage renal failure when switched from morphine to hydromorphone, and adverse effects improved.[33] Although the subjects were described as end-stage renal failure, there was a wide range of values given for their blood urea nitrogen (BUN) and creatinine levels, and without the GFR and/or creatinine clearance values, the degree of renal failure cannot be reliably determined. Another review quoted the author's personal experience of no adverse effects with standard dosing in the renal failure population.[34]

Oxycodone

Pöyhiä et al. found that 8–14% of oxycodone is excreted as conjugated and free oxycodone, but gave no figures for the remaining metabolites they found: noroxycodone, conjugated oxycodone, conjugated oxymorphone, and oxymorphone.[35] Plasma levels of oxymorphone, the only active metabolite, were negligible. The elimination half-life of oxycodone is lengthened in uremic patients, and excretion of metabolites is severely impaired.[36] Although Kaiko et al.[37] and Heiskanen et al.[38] have shown that oxymorphone has no significant pharmacodynamic effect in subjects with normal renal function, it is not known how much effect its accumulation has in renal failure. Fitzgerald found little data, but reports personal experience of CNS toxicity and sedation with usual doses in renal failure patients.[34]

Codeine

Codeine is metabolized to codeine-6-glucuronide (81.0%), norcodeine (2.16%), morphine (0.56%), morphine-3-glucuronide (2.10%), morphine-6-glucuronide (0.80%), and normorphine (2.44%).[39] Both codeine and codeine-6-glucuronide are excreted renally.[39] In a single-dose study, Guay et al. found significantly reduced renal clearance of codeine, codeine glucuronide, morphine, and morphine glucuronide in patients with advanced renal failure, but comparison of other pharmacokinetic parameters did not reach significance, probably because of large between-patient variability in the renal failure group.[40] There is a report of respiratory arrest, attributed to the morphine-6-glucuronide metabolite, in a child with renal failure who was given codeine for post-operative pain,[41] and earlier Matzke et al. had reported profound narcolepsy in three renal failure patients given codeine.[42]

Methadone

Methadone is metabolized primarily to a pyrrolidine, and then to a pyrroline, both of which may be hydroxylated. Minor pathways may produce pyrrolidone, and the possibly active methadol metabolites.[43] Normally, 20–50% is excreted in urine as methadone or its metabolites, and 10–45% in feces as the pyrrolidine metabolite.[44] In one study, an oliguric subject excreted 15% of the daily dose in the feces, of which 3% was unchanged methadone, and an anuric patient excreted nearly all the dose in the feces, but still only 3% as unchanged methadone.[44] The author concludes that methadone is safe to use in patients with renal disease.

Fentanyl and Sufentanil

Fentanyl is metabolized in the liver primarily to norfentanyl (>99%), with smaller amounts of despropionylfentanyl and hydroxyfentanyl, and also some duodenal metabolism to norfentanyl.[45] There is no evidence that any of these metabolites are active. Mercadante et al. reported the use of a fentanyl infusion over two days in a patient with bowel obstruction and renal failure, with good pain control and no adverse effects.[46] Fyman et al. studied the use of a six-hour sufentanil infusion in ten patients undergoing renal transplantation. Although the conclusion of the study was that no dosage adjustments are necessary in renal failure, the authors point out that the fact that the patients all had a functioning kidney at the end of the six hours may mean that their results are not applicable to chronic renal failure patients.[47] A similar study found that fentanyl clearance is reduced in patients with moderate to severe uremia (BUN > 60mg/dL [21.5 mmol/L]), and could depress respiration post-operatively because of decreased clearance.[48] Although no significant difference in clearance and half-life of sufentanil was found between adolescents with chronic renal failure (CRF)

and normal adolescent controls, there was more variability in patients with CRF.[49] From the limited data available, it appears that fentanyl and sufentanil can be used in patients with renal failure, but such patients should be monitored for signs of gradual accumulation of the parent drug.

Dialysis

The role of dialysis in the clearance of a drug and/or its metabolites is very complex. The properties of the parent drug, and its metabolites, have to be considered, as well as technical factors related to the dialysis procedure. The "plasma clearance" of a drug is the sum of its renal and non-renal clearances. Thus, if a drug is mostly cleared by non-renal mechanisms (usually the liver), dialysis will have little effect upon that drug's clearance.

The likelihood of removal of any molecule in blood by dialysis depends upon the molecular weight of the molecule, its water solubility, and its volume of distribution. The molecule's degree of protein binding also affects its dialyzability, but the degree of protein binding can be altered in uremia.[50] These characteristics, where known, are listed in Table 2. The lower the molecular weight, the more likely the free molecule is to pass through a given dialysis filter, but the greater the protein binding, the less likely that the molecule will be removed in any great amount. Similarly, the greater the water solubility, the more likely the molecule will be removed, but the greater the volume of distribution, the less is removed per unit time.

Turning to the dialysis procedure itself, removal of any molecule is influenced by the flow rates of the dialysis solution and the patient's blood; the surface area, pore size, and "geometry" of the filter; and the technique used. As well as standard hemodialysis, there are several "high-efficiency" (also known as "high-flux" and/or "high permeability") techniques now available, and also a group of procedures collectively referred to as continuous renal replacement therapy (CRRT). The "high-efficiency" techniques use more permeable dialysis membranes, and higher blood and dialysate flow-rates, all of which affect the removal of a drug molecule. Generally, removal of a drug by high-efficiency dialysis is greater than by standard hemodialysis. This can be so efficient that removal of the drug from plasma exceeds the transfer of drug from other tissues, so that following dialysis there is a "rebound" effect as plasma levels of the active drug rise again.

In peritoneal dialysis, the filter is the peritoneum, so the pore size is fixed, and the "flow rate" is determined by the volume and frequency of "exchanges" (the more frequent the exchanges, the more drug is removed).

With the above information, some estimate can be made as to how the individual opioids will behave.

Morphine

Morphine has low protein-binding that is somewhat reduced in uremic patients, and significantly reduced in anephric patients.[50] It has moderate water-solubility and so is likely to be removed by most dialysis procedures. Reports have confirmed this,[51,52] but other studies have shown that the much slower (40 times less) flow rates of hemofiltration and hemodiafiltration remove a much smaller amount of morphine.[53] Morphine-6-glucuronide is also removed by hemodialysis, but diffuses out of the CNS very slowly, delaying the response to dialysis.[12]

Table 2
Physico-Chemical Properties of Some Opioids

Drug	Volume of Distribution (L/kg)	Plasma Protein Binding (%)	Water Solubility	Molecular Weight
Morphine sulfate	3.2	35	1:21	758.8
Hydromorphone hydrochloride	1.22	N/A[a]	1:3	321.8
Oxycodone hydrochloride	2.6	45	1:6	405.9
Codeine phosphate	2.6	7	1:4	406.4
Methadone hydrochloride	3.8	89	1:12	345.9
Fentanyl citrate	4	80	1:40	528.6

Sources: Martindale Pharmacopeia; Goodman & Gilman's Therapeutics; Micromedex (Drug information computer program); Remington's Pharmaceutical Sciences.
[a]There are no data in the above sources on hydromorphone protein binding, but Sarhill et al. state in their article that serum protein binding is 7.1%.[39]

An early study in patients with acute renal failure found that morphine and the glucuronides were cleared by peritoneal dialysis,[7] but a more recent one in patients with chronic renal failure undergoing continuous ambulatory peritoneal dialysis determined that only about 12% of the parent compound and its glucuronide metabolites are removed per exchange. Extrapolation of these results suggests that with chronic dosing, morphine would not accumulate but the glucuronides would.[11]

Hydromorphone

Hydromorphone has a low volume of distribution, high water solubility, and low molecular weight. Data on protein binding could not be found in the usual sources, but Sarhill et al. make an unreferenced statement that serum protein binding for hydromorphone is 7.1%.[54] From these figures, one would expect hydromorphone to be dialyzable, and Durnin et al. reports that hemodialysis reduces plasma levels to 40% of pre-dialysis levels.[28] Fitzgerald reports personal experience,[34] supported to a limited extent by Lee et al.'s retrospective study that included two hemodialysis patients,[33] of safe and effective use of hydromorphone in dialysis patients.

Oxycodone

Oxycodone has a greater volume of distribution than hydromorphone, is nearly 50% protein-bound, and is quite water-soluble. No data on dialysis of oxycodone were found, but its physicochemical properties suggest that it is likely to be dialyzable to some extent.

Codeine

Guay et al. found significant differences in codeine pharmacokinetics when comparing a group of healthy subjects with a group on hemodialysis.[40] This was a single-dose study, but he extrapolated the results to suggest that chronic dosing would cause accumulation to toxic levels in two-thirds of the hemodialysis patients. Plans to continue the study to assess repeat dosing were abandoned when two of the six hemodialysis subjects had severe adverse reactions to a single dose of codeine. Guay et al. conclude that dosage adjustment may be needed in some uremic patients taking codeine.[40]

Methadone

Methadone has high protein binding and a high volume of distribution, moderate water solubility, and low molecular weight. The first two properties would suggest that it is poorly removed by dialysis, and one single-patient report has indicated this to be the case, although the author cautions about the possibility of patient variability. The inactive, more water-soluble metabolite is more readily removed, but with no clinical consequences.[55]

Fentanyl and Sufentanil

Fentanyl has high protein binding and low water solubility, as well as a high volume of distribution, and a moderately high molecular weight. Thus one would not expect it to be dialyzable, which is supported by the reports,[52,56] although one of the reports suggested that a particular type of dialysis filter (CT 190) might remove fentanyl by adsorbing it onto its surface, as fentanyl appeared to be removed from the blood, but did not appear in the dialysate solution.[56] There are no data on sufentanil and dialysis, but because of similar pharmacokinetic properties to fentanyl, one would expect sufentanil not to be dialyzable.

Recommendations

Although some authors have recommended dosage reduction of opioids based on the calculated GFR value,[2] the basis for such recommendations is not entirely clear. An alternative approach, based on the preceding review, is given below. Ideally, the degree of renal failure should be determined in terms of the GFR (and/or creatinine clearance), but many of the studies use serum BUN or creatinine levels. In addition, the studies have been of very mixed design, and mostly on opioid-naive patients or volunteers. The problem of the development of renal failure while taking opioids has not been addressed. Based on the data, one would surmise that as renal failure develops, the excretion of the metabolites and/or parent drug would decrease, and gradual accumulation would occur, with associated clinical effects. The signs and symptoms of opioid overdose in the renally compromised patient, compared with those in the person with normal renal function, have not been reported in the literature.

These recommendations are based on the limited literature extant. Clearly, the use of opioids other than morphine in renal failure and dialysis patients is an area that needs much more study.

Renal Failure

Morphine. Do not use, due to the difficulty of managing the complicated adverse effects of the metabolites.

Hydromorphone. Use carefully. Although the 3-glucuronide metabolite is neuro-excitatory and can accumulate in renal failure,[32] hydromorphone has been used in renal failure patients with no adverse effects.[33]

Oxycodone. There are insufficient data to make a recommendation. If used, administer with great caution and careful monitoring. The active metabolite, free oxymorphone, is produced in very small amounts,[35] but does accumulate, along with the parent drug, in renal failure.[36] There is an anecdotal report of its toxic and CNS-depressant effects in patients with renal failure.[34]

Codeine. Do not use. The active metabolites accumulate in renal failure,[40] and there are reports of serious adverse effects in renal failure patients.[41,42]

Methadone. Appears safe. The metabolites are apparently inactive,[43] and in renal failure, the parent compound and the metabolites are excreted into the gut.[44] These results are from studies on a very small number of patients, and it is possible that there may be patient variability. Some authors recommend dose reduction in severe renal failure (GFR <10 mL/min), but it is not clear why.[2] The usual precautions taken when prescribing methadone should still be observed.

Fentanyl. Probably safe, at least in the short term. Although there are reports of the parent compound accumulating in renal failure,[49] clinical experience is that there are no adverse effects.[46] However, if being used long-term in renal failure patients, careful monitoring of pharmacodynamic effects is advised.

Dialysis

Morphine. Both the parent compound and the metabolites can be removed by dialysis,[12,52] but be alert for "rebound" as drugs and/or metabolites re-equilibrate between CNS and plasma.[12] Metabolites would accumulate in between dialysis sessions, and extra dosing may be needed during or after dialysis. There are better alternatives, so morphine is best avoided in dialysis patients.

Hydromorphone. Use carefully, and monitor the patient. Hydromorphone has been used without adverse effects in dialysis patients.[33] The parent drug is partly removed by dialysis,[28] but there are no data concerning dialysis of the metabolites, and metabolite accumulation is a risk.

Oxycodone. There are no data on the dialysis of oxycodone and its metabolites. Until such data are obtained, the use of oxycodone in dialysis patients is best avoided.

Codeine. Do not use. The metabolites accumulate in renal failure, and serious adverse effects from codeine have been reported in dialysis patients.[40]

Methadone. The metabolites are inactive, and it is not dialyzed.[55] No dose adjustments are required in dialysis patients. The usual precautions taken when prescribing methadone should still be observed.

Fentanyl. Appears safe, at least over short periods. The metabolites are inactive, and although there is some concern that the parent compound may accumulate in renal failure, the clinical significance of this is not known. It is not dialyzed,[52,56] so in most cases, no dose adjustments have to be made for dialysis patients. However, fentanyl may adsorb onto one type of filter,[56] in which case changing the filter is recommended, but if that is not possible, changing to methadone is recommended.

One final note of caution—the "safe" opioids (fentanyl and methadone) are not dialyzable, so, as with all of the opioids, caution is needed in titrating these drugs in renal failure/dialysis patients, and close monitoring is advised for a protracted period of time.

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