



Prise en charge de la douleur aiguë de type nociceptive chez l'insuffisant rénal chronique

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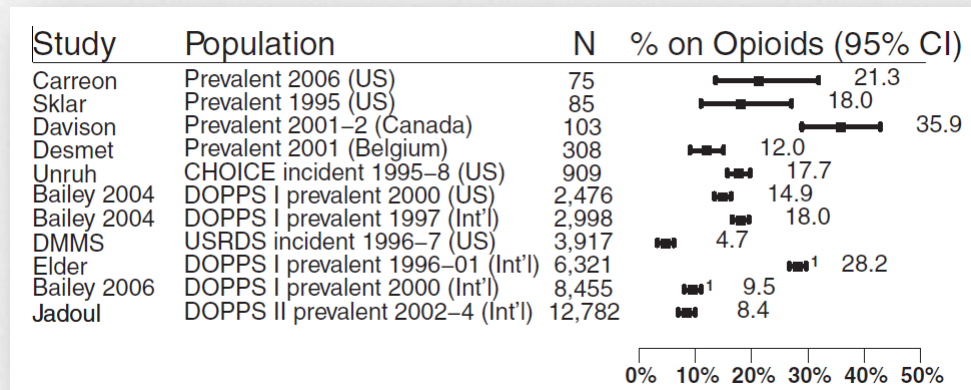
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Epidémiologie

- ✓ USA : 50% insuffisant rénaux chroniques (IRC)hémodialysé (HD) douloureux
- ✓ USA : 83% cas douleur modérée à sévère

Butler et al. Am J Kidney Dis. 2014 january;63(1):171-173
Etude rétrospective, 146000 patients 2006-2008

- ✓ Recours aux opiacés : 5% [IC 95%, 4,1-5,1] à 36% [IC 95%, 27,3-45,5]



- ✓ Contrôle de la douleur : 17% [IC95%,13,6-21,3] à 38% [IC95%,29,1-47,5%]

Wyne et al. Clin J Am Soc Nephrol 6:326-333,2011
Meta-analyse USA, canada, Belgique : 26000 patients

Comment soulager une douleur chez l'IRC ?

- ✓ Evaluer la douleur
- ✓ Définir le type ? Nociceptive, neuropathie, aigue ou chronique
- ✓ Stade de l'insuffisance rénale
- ✓ Douleur nociceptive : paliers OMS modifiés pour l'insuffisant rénal

Acetaminophen Non-steroidal anti-inflammatory drugs (NSAIDs), Cyclo-oxygenase-2 (Cox-2) inhibitors [only for short-term]* Carbamazepine Gabapentin Pregablin Tricyclic antidepressants	Non-opioid ± Adjuvant	Mild pain Score 1-3	Step 1
± Tramadol (0.2) Oxycodone with acetaminophen	Non-opioid ± Adjuvant ± Weak opioid	Moderate pain Score 4-6	Step 2
± Oxycodone (2) Hydromorphone (3.5-7.5) Fentanyl/alfentanil (50-100) Methadone (10) Buprenorphine (30-60)	Non-opioid ± Adjuvant ± Strong opioid	Severe pain Score 7-10	Step 3

Launay-Vaucher et al. *J Pain* 2005;6(3):137-48
Barakzoy AS et al. *J Am Soc Nephrol* 17: 3198-3203, 2006

N'apparaissent pas :

- Nefopam
- Nalbuphine
- Morphine

Comment soulager une douleur chez l'IRC ?

✓ Facteurs de risque de complications des antalgiques

- ❖ Age > 70 ans
- ❖ Comorbidités multiples

Bourquin V et al. Rev Med Suisse 2008; 4:2218-23

✓ Facteurs de risque de complications des opiacés :

Factors contributing to opioid toxicity in chronic kidney disease		
Patient factors		Exogenous factors
<u>Independent of kidney function</u> • Age – extremes of age, increases sensitivity • Gender – women more sensitive • Genetic – absence of A118G SNP* • Route of administration§ • Enterohepatic circulation • Hypoalbuminemia • Concomitant illness(es) – Sepsis, liver disease		<u>Drug-drug interactions</u> • Cytochrome P450 2D6 system® • P-glycoprotein inhibitors¶ • Concomitant antibiotic use°
<u>Dependent on kidney function</u> • Decreased clearance – accumulation of parent drug and active metabolites • Decreased threshold • Change in volume of distribution (V_d) • Change in protein binding • Impaired ventilatory response to carbon dioxide in CKD		

* A118G polymorphism protects against M6G-related opioid toxicity²⁸.

§ Routes that use first pass metabolism results in higher production of metabolites than those that bypass it.

¶ P-glycoprotein inhibitors increase uptake of M6G across blood brain barrier^{16,17}.

° Concomitant antibiotics by altering bacterial flora reduces bacterial glucuronidase, resulting in reabsorption of M6G.

® Extensive 2D6 metabolism may occur in up to 1/3rd of patients of east African heritage – increasing the risk of opioid overdose from codeine.

Parmar MS et al. F1000Research 2013, 2:28

Particularités des antalgiques paliers I

Paracétamol

- ✓ Métabolisme hépatique
- ✓ Elimination métabolites et sous forme inchangé (<5%) : urinaire
- ✓ Lésion glomérulaire et tubulaire possibles chez l'IRC

*Trinn C, Acta Physiol Hung, 1996
JonesJ, Clin Pharm Ther, 1993*

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Adaptation posologie chez IRC modéré et sévère : 1g/8h

Particularités des antalgiques paliers I

Anti inflammatoire : AINS et anti Cox2

- ✓ CI dans l'insuffisance rénale sévère
- ✓ Dans l'insuffisance rénale modérée :
 - ❖ Possible
 - ❖ Courte durée : 5 - 7 jours
 - ❖ Faible doses
 - ❖ Surveillance fonction rénale

*Parmar MS et al. F1000Research 2013, 2:28
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Fuzier R et al SFAR 2007: 677-683*

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✓ Pharmacocinétique ***non influencée*** par l'insuffisance rénale (IR) :

- ❖ Ibuprofene
- ❖ Indomethacine
- ❖ Diclofénac
- ❖ piroxicam

*Helleberg L et al. Clin Pharmacokinet 1981;6:245-58
Stein G et al. Int J Clin Pharmacol Biopharm 1977; 15: 470-3
Brogden RN et al. Drugs 1984;28:292-323
Olkkola KT et al. Pharmacokinet 1994;26:107-20
Todd PA et al. Drugs 1988; 35:244-85*

Particularités des antalgiques paliers I

Nefopan

- ✓ Recommandé en postopératoire chez l'insuffisant rénale par la SFAR 2007

Fuzier R et al SFAR 2007: 677-683

- ✓ Liaison protéine 76%
- ✓ Elimination urinaire de 3 métabolites
- ✓ Un cas de surdosage fatal décrit

Bourquin V et al. Rev Med Suisse 2008; 4:2218-23

***Prudence et réduction posologique chez l'IRC, HD
Administration : après la séance de dialyse***

Particularités des antalgiques paliers II-III

molécule	Puissance / morphine	T _{1/2} Non IR	T _{1/2} IRC	Métabolites actifs	dialysable	Voie d'élimination	Impact clinique
Codéine		3-4h	18 à 69h	Oui nombreux	NC	80% rénale	- Non recommandée chez l'IR sévère et dialysé - Polymorphisme CYP2D6
Tramadol	0,2	6-8h	12h	1 actif M1	oui	> 90%	- Diminuer posologie - Augmenter l'intervalle - Polymorphisme CYP2D6
Morphine	1 M6G : 10	2-3h bolus IV	M6G : - 17h : non HD - 27h : HD	Oui M6G	Oui	rénal	- A éviter chez IR sévère et HD, plutôt bolus unique ou répété /24-48h selon EVA - Diminuer posologie - Augmenter l'intervalle - Si HD : clairance cérébrale retardée et réapparition de la douleur possible en post HD Surveillance prolongée apnée retardée > 48h

Nicola P et al. *Current drug targets*, 2010,11 752-758
 Parmar MS et al. *F1000Research* 2013, 2:28
 Fuzier R et al *SFAR* 2007: 677-683
 Stamer UM et al. *Pain* 105 (2003) : 231-238

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Oxycodone (oxynorme®)	2	LP :12h Non LP:3-6h	4,5h	Oui nombreux	oui	rénale	- Diminuer posologie - Augmenter l'intervalle
Hydromorphone (sophidone®)	Oral : 5-6 IV : 8,5	2,5h	<u>Non modifiée</u>	<u>non</u>	Drogue mere oui Métabolites non	rénale	- Diminuer les posologies - neurotoxicité des métabolites (agitation, confusion, hallucination)
Fentanyl patch (Durogesic®)	50-100	24h après ablation patch	<u>Non modifiée</u>	<u>non</u>	peu	rénale	- Diminuer posologie
Buprenorphine Oral, patch	30-60	30h	<u>Non modifiée</u>	<u>non</u>	non	Selles +++	- Drogue sûre - Pas d'adaptation posologique
Methadone	10	8-75h	<u>Non modifiée</u>	<u>non</u>	Non	Drogue mère : selles	- Augmenter l'intervalle car longue demi vie - Douleur chronique

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CAT devant douleur chez l'insuffisant rénal chronique adulte

Clairance créatinine sérique + EVA

< 30ml/min ou dialysé

30 à 60ml/min

> 60 ml/min

Echelle « sûre »

- ✓ Palier I : Paracétamol
- ✓ Palier II : Tramadol
- ✓ Palier III : Fentanyl (douleur chronique)

> 70 ans
Comorbidités multiples

Echelle OMS modifiée
Adapter posologies opiacés

Analgésie
selon paliers OMS
sans adaptation
posologique

Si Echech

- ✓ Hydromorphone
- ✓ Oxycodone
- ✓ Morphine
- ✓ Si hospitalisé :
Anesthésie locorégionale

Surveillance clinique rapprochée
sur plusieurs jours.

Bourquin et al. Rev Med Suisse
2008; 4:22:8-23

Tableau 2. Adaptation posologique des différents analgésiques couramment utilisés en fonction de l'insuffisance rénale
(Modifié selon Aronoff et coll.⁴).

Antalgiques	Dosage habituel (per os)	< 30 ml/min	30-60 ml/min	> 60 ml/min
Codéine	15-120 mg toutes les 4-6 heures	50%	75%	100%
Tramadol	50-100 mg toutes les 4-6 heures max 400 mg/j	50-100 mg toutes les 12 heures max 200 mg/j		100%
Morphine	5-120 mg toutes les 4-6 heures max 1,5 mg/kg/j	50% en dose unique	75%	100%
Oxycodone	2,5-5 mg toutes les 6 heures	50% en dose unique	75%	100%
Méthadone	2,5-10 mg toutes les 6-8 heures	Toutes les 12-24 heures	Toutes les 8-12 heures	100%
Fentanyl	25-50 µg selon patch	100%	100%	100%
Buprénorphine	0,3 mg toutes les 6-8 heures	100%	100%	100%

Les devises Shadok



SI GA FAIT MAL C'EST QUE
GA FAIT DU BIEN !!

Merci de votre
attention

Table 3. Pain management in CKD.

Pain intensity	WHO analgesic step	Agent(s) of choice	Comments
Mild pain Score 1–3	Non-opioid ± Adjuvant	Acetaminophen 500 mg q6h (by the clock) and 325 mg every 6–8h as required	Not to exceed total dose of 3 g in 24-hours; If unable to take orally, then consider suppository NSAIDs/Cox-2 inhibitors are <i>not recommended</i> , but may consider, for short-term ONLY, under close observation
Moderate pain Score 4–6	Non-opioid ± Adjuvant ± Weak opioid	± Tramadol 50 mg every 12h, if required or Oxycodone 2.5 mg every 8–12h	Maximum dose 200 mg in stage 4 CKD and 100 mg in stage 5 CKD, dose after dialysis
Severe pain Score 7–10	Non-opioid ± Adjuvant ± Strong opioid	± Hydromorphone 1.3 mg every 8h or Oxycodone 2.5 mg every 8–12h or Fentanyl 25–50 mcg SQ every 4–6h or Buprenorphine 0.3 mg every 6h IM/IV 8–16 mg sublingual daily Transdermal Patch – 5 mcg/hr–20 mcg/hr or Morphine 1.25–2.5 mg every 8–12h (for short-term use)	Use laxatives to avoid constipation, when using opioids Do not write standing (or long-term) orders for opioids Reassess the need and dose of opioids every 24–48 hours Monitoring for CNS and respiratory effects is required for protracted periods Fentanyl and methadone are highly protein bound and not dialyzable Avoid fentanyl transdermal patch in opioid-naïve patients

Management of acute and post-operative pain in chronic kidney disease [v3; ref status: indexed, <http://f1000r.es/10f>]

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Table 6. Severe and end stage renal impairment

Recommendations for the use of opioids in cancer related pain:

Estimated glomerular filtration rate (GFR) <30ml/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	<u>Opioid naïve patient</u> 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 <u>If converting from another opioid</u>	-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 -Buccal/sublingual or intranasal fentanyl may be used but are not appropriate for titration of dose -Monitor closely for toxicity
Alfentanil	2nd Line	Standard conversion tables can be used but a reduction of 20% is suggested 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 naïve 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, remifentanyl 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.

Palliative Medicine

<http://pmj.sagepub.com/>

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

S King, K Forbes, GW Hanks, CJ Ferro and EJ Chambers

Palliat Med 2011 25: 525

DOI: 10.1177/0269216311406313

The online version of this article can be found at:

<http://pmj.sagepub.com/content/25/5/525>

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)
Remifentanyl	Limited evidence	Limited evidence
Sufentanyl	Limited evidence	Limited evidence

^aWhether an opioid is dialysable is a more complex issue than 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.

^bCaution should be used with all opioids in renal impairment and consideration given to reducing dose and frequency of administration

^cThe evidence base consists largely of case reports and clinical experience and has not been systematically reviewed in this publication. Clinical practice varies amongst nephrologists.

^dSome 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

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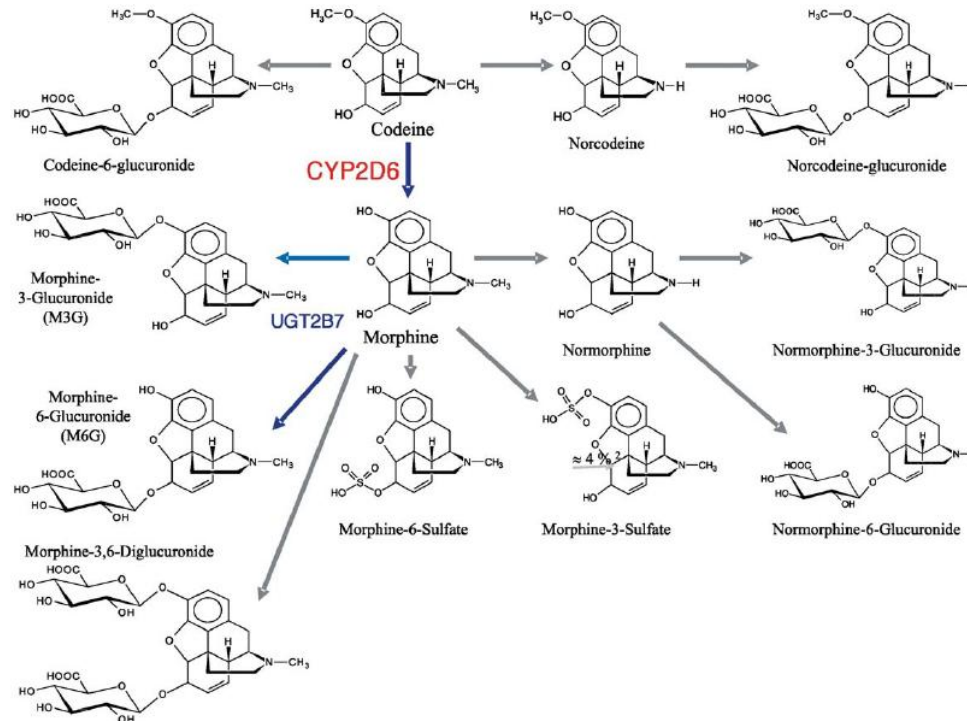


Fig. 3. Metabolism of codeine and morphine metabolism.

Proceedings of the Symposium "Updates of the Clinical Pharmacology of Opioids with Special Attention to Long-Acting Drugs"

Opioid Metabolites

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Tableau 1. Classification K/DOQI selon le GFR de l'insuffisance rénale chronique

K/DOQI: Kidney disease outcome quality initiative; GFR: glomerular filtration rate (taux de filtration glomérulaire).

Stades	Descriptions	GFR (ml/min/1,73 m ²)
1	Maladie rénale avec GFR normal	≥ 90
2	Maladie rénale avec faible baisse du GFR	60-89
3	Baisse modérée du GFR	30-59
4	Baisse sévère du GFR	15-29
5	Insuffisance rénale terminale	< 15 ou dialyse

Rev Med Suisse 2008; 4: 2218-23

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Tableau 3. Effets pharmacologiques des opioïdes selon les récepteurs

(Modifié selon Ford et coll.³⁶).

	Récepteurs	Effets pharmacologiques
Mu (μ)	μ_1	Analgesie supraspinale (produit la plus grande partie de l'effet analgesique), analgesie peripherique
	μ_2	Analgesie spinale, myosis, depression respiratoire, euphorie, dependance physique, diminution de la motilite gastrique (constipation)
Kappa (κ)	κ_1	Analgesie spinale, myosis (moins que μ_2)
	κ_2	Dysphorie, <i>psychotomimesis</i> (desorientation et/ou impression de depersonnalisation)
	κ_3	Analgesie supraspinale
Delta (δ)	δ	Analgesie spinale

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