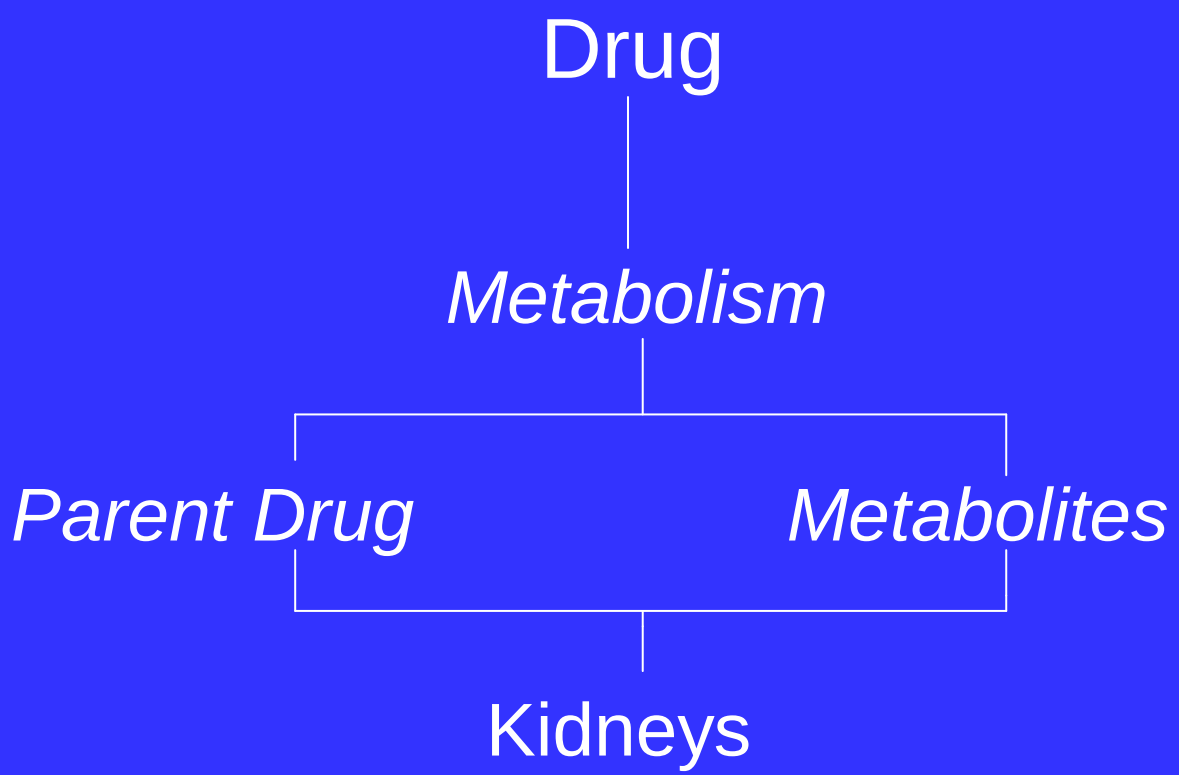
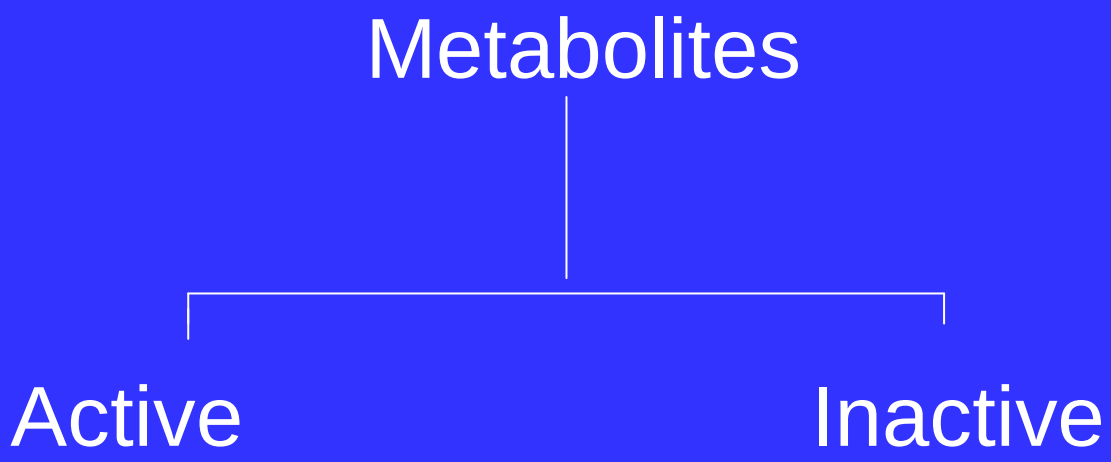
Renal Palliative Care Medication Guidelines

- General principles
- Challenges
- Commonly used medications in Palliative Care in the context of CKD
- Analgesics

Pharmacology in the context of CKD is complex

For many medications, the parent medication and/or their metabolites are renally excreted.


Drug
Metabolism
Parent Drug
Metabolites
Kidneys


Metabolites
Active
Inactive

The clinical imperative to modify the drug dosing regimen in patients with renal impairment or a kidney transplant is dependent on a variety of factors.

Cervelli M. (ed). The Renal Drug Reference Guide. 2007

1. The Fraction of the Active Drug and/or Active Metabolites that is excreted directly by the Kidneys

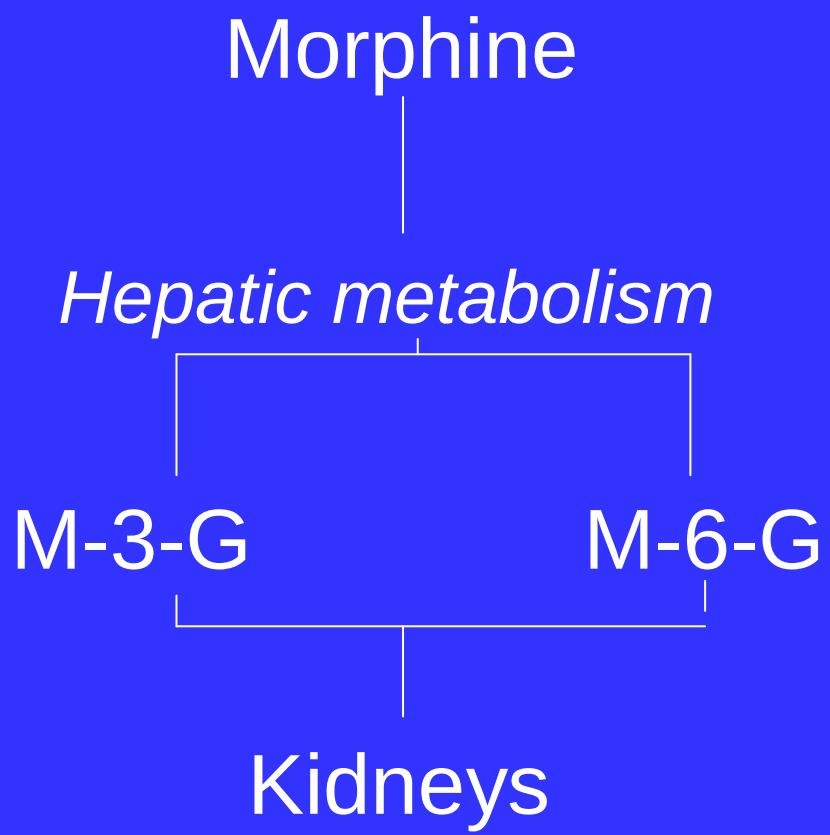
The greater the fraction of an active drug that is directly excreted by the kidneys, the greater the need for dose modification.

Generally speaking, it is usually only necessary to modify the dosing of a drug if more than 25-50 % of the active component is excreted unchanged in the kidney.

Cervelli M. (ed). The Renal Drug Reference Guide. 2007

Active metabolites should be assessed for their dependence on renal excretion in the same way as the parent drug

Active metabolite toxicity is often the reason for recommendations to avoid or modify the drug dosing regimen in patients with renal impairment


Morphine
Hepatic metabolism
M-3-G
M-6-G
Kidneys

2. Degree of Renal Impairment

Generally, dose modifications are only clinically required when the Renal function falls below a GFR of 30-60ml/min

- The estimation of renal function is not precise.

- There are several methods of calculating renal function for the purposes of evaluating renal disease and estimating drug clearance for drug regimen design.

Cockcroft-Gault Method

Creatinine Clearance

MDRD Formulae

eGFR

Nankivell Method

GFR in patients with Kidney transplantation

The drug dosing in renal impairment published in the literature is based on the Cockcroft-Gault calculation. This should be used unless references state that drug dosing has been expressed for normalising eGFR.

Brown E et al. *End of Life Care in Nephrology -from Advanced Disease to Bereavement* 2007Oxford Specialist Handbooks, p. 280.

3. Effect of Renal Impairment on physiological mechanisms

Uraemia may effect :

1. Bioavailability of the drug
2. Absorption of the drug
3. Metabolism of the drug

ESRD is associated with reduced serum Albumin

Volume of distribution

Following absorption ,

all drugs are distributed to different sites in the body depending on their Volume of Distribution

$$Vd = \frac{\text{Administed Drug}}{\text{Plasma concentration}}$$

4. The effect of the drug/ metabolites on the Kidneys themselves

NSAIDs

Aminoglycosides

5. Drug Interactions

Especially important in the context of the interaction of Immunosuppressive agents and medications that inhibit or induce hepatic enzyme systems

6. Effect of dialysis on drug clearance

Multiple gaps in knowledge

- Limited data available for patients on HD
- Less information on CAPD

- Technical aspects of dialysis changes with evolving technology

- Selection of medications, dosage and regimes that are safe, can be difficult.

In practical terms, if a drug is significantly cleared by dialysis,

doses are given following dialysis.

Challeges

This is a complex area

There are multiple factors to consider

Recommendations in published data occasionally conflict on the specific doses of medications to be used.

Indeed, a systematic comparison of 4 sources of drug information on dose adjustment in CKD found :

1. Scarce details of evidence for recommendations.
2. Variations in definition of Renal Failure.
3. Differing recommendations for both drug dosage and dosing interval

Vidal L et al. Systematic comparison of for sources of drug information regrading adjustment of dose for renal function.BMJ 2005; 331:263.

Gaps in knowledge

Steering a middle course between efficacy and safety

Commonly used Palliative medications in the context of CKD

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Analgesics

Paracetamol

- Metabolised in liver
- 2-5 % excreted unchanged renally
- Inactive metabolites
- No dose adjustment = 1g qid

NSAIDs

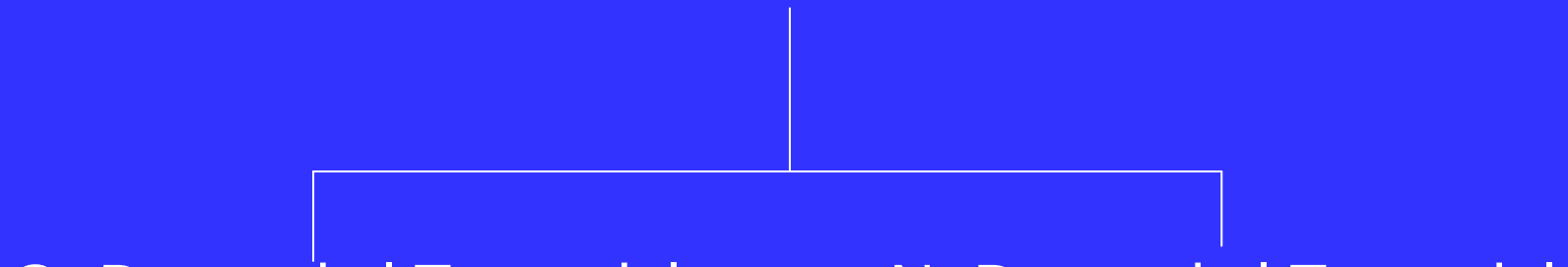
- Potentially nephrotoxic
- Sodium/Water retention
- Hyperkalaemia

- Reduce doses in mild renal impairment.
- Avoid in moderate to severe Renal failure

Tramadol

86% Metabolised in Liver

Tramadol



O- Desmethyl Tramadol (M1) (Active)

N- Desmethyl Tramadol (Inactive)

90 % of Tramadol and its metabolites are Renally excreted

Need for dose adjustment

If on Dialysis or
on Conservative pathway eGFR 15-30

Commence 50mg bd

Maximum 100mg bd

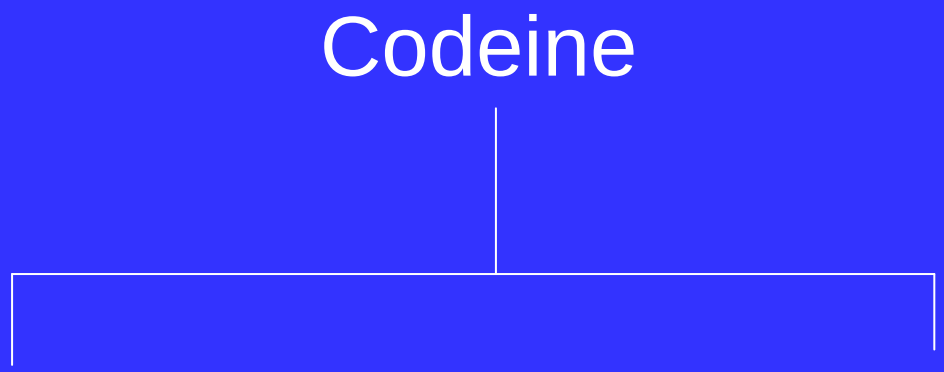
If on Conservative pathway

eGFR < 15

Tramadol 50mg bd (maximum)

Codeine

Metabolised in Liver



"We advise caution with chronic use of codeine in CKD patients and suggest limiting doses to 120mg or less per day."

Davison S, Ferro CJ. Management of Pain in CKD. *Progress in Palliative Care* 2009; 17: 186-195.

Morphine

Not recommended

Hydromorphone

Metabolised in Liver

Hydromorphone

Hydromorphone -3- Glucuronide

- Safe and effective
- Some caution expressed

- Commence low and qid.
- If tolerated – q4hours
- Titrate up dose carefully – once pain well controlled aim to convert to Fentanyl patch

Oxycodone

Short-acting	Long-acting
Endone	Oxycontin
Oxynorm	

- Metabolised by liver
- Active metabolites are eliminated mainly by hepatic metabolism
- Single dose study showed prolongation of oxycodone and its metabolites

"There are no long term studies of chronic use in renal failure and the conflicting case reports mean there is insufficient evidence currently for a recommendation."

Davison S, Chambers EJ, Ferro CJ. Management of pain in renal failure. In Chambers EJ et al (eds) *Supportive Care for the Renal Patient* 2010, 2nd ed, OUP.

Methadone

- Metabolised in liver
- Excreted mainly in the feces. Some renal excretion of Methadone and its metabolites
- Not dialysed
- Safe to use, but requires skill in dosing regimen – specialist use.

Fentanyl

- Metabolised in Liver
- Inactive metabolites
- 5-10 % excreted unchanged renally
- Fentanyl is not dialysed

Fentanyl is safe to use at standard doses

Buprenorphine

= Norspan

Buprenorphine – 3 – Glucuronide (B-3-G)

Norbuprenorphine (NorB)

Both accumulate in CKD

B-3-G is inactive ; NorB has minor analgesic quality

"There is lack of evidence about longer term use in ESRD"

Brown E et al (eds) *End of Life Care in Nephrology*. 2007, p. 99.

" …it may be a potentially useful analgesic for use in patients with CKD, although until there are longer term studies the authors remain cautious about recommending it."

Davison S, Chambers EJ, Ferro CJ. Management of pain in renal failure. In Chambers EJ et al (eds) *Supportive Care for the Renal Patient* 2010, 2nd ed, OUP.

Conclusion

- Pharmacology of CKD is complex
- Gaps in knowledge
- Increasing levels of experience
- Balance of efficacy and safety

Commonly used Palliative medications in the context of CKD