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.

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.

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.

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.
\[ V_d = \frac{\text{Administered Drug}}{\text{Plasma concentration}} \]
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.
Challenges
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:

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

Gaps in knowledge
Steering a middle course between efficacy and safety
Commonly used Palliative medications in the context of CKD
Acknowledgements

Dr Andrew Broadbent
Palliative Care Physician
Greenwich Hospice,
Hope Health Care Sydney

Aine Heaney
Pharmacist
National Prescribing Service
Renal Palliative Care Working Group
St George Hospital

Liz Josland, Renal CNC
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

Codeine

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

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
Endone
Oxynorm

Long-acting
Oxycontin
• 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.”

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

- 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”

“...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.”

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