Analgesic use in renal failure

Traditionally serum creatinine has been used as a measure of renal function. This is inaccurate as patients may have a clinically significant deterioration in renal function while still having a serum creatinine within the normal reference range. (Lamb et al)

Glomerular filtration rate (GFR) is a preferable measure of renal function. There are two generally accepted methods of estimating GFR
1. Cockcroft + Gault equation
2. 4 variant modification of diet in renal disease equation (4vMDRD)

Both methods are inaccurate at extremes of age and body weight. Estimated GFR (eGFR) is now provided with biochemistry results and is based on the 4vMDRD calculation. It will not have been adjusted for body total surface area.

eGFR classification of renal impairment

Degree impairment	**Chronic Kidney Disease (CKD) stage**	**GFR ml/min/1.73m^2**	**Creatinine clearance ml/min**
Normal renal function	1	>90	120
Mildly reduced renal function in presence of renal disease. In absence of renal disease eGFR>60 is considered normal	2	60-89	20-50
Moderately reduced renal function	3	30-59	10-20
Severely reduced renal function	4	15-29	<10
Very severe. Established (end-stage) renal failure	5	<15	<10

Modifying drug dose based on renal function

In patients known to have chronic renal impairment or those at high risk of renal impairment renal function should be checked before prescribing a drug that may require dose modification. A baseline eGFR can help to indicate the need for dose modification.

Dose adjustments should be made following advice in BNF, Palliative Care Formulary, manufacturers SPC's and the Renal Drug handbook.

For prescribing purposes renal impairment is arbitrarily divided into mild, moderate and severe, corresponding to creatinine clearances of 20-50 ml/min, 10-20 ml/min and < 10 ml/min.

Renal failure can make patients more susceptible to adverse effects of drugs. In particular it causes:

- An increased bleeding tendency, therefore the risks of NSAIDs and anticoagulants are increased.
- Increased blood-brain barrier permeability, therefore increased sensitivity to CNS side effects of drugs e.g. sedation

Renal failure can change analgesic pharmacokinetics in the following ways:

- Reduced excretion of drug or metabolites
- Altered drug distribution: especially if drug is plasma protein bound
- Reduced oral absorption: vomiting diarrhoea or mucosal oedema

Analgesics can still be prescribed according to the WHO analgesic ladder.

STEP 1 ANALGESICS

Paracetamol:
GFR 20-50 = no dose adjustment
GFR 10-20 = no dose adjustment
GFR <10 500mg-1g tds
NSAIDs: Should be avoided even in mild renal impairment. Can still be used in dialysis patients if they have no significant residual renal function (anuric patients)

STEP 2 ANALGESICS

Codeine: co-dydramol, co-codamol, codeine phosphate, dihydrocodeine: Half life significantly prolonged in chronic renal failure.
Mild renal failure – maintain normal dose
Moderate renal failure – 75% dose
Severe renal failure – 50% dose
Tramadol: Active metabolite excreted renally.
Mild renal failure- normal dose 50-100mg qds
Moderate renal failure – increase dosing interval 50-100mg bd
Severe renal failure – avoid
Buprenorphine: metabolised in the liver to inactive norbuprenorphine. Therefore safe to use in patients with renal impairment. No dose adjustments in Transdermal preparations. Reduce dose of SL buprenorphine by 25% in severe renal impairment.

STEP 3 ANALGESICS

Morphine: morphine and its metabolites accumulate in renal failure and should therefore be avoided.
Diamorphine: avoid in renal failure
Oycodone: Half life shown to be mildly prolonged. Suggest use with great caution in severe renal failure
GFR 20-50 = no dose adjustment
GFR 10-20 = no dose adjustment. Avoid modified release preparations.
GFR < 10 avoid
Fentanyl: metabolised to norfentanyl and inactive metabolites. Theoretical and clinically observed reduction in toxicity in renal failure. Although metabolites are inactive there is some concern that the parent drug may accumulate in moderate-severe renal impairment hence the recommendation to reduce dose:
GFR 20-50 = normal dose
GFR 10-20 = 75% dose
GFR<10 = 50% dose
Alfentanil: similar pharmacologically to fentanyl. Inactive metabolites.10 times as potent as SC diamorphine. Can be administered via CSCI and is safe even in severe renal impairment. No dose adjustment is required.
Methadone: renal impairment does not affect methadone clearance. Can be used in severe renal failure but dose adjustment required.
GFR 20-50 = no dose adjustment
GFR 10-20 = no dose adjustment
GFR <10 = 50% dose reduction

ADJUVANT ANALGESICS

Amitriptyline: starting dose needs no adjustment but must be titrated carefully to avoid sedation.
Gabapentin: requires significant dose reduction
GFR 20-50 = 300mg bd maximum
GFR10-20 = 300mg od maximum
GFR<10 = 300mg alternate days maximum
Pregabalin: Require significant dose reduction
GFR 20-50 = starting dose 75mg od . Max 300mg/day in divided doses
GFR 10-20 = starting dose 25-50mg od. Max 150mg/day in divided doses
GFR <10 = starting dose 25mg od. Max 75mg od
Sodium Valproate: start with normal dose but titrate carefully. Beware increased sedation in renal failue.
Dexamethasone: does not require dose adjustment but may be complicated by fluid retention
Clonazepam: no dose adjustment required but beware increased risk of sedation.
Ketamine: inactive metabolites. Safe in renal failure. No dose adjustments required

REFERENCES

- Farrell A, Rich A. Analgesic use in patients with renal failure.Eur J.Pall.Care 2000; 7(6):201-205
- Davies G, Kingswood C, Street M. pharmacokinetics of opioids in renal dysfunction. Clinical Pharmacokinetics 1996; 31(6):410-422
- Kaiko D, Benziger C, Cheng Y et al. Clinical pharmacokinetics of controlled release oxycodone in renal impairment. Clin Pharmacol Ther 1996; 59: 130-137
- Hunt R, Fazekas B, Thorne D et al. A comparison of subcutaneous morphine and fentanyl in hospice cancer patients. Journal Pain and Symptom Management. 1999; 18:111-118
- Farrell A and Rich A. Analgesic use in patients with renal failure. European Journal of Palliative care. 2000; 7(6)
- Dean M. Opioids in renal failure. Journal of pain and symptom management. 2004; 28 (5) 497-504
- Ashley C, Currie A .2004. The Renal Drug Handbook Second Edition. Oxford Radcliffe Medical Press
- Davies G, Kingswood C and Street M. Pharmacokinetics of opioids in renal dysfunction. Clinical Pharmacokinetics. 1996; Dec 31(6) 410-422
- Lamb, Tomson, Roderick. Annals of clinical biochemistry 2005 .42(5): 321-345
- Devaney A, Ashley C, Tomson C. How the reclassification of kidney disease impacts on dosing adjustments. Pharmaceutical journal 2006; 277:403-405
- Department of health. NSF for renal services: part two.2005 .Chronic Kidney disease, acute renal failure and end of life care
- Froissart M, Rossert J, Christian Jacquot C, et al. Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. J Am.Soc. Nephrology 2005 16: 763-773