Acute Pain Relief in Children with Renal impairment

Document Type	Guideline
Function	Clinical Practice
Directorate(s)	Child Health
Department(s) affected	All who manage children with renal impairment
Applicable for which patients, clients or residents?	All children with acute or chronic renal impairment
Applicable for which staff members?	All Starship clinicians but primarily anaesthesia, PICU, surgical and nephrology staff
Key words (not part of title)	Analgesia, renal failure, dialysis, chronic kidney disease
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1. Purpose of policy or guideline

This document contains information and clinical practice guidelines on the administration of analgesia for acute pain in paediatric patients (3 months – 18 years) with acute or chronic renal impairment.

2. Definitions

Acute or chronic renal impairment, defined as an estimated or measured glomerular filtration rate (GFR) <50mL/min/1.73m^2. This includes patients described as having chronic kidney disease (CKD) stage 3, 4 and 5. It also includes kidney transplant recipients with decreased GFR.

3. Introduction

Special considerations must be given to patients with renal impairment to minimize direct analgesic-induced renal-related complications and other drug-accumulation-related complications due to reduced renal clearance. Impaired renal function may lead not only to an accumulation of ingested components that are predominantly excreted by the kidney, but active or toxic metabolites may accumulate as well and increase the frequency of adverse reactions.

Modification of drug doses in renal disease is usually necessary only when the GFR is less than 30–40 mL/min/1.73m^2.

When choosing appropriate analgesia for patients with renal impairment or on renal replacement therapies (haemodialysis (HD), peritoneal dialysis (PD), continuous renal replacement therapy (CRRT), renal transplant), one should consider all of the following:

- Type of renal impairment – should all potentially nephrotoxic agents be avoided? Does this patient have acute or chronic renal failure? If chronic, is there residual urine output to preserve?
- Degree of renal impairment – what is the eGFR? Is the patient on dialysis and if so what type?
- Usual mechanism of clearance of the drug or its metabolites – should dosing be adjusted and how?
- Degree of removal of the drug by renal replacement therapies – is supplementary dosing required?
- What other drugs is the patient on and what might potential interactions be?
- What other co-morbidities (hepatic dysfunction) / drug allergies or intolerances does the patient have?

Additional caveats/ important points:

1. Weight – use ideal body weight if obese or estimated dry weight if fluid overloaded.
   2. Estimated GFR – any patient on dialysis / oliguric is categorized as <10, for others use simplified Schwartz equation as a general estimation: 36.5 x height (cm)/creatinine.
   a. No estimating GFR formulae are validated for use in acute renal failure; they have poor accuracy in the setting of fluctuating / changing renal function.
   b. Remember creatinine production is proportional to muscle mass, resulting in potential overestimation of GFR in subjects with low muscle mass. Additionally, creatinine is excreted by glomerular filtration and tubular secretion. The relative contribution of tubular secretion to total creatinine clearance increases with falling GFR, resulting in overestimation of GFR in patients with reduced renal function.
3. When several drugs are administered simultaneously, accumulating metabolites may result in unknown or unexpected interactions. Therefore, as a general principle, drug therapy in patients with impaired renal function should be limited to the smallest possible number of substances.

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4. Drug details

Drug	**PARACETAMOL**	
Dose in normal renal function	Oral	10-15mg/kg (maximum of 1g per dose) every 4 to 6 hours. Maximum of 90mg/kg/day or 4g/day (whichever is least)
Dose adjustment in dialysis	10-15 mg/kg (maximum 1 g per dose) every 8 hours. Maximum of 3 doses/day	
	Cleared via HD - will need re-dosing post HD session Not cleared via PD – no supplementary doses required	
Additional considerations	Caution in hepatic impairment / jaundice	

Drug	**NON-STERIODAL ANTI-INFLAMMATORIES (NSAIDs)**	
Information	Includes ibuprofen and diclofenac	
Dose in normal renal function	**Ibuprofen :** > 1 month	5-10mg/kg (maximum of 400mg) every 6 to 8 hours
	Diclofenac : > 6 months	0.5- 1.5mg/kg (maximum of 75mg) every 8 hours, maximum of 3mg/kg/day
Dose adjustment in renal impairment	Acute kidney injury (irrespective if on dialysis)	Contraindicated
	CKD/kidney transplant	Best avoided*
Dose adjustment in dialysis	ESKD on dialysis Urine output (> 100 mL/day)	Best avoided*
	ESKD on dialysis No urine output (< 100 mL/day)	Dose in normal renal function
	No clearance via HD or PD; no supplementary doses required	
Additional considerations	In patients with residual kidney function, NSAIDS may exacerbate hypertension, oedema, hyponatraemia, hyperkalaemia. Caution in severe asthma, coagulation defects ** In certain settings NSAIDs may be considered after discussion with the renal consultant*	

Drug	**TRAMADOL**	
Information	Not registered for use in children under 2 years, use as directed by Acute Pain Service in this age group.	
Dose in normal renal function	> 1 year or > 10kg:	1-2 mg/kg (maximum 100mg) every 6 hours
Dose adjustment in renal impairment	GFR 10-30mL/min/1.73m^2 (CKD 4)	0.5-1 mg/kg (maximum 50mg) every 12 hours
	Avoid long acting tramadol preparations	
Dose adjustment in	0.5mg/kg (maximum 50mg) every 12 hours	

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dialysis	Clearance with high permeability filter. None/minimal clearance via conventional HD. May need re-dosing post HD session depending on dialysis filter. No data available on clearance via PD.
Additional considerations	Pharmacologically active metabolites formed by CYP2D6. Co-prescription with enzyme inducers/inhibitors cautioned (see Appendix 2). Avoid in patients with seizure disorder. Co-prescription with serotonergic medicines (carbamazepine, sumatriptan, illicit drugs, morphine, and anti-depressants) can increase the risk of serotonin syndrome.

Drug	**OXYCODONE**	
Information	Considered the first choice opiate for paediatric pain in renal impairment	
Dose in normal renal function	**Oral**	0.1-0.2 mg/kg/dose (maximum 10mg/dose) every 4 to 6 hours
	IV injection < 6 months	0.02mg/kg/dose every 5 minutes
	IV injection > 6 months	0.04mg/kg/dose every 5 minutes
	IV injection > 50kg	2mg per dose every 5 minutes
Dose adjustment in renal impairment	**Oral:** GFR 10-50 mL/min/1.73m^2 (CKD 3&4) or CRRT	0.1-0.2 mg/kg/dose (maximum 10mg/dose) every 8 to 12 hours
	IV injection: GFR 10-50 mL/min/1.73m^2 (CKD 3&4) or CRRT	Standard dosing, but bolus doses only. No background infusions given unless directed by Acute Pain Service.
Dose adjustment in dialysis	**Oral**	0.025-0.05 mg/kg/dose every 8 to 12 hours. Maximum starting dose of 2.5mg.
	IV	Standard dosing, but bolus doses only. No background infusions given unless directed by Acute Pain Service.
	Clearance with high permeability filter. No data regarding clearance via conventional HD or PD. May need re-dosing post HD session, review on case-by-case basis.	
Additional considerations	Mainly hepatically metabolized (90%). Pharmacologically active metabolite (oxymorphone) accumulates in renal failure. Oxymorphone is converted from oxycodone via CYP2D6 pathway. Co-prescription with CYP2D6 enzyme inducers or CYP3A4 inhibitors cautioned. Caution if patient post anaesthetic or co-prescribed sedatives. Careful monitoring for sedation/ depressed respiration/hypotension required in those with advanced renal impairment	

Drug	**FENTANYL**	
Information	Second choice opiate for IV infusion if oxycodone contraindicated.	
Dose in normal renal function	**IV injection:**	0.5-1 micrograms/kg every 15 minutes *Maximum of 50 micrograms/dose*
	IV infusion <3months: **IV infusion >3 months**:	0.2-0.8 micrograms/kg/hour 0.5-1 micrograms/kg/hour *Maximum of 50micrograms/hour*
Dose adjustment in renal impairment	GFR 10-50 mL/min/1.73m^2 (CKD 3&4) or CRRT:	Reduce dose by 50%
Dose adjustment in	Reduce dose by 75%	

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dialysis	Not substantially cleared by HD (supplemental doses not required) No data available for PD
Additional considerations	Although mostly hepatically metabolised (10% renal) and no active metabolites, accumulation can occur in patients with moderate to severe renal impairment due to increased volume of distribution and reduced clearance. There is considerable inter-patient variability in fentanyl pharmacokinetics in these patients. Caution if patient post anaesthetic or co-prescribed sedatives. Careful monitoring required for sedation / depressed respiration / hypotension in those with advanced renal impairment.

Drug	**MORPHINE**		
Information	Not to be prescribed "as per IV protocol" or used in PCA / NCA. Recommended for short-term use only - doses should be reassessed every 24 to 48 hours		
Dose in normal renal function	**Oral:**	<15kg	0.15-0.3 mg/kg/dose every 2 hours
		15-30kg	5 – 10 mg/dose every hour
		>30kg	10 mg/dose every hour
	Slow IV bolus:		0.05-0.1 mg/kg/dose when required
	"As per protocol":	<6 months	0.02 mg/kg/dose every 5 minutes
		>6months	0.04 mg/kg/dose every 5 minutes
		>50kg	2 mg every 5 minutes
Dose adjustment in renal impairment	GFR 30-50mL/min/1.73m^2 (CKD3)		Reduce dose by 25% and change dosing interval to every 6 hours
	GFR 10-30mL/min/1.73m^2 (CKD 4)		Reduce dose by 25-50% **and** change dosing interval to every 8 hours
Dose adjustment in dialysis	Reduce dose by 50 – 75% and give 8 hours apart. Maximum of 2 doses.		
	Clearance of morphine and morphine-6-glucuronide (M6G) with high permeability filter, minimal data re conventional HD but likely some clearance. M6G diffuses out of CNS very slowly, thus limiting and delaying response to dialysis. Supplemental doses not required. Not sufficiently cleared via PD.		
Additional considerations	Caution if patient post anaesthetic or co-prescribed sedatives. Careful monitoring required in those with advanced renal impairment for sedation/respiratory depression/hypotension. Low threshold for pulse oximetry monitoring and is mandatory in < 6 month old patients. See Appendix 1 for naloxone dosing.		

5. Supporting evidence

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- Taketomo CK, Hodding JH, Kraus DM, Editors. Pediatric & Neonatal Dosage Handbook. 19th Edition. Hudson (OH): Lexi-Comp; 2012
- http://nzfchildren.org.nz/New Zealand Formulary for Children release 35—1 May 2015 | ISSN: 2350-2916

6. Associated Auckland DHB documents

- Pain Management - Analgesia Overview - Paed

7. Disclaimer

No guideline can cover all variations required for specific circumstances. It is the responsibility of the health care practitioners using this Auckland DHB guideline to adapt it for safe use within their own institution, recognise the need for specialist help, and call for it without delay, when an individual patient falls outside of the boundaries of this guideline.

8. Corrections and amendments

The next scheduled review of this document is as per the document classification table (page 1). However, if the reader notices any errors or believes that the document should be reviewed ***before*** the scheduled date, they should contact the owner or the Clinical Policy Advisor without delay.

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Appendix 1: Naloxone

Indications and Dosing:

Excessive sedation/ respiratory depression	1-2 micrograms/kg IV Call code pink
Respiratory arrest	10 micrograms/kg IV maximum 400 micrograms Repeat every q2-3 minutes Call code blue

Due to the short duration of action of naloxone repeated doses may be needed or an infusion commenced. In this circumstance, contact PICU for further advice.

Appendix 2: More common CYP450 enzyme inducers / inhibitors (not exhaustive list)

2D6 inhibitors	SSRIs (fluoxetine, paroxetine, sertraline), terbinafine, chlorpromazine, cimetidine
2D6 inducers	rifampicin
3A4 inhibitors	clarithromycin, some antivirals, azole antifungals, erythromycin, ciprofloxacin, norfloxacin, grapefruit juice

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