

Title KETAMINE FOR ANALGESIA AND SEDATION

This medication guideline has been prepared to standardise the prescribing, administration and dispensing of this ketamine for analgesia and sedation for adult inpatients at Alfred Health. For the use of ketamine in status epilepticus refer to Status Epilepticus Management in Adults Guideline. For paediatric sedation in ED, Alfred Health has adopted the Royal Children's Hospital (RCH) clinical practice guideline Ketamine use for procedural sedation, endorsed by the Paediatric Improvement Collaborative. The RCH guideline endorses use of ketamine in children from 3 months, but ketamine should not be used at Alfred Health for procedural sedation in children under two years of age without anaesthetic consultation.

Additional information relating to this drug can be found in the references listed and by contacting the Alfred Medicines Information Service on 62002.

Areas Applicable: Operating Suites, ICU, ED, Trauma Unit Ward 5W Procedure Room, Ward 6W DUS Procedure Room, and general wards under Acute Pain Service, Palliative Care Unit or Neurology guidance.

Introduction

Ketamine is a phencyclidine derivative, mediating the majority of its actions via N-methyl-D-aspartate (NMDA) receptor antagonism. At low doses it produces analgesia and sedation, but at higher doses produces a dissociative anaesthetic state. Whilst airway tone, protective airway reflexes and ventilation are better maintained compared to anaesthetic states produced by other agents, they cannot be guaranteed. Clinicians using ketamine boluses must have the necessary airway skills to obtain and maintain an airway and provide adequate ventilation when they are compromised.

Tissue damage causing persistent nociception, or neuropathic pain states, may activate N-methyl-D-aspartate (NMDA) receptors in the spinal dorsal horn, producing the phenomenon of "wind-up", with the spinal hyperexcitability, allodynia and hyperalgesia (central sensitisation). NMDA antagonists, such as ketamine, can be used to attenuate this central sensitisation with consequent improved analgesia. Ketamine is often used in addition to opioids and has been shown to have an opioid-sparing effect.

Description	
Drug Presentation	 200 mg (base)/2 mL (Ketalar® or alternative brand) – MUST BE DILUTED with compatible solution before administration 25mg wafer (Wafermine®) - for sublingual administration
Prescribing & Administration Requirements /Restrictions for Medical Staff	 To reduce the risk of iatrogenic patient harm, the following restrictions apply: Acute Pain Service (APS) Ketamine wafers are restricted to APS for analgesia during dressing changes in patients with burns (see Appendix 2) Anaesthetic Staff For Anaesthesia and Procedural Sedation:

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	Care Unit (PACU) by appropriately experienced staff		
	ED refer to Appendix 1		
	• ICU		
	 For Anaesthesia and Procedural Sedation: Only to be used under the supervision of, and after discussion with, an ICU consultant or senior registrar For Analgesia: 		
	-The decision to use ketamine as an analgesic adjunct infusion should be made after discussion with an ICU consultant or senior registrar		
	Neurology Unit		
	 Only used with the supervision of a Neurology Unit Consultant Predominantly used as an intravenous infusion for treatment of migraine and neuropathic pain (does not require APS consult) 		
	Palliative Care Unit		
	 Only used with the supervision of a Palliative Care Consultant Predominantly used as a subcutaneous infusion 		
	Trauma Unit in 5W Procedural Room		
	 Only used by credentialed consultant staff per <u>Appendix 3</u> 		
Drug Storage/ Availability	S8 – stored in DD cupboard		
Actions (Pharmacology)	 NMDA receptor antagonist In Australia, ketamine is a racemic mixture of the 'r' and 's' enantiomers in a 1:1 ratio Rapid onset of dissociative anaesthesia, characterised by Cataleptic state, often with eyes remaining open Relative maintenance of pharyngeal/ laryngeal reflexes (subanaesthetic doses), but does not guarantee protection against aspiration in unfasted patients Increased salivation, that can precipitate laryngospasm Maintenance of minute ventilation (subanaesthetic doses) Cardiovascular stimulation, with relative preservation of mean arterial pressure (MAP) Normal or slightly enhanced skeletal muscle tone Profound analgesia in sub-anaesthetic doses, and is opioid sparing Reduces 'wind-up' and may be useful in the treatment of neuropathic pain, and the prevention of chronic pain. Elimination half-life = 2 to 3 hours Metabolised to nor-Ketamine, which is an active metabolite with 20-30% activity of the parent compound 90% of ketamine excreted in urine (mostly as metabolites) Anaesthesia persists for only 5 to 10 minutes after an induction dose of ketamine; re-administration is necessary to maintain effective anaesthesia 		
Indications	 1. INDUCTION OF ANAESTHESIA In ED, Operating suites, and ICU Only by clinicians with detailed knowledge of ketamine's pharmacology and adequate experience with its clinical use. These staff must also have the requisite skills to manage a compromised airway and ventilation. Credentialing by each department/unit is defined in the Prescribing & Administration Requirements/Restrictions for Medical Staff section. Choice as induction agent for various operations, procedures, or 		

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emergency intubation by appropriately credentialed clinician

 Usual dose as sole induction agent is 1-2mg/kg, and this may need to be significantly reduced in haemodynamically compromised patients, patients with reduced conscious states from any cause, and the elderly

2. PROCEDURAL SEDATION/ANALGESIA

- In ED, Operating suites, ICU, Trauma Unit Ward 5W Procedure Room, and 6W Procedure Room for Burns Dressings under Sedation (DUS)
- Only by clinicians with detailed knowledge of ketamine's pharmacology and adequate experience with its clinical use. These staff must also have the requisite skills to manage a compromised airway and ventilation. Credentialing by each department/unit is defined in the Prescribing & Administration Requirements/Restrictions for Medical Staff section.
- Choice as sedation agent for various procedures by appropriately credentialed clinician
- Usual dose to obtain conscious sedation is 0.5-1mg/kg, and this may need to be reduced in haemodynamically compromised patients, patients with reduced conscious states from any cause, and the elderly
- Patients must be adequately monitored to ensure adequate respiration and oxygenation
- As depth of sedation is increased, protective airway reflexes cannot be guaranteed, and unfasted patients are at risk of aspiration

3. ANALGESIA

- Intravenous, subcutaneous, and sublingual routes of administration
- Can be utilised on any general ward as follows:
 - Prescribed by APS as part of multi-modal analgesic regimen for any patient with severe pain, inadequately managed with opioids and conventional adjuvants.
 - Prescribed by Palliative Care physicians, as per the relevant guideline, in the treatment of severe chronic and/or cancer-related pain, especially those already on large doses of opioids.
 - Prescribed by the Neurology Unit, for the treatment of severe chronic migraines unresponsive to other agents, neuropathic pain with features of central sensitisation, Complex Regional Pain Syndrome (CRPS), and in patients in whom discontinuation of opiates is desirable.

Absolute

- Known hypersensitivity to ketamine products
- Previous severe adverse reactions, especially psychogenic

Relative

Contraindications

Use with caution if:

- Known or suspected difficult airway
- Unfasted and risk of aspiration
- Acute myocardial ischaemia
- Poorly controlled heart failure
- Uncontrolled hypertension
- Acute psychotic states and recent methamphetamine use
- Whilst not contra-indicated in patients with traumatic brain injury (TBI) and

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	 raised intracranial pressure (ICP), the literature does not support its use a a sole agent, because it increases cerebral metabolic activity heterogeneously Whilst ketamine is probably safe to use in acute porphyrias, it is not the drug of choice, that being propofol. 				
	Use with caution:				
	Conditions where hypertension is hazardous (e.g. cardiovascular disease, heart failure, uncontrolled hypertension, recent AMI, recent stroke, cerebral bleeding or mass). Problems unlikely at doses <0.3 mg/kg/hr by continuous infusion. Avoid bolus doses.				
	Alcohol intoxication or a history of alcohol abuse				
	Adverse psychogenic sequelae can be severe and occur in up to 15% of patients receiving anaesthetic doses. They are minimised by administering ketamine as an infusion and avoiding bolus doses. Due to the risk of these adverse psychological events, ketamine should be used in caution in				
Precautions	patients with psychiatric illness, acute psychotic states, or recent				
	 methamphetamine use, whilst noting that it is recommended as third line treatment for the sedation of patients with acute behavioural disturbances in the ED, See Sedation for Acute Behavioural Disturbance in Emergency Department Guideline and Safer Care Victoria's Caring for people displaying acute behavioural disturbance. Glaucoma or elevated intraocular pressure, globe injuries. Hyperthyroidism (increased risk of hypertension, tachycardia) Do not use alone in surgery or diagnostic procedures of pharynx, larynx, or bronchial tree Consider dose reduction in patients with cirrhosis or hepatic impairment Potential abuse as a recreational drug 				

Administration

Dose Range

For IV Infusion Analgesia:

 Usual Dosage Range: 0.1 - 0.3 mg/kg/hr (unless otherwise specified by the Consultant in charge)

Usual Dose Range: 7 - 24 mg/hrInfusion Rate (4 mg/mL): 1.75 - 6 mL/hr

IV Loading Dose prior to infusion*

Loading doses are *generally not recommended*, particularly on the general wards. A loading (bolus) dose should only be given to achieve adequate ketamine blood levels on initiation of infusion.

- Dose: 0.1 mg/kg over at least 1 minute to a maximum bolus dose of 10 mg IV. Consideration should be given to the addition of a bolus of midazolam 0.5 mg IV, particularly those predisposed to psychological manifestations.
- Dilute ketamine 200mg/2mL ampoule to 20mL with compatible fluid to produce a final concentration of 10mg/mL

*Bolus doses increase the risk of unpleasant psychological manifestations which include hallucinations and in some cases have caused susceptible patients to develop post-traumatic stress disorder. Bolus dosing should only be done by appropriately trained staff.

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	For Subcutaneous Infusion Analgesia:			
	Acute Pain Service			
	Same dosage range as above, and generally given via the PCA pump as a			
	continuous infusion (at concentration as above for IV infusion)			
	Palliative Care Unit Constally start at decay of 100 mg/24 hours and increase incrementally up to			
	Generally start at doses of 100 mg/24 hours and increase incrementally up to doses of 500 mg/24 hours, via Niki T34 pump. Loading doses are not			
	recommended in the Palliative Care setting. Note: For further advice on			
	administration for continuous subcutaneous infusions liaise with Palliative care			
	daniminos del continuodo suboutanodos inidistrio liaise with i aliative care			
	For migraine and neuropathic pain management by Neurology: Refer to IV Infusion Analgesia section.			
	For use in ED: Refer to Appendix 1			
	For Sedation + Analgesia in ICU:			
	• 0.05– 0.4 mg/kg/hr			
	 Higher IV doses have been used for sedation and analgesia⁴ but requires careful titration 			
	For Sublingual Analgesia (APS only): Refer to Appendix 2			
Duration of Therapy	Need for ongoing therapy to be decided by Acute Pain Service, Palliative Care Unit, Neurology or ICU			
	Titrate under direction of Acute Pain Service, Palliative Care Unit, ICU or			
	Neurology for the approved indications			
	Start at the lower end of the dose range to minimise side effects.			
Titration Parameters	Review at one hour – if pt comfortable leave at this rate, if patient has Project the project of the			
	persistent pain consult relevant specialist team, i.e. Acute Pain Service, Palliative Care, Neurology or ICU			
	Review at 6–12 hours – if comfortable leave at this rate, if not contact			
	relevant specialist team and consider alternative techniques			
	ICU and General Wards (use IV Ketamine powerplan)			
	Drug Dose: 200 mg (2 mL)			
	Make up infusion TO : 50 mL in IV syringe			
	Compatible Solutions: 0.9% sodium chloride, 5% glucose			
	Final Concentration: 4 mg/mL			
Intravenous Infusion	• 1mL/hr = 4 mg/hr			
minutorious imagion	Infusion pump: PCA pump (wards) or Alaris (ICU) (In the support that a leaterning infusion is parameters at the ARS in ER. the RCA.)			
(In the event that a ketamine infusion is commenced by APS in ED, pump should be used unless the patient is to be transferred to ICU)				
	Mildomologo addition (ADC On to):			
	Midazolam addition (APS Only):			
	Reduces the incidence of hallucinations in high risk patient groups ie. patients with peurotic traits or psychiatric illness.			
	 patients with neurotic traits or psychiatric illness 1mg Midazolam added to the 200mg/50mL syringe 			
	MUST have IV fluids running with the ketamine infusion at a minimum of 5mls			
	per hour via an infusion pump, to prevent cannula occlusion and maintain drug			

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	flow to the patient. The ketamine infusion line should be attached to the side arm of the IV maintenance line downstream of a non reflux valve or run with an existing infusion, if compatible. Note: Consultation with Acute Pain Service, Palliative Care or Neurology unit should occur prior to use on general wards			
Ceasing infusion	This can usually be done over a few hours			
Incompatibilities	Barbiturates, diazepam, thiopentone			
Y-Site Compatibility	Morphine sulphate, oxycodone, midazolam, lignocaine (based on clinical practice). For other drug combinations please contact medicines information on ext 62002 or your clinical pharmacist.			
Subcutaneous Syringe Compatibility ⁷	Midazolam, morphine sulphate. For other drug combinations please contact medicines information on ext 62002 or your clinical pharmacist.			
Practice Points				
Side Effects	 Side effects at analgesic doses are less common than at anaesthetic doses, but can be quite distressing to patients, especially hallucinations and related phenomena. Doses may need to be reduced or even ceased. Common Increased salivary and tracheobronchial secretions Psychological manifestations varying in severity including (may occur during therapy and for up to 24 hours after therapy stopped): Pleasant dream-like states, floating sensations Emergence delirium Vivid imagery/hallucinations Confusion, insomnia, excitement, and irrational behaviour Treatment: Consider reducing rate of ketamine, or give low dose benzodiazepines (e.g. 0.5 mg IV/SC midazolam or sublingual 1 mg lorazepam using tablets) or haloperidol Note: These psychological effects occur to a lesser extent with the subanaesthetic analgesic doses and generally can be controlled by the treatment as recommended above. 			
	Serious Increased blood pressure (frequent) Tachycardia (frequent) Increased intraocular pressure Muscle hyperactivity (frequent), may resemble tonic/clonic seizures – more so at anaesthetic doses Respiratory depression (dose related or too rapid administration rate) Laryngospasm Other Urinary tract toxicity/bladder dysfunction			
	 Rash, vomiting Local inflammation at subcutaneous infusion site 			

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	- For ketemine influsions	_			
	For ketamine infusions FIRST 4 HOURS				
	1 Hourly	2 Hourly	4 Hourly thereafter		
	Heart Rate	Heart Rate	Heart Rate		
	Blood Pressure Blood Pressure		Blood Pressure		
	Respiratory Rate Respiratory Rate		Respiratory Rate		
	Sedation Score (0-3)	Sedation Score (0-3)	Sedation Score (0-3)		
	O2 Saturations	O2 Saturations	O2 Saturations		
Monitoring	Pain Score (VNRS 0-10)	Pain Score (VNRS 0-10)	Pain Score (VNRS 0-10)		
	Functional Activity Score (FAS)	Functional Activity Score (FAS)	Functional Activity Score (FAS)		
	 Monitor for hallucinations and vivid dreams. If patient experiences disturbing or distressing symptoms, cease ketamine and refer to medical team. Monitor for signs of emergence delirium symptom. Monitor patient's liver and renal function Monitor SC injection site for local inflammation 				
Drug Interactions	 Theophylline (decreases seizure threshold) Use with caution if using with other medications that can increase the BP or heart rate. Monitor combinations closely. Thyroxine (sustained rises in arterial blood pressure reported) Potent cytochrome 3A4 inhibitors eg clarithromycin as ketamine is metabolised by this enzyme Atracurium (ketamine may potentiate the neuromuscular blocking effects) The use of ketamine with other central nervous system (CNS) depressants. Reduced doses of ketamine may be required with concurrent administration of other anxiolytics, sedatives and hypnotics St. John's Wort (an increased risk of cardiovascular collapse and/or delayed emergence from anaesthesia). Cease St John's Wort 5 days prior to ketamine administration. Use with caution if using with drugs which prolong QTc interval (list available at https://www.crediblemeds.org/) This list only includes some common drugs and is not exhaustive. Contact your Clinical Pharmacist or Medicines Information on 62002 for details relating to 				
Use in Pregnancy/Lactation	 See <u>The Women's Pregnancy and Breastfeeding Medicines Guide</u> 				
Other Considerations		ported being used as a dr Prior to Sublingual dose r	•		
Nurse Practitioner/ Candidate Considerations	 For Patient Education Prior to Sublingual dose refer to <u>Appendix 2</u> A Nurse Practitioner/candidate who works with the Acute Pain Service can prescribe a Ketamine infusion within the usual dose range parameters Treatment of side effects extends to reduction or cessation of infusion only 				

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A patient who continues to have severe pain or intolerable side effects should be reviewed by an Acute Pain Service Consultant

APPENDICES

- 1. Administration in the Emergency Department
- 2. Ketamine Sublingual Administration For Dressing Change (INPATIENT USE ONLY)
- 3. Ketamine For Procedural Sedation In Ward 5 West Procedural Room

KEY RELATED DOCUMENTS

- Key aligned policy
 - Alfred Health Medication Safety Policy
 - **Team Time Out Policy**
- Key legislation, acts & standards:
 - Charter of Human Rights and Responsibilities Act 2006 (Vic)¹
- Other relevant documents:
 - Acute Pain: Pharmacological and Non-Pharmacological Management in Adults Guideline
 - Referrals to Pain Management Services Guideline
 - Analgesia for Burns Dressing Changes Guideline
 - Patient Controlled Analgesia (PCA) Management Guideline
 - Recovery Room Management of Acute Pain in Adults Guideline
 - Sedation For Acute Behavioural Disturbance in the Emergency Department
 - ICU Sedation and Analgesic Titration Algorithm
 - Standardised Intravenous Bolus and Continuous Drug Infusions Table Guideline
 - **Fasting Patient**

REFERENCES

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¹ REMINDER: Charter of Human Rights and Responsibilities Act 2006 – All those involved in decisions based on this guideline have an obligation to ensure that all decisions and actions are compatible with relevant human rights.



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General resources also used in the preparation of this monograph include: MIMS [On-Line] (accessed 09/04/19); Australian Medicines Handbook [On-Line] (accessed 09/04/2019); Burridge N (ed) Australian Injectable Drugs Handbook [On-Line] (accessed 09/04/19); The Women's Pregnancy and Breastfeeding Medicines Guide [On-Line] (accessed 09/04/19].

KEYWORDS

Ketamine

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Amendment approved by Alfred Health Drug and Therapeutics Committee Date: 14th July 2021			
Disclaimer: This procedure has been developed within the context of Alfred Health service delivery. Alfred Health shall not be responsible			

for the use of any information contained in this document by another organisation outside of Alfred Health.

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Appendix 1 – Administration in the EMERGENCY DEPARTMENT

Only to be used under the supervision of, and after discussion with, an Emergency Physician, or ED Fellow/Senior Registrar if at night.

- Pre-Primary Exam trainees are not to administer ketamine without direct supervision by an Emergency Physician
- Post-primary Exam trainees can administer ketamine after discussion with an Emergency Physician or ED Fellow.

In addition to above, trainees administering ketamine must have completed their LEX module for Procedural Sedation.

Administration

Dosing#

1. Intractable pain

- Where maximal doses of narcotics have been reached, or if patient instability necessitates use
- Dose*: IV 0.1-0.5mg/kg over at least 1 minute#
- Consideration should be given to the addition of a bolus of midazolam 0.5 mg IV
- Note: Early notification of the Acute Pain Service is required if difficult analgesic requirements are anticipated or if more than two bolus doses are needed.

*A maximum of two bolus doses may be used in the ED by experienced medical staff, prior to consultation with the Acute Pain Service.

2. Procedural Sedation

- When indicated due to patient instability, fasting status or where other agents are less appropriate and procedure cannot be delayed
- <u>Dose:</u> 0.5-1mg/kg plus a further 0.5mg/kg if required. Give by slow IV push.
- Consider giving midazolam prior to ordering procedure to limit psychological manifestations, particularly in susceptible patients.

3. Induction of Anaesthesia

- When indicated due to patient instability, or where considered to be the safest agent (e.g. airway issues, bronchospasm).
 May be used as a single agent or in combination (e.g. with benzodiazepines)
- <u>Dose:</u> IV 1-2mg/kg.# Give by slow IV push.
- Use caution in hypertensive patients

Note- Prior agents used for analgesia, particularly high dose opioids, may necessitate a reduction in the bolus dose to be given. Without dose reduction, maintenance of normal airway reflexes and ventilation may be compromised.

*Dilute ketamine 200mg/2mL ampoule to 20mL with compatible fluid to produce a final concentration of 10mg/mL

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Appendix 2 - Ketamine Sublingual Administration For Burns Dressing Change (INPATIENT USE ONLY)

Presentation – Sublingual dose

- 25mg wafer (Wafermine®)
- S8 stored in DD cupboard on ward

Administration

Dosing

To be used in ICU and General wards following consultation with Acute Pain Service

- LOADING DOSE: Sublingual ketamine (25 mg) administered 10 minutes prior to commencement of dressing change (I.e. before dressing removal).
- BOLUS DOSES: The patient can receive extra doses of sublingual ketamine during the dressing change as they require (5 minutely up to 3 times PRN). The boluses doses are only to be patient initiated (at the patient's request). The maximum total dose that the patient receives is at the acute pain services discretion and will vary from patient to patient.

Counselling

Patient Education Prior to Sublingual dose

- Advise patient that the dose is to be placed under the tongue and the
 patient should try to not swallow the medication for as long as possible
- Prior to commencement of sublingual ketamine, the patient should be educated on the medication and the possible side effects such as:
 - Bitter taste
 - Can give a "warm" or "weird" effect,
 - Hallucinations are possible but unlikely
 - Older patients may not like dysphoric effect
 - Short acting
 - Do not repeat dose if patient disliked the effects

Patient Education on Discharge

Advise patient that the effect of ketamine can last for up to 24 hours after the last dose.

- Patient to remain in bed for 60mins after final ketamine dose
- They should be cautioned about driving or engaging in hazardous activities etc during this time period
- Counselled that emergent psychological reactions may occur

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Appendix 3 – Ketamine For Procedural Sedation in Ward 5 West Procedural Room

** Only credentialed CONSULTANT Trauma medical staff are authorised to administer ketamine sedation on 5 West **

In general, to be *credentialed* to administer IV ketamine sedation on 5 West, practitioners must be:

- An emergency physician (FACEM) and be credentialed to use ketamine sedation in ED, or
- · A specialist anaesthetist (FANZCA), or
- A trauma consultant (FACEM, FANZCA, FCICM, FRACS or equivalent) and,
 - o Have had previous experience in the use of ketamine sedation, or
 - Competed training in the use of ketamine sedation (including observing ketamine sedation and performing ketamine sedation under supervision)

Indications

Procedures requiring IV sedation (e.g. insertion of intercostal catheters)

Staffing

- In accordance with joint ANZCA/ACEM PS09 guideline, ¹⁶ a minimum of three staff are required:
 - o 1 credentialed consultant doctor (the sedationist),
 - o A second doctor (the proceduralist), and
 - o A third assistant (nursing or medical staff)

Consent / Assessment

- Consent should be obtained for procedural sedation either from the patient or, if not possible, from the appropriate medical decision maker
- Pre-sedation assessment should include, as a minimum:
 - Airway assessment any suspected difficult airway should not have procedural sedation without consultation with anaesthesia
 - A fasting assessment patients should be fasted in accordance with Alfred Health fasting guidelines
 - A pre-procedure assessment including allergies, past medical history, and current medications
- A "time-out" should occur prior to the procedure in accordance with Alfred Health guidelines

Monitoring

- Patients should be monitored with a minimum of 16:
 - o Pulse oximeter and
 - Non-invasive blood pressure
- All patients should be provided with supplemental oxygen while sedation occurs
- Equipment for monitoring end-tidal carbon dioxide should be available on the ward, as should emergency drugs, ECG monitoring and equipment for endotracheal intubation
- Suction equipment should be available and checked prior to commencing each sedation case

Prescribing / Dosage

- Dilute ketamine 200mg/2mL ampoule to 20mL with sodium chloride 0.9% to produce a final concentration of 10mg/mL
- IV access patency should be confirmed prior to commencing injection of ketamine
- Sedation with ketamine should commence with slow IV injection, and the initial dose should not exceed 0.5mg/kg
- The total dose of ketamine for sedation should not exceed 1mg/kg

Recovery

 Patient should remain in the procedure room (or other appropriately monitored environment), with 1:1 nursing and minimum monitoring (pulse oximetry and BP) until conscious or for a minimum of 30 minutes after the procedure.

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