Ketamine: current applications in anesthesia, pain and critical care


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Pharmacokinetics:
- Highly lipid soluble
- Rapid breakdown and redistribution
- Norketamine (main metabolite; 1/3 tot 1/5 as potent)
- Excretion in urine and faeces
- Cumulative effect

Pharmacodynamics:
- Stimulation cardiovascular system (increase in HR, RR and CO mainly through sympt. NS)
- Minimal effect on central respiratory drive
- Airway relaxation
- Increases salivation and muscle tone
- Cataleptic, amnestic, profound analgesic, and dose dependent anesthetic actions
- Induces a dissociative state
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Mechanism of actions:

- noncompetitive antagonism of the N-methyl D-aspartic acid (NMDA) receptor

- opioid receptors, monoamine, cholinergic, purinergic and adrenoreceptor systems and local anesthetic effects
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Newly found mechanisms of action with newer clinical applications:

- plays a role in the opioid induced antihyperalgesic effects of ketamine
- subanesthetic doses potentiate opioid analgesia
- a protective antiinflammatory effect against sepsis process

Also:
- hypnotic effects of ketamine are caused by a combination of immediate channel blockade of NMDA and hyperpolarization-activated cation channels
- antiproinflammatory effects may be responsible for its antihyperalgesic effects
- immediate analgesic effects are mediated predominantly by a combination of opioid system sensitization and antinociception
- inhibits tumor necrosis factor-alpha and interleukin-6 gene expressions in macrophages. [NMDA receptor blockade by ketamine inhibits extracellular signal regulated kinase ½ pathway and proliferation of carcinoma cells by cell cycle arrest
- Downstream “postdrug” effects such as activity induced increase in structural synaptic connectivity lead to the prolonged antidepressant effects of ketamine.
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Old well-established applications where the role of ketamine remains unchallenged

1. IV induction agent in the emergency setting in shocked or hypotensive patients
2. Reactive airways disease
3. Induction of patients especially children with congenital heart disease with right to left shunt
4. Burn patients (IM injection)
5. Prehospital and battlefield medicine
6. IV supplement to local and regional anesthesia
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Intermediate clinical applications currently in use with moderate scientific evidence and where ketamine is used as an option to other agents:

1. Pediatrics: premedication, attenuation of sevoflurane induced emergence agitation and adjunct to caudal block

2. Adjunct to IV regional anesthesia, peripheral nerve blocks, stellate ganglion blocks

3. Prevention of postanesthesia shivering
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Recent clinical applications of ketamine with moderate scientific evidence and based on a renewed interest in low dose ketamine regimes:

1. Procedural sedation for adults and children (in combination with low doses of propofol)

2. Sedation and analgesia in the critical care unit
   
   In a study in patients with intracranial hypertension undergoing mechanical ventilation, ketamine effectively decreased intracranial pressure (ICP) and prevented untoward ICP elevations during distressing interventions without lowering blood pressure and cerebral perfusion pressure. Thus, ketamine can be used in combination with a benzodiazepine for patients with traumatic brain injury and intracranial hypertension and in trauma emergency situations

3. Co-induction and total IV anesthesia (TIVA)
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Recent clinical applications with limited scientific evidence
the role of the NMDA-receptor in pain modulation / anti-inflammatory properties

Acute pain management
1. Perioperative analgesia
   low dose ketamine 0.5mg/kg followed by 50-500 ug/kg/h
   - pre-emptive analgesia
   - reduction of opioid induced hyperalgesia

2. the role of multimodal pain therapy including ketamine in preventing postoperative chronic pain.

Chronic pain management
- (non-)cancer chronic pain
- short term relief of refractory neuropathic pain
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LIMITATIONS AND WARNINGS FOR KETAMINE USE:

1. The increase in muscle tone produced by ketamine makes it unsuitable for operations where muscle relaxation is needed

2. It is not indicated in conditions like hypertension, schizophrenia and raised intraocular pressure

3. Though ketamine well maintains the airway, some form of airway compromise needing manipulation can occur

4. The increase in salivation produced by ketamine can be troublesome and may produce laryngospasm in children. Premedication with an antisialogogue may be needed

5. It produces dose dependent psychological manifestations like emergence reactions, dreams, hallucinations and long-term psychotomimetic effects
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**Conclusion:**

The use of ketamine is extending now beyond the field of anesthesia into pain, palliative care, intensive care, and procedural sedation. It is being used more in low doses and as an adjunct to other drugs!!