# Ketamine (Ketalar): Mechanism of Action, Uses and Effects

Ketamine (Ketalar) is a commonly used intravenous anesthetic agent that is a noncompetetive inhibitor of N-methyl-D-aspartate (NMDA) . It got its start as an anesthetic drug in the 1960s and approved for human use in 1970 when it was used on the battlefields of the Vietnam War.

Ketamine is a congenor or derivative of psychotomimetic agent known as phenycyclidine (PCP). Ketamine is related to phencyclidine but with less than 10% of the potency of pure phencylidine.

This anesthetic agent is known to be a cardiovascular stimulant and its use may lead to an increases intracranial pressure.

Ketamine is classified as category A in pregnancy and is primarily sold under the brand name Ketalar.

It can also be used to minimize discomfort associated with surgical manipulation or injection of local anesthetics.

It has two reisomers S-ketamine S (+) and R ketamine R(-). S-Ketamine exhibits dextrorotationandR-Ketamineexhibits levorotation. Of these S is more potent.

It is available in a clear liquid or off-white powder form that is used for intravenous injection.

Ketamine is known to cause dissociative anesthesia.

## What is dissociative anesthesia ?

This is a kind of anesthesia produced by ketamine whereby a patient remains conscious but has marked catatonia, analgesia and amnesia (short-term memory loss).

Dissociative anesthesia is observed after induction with ketamine. The patient has eyes open with a cataleptic state which is a state with slow nystagmic activity.

Dissociative drugs cause distortion of color, sights,and sounds, self, and one's environment. Other examples of drugs with dissociative effects are include phencyclidine (PCP) and dextromethorphan (DXM).

## Indications of ketamine

Ketamine is indicated for induction and maintenance of anaesthesia. It is primarily used for surgical procedures which dont require skeletal muscle relaxation

This agent is also being studied on its possibility as a treatment for severe depression in difficult cases.

It is also used in the prevention of opioid-induced hyperalgesia.

Supplementation of spinal or epidural anesthesia using low doses.

It is the drug of choice for people in traumatic shock who are at risk of hypotension.

Ketamine is sometimes used in the treatment of status epilepticus that has failed to adequately respond to standard treatments

## Mechanism of action of ketamine

Ketamine works by antagonizing the N-methyl-D-aspartate receptor complex affecting muscarinic receptors, opioid receptors and voltage sensitive calcium channels in the brain, spinal cord and descending monoaminergic pain pathway.

It binds specifically to the dizocilpine (MK-801) site of the N-methyl-D-aspartate receptor complex, near the channel pore as an uncompetitive antagonist.

Ketamine is also known to interact with and antagonize the NMDAR via another allosteric site on the receptor. Due to its complex mechanism of action and its ability to interact with several receptor systems, it is known as 'a pharmacologist's nightmare

It disrupts the neurotransmitter known as glutamate. Glutamate is a brain chemical that is involved with learning, memory, emotion, recognition of pain.

## Pharmacokinetics and pharmacodynamics

Ketamine can be absorbed by IV, IM, oral, and topical routes because of its water and lipid solubilities.

Clinically it is usually administered intravenously or intramuscularly.

Ketamine is highly lipid soluble but low protein binding agent. (12-47 % protein bound). This makes it suitable for rapid onset of action.

Its volume of distribution at a steady state (Vdss) is 3.1 L/kg.

It has an distribution half-life of 11-16 minutes and an elimination half-life of 2-4 hours.

Its CL is 12-17 ml/kg/minute.

It is metabolized in the liver through the process of N-demethylation by the cytochrome P450 enzyme (CYP 3A4 and CYP 2B6) to produce a primary active metabolite known as Norketamine and Dehydronorketamine. This is then hydroxylated and conjugated to form a water soluble inactive metabolite which is then eliminated via urine 91%.

Its effect is usually reduced by redistribution to other body tissues after a bolus infusion because of its high lipophilicity.

It also rapidly crosses the blood–brain barrier and enters into the central nervous system.

It has a moderate duration of action of about 5-10 minutes.

## Dosage and administration

This agent is an important alternative to other intravenous anesthetic agents due to its unique features mentioned above.

It is given as a slow intravenous infusion over at least 60 sec so as to prevent development of hypertension and respiratory depression.

Do not give 100 mg/mL preparation undiluted

**Induction;**

- It is given intravenously at the rate of 1-4.5 mg/kg slow intravenously.
- 0.5-2 mg/kg slow IV if adjuvant drug such as midazolam is used, OR
- Intramuscularly: 6.5-13 mg/kg once
- Alternatively it can be given as 4-10 mg/kg IM once if adjuvant drug is used.

**Maintenance**

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    - 50% of IV ketamine induction dose administered as needed, OR
    - 0.1-0.5 mg/min IV continuous infusion

General anesthetic effect of ketamine is achieved with an intravenous infusion at the rate of 15-45 mcg/kg/minute plus 50-70% low potency nitrous oxide gas. Alternatively this can be achieved with ketamine alone at the rate of 50-90 mcg/kg/minute.

During regional anesthesia, ketamine is used at a small bolus dose of 0.2-0.8 mg/kg intravenously when additional analgesia is desired.

As mentioned above, ketamine provides analgesia without causing a respiratory or airway compromise.

A subanalgesic dose of 3-5 mcg/kg/minute may be used when it is employed as an adjunt to limit opioid tolerance.

## What are its effects in major body systems?

In the cardiovascular system, this agent is better tolerated with minimal effects therefore it fits most patients.

Sometimes it is associated with elevated blood pressure, increased heart rate (tachycardia) and increased cardiac output through centrally mediated sympathetic stimulation.

The agent is also known to have a direct myocardial depression although this effects is masked by

its sympathetic nervous system stimulation.

In the central nervous system, ketamine is known to produce cerebral vasodilation. This effect leads to increased cerebral blood flow as well as CMRO2. This effect makes ketamine not to be recommend for use in patients who may be having central nervous system pathology due to an increased risk of developing increased intracranial pressure.

Also its use is associated with the development of emergent reactions that are looked at within the article.

In the respiratory system, its use is associated with a better preserved bronchodilation therefore suitable for patients who have a reactive airway.

Its use has no respiratory depression. The patients usually have an intact respiratory response to hypercapnia (increased blood carbon(IV) levels) and stable blood gases.

Its ability to cause increased salivation can be countered by administration of anticholinergics to dry the membranes.

Neuromuscular and skeletal, it may cause increased skeletal muscle tone (tonic-clonic movements)

Ocular/vision. Its use may cause double vision, increased intraocular pressure, involuntary eye movements or tunnel vision

## Contraindications

Its use is contraindicated in patients with ketamine hypersensitivity and those at higher chances of developing hypertensive state such as hypertensive patients.

It is contraindicated in patients with psychiatric disorders because of its ability to cause hallucinations, and therefore may exacerbate the symptoms of certain psychiatric disorders.

It is also contraindicated in patients with penetrating eye injury : because it can increase risk of loss of eye contents, due to increased intraocular pressure.

A rapid administration of the drug causes respiratory depression

It should not be mixed with diazepam or barbiturates in same syringe.

Acute porphyria because it is considered to be porphyrinogenic.

It should not be used alone in surgeries involving the pharynx or bronchial tree, mechanical stimulation of the pharynx, larynx, or bronchial tree; avoid mechanical stimulation of the pharynx if ketamine used alone

Glaucoma or acute globe injury may be considered a relative contraindication

Drug interactions

There are no known severe reactions associated with its use.

Serious interactions of ketamine include:

- doxapram
- elvitegravir/cobicistat/emtricitabine/tenofovir df
- epinephrine
- fentanyl
- idelalisib
- isocarboxazid
- ivacaftor
- memantine
- norepinephrine
- phenelzine
- rasagiline
- selegiline
- sodium oxybate
- tranylcypromine

## Adverse Drug Reactions (ADRs) of Ketamine

Ketamine is generally well-tolerated but can lead to a range of adverse effects, particularly related to its CNS action and sympathetic stimulation:

**Central Nervous System (CNS)**

- **Emergence phenomena** : vivid dreams, hallucinations, and delirium upon waking. These effects are more common in adults and can be minimized by co-administration of benzodiazepines (e.g., midazolam).
- **Confusion, dizziness, and agitation** : especially during recovery.
- **Sedation or excessive somnolence**

**Cardiovascular System**

- **Hypertension** and **tachycardia** due to sympathetic stimulation
- Rarely, **arrhythmias** or **myocardial ischemia** in susceptible patients

**Respiratory System**

- **Increased salivation** , which can cause airway obstruction in rare cases; anticholinergics such as atropine or glycopyrrolate are often co-administered
- **Laryngospasm** or **apnea** may occur with rapid IV injection or overdose

**Gastrointestinal System**

- **Nausea and vomiting** , especially during recovery

**Musculoskeletal**

- **Involuntary movements** , increased muscle tone or tonic-clonic activity

**Ocular**

- **Diplopia** , **nystagmus** , **elevated intraocular pressure** , **blurred or tunnel vision**