

New Zealand Data Sheet

Name

Ketamine Infusion 1 mg/ml (bags), 2 mg/ml, 4 mg/ml and 10 mg/ml (syringes).

Description

Ketamine (as hydrochloride) (CAS number 1867-66-9) is a non-barbiturate anaesthetic chemically designated dl-2-(o-chloro-phenyl)-2-(methylamino) cyclohexanone hydrochloride. Ketamine is a racemic mixture. The molecular weight is 274.2 and the empirical formula is $C_{13}H_{16}ClNO.HCl$. It is formulated as an acid (pH 3.5 to 5.5) solution for intravenous infusion in concentrations containing the equivalent of 4 and 10 mg ketamine base per millilitre and contains no preservatives. Ketamine is freely soluble in water and methyl alcohol and is soluble in alcohol.

Pharmacology

Actions

Ketamine is a rapid-acting, general anaesthetic producing an anaesthetic state characterised by profound analgesia, normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and respiratory stimulation, and occasionally, a transient and minimal respiratory depression.

A patent airway is maintained, partly by virtue of relatively unimpaired pharyngeal and laryngeal reflexes (see **Precautions**).

The anaesthetic state produced by ketamine has been termed 'dissociative anaesthesia' in that it appears to selectively interrupt association pathways of the brain before producing somaesthetic sensory blockade. Ketamine may selectively depress the thalamoneocortical system before significantly obtunding the more ancient cerebral centres and pathways (reticular-activating and limbic systems).

Elevation of blood pressure begins shortly after injection, reaches a maximum within a few minutes and usually returns to pre-anaesthetic values within 15 minutes after injection. The median peak rise has ranged from 20 to 25% of pre-anaesthetic values.

Pharmacokinetic Properties

Distribution

Ketamine (as hydrochloride) is rapidly and extensively distributed throughout the body into highly perfused tissues including the brain. Mean volume of distribution is reported to range from approximately 1 to 3 L/kg, and the distribution half-life is approximately 7 to 11 minutes. Ketamine (as hydrochloride) is approximately 20-50% bound to plasma proteins. Ketamine is likely to be excreted in breast milk, but this is unlikely to be clinically relevant. The drug crosses the placenta in induction doses but in amounts that have no adverse effects on the neonate (see **Use in Pregnancy** and **Use in Lactation**).

Metabolism

Ketamine undergoes extensive hepatic metabolism. The biotransformation includes N-dealkylation to norketamine (metabolite I), hydroxylation of the cyclohexone ring

(metabolites III and IV), conjugation with glucuronic acid and dehydration of the hydroxylated metabolites to form the cyclohexene derivative (metabolite II). Norketamine (metabolite I) has about 1/6 of the potency of ketamine and is formed at concentrations in the plasma similar to those of the parent compound.

Elimination

After intravenous bolus administration, ketamine shows a bi- or triexponential pattern of elimination. The alpha phase lasts about 45 minutes with a half-life of 10 to 15 minutes. This first phase, which represents the anaesthetic action of ketamine, is terminated by redistribution from the CNS to peripheral tissues and hepatic biotransformation to an active metabolite. The beta phase half-life is about 2.5 hours. About 90% of ketamine is excreted in the urine, mostly as metabolites, with only about 2 to 4 % as the unchanged drug. Approximately 5% is recovered in the faeces. The renal clearance of ketamine hydrochloride is 15 ± 5 mL/min/kg.

Paediatric Patients

Plasma half-life, clearance and volume of distribution (relative to body weight) are not significantly different between adults and children.

Clinical Studies

Ketamine (as hydrochloride) has been studied in over 12,000 operative and diagnostic procedures involving over 10,000 patients from 105 separate studies. During the course of these studies, ketamine was administered as the sole agent, as induction for other general anaesthetic agents, or to supplement low potency agents. In these studies, the anaesthesia was rated either "excellent" or "good" by the anaesthetist and the surgeon at 90% and 93% respectively. In a second method of evaluation, the anaesthesia was rated "adequate" in at least 90% and "inadequate" in 10% or less of procedures. Specific areas of application have included the following:

1. debridement, painful dressings and skin grafting in burn patients as well as other superficial surgical procedures;
2. neurodiagnostic procedures such as pneumoencephalograms, ventriculograms, myelograms and lumbar punctures;
3. diagnostic and operative procedures of the eye, ear, nose and mouth including dental extractions;
4. diagnostic and operative procedures of the pharynx, larynx or bronchial tree; Note: muscle relaxants with proper attention to respiration, may be required (see **Precautions**)
5. sigmoidoscopy and minor surgery of the anus and rectum and circumcision;
6. extraperitoneal procedures used in gynaecology, such as dilation and curettage;
7. orthopaedic procedures such as closed reductions, manipulations, femoral pinning, amputations and biopsies;
8. as an anaesthetic in poor-risk patients with depression of vital functions;
9. in cardiac catheterisation procedures.

Indications

Ketamine infusion is recommended:

1. as the sole anaesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketamine is best suited for short procedures and it can be used with additional doses, for longer procedures;

2. for the induction of anaesthesia prior to the administration of other general anaesthetic agents;]
3. to supplement low-potency agents, such as nitrous oxide.

Contraindications

Ketamine is contraindicated in patients with any condition in which a significant elevation of blood pressure would be hazardous such as: severe cardiovascular disease, heart failure, severe or poorly controlled hypertension, recent myocardial infarction, history of stroke, cerebral trauma, intracerebral mass or haemorrhage. Ketamine is also contraindicated in those who have shown hypersensitivity to the drug or its components.

Precautions

1. Ketamine should be used by or under the direction of medical practitioners experienced in administering general anaesthetics and in maintenance of an airway and in the control of respiratory support.
2. Barbiturates and ketamine, being chemically incompatible because of precipitate formation, **should not** be injected from the same syringe.
3. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with ketamine.
4. Post-operative confusional states may occur during the recovery period (see **Precautions, Emergency Reaction**).
5. Because pharyngeal and laryngeal reflexes are usually active, ketamine should not be used alone in surgery or diagnostic procedures of the pharynx, larynx or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if ketamine is used alone. Muscle relaxants with proper attention to respiration, may be required in both of these instances.
6. Resuscitative equipment should be ready for use.
7. Rapid administration may result in respiratory depression or apnoea and enhanced pressor response.
8. In surgical procedures involving visceral pain pathways, ketamine should be supplemented with an agent, which obtunds visceral pain.
9. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.
10. An increase in cerebrospinal fluid pressure has been reported following administration of ketamine. Use with extreme caution in patients with pre-anaesthetic elevated cerebrospinal fluid pressure.
11. In patients with significant renal or hepatic impairment, the elimination of ketamine could potentially be delayed. Dose reductions should be considered in patients with cirrhosis or other types of liver impairment.
12. Patients should be cautioned that driving an automobile, operating machinery or engaging in other hazardous activities should not be undertaken for 24 hours or more (depending on dose and other drugs employed) after anaesthesia.
13. Use with caution in patients with increased intraocular pressure (eg. glaucoma) because the pressure may increase significantly after a single dose of ketamine
14. Use with caution in patients with neurotic traits or psychiatric illness (eg. schizophrenia and acute psychosis).

15. Use with caution in patients with acute intermittent porphyria.
16. Use with caution in patients with seizures.
17. Use with caution in patients with hyperthyroidism or patients receiving thyroid replacement (increased risk of hypertension and tachycardia).
18. Use with caution in patients with pulmonary or upper respiratory infection (ketamine sensitises the gag reflex, potentially causing laryngospasm).
19. Use with caution in patients with intracranial mass lesions, a presence of head injury, globe injuries, or hydrocephalus.

Emergence Reaction

Treatment-emergent adverse reactions have occurred in approximately 12% of patients. The psychological manifestations vary in severity between pleasant dream-like states, vivid imagery, hallucinations, nightmares or illusions and delirium (often consisting of dissociative or floating sensations). In some cases, these states have been accompanied by confusion, excitement and irrational behaviour, which a few patients recall as an unpleasant experience. The duration ordinarily lasts no more than a few hours; in a few cases, however, recurrences have taken place up to 24 hours post-operatively. No residual psychological effects are known to have resulted from use of ketamine

The incidence of these treatment-emergent adverse events is least in the young (15 years of age or less) and elderly (over 65 years of age) patient. These reactions may be reduced if verbal, tactile and visual stimulation of the patient is minimised during the recovery period.

This does not preclude the monitoring of vital signs. In addition, the use of a small hypnotic dose of a short-acting or ultra-short-acting barbiturate may be required to terminate a severe treatment-emergent adverse reaction. The incidence of emergence reactions is reduced as experience with the drug is gained. When ketamine is used on an out-patient basis, the patient should not be released until recovery of anaesthesia is complete and should be accompanied by a responsible adult at discharge.

Cardiovascular

Because of the substantial increase in myocardial oxygen consumption, ketamine should be used with caution in patients with hypovolemia, dehydration, or cardiac disease, especially coronary artery disease (eg. congestive heart failure, myocardial ischaemia, and myocardial infarction). In addition ketamine should be used with caution in patients with mild-to-moderate hypertension and tachyarrhythmias.

Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.

Abuse Potential

Ketamine has been reported being used as a drug of abuse. Reports suggest that ketamine produces a variety of symptoms including, but not limited to, flashbacks, hallucinations, dysphoria, anxiety, insomnia, or disorientation. Ketamine dependence and tolerance may develop in individuals with a history of drug abuse or dependence. Therefore, ketamine should be prescribed and administered with caution.

Use In Pregnancy

Category B3

Limited studies in animals have not shown that ketamine causes birth defects; however, it crosses the placenta. Histological changes in the heart (degeneration and

oedema of cardiac muscle), liver (diffuse haemopoietic cell infiltration, parenchymal cell degeneration) and kidneys (proximal convoluted tubule degeneration) were observed in foetuses following administration of ketamine to pregnant rats during the period of organogenesis at doses similar to the maximum human dose, on a body surface area basis; a NOEL for these effects was not established. Ketamine administration to pregnant monkeys near term was associated with increased blood pCO₂ and a dose-dependent respiratory depression in neonates, at a dose about one sixteenth the maximum human dose on a body surface area basis.

With the exception of administration during surgery for abdominal delivery or vaginal delivery, no controlled clinical studies in pregnancy have been conducted. The safe use of ketamine in pregnancy has not been established, and such use is not recommended.

Australian categorisation definition of Category B3:

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Use in Lactation

Ketamine is likely to be excreted in breast milk and therefore breastfeeding should be discontinued when ketamine is in use.

Interactions with other Medicines

Halogenated hydrocarbon inhalational anaesthetics may prolong the half-life of ketamine; recovery from anaesthesia may be prolonged following concurrent use. Concurrent use of ketamine (especially in high doses or when rapidly administered) with halogenated anaesthetics can increase the risk of developing bradycardia, hypotension, or decreased cardiac output.

Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with ketamine.

Benzodiazepines may prolong the half life of ketamine; recovery from anaesthesia may be prolonged following concurrent use.

Co-administration of drugs with a hypertensive effect (eg. ergometrine) should be avoided.

Sustained rises in arterial pressure have been reported in patients receiving concomitant ketamine and thyroxine.

Clinically apparent reduction in seizure threshold has been reported in patients receiving concomitant ketamine and theophylline. Unpredictable extensor-type seizures have been reported with concurrent administration of these agents.

There is no information available on the interactions between ketamine and antihypertensive agents. However, given the marked increase in arterial pressure following administration of ketamine, cardiac function should be monitored (see **Precautions**).

Barbiturates and ketamine, being chemically incompatible because of precipitate formation, **should not** be injected from the same syringe.

Ketamine is clinically compatible with the commonly used general and local anaesthetic agents when an adequate respiratory exchange is maintained.

Ketamine may potentiate the neuromuscular blocking effects of atracurium and tubocurarine, including respiratory depression with apnoea.

The use of ketamine with other central nervous system (CNS) depressants (eg. ethanol, phenothiazines, sedating H₁-blockers, or skeletal muscle relaxants) can potentiate CNS depression and/or increase risk of developing respiratory depression. Reduced doses of ketamine may be required with concurrent administration of other anxiolytics, sedatives, and hypnotics.

Ketamine has been reported to antagonise the hypnotic effect of thiopental.

Patients taking thyroid hormones have an increased risk of developing hypertension and tachycardia when given ketamine.

Concomitant use of antihypertensive agents and ketamine increases the risk of developing hypotension.

Effects on Laboratory Tests

There is no information available regarding the possible effects of ketamine on clinical laboratory tests.

Adverse Effects

Cardiovascular

Blood pressure and pulse rate are frequently elevated following administration of ketamine. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

Respiration

Although respiration is frequently stimulated, severe depression of respiration or apnoea may occur following rapid intravenous administration of high doses of ketamine. Laryngospasm and other forms of airway obstruction have occurred during ketamine anaesthesia.

Eye

Diplopia and nystagmus have been noted following ketamine administration. Ketamine may also cause a slight elevation in intraocular pressure measurement.

Psychological (see Precautions- Emergence Reaction)

Neurological

In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements, sometimes resembling seizures (see **Dosage and Administration**).

Gastrointestinal

Anorexia, nausea and vomiting have been observed. However this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness (see **Dosage and Administration**). Hypersalivation has also been observed.

Abuse Potential (see Precautions)

Immune System Disorders

Anaphylaxis has been observed.

General

Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

Dosage and Administration

Pre-Operative Preparation

1. While vomiting has been reported following ketamine administration, airway protection is usually afforded because of active laryngeal-pharyngeal reflexes. However, because these reflexes may also be diminished by supplementary anaesthetics or muscle relaxants, the possibility of aspiration must be considered. Ketamine is recommended for use in the patient whose stomach is not empty only when, in the judgement of the medical practitioner, the benefits of the drug outweigh the possible risks.
2. Atropine, hyoscine or other 'drying' agents should be given at an appropriate interval prior to induction.

Dosage

As with other general anaesthetic agents, the individual response to ketamine is somewhat varied depending on the dose, route of administration and age of patient, so that the dosage recommended cannot be absolutely determined in a fixed manner. The drug should be titrated against the patient's requirements.

Onset and Duration

Because of rapid induction following the initial intravenous injection, the patient should be in a supported position during administration. The onset of action of ketamine is rapid; an intravenous dose of 2 mg/kg of body weight usually produces surgical anaesthesia within 30 seconds after injection, with the anaesthetic effect usually lasting 5 to 10 minutes. If a longer effect is desired, additional increments can be administered to maintain anaesthesia without producing significant cumulative effect.

Induction

The initial dose of ketamine administered intravenously may range from 1 mg/kg to 4.5 mg/kg. The average amount required to produce 5 to 10 minutes of surgical anaesthesia has been 2 mg/kg. It is recommended that ketamine infusion be administered slowly (over a period of 60 seconds). More rapid administration may result in respiratory depression and enhanced pressor response. Dose reductions should be considered in patients with cirrhosis or other types of liver impairment (see **Precautions**).

Maintenance of Anaesthesia

Increments of one half to the full induction dose may be repeated, as needed, for maintenance of anaesthesia. However it should be noted that involuntary and tonic-clonic movements of extremities might occur during the course of anaesthesia. These movements do not imply a level of attenuated anaesthesia and are not indicative of the need for additional doses of the anaesthetic. It should be recognised that the greater the total dose of ketamine administered, the longer will be the time to complete recovery.

This product is for one dose in one patient only. Discard any remaining contents.

Overdosage

Respiratory depression may occur with overdosage or too rapid rate of administration of ketamine, in which case, supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

Ketamine has a wide margin of safety; several instances of unintentional administration of overdoses of ketamine (up to 10 times that usually required) have been followed by prolonged but complete recovery.

In case of overdose, immediately contact the Poisons Centre for advice, call 0800 764 766.

Presentation and Storage Conditions

Ketamine Infusion 1 mg/ml is available in flexible bags, are to be stored at 15 – 25 °C and have a shelf life of 12 months from the date of manufacture.

Ketamine Infusions 2 mg/ml and 4 mg/ml are available in 50 ml syringes. The 10 mg/ml strength is available in 10 ml syringes. Syringes of all strengths are stored at 15 - 25 °C and have a shelf life of 6 months from the date of manufacture.

The infusions should not be used if they are coloured and/or contain particulate matter.

Medicine Classification

Controlled Drug C4

This medicine has been granted provisional consent under section 23 of the Medicines Act 1981.

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