KETAMINE - SUBLINGUAL WAFER

Introduction

Ketamine wafer (trade name in Australia "**Wafermine**") is a novel formulation of ketamine suitable for **sublingual** administration.

There is ongoing evaluation, but the agent shows promise as the first powerful oral analgesic *alternative* or *adjunct* to the opioids.

Ketamine **wafer** has comparable bioavailability with other oral transmucosal formulations of ketamine but with **markedly reduced inter-subject variability**.

It is indicated for:

1. Moderate to severe acute postoperative pain.

2. Moderate to severe acute procedural pain.

Ketamine wafer is currently available in Australia under **exemption Schedule 5A (item 5)** of the Australian Therapeutic Goods Regulations.

Important advantages of sublingual ketamine wafer, over opioids include:

- **Quicker onset of analgesia (within 10 minutes)**
- **Easier to titrate to clinical effect**
- **More predictable clinical response**
- **Less respiratory depression**
- **Less potential for addiction.**
- **Avoids the need for an IV**

See also separate document on:

- **Ketamine -Parenteral (in Drugs folder).**

History

Ketamine was first synthesized in **1961** by **Dr. Calvin Lee Stevens**, (1923 - 2014) a professor of organic chemistry who worked at Wayne State University and Parke - Davis Laboratories.

After promising preclinical research in animals, ketamine was introduced to testing in human prisoners in 1964. These investigations demonstrated ketamine's short duration of action and reduced behavioural toxicity made it a favourable choice over phencyclidine (PCP) as a dissociative anaesthetic

It was approved for human use in 1965.

It was given FDA approval as an anaesthetic agent in 1970.

It was then used for wounded soldiers during the Vietnam War.

During the 1980s it began to be used as a drug of abuse, favoured because of its dissociative effects. In 1995 it was listed by the DEA as an emerging drug of abuse.

In 1999 ketamine was listed as a controlled substance in the United States.

Chemistry

Ketamine, is a phencyclidine derivative.

With the sublingual formulation there is rapid disintegration upon contact with saliva of the hydrophilic wafer matrix.

Lyophilised ketamine is then absorbed via the sublingual route.

Preparations

Racemic mixture of ketamine hydrochloride as:

Sublingual wafers:

- 25 mg
- 50 mg

Mechanism of Action

Ketamine is an **N-methyl-D-aspartate (NMDA) antagonist** that induces dissociative anaesthesia due to dissociation between the thalamocortical and limbic systems, effectively dissociating the central nervous system from all outside stimuli (touch, sight, sound, taste, smell).

It also interacts with opioid receptors.

Pharmacodynamics

Studies to date have shown rapid analgesic responses with a reduction in pain intensity scores occurring within **10 minutes** of sublingual administration.

Peak analgesic response occurred between **20-30 minutes** post dosing.

The duration of action after a single dose is up to **2 - 3 hours**.

Pharmacokinetics

Absorption:

- **Sublingual** ketamine is rapidly absorbed.

  The wafer dissolves within 1 - 2 minutes of being placed sublingually.

  Because of high hepatic first pass metabolism, **oral** formulations of ketamine have low bioavailability. When these are administered **sublingually** as a liquid formulation or as a tablet, systemic absorption seems about the same or at most only about 50% higher than after oral administration. This fact suggests that most of the sublingually administered drug actually ends up being swallowed by patients! [2]

  The novel **rapidly dissolving** sublingual **wafer** formulation however, by releasing the drug in a **small volume immediately adjacent to the mucosal membranes**, allows for significant **direct** sublingual absorption with higher overall bioavailability than other oral formulations.[2]

- The absolute bioavailability of sublingual ketamine is around 30 %

  This suggests that a **sublingual** dose of **50 mg** would produce a similar drug exposure to approximately **15 mg** of **intravenous** ketamine.

Distribution

- Ketamine (as a hydrochloride) is rapidly and extensively distributed throughout the body into highly perfused tissues including the brain.
- Ketamine is highly lipid soluble and not highly protein bound
- The mean volume of distribution ranges from approximately 1 - 3 L/kg
- It is unknown if whether ketamine is excreted into human breast milk
- Placental transfer in humans can occur.

Metabolism and excretion:

- Ketamine undergoes extensive hepatic metabolism by the cytochrome P450 system, mainly by CYP3A4 and 2B6.
- Some metabolites are active, including norketamine which is about 1/3 to 1/5 as potent as ketamine
- Redistribution half - life is 5 - 15 min and the elimination half - life is about 1 - 2 hours.

Indications

Sublingual ketamine is indicated for:

1. Moderate to severe acute postoperative pain.
2. Moderate to severe acute procedural pain.

Contra-indications/precautions

Contraindications/ precautions from the parenteral formulation include:

1. Non-fasted patients (as with any anaesthetic agent).
2. Conditions that may be worsened by an **increase in blood pressure** and/or heart rate:
    - Poorly controlled hypertension, stroke, intracerebral haemorrhage, angina, recent MI, stenotic valvular heart disease, tachyarrhythmias, chronic heart failure, thyrotoxicosis.
3. Procedures that will stimulate the posterior pharynx.
    - Major procedures stimulating the posterior pharynx (e.g., endoscopy) increase the risk of laryngospasm, whereas typical minor ED oropharyngeal procedures do not.
4. Caution when used in association with other CNS depressant drugs, including **ethanol.**

Seizure disorders are no longer considered contraindications to ketamine use

Pregnancy

Ketamine is classified as a category B3 drug with respect to pregnancy.

B3 drugs are those 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 foetal damage, the significance of which is considered uncertain in humans.

Reports of congenital malformations following ketamine use during pregnancy have not been located.

However, maternal use of ketamine, especially at high doses or prolonged use near term may increase the risk of maternal and neonatal complications such as increased maternal blood pressure, increased uterine tone, respiratory depression and increased skeletal musculature tone in newborns.

Ketamine is considered safe to during pregnancy when used at the lowest effective dose for the shortest duration possible.

Breast feeding

There is limited information describing the use of ketamine during breastfeeding.

Ketamine undergoes rapid degradation in the plasma, which may limit the amount of ketamine excreted into breast milk.

Ketamine is considered safe to use during breastfeeding when used at the lowest effective dose for the shortest duration possible.

However, observe the breastfed infant for potential adverse effects, such as drowsiness, poor feeding and sleeping pattern changes.

Adverse Effects

Adverse events via the sublingual route are usually only mild and transient.

Adverse reactions from the *parenteral* formulation include:

1. Transient **apnoea or respiratory depression**

    - This is the most common potentially serious adverse effect.

    - Although mild stimulation of respiration is most commonly seen, respiratory depression, even apnoea, can occur, usually in the setting of excessively rapid and high dose IV administration.

2. Hypersalivation:

- Gentle suctioning is useful to remove excess secretions, but this should only be at the **anterior** buccal cavity. Deeper airway suction may aggravate airway reflexes.

- *Prophylactic* anticholinergics are **no longer** recommended.

- Atropine **(0.02 mg/kg to a maximum of 0.6 mg IV/IM)** or glycopyrrolate may be considered if hypersalivation occurs that is not readily controlled by gentle suction.

3. Transient laryngospasm

4. Vomiting, (uncommon, risk slightly greater by IM route)

   - Prophylactic ondansetron can slightly reduce vomiting

5. Myoclonic jerking movements

6. Allergic reactions, (very uncommon):

   - A benign evanescent patchy erythematous rash about the upper torso may be seen, (presumably due to an "anaphylactoid" type histamine release).

   - True anaphylaxis is very rare, but has been well described in isolated case reports. [11]

7. **Emergence phenomena:**

   - Emergence reactions are relatively frequent occurring in approximately 10 % of patients.

   - These may take the form of hallucinations, both visual and auditory.

     Severity may range from pleasant dream-like states or depersonalisation, to very vivid hallucinations to frank delirium.

   - Most patients cannot recall the reactions but a few can recall them as an unsettling experience.

   - Emergence phenomena, occur more commonly beyond mid-adolescence (after about 15 years). They are also more common in the elderly (> 65 years).

   - The duration of these reactions is usually no more than a few hours.

   - **Simple and constant reassurance** is usually sufficient treatment, but occasionally benzodiazepine sedation may be required.

Prophylactic benzodiazepines are no longer recommended.

Maintaining minimal sensory stimulation will help reduce the effects of emergence phenomenon.

Maintain the patient in a quiet area with **dim lighting**, when possible.

Dosing

Ketamine wafers are administered sublingually .

To ensure the sublingual mucosa is moist prior to wafer administration, patients should be instructed to rinse their mouth with approximately 20 mLs of water and then to swallow the water completely.

The wafer should then be placed posteriorly towards the base of the tongue and medially on either side of the frenulum in the sublingual space.

The patient should then be informed not to chew or swallow the wafer, but rather just let it sit under the tongue to be dissolved.

Usual adult dosing has not been clearly established.

The following regime has been used successfully:

- SL **25 - 50 mg**, 10 minutely PRN, (up to 3 - 5 doses may be required)

A maximum dose per procedure has not been established.

References

1. Wafermine- Prescriber Information Sheet - Biopharma & Syrinx Pharmaceuticals; October 2017.

2. Paul Edward Rolan, et al. The absolute bioavailability of racemic ketamine from a novel sublingual formulation. Br J Clin Pharmacol. 2014 Jun; 77(6): 1011 - 1016.

3. Ketamine in RWH Pregnancy & Breast feeding Guidelines, 15 February 2017

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