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Chapter

Use of Oral Ketamine in Palliative Care

Mateja Lopuh

Abstract

Ketamine, an N-methyl-D-Aspartate receptor antagonist, has been used for more than 50 years. From its initial potential as an anesthetic drug, its use has increased in the fields of pain medicine, psychiatry, and palliative care. It is available in different formulations, of which oral use is promising due to its active metabolite, norketamine which reaches 2–3 times higher levels when administered orally in comparison with parenteral use. Oral use is also more feasible and easier to use in settings, where medical staff is not that present, such as home care or hospices. Oral solution of ketamine has not yet been officially licensed for use although there have been several reports which recommend its use in neuropathic pain, severe depression, airway obstruction, and anxiety. Palliative care is defined as total care for patients whose diseases do not respond to curative treatment. It encompasses good control of physical symptoms, and psychological, social and spiritual problems. Patients often experience pain, despite high doses of opioids, depression and anxiety, and dyspnea. Oral ketamine does not have the side effects of opioids therefore it represents a good alternative. It may also reduce the need for high opioid doses and be more suitable for patients who wish to avoid the necessary sedation.

Keywords: oral ketamine, neuropathic pain, opioids, symptom control, palliative care

1. Introduction

Ketamine is a potent noncompetitive NMDA receptor antagonist. It is primarily marketed as a general anesthetic, but it also shows analgesic properties at lower, subanesthetic doses [1]. It is used as a chlorhydrate in a slightly acid aqueous solution. It is a racemic mixture of two enantiomers of equal quantity of which only the S (+) enantiomer is active and is two times stronger than the racemic mixture and four times stronger than the R (−) enantiomer. In equianalgesic doses, the S-enantiomer is associated with lower levels of undesirable effects.

Ketamine metabolism is characterized by low binding to plasma proteins, about 10–30%. It is highly liposoluble and has therefore an extensive distribution. The central compartment volume is 70 liters and the distribution volume at steady state is around 200 liters. Oxidation is the primary process in the metabolism of ketamine, resulting in norketamine (80%), which is an active metabolite that itself is principally hydroxylated in 6-hydroxy-norketamine and finally excreted in bile and urine after glucurononconjugation. Ketamine elimination clearance is dependent on the liver blood flow, half time is 2–3 hours, and it may be 20% higher in women than men [2].
Ketamine is commonly administered via the intravenous, intramuscular, subcutaneous, or oral route. The subcutaneous route appears to be very practical because it avoids potential delays in treatment caused by the inability to establish intravenous access, has a rapid onset of action, and can be used by less skilled personnel, too [3].

The oral route availability of ketamine is incomplete and erratic. Only about 16–20% of an oral dose reaches systemic circulation due to extensive hepatic first-pass elimination. The bioavailability of intranasal ketamine was found to be 50%. Peak plasma concentrations are being reported within 30 minutes of oral administration. Norketamine as an active metabolite reaches 2- or 3-times higher levels when ketamine is administered orally than parenterally and the duration of action of oral ketamine is longer. To achieve a good analgesic effect, doses of oral ketamine can be one-third of the parenteral one, due to the active effect of norketamine [3]. In chronic use, norketamine may be the main analgesic agent. Because of norketamine accumulation the need for ketamine when given for a longer period of time, decreases over time. Norketamine is 33% as potent as the parent compound [4].

In palliative care patients often exhibit a variety of symptoms. They float between the desire to keep autonomy for as long as possible and the wish to avoid the unnecessary suffering, caused by poorly relieving symptoms. Many patients are afraid of opioids, especially morphine, and are reluctant to use them. Some physicians still believe that morphine accelerates death, and they would only use it when patients already entered the dying phase. Ketamine with its analgesic properties may be a good option to keep the opioid levels low as long as possible.

Ketamine has not yet been widely used in palliative care probably because it has always been marketed as an anesthetic drug and therefore reserved for use in the operating theaters. Even its use has not been very prominent due to the psychomimetic side effects when used in anesthetic dosage. Its domains of use expanded in pain medicine, where the doses can be lower, but it was used parenterally, therefore intravenous or subcutaneous access was needed. Longer subcutaneous use often resulted in necrosis of subcutaneous tissue and reduced flow from elastomeric pumps.

Oral and nasal use of ketamine has not been officially licensed although several papers have already been published which suggest that both routes are safe and feasible. These two routes seem to offer advantages over the intravenous and subcutaneous approaches as they allow the patient to be self-sufficient and autonomous in drug administration.

Some pharmacokinetics data are summarized in Table 1.

Palliative care may expand over the whole trajectory of the incurable disease. Ketamine is used as a co-analgesic in poorly controlled pain, especially neuropathic pain, to reduce the dose of opioids, to relieve anxiety and depression, severe epileptic seizures, and as bronchodilator. The long-term use of ketamine has not been studied extensively. In palliative care, the studies are limited because symptoms accumulate in the course of the disease and that makes the observation of side effects more difficult.

<table>
<thead>
<tr>
<th></th>
<th>Bioavailability (%)</th>
<th>Onset of action (min)</th>
<th>Duration of action (h)</th>
<th>Elimination half time (h)</th>
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<tr>
<td>Parenteral route</td>
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<td>0.5</td>
<td>0.5–2</td>
<td>2</td>
</tr>
<tr>
<td>Oral route</td>
<td>17–25</td>
<td>30</td>
<td>4–6</td>
<td></td>
</tr>
<tr>
<td>Nasal route</td>
<td>50</td>
<td>20</td>
<td>Up to 3</td>
<td>2</td>
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Table 1. Pharmacokinetics of ketamine.
This chapter focuses on the oral/nasal route of ketamine administration in patients with palliative diseases, its useful properties in clinical practice, and its side-effects. Some suggestions are given about the formulation of the drug and the dosage regimens.

2. Clinical uses of ketamine

Ketamine is approved as a general anesthetic agent. At subanesthetic doses, it can be considered for use in a palliative care setting for pain refractory to opioids and as an adjuvant analgesic. Ketamine was approved by FDA for antidepressant use in 2019 as a nasal spray. Ketamine has no reversal agent [5].

Ketamine can be used in the intensive care units as a sedative and analgesic drug. It can be safely used in patients with traumatic brain injury as it does not raise the intracranial blood pressure, caution is needed when used with raised intraocular pressure. When used as an analgesic drug, it may reduce pain scores, opioid consumption, and postoperative nausea and vomiting.

In chronic, non-cancer pain, ketamine can be used as add-on therapy when other therapeutic options have failed. The long-term effects remain controversial.

In cancer pain, ketamine is considered an essential adjuvant drug but the evidence for its efficiency is low [6, 7].

Ketamine has proven to be efficient in treating major depression, bipolar disorders, and suicidal behavior. It acts very fast, and relieves depression in less than 2 hours. In the approved nasal spray only the S (+) enantiomer is used [8, 9].

Other uses of ketamine with the low level of evidence are alcohol withdrawal, status epilepticus, and persistent bronchospasm in critical care settings [8].

Suggested mechanisms of ketamine action are summarized in Table 2.

3. Oral formulations

Ketamine is not licensed for oral use. Physicians should properly inform the patients about the advantages and possible side-effects of the drug and the route of administration.
A parenteral formulation is utilized for oral formulations of ketamine. Use generic ketamine 50 mg/ml 10 ml vials and purified water. Alternatively, one can use flavored syrup instead of water, but most patients find it too sweet.

To prepare 100 ml of oral solution with a concentration of 50 mg/5 ml use two 10 ml vials of ketamine 50 mg/ml for injections and 80 ml of purified water. The solution can be refrigerated with an expiry date of 1 week from manufacture [1].

It is useful to provide the patient with a syringe to ease the administration of ketamine.

4. Nasal route

Ketamine is not licensed for nasal use. Physicians should properly inform the patients about the advantages and possible side-effects of the drug and the route of administration.

The nasal route appears very promising as it allows the patient to self-administer the drug when needed due to the rapid onset of action which is similar to intramuscular injection. As the capacity of the human nostrils is 0.2 ml, a greater volume may be swallowed or may run out of the nose. Ketamine may be administered via MAD which delivers a mist of atomized medication or via metered-dose nasal spray. The concentration of ketamine, commercially available is 100 mg per ml or 10 mg per ml. Up to 40 mg can be reliably delivered intranasally. Higher doses are ingested [10].

Patients can be prescribed oral ketamine basal treatment and use nasal formulation for treating breakthrough pain.

5. Regimens for switching from parenteral to oral administration

Ketamine has been predominantly used parenterally as a co-analgesic in addition to opioids and co-adjuvant drugs. Oral use has obvious advantages: it is not necessary to carry the pump around, which needs frequent refilling and it avoids inflammation on the site of subcutaneous administration. It has been proven in studies that a 1:1 dose ratio is safe and effective in switching from parenteral to oral administration [11]. Another report suggested switching to one-third of the parenteral dose as a result of the effect of norketamine. Oral ketamine may in fact be a more potent analgesic and produce adverse effects less frequently than parenteral ketamine. After oral administration of 0.5 mg/kg ketamine approximately 20% is absorbed and its analgesic action seems to be mediated by its first metabolite norketamine, which has a half-life of 12 hours [12].

A good therapeutic response to parenteral ketamine suggests a greater likelihood of benefit from oral dosing. Patients who could benefit from switching to oral use of ketamine are those whose pain has been stable for 48 hours after subcutaneous infusion of ketamine, patients who wanted to be discharged home and had good pain control with ketamine, patients with a life expectancy longer than 2 weeks, and patients who could swallow or had a possibility to be tube fed.

When switching from parenteral to the oral route, benzodiazepines are discontinued [12].

The usual starting dose is 10–25 mg three or four times daily plus when needed. The dose can be increased in steps of 10–25 mg up to 100 mg three times daily [13].

Authors of the so far published studies differ in their recommendations about oral ketamine initiation. Some recommend one should always begin first with
parenteral application and then switch to oral ketamine. The parenteral route could be either intravenous or subcutaneous. When used as an adjuvant to oral morphine, patients begin as well with oral ketamine [14, 15]. For the patient, who are, due to advanced disease, unable to swallow, the nasal route is more suitable [10].

6. Useful properties in the palliative care setting

6.1 Analgesic properties

Ketamine is considered one of the World Health Organization’s essential drugs for the management of refractory pain and is associated with reduced opioid consumption and reduced opioid tolerance. It can be used in the treatment of acute and chronic pain as a co-analgesic and for alleviating the breakthrough pain episodes. Prescribing subanesthetic doses of ketamine can reduce postoperative morphine necessity and so diminish the side-effects of morphine.

The use of ketamine in the treatment of pain as an adjuvant analgesic is not licensed but the evidence for its efficiency is considerable. Its use has been recommended in the Scottish Palliative Care Guidelines and the Palliative Care Formulary. When used, a prescribing physician should notify the patient.

Ketamine is indicated for the treatment of neuropathic pain which has not responded to other medications, including strong opioids, anticonvulsants (gabapentin), and tricyclic antidepressants, including a trial of high dose dexamethasone.

Experimental data provide evidence that norketamine is effective in preventing central sensitization and in reversing an established hyperalgesia.

Although clinical evidence has been adding up, there are just a few comparative studies, and the majority of evidence is in the form of case reports [16–18].

A usual starting dose of oral ketamine is 10 mg four times daily initially, increasing to a maximum of 100 mg four times daily according to the response. Frail patients may be started at a lower oral dose: 25–30 mg over 24 hours. The maximum reported dose is 200 mg three times daily. It is possible to withdraw ketamine for several weeks after good pain control is achieved and restart the regimen when the pain returns.

Occasionally oral ketamine or sublingual/buccal ketamine is used as required. Usual dose is 2.5–5 mg (using 50 mg/5 ml solution). This dose is an individual decision.

There is no time limit to the treatment, but the success of pain relief should be regularly assessed, and the dose adjusted when needed [19–21].

6.2 Antidepressant and anxiolytic actions

Ketamine can produce rapid relief of major depression, bipolar disorders, and suicidal ideation. The mechanism for this effect is not yet fully understood but the major depressive disorder is associated with synaptic downregulation in the prefrontal cortex and hippocampus and it is believed that ketamine causes a glutamate surge that leads to a series of events resulting in synaptogenesis and reversal of the negative effect of depression and chronic stress. It appears that ketamine normalizes depression-related prefrontal dysconnectivity.

The rapid effect of ketamine on stress, anxiety, and depression may be of huge importance for the treatment of psychiatric conditions of patients in palliative care. Anxiety and depression are related to lower quality of life [22–24].
The positive psychological effect of ketamine is attributed to an induction of neuroplasticity which reverses the negative effect of stress and depression on neural cells and synapses [25].

There are various dosage regimens described in studies, in one case report patients received a bolus of one single dose of ketamine racemate (0.5 mg/kg). The reduction in anxiety was more pronounced in the first 4 days. After daily oral administration over 28 days of ketamine racemate, a significant effect was sustained with a large effect size for anxiety and depression. There was a significant response after the first 3 days [25, 26].

FDA-approved nasal spray formulation for the treatment of anxiety and depression [27, 28].

6.3 Bronchodilatatory effects

Ketamine produces bronchodilation, allowing secure induction of anesthesia in a patient with a life-threatening asthma and intense acute bronchial constriction. It is reported that ketamine doses of 0.1–0.2 mg/kg followed by 0.15–2.5 mg/kg/h can be used in patients with refractory bronchospasm and intensive status of asthma. The proposed mechanism of action is inhibition of inflammatory cascade and reduction in markers of inflammation and bronchodilation [29].

6.4 Topical ketamine in the treatment of mucositis pain

Ketamine oral rinse significantly reduced radiation-induced mucositis pain and hyperalgesia in a patient with head and neck cancer and so preserved the possibility of oral intake. It is speculated that the analgesia could be produced locally and systemically due to the absorption across the oral mucosa. The possibility of systemic absorption may result in psychomimetic and sedative effects. In the published paper the dose of 20 mg was arbitrarily chosen, being twice as the usual empiric starting dose for sublingual administration. As the literature is scarce on data for the topical use of ketamine further studies are needed before its use can be routinely recommended [30].

6.5 Refractory status epilepticus

Evidence suggests that the activity as well as the number of NMDA receptors is increased in refractory status epilepticus. Ketamine reduces the NMDA receptor-induced neurotoxicity and also has a neuroprotective role. On the other hand, evidence also shows that ketamine, at usual doses, has an epileptogenic potential and should be avoided in patients with epilepsy. From the so far published studies, no conclusive results can be drawn and further clinical trials are needed to assess the safety and efficiency of ketamine in both adult and pediatric populations [31].

7. Side effects of ketamine use

Side effects of ketamine use are dose-dependent. They are more common when ketamine is used as an anesthetic. Very common side effects are vivid dreams, hallucinations, dysphoria, and sedation. Incidence of psychotic effects can be reduced by using haloperidol or benzodiazepines. Sometimes can be enough just to reduce the dose of ketamine. Among less common side effects are cardiovascular side effects which are normally not serious. An increase in blood pressure and heart rate may occur. There are several reports about urinary tract symptoms that might require
discontinuation of ketamine infusion. The bladder is most severely affected. There is a strong correlation between higher age (older than 30 yrs), longer duration of use (more than 24 months), and co-use of illicit drugs.

Other side effects include increased muscle tone, involuntary movements, dizziness and nausea, liver toxicity, and neuropsychiatric toxicities [32, 33].

8. Recommendations for use of ketamine in palliative care

Palliative care aims to relieve symptoms of the advanced incurable disease and improve the quality of life throughout illness and in the bereavement period so that the patients and families can realize their full potential to live even the life is approaching its end.

Patients in palliative care may report a variety of symptoms among which poor pain control merits full attention. The concept of total pain is applicable as pain may occur on a physical, psychological, social, and spiritual level. Physical pain and psychological distress are connected. About two-thirds of patients with advanced cancer suffer from pain and more than half of those experience moderate to severe pain. Following the WHO cancer pain relief guidelines, one can achieve acceptable pain relief in over 50% of treated patients. About 50% of the patient may have poor pain control.

Many of the symptoms in palliative care require a pharmacological approach and drug prescription. Most strong analgesics have a strong sedative effect and therefore impact patients’ cognition. Many patients, who list as their value being able to think clearly, are reluctant to use them. Some are also afraid of the addiction potential of these drugs.

Having in mind that many patients in palliative care have psychiatric symptoms and sometimes they cannot wait for the classic antidepressant drugs to act, ketamine is promising due to its rapid action. Up to 42% of hospice patients have symptoms of depression and up to 70% have symptoms of anxiety. Untreated psychiatric symptoms are associated with significant morbidity and mortality, when left untreated, these symptoms can also interfere with their ability to make decisions and make realistic goals.

Oral ketamine may prove particularly useful for hospice patients who wish to remain home instead of receiving treatment in the hospital. To fasten the onset of oral ketamine, it was suggested to start patients on parenteral dosing before switching to oral administration. Another alternative to oral ketamine is an intranasal spray, which has been approved for the treatment of depression, but it might be more difficult to use [33–36].

9. Summary

Although ketamine has been in clinical practice for many years, it has been predominantly used as an anesthetic drug. Newer insight into its action shows its effectiveness in treating pain, anxiety, depression, bronchial spasm, refractory status epilepticus, and radio-induced mucositis.

This is especially important in the palliative setting, where patients commonly have pain combined with some other symptoms. They usually become refractors to high doses of opioids, with a detrimental quality of life.

Ketamine has a sparing effect on opioid consumption which may prolong their analgesic effect, reduce their dose and make pain treatment effective again. It can be used as an adjuvant as a baseline treatment or and as a breakthrough medication.
Besides it, rapid relief of anxiety with just a single dose of ketamine is promising as well as the fact that the effect is sustainable. Oral and nasal routes appear to be a good alternative for patients who are not institutionalized and who wish to avoid painful injections. Further studies are needed to define a suitable dosing protocol for ketamine.

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