Therapeutic Reviews

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Therapeutic Reviews aim to provide essential independent information for health professionals about drugs used in palliative and hospice care. The content is also available on www.palliativedrugs.com and will feature in future editions of the Hospice and Palliative Care Formulary USA and its British and Canadian counterparts. The series editors welcome feedback on the articles (hq@palliativedrugs.com).

Ketamine* AHFS 28:04

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The use of ketamine is associated with neuropsychiatric, urinary tract and hepatobiliary toxicity. Although most reports involve long-term recreational abusers, it has also arisen after only 1–2 weeks of therapeutic use (Box A). Accordingly, the use of ketamine should be restricted to specialists in pain or palliative care for patients who have failed to obtain relief from standard drug and non-drug treatments.

Class: General anesthetic.

Indications: Induction and maintenance of anesthesia; †neuropathic, inflammatory, ischemic limb and procedure-related pain unresponsive to standard treatments.[1,2]

Contra-indications: Any situation in which an increase in blood pressure would constitute a hazard.

Pharmacology

Ketamine, a derivative of phencyclidine (PCP), is a dissociative anesthetic which has analgesic properties in sub-anaesthetic doses.[2,3] Ketamine is the most potent NMDA-receptor-channel blocker available for clinical use, binding to the PCP site when the channels are in the open activated state (Fig. 1).[3] It also binds to a second membrane-associated site which decreases the frequency of channel opening.[3]

The NMDA receptor-channel complex is closely involved in the development of central sensitization of dorsal horn neurons which transmit pain signals.[4] At normal resting membrane potentials, the channel is blocked by magnesium and is inactive.[3] When the resting membrane potential is changed as a result of prolonged excitation, the channel unblocks and calcium moves into the cell. This leads to neuronal hyperexcitability and results in hyperalgesia and allodynia, and a reduction in opioid-responsiveness. These effects are probably mediated by the intracellular formation of nitric oxide and cyclic guanosine monophosphate.[3]

The reduction in opioid-responsiveness arises from cross-talk between opioid receptors and the NMDA receptor-channel. Opioid receptor activation results in phosphorylation and opening of the NMDA receptor-channel leading to a cascade of events which ultimately down-regulates the opioid receptor and its effects, thereby contributing towards tolerance and hyperalgesia.[3]

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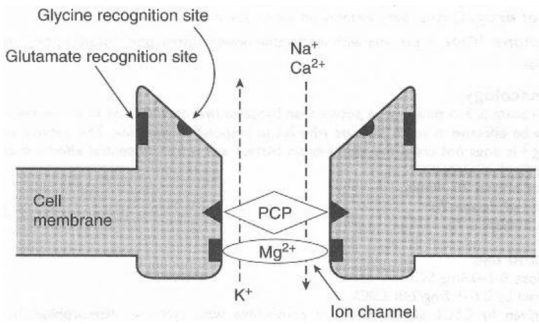

Fig. 1. Diagram of the NMDA (excitatory) receptor-channel complex. The channel is blocked by magnesium (Mg^{2+}) when the membrane potential is at its resting level (*voltage-dependent block*) and by drugs which act at the phencyclidine (PCP) binding site in the glutamate-activated channel, e.g. dextromethorphan, ketamine, methadone (*use-dependent block*).[4]

In addition to blocking the NMDA receptor-channel, ketamine has other actions, some of which may contribute to its analgesic effect.[2] These include opioid-like and anti-inflammatory effects,[5] and interactions with, e.g.:

- other calcium, potassium and sodium channels, e.g. HCN, AMPA
- cholinergic, dopaminergic and noradrenergic transmission
- descending inhibitory pathways.

Resultant changes in cellular processes, e.g. in gene expression and protein regulation, could explain ongoing benefit even after discontinuation of ketamine.[6]

Ketamine is generally administered PO or SC/CSCI.[7,8] It can also be administered IM, IV, SL, intranasally, PR and spinally (preservative-free formulation).[9–16] However, for spinal routes, concerns have been raised about the potential for neurotoxicity.[17] Ketamine has been given by CIVI in adults and children in combination with opioids (fentanyl, morphine) ± midazolam to control intractable pain and agitation.[18–20]

Although in some countries both racemic ketamine and the *S*–enantiomer are available for clinical use, in the USA only the racemic mixture is marketed. Because of its greater affinity and selectivity for the NMDA-receptor, the *S*–enantiomer as a parenteral analgesic is about 4 times more potent than the *R*–enantiomer, and twice as potent as the racemic mixture.[21–23] When equi-analgesic doses are compared, the *S*–enantiomer is also associated with lower levels of undesirable effects, e.g. anxiety, tiredness, cognitive impairment.[22,24]

About 90% of a parenteral dose of ketamine is excreted in the urine, mostly as conjugates of hydroxylated metabolites. Less than 5% is excreted unchanged via the faeces and urine. Ketamine undergoes hepatic metabolism mainly to norketamine. Because of extensive first-pass metabolism, a greater proportion of a PO dose of ketamine is converted to norketamine compared to one administered by injection.[25] Norketamine has a lower affinity for the NMDA-receptor-channel than ketamine. Although norketamine (particularly S-norketamine) is analgesic in rodents, this remains to be clarified in humans.[26–28] Norketamine is further metabolized to the inactive dehydronorketamine.

Ketamine causes hepatic enzyme induction and enhances its own metabolism. The implications of this for the efficacy or tolerability of therapeutic ketamine is unknown. However, in abusers, it may contribute towards the relatively rapid tolerance to the desired 'high', with those taking it most days of the week reporting about a 7-fold increase in dose after the first 2 months of use.[29]

Ketamine increases sympathetic nervous system activity and causes tachycardia and intracranial hypertension. When ketamine is used for procedural anesthesia, a quarter of patients experience vivid dreams, misperceptions, hallucinations and alterations in body image and mood as emergent (psychotomimetic) phenomena, i.e. as the effects of a bolus dose wear off. The incidence is reduced to <10% by the concurrent use of midazolam.[30] Emergent phenomena occur to a lesser extent with the sub-anaesthetic analgesic doses given PO or CSCI, and generally can be controlled by concurrent administration of a benzodiazepine (e.g. diazepam, midazolam) or haloperidol.[13,31,32] Sub-anaesthetic doses of ketamine are associated with impaired attention, memory and judgement, and it is used as a pharmacological model for acute schizophrenia.[3]

Although it is used as an analgesic in various clinical settings (including postoperatively[33,34]), the increasing concern about the potential for neuropsychiatric, urinary tract and hepatobiliary toxicity (Box A) will probably result in a decline in the use of ketamine for chronic non-cancer pain, and possibly cancer pain. In the palliative

care setting, ketamine should generally be reserved for pain which has failed to respond to standard analgesic drugs, including opioids and adjuvants.

Chronic non-cancer pain

A review of sub-anaesthetic doses of ketamine for chronic non-cancer pain (mostly neuropathic but also ischemic, fibromyalgia, post-whiplash, etc.) identified 29 RCTs and concluded that:

- ketamine provides relief
- undesirable effects can limit its use
- long-term use should be restricted to a controlled trial.[35]

A systematic review of analgesics for phantom limb pain reached similar conclusions.[36] There is RCT evidence of benefit in complex regional pain syndrome type 1, with relief persisting 4–6 weeks beyond the duration of the ketamine infusion.[37–39]

Cancer pain

A systematic review of ketamine as an adjunct to opioids in cancer pain found only two studies of sufficient quality[13,40] and concluded that there is insufficient robust evidence to assess potential benefits and harms.[41] Thus, in patients with cancer, evidence of ketamine's efficacy as an analgesic is mostly from case reports, retrospective surveys or uncontrolled studies in patients with refractory neuropathic, bone, and mucositis-related pain.[7,8,13,40,42–52] Results from a large RCT of PO racemic ketamine in cancer-related neuropathic pain are pending.[53]

Short-term 'burst' treatment with ketamine may sometimes have a relatively long-lasting effect (i.e. several days to weeks and occasionally for months).[54,55] For example, ketamine 100mg/24h by CIVI for 2 days in a cancer patient, repeated a month later, reduced opioid requirements by 70%.[56] Similarly, in non-cancer pain, patients taking regular strong opioids for ischemic limb pain, a single 4h IV infusion of ketamine 600microgram/kg reduced opioid requirements during the next week.[57]

However, in a large case series, about a quarter of patients experienced severe undesirable effects from higher-dose 'burst' CSCI ketamine involving rapid dose escalation 100 → 300 → 500mg/24h over 3–5 days.[54] Further, in a 5-day RCT in cancer patients using the same regimen, there was no difference in the proportion responding in the ketamine and placebo arms (about 50% in each, based on average pain score).[58] There were fewer treatment failures at the maximum dose (25 vs. 50%) but more undesirable effects and withdrawals due to toxicity (19 vs. 2%).[58] *These results suggest that rapid titration involving such doses of CSCI ketamine is generally inadvisable.*

Miscellaneous

PO/IV ketamine (generally in combination with morphine or midazolam) can provide analgesia in severe cancer treatment-related mucositis,[59] during painful procedures, e.g. change of dressings,[60–62] and orthopaedic emergencies.[63]

Topical ketamine has been applied to the skin in various non-cancer pains,[64,65] and used as an oral rinse in radiation-induced mucositis.[66]

Ketamine has a rapid antidepressant effect in patients with major depression and bipolar disorder, including a reduction in suicidal ideation.[67] Following a single IV dose (typically 500microgram/kg over 40min), up to 70% of patients respond, with improvements seen within hours. However, duration of benefit is generally ≤1 week.[67,68] These effects are accompanied by a more rapid restoration of neuroplasticity than that seen with conventional antidepressants. The exact mechanism is unclear but includes the release of brain-derived neurotrophic factor which helps to restore neuroplasticity, e.g. through the formation of new synapses.[68] Although case reports of benefit are emerging from the palliative care setting,[69–73] the use of ketamine to treat major depression is experimental, and should ideally be restricted to RCTs. Other drugs which act on the NMDA receptor-channel complex are undergoing clinical trials in depression.[74]

The use of CIVI ketamine has been explored in the treatment of refractory status epilepticus, but its place in clinical practice remains to be determined.[75]

Bioavailability 93% IM; 45% nasal; 30% SL; 30% PR; and 20% PO.[76,77]
Onset of action 5min IM; 15–30min SC; 30min PO.
Time to peak plasma concentration no data SC; 30min PO; 1h norketamine.[78]
Plasma halflife 1–3h IM; 3h PO; 12h norketamine.[79]
Duration of action 30min–2h IM; 4–6h PO, sometimes longer.[80]

Cautions

History of psychiatric disorder; epilepsy, glaucoma, hypertension, heart failure, ischemic heart disease, CVAs, acute intermittent porphyria.[81] Hyperthyroidism (increased risk of hypertension and tachycardia). Conditions

causing excessive upper airway secretions; ketamine both increases salivation and sensitizes the gag reflex, leading on rare occasions to laryngospasm. Severe hepatic impairment (consider dose reduction).

Because of reports of ketamine increasing CSF pressure, raised intracranial pressure (e.g. as a result of head injury, intracranial tumour, hydrocephalus) is a traditional caution. However, systematic reviews report no such concerns in ventilated patients with traumatic or non-traumatic brain injury.[82,83]

Drug interactions

Reports involving the CYP450 enzyme system are mostly limited to PO *S*-ketamine:

- clarithromycin and grapefruit juice (potent CYP3A4 inhibitors) increase the plasma concentration of *S*−ketamine and reduce that of norketamine[84,85]
- ticlopidine (potent CYP2C19 and weak CYP2B6 inhibitor) increases the area under the plasma concentration-time curve[86]
- rifampin and St. John's wort (potent CYP3A4 inducers) decrease the plasma concentration of *S*−ketamine; rifampin also following IV *S*−ketamine.[87,88]

The clinical relevance of these interactions is unclear. Other potent inhibitors or inducers of these enzymes could have similar effects.

Undesirable effects

Ketamine can be abused or diverted; careful monitoring is essential.

Dose-related psychotomimetic phenomena occur in about 40% of patients with CSCI ketamine, less with PO: euphoria, dysphasia, blunted affect, psychomotor retardation, vivid dreams, nightmares, impaired attention, memory and judgement, illusions, hallucinations, altered body image.

Delirium, drowsiness, dizziness, diplopia, blurred vision, nystagmus, altered hearing, hypertension, tachycardia, hypersalivation, nausea and vomiting. At higher anesthetic doses, tonic-clonic movements are very common (>10%) but these have not been reported after PO use or with analgesic parenteral doses.

Erythema and pain at injection site. Neuropsychiatric, urinary and hepatobiliary toxicity (Box A).

Box A. Ketamine and neuropsychiatric, urinary and hepatobiliary toxicity

Neuropsychiatric

There are no studies of neuropsychiatric effects in patients receiving therapeutic ketamine long-term. Most participants in the studies below also abused multiple other drugs.

Long-term ketamine abusers have a dose-related increase in subclinical psychotic symptoms, e.g. delusions, dissociation and schizotypy. The relevance is uncertain; no definite link exists between ketamine abuse and psychosis.[89]

In frequent abusers of ketamine (≥5 days/week), both short- and long-term memory are affected with dose-related impairments in visual recognition memory (tested by remembering patterns) and spatial working memory (tested by remembering which boxes contained hidden tokens).[89,90]

MRI changes were evident with *total estimated lifetime doses* of ≤3g.[91,92] Functional MRI show dose-related alterations in the anterior cingulate cortex (decrease) and in the left precentral frontal gyrus (increase).[91]

These effects may be the consequence of long-term NMDA-receptor-channel blockade. Dopamine depletion in the prefrontal cortex, a key area involved in working memory, is also reported in those abusing ≥200mg/week.[93] Ketamine is also directly neurotoxic, with dose-related MRI changes suggestive of disruption or damage to the white matter in the frontal and left temporoparietal regions.[92]

Memory impairments appear to improve with abstinence, but former abusers continue to score higher than controls on delusional symptoms.[89]

Urinary tract

In three patients with chronic pain, urinary symptoms developed after receiving ketamine PO 650−800mg/24h for 5−18 months.[94] In another patient, severe damage necessitated cystectomy after three years of

ketamine PO 240mg/24h for chronic back pain.[95] However, urinary symptoms developed after only 9 *days* in a 16 year-old receiving ketamine PO 8mg/kg/24h.[96]

Urinary symptoms have been reported in abusers of 'street' ketamine, generally taken as powdered ketamine via nasal insufflation. The risk appears related to both dose and frequency of use.[97]

Symptoms include frequency, urgency, urge incontinence, dysuria, hematuria and lower abdominal pain.[97–99] The exact mechanism of the damage is unclear, but ketamine has a direct irritant effect on the upper and lower urinary tract.[100]

Investigations (e.g. cystoscopy and biopsy, CT urogram) may show interstitial cystitis, detrusor overactivity, decreased bladder capacity, vesico-ureteric reflux, hydronephrosis, papillary necrosis, and renal impairment. Irreversible damage leading to renal failure has occurred.

Animal studies have found an increased expression of P2X1 purinergic receptors (activated by ATP) but not muscarinic receptors on bladder smooth muscle, which may explain the reports of limited benefit from anti-muscarinic antispasmodics.[101]

Consequently, when patients receiving therapeutic ketamine experience urinary symptoms without evidence of bacterial infection, practitioners should consider stopping the ketamine and seeking the advice of a urologist.

Symptoms generally settle several weeks after stopping ketamine. However, in some abusers, symptoms have persisted despite abstinence.[97,102]

Hepatobiliary

Abnormal LFTs have been associated with both ketamine abuse and therapeutic use, e.g. IV for maintenance anesthesia (>10h) or infusions for pain relief (≥4 days).[103–106] In the latter, although abnormal LFTs were sometimes apparent after 4–5 days, in others it occurred only with a second infusion some 2 weeks later.[106]

In abusers, abdominal pain has been reported and, in some, dilation or strictures of the common bile duct.[104,107,108]

The cause is unknown, but possibilities include a direct toxic effect of ketamine or a metabolite, or ketamine-related dysfunction of the sphincter of Oddi.[103,109]

With abstinence, the LFTs, abdominal pain and biliary duct dilation generally improve. Some recommend regular monitoring of LFTs during the long-term therapeutic use of ketamine.[106]

Dose and use

Because of the undesirable effects profile of ketamine, which includes neuropsychiatric, urinary tract and hepatobiliary toxicity, prescription of ketamine as an analgesic should be restricted to specialists in pain or palliative care for patients who have failed to obtain adequate relief from standard non-drug and drug treatments, including the optimal use of opioids, non-opioids and adjuvant analgesics. A toxicity monitoring form is available.[110]

In patients with a prognosis of more than a few weeks, once analgesia has been obtained, an attempt should be made to withdraw ketamine over 2–3 weeks. Benefit from a short course can last for weeks or even months, and can be repeated if necessary.[53] Thus, apart from patients with a prognosis of just days–weeks, long-term continuous ketamine should be used only as a last resort, i.e. in those patients with unsatisfactory analgesia from a short course approach.

Note: whole body hyperalgesia and allodynia may occur if ketamine is abruptly stopped after ≥3 weeks of use.[111]

All doses in this section relate to racemic ketamine

Dose recommendations vary widely, but ketamine is often started low dose PO (see below). In some centres, an initial test dose is given to assess tolerability and efficacy. The prophylactic concurrent administration of a

benzodiazepine or an antipsychotic is also routine in some but not all centres, where it is reserved for more select circumstances (see below). Long-term success, i.e. both pain relief and tolerable undesirable effects, varies from <20% to about 50%.[10,11,47,112]

Some practitioners routinely reduce the background opioid dose by 25–50% when starting parenteral ketamine. If the patient becomes drowsy, the dose of opioid should be reduced. If a patient experiences dysphoria or hallucinations, the dose of ketamine should be reduced and a benzodiazepine prescribed, e.g. diazepam 5mg PO stat & at bedtime, lorazepam 1mg PO stat & b.i.d., midazolam 5mg SC stat and 5–10mg CSCI, or haloperidol, e.g. 2–5mg PO stat & at bedtime, or 2–5mg SC stat and 2–5mg CSCI.[32] In patients at greatest risk of dysphoria (those with high anxiety levels), these measures may be more effective if given before starting ketamine.

When switching from CSCI to PO after just a few days, a conversion ratio of 1:1 should be used.[48,113] However, after weeks–months of use, some have found that a *smaller* total daily dose (25–50% of the parenteral dose) can maintain a similar level of analgesia, e.g. CSCI 400mg/24h → PO 150mg/24h.[46] In both instances, the patient should be monitored closely and the dose titrated accordingly. When switching from PO to CSCI or CIVI, it is advisable to commence on a small dose and titrate as required.

By mouth[7,8,114–116]

An oral solution can be prepared by a local pharmacy (Box B). When this option is not available, use direct from a vial or dilute for convenience (immediately before administration) to 50mg/5mL; add a flavouring of the patient's choice, e.g. fruit cordial, to mask the bitter taste:

- start with 10–25mg t.i.d.–q.i.d. and p.r.n.
- if necessary, increase dose in steps of 10–25mg up to 100mg q.i.d.
- maximum reported dose 200mg q.i.d.[114,116]
- give a smaller dose more frequently if psychotomimetic phenomena or drowsiness occurs which does not respond to a reduction in opioid.

Box B. Preparation of ketamine oral solution: pharmacy guidelines

Use ketamine 100mg/mL 10mL vials because this is the cheapest concentration. Simple Syrup USP can be used for dilution but this is too sweet for some patients. Alternatively, use purified water as the diluent and ask patients to add their own flavouring, e.g. fruit cordial, just before use to disguise the bitter taste.

To prepare 100mL of 50mg/5mL oral solution:

- 10mL vial of ketamine 100mg/mL for injection
- 90mL purified water.

Store in a refrigerator with an expiry date of 1 week from manufacture.

Subcutaneous[8]

- typically 10–25mg p.r.n., some use 2.5–5mg
- if necessary, increase dose in steps of 25–33%.

CSCI[7,31,42,43,45,117]

Because ketamine is irritant, dilute to the largest volume possible, and consider the use of 0.9% saline as the diluent. Consider the use of prophylactic diazepam, lorazepam, midazolam or haloperidol (see text above).

- start with 1–2.5mg/kg/24h
- if necessary, increase by 50–100mg/24h
- continue to titrate until adequate pain relief
- usual maximum 500mg/24h
- maximum reported dose 3.6g/24h.

CSCI compatibility with other drugs: There are 2-drug compatibility data for ketamine in WFI with metoclopramide, midazolam and morphine sulfate. For more details see *www.palliativedrugs.com*.

There are 2-drug compatibility data for ketamine in 0.9% saline with alfentanil, clonazepam, dexamethasone (low-dose), diamorphine (not USA), haloperidol, hydromorphone, levomepromazine, metoclopramide, midazolam, morphine sulfate and oxycodone (not USA). For more details see *www.palliativedrugs.com*.

Intravenous[8,118]

For cancer pain:

- typically 2.5–5mg p.r.n.

To cover procedures which may cause severe pain:

- 500microgram–1mg/kg (typically 25–50mg; some start with 5–10mg), given over 1–2min preceded by, e.g. IV lorazepam 1mg or IV midazolam 100microgram/kg (typically 5–10mg; some start with 1–2mg) to reduce emergent phenomena
- use a maximum concentration of ketamine 50mg/mL; 0.9% saline or 5% glucose are suitable diluents.

The right dose should provide analgesia within 1–5min lasting for 10–20min.

There is a risk of marked sedation when ketamine and a benzodiazepine are given concurrently. Use only if competent in airway management and the patient can be adequately monitored.

Procedures of longer duration may require ketamine CIVI; obtain advice from an anesthetist.

CIVI[20,119,120]

Dilute to a concentration of 1mg/mL with 0.9% saline or 5% glucose.

- give a single 'burst' of 600microgram/kg up to a maximum of 60mg over 4h (reduce dose by 1/3–1/2 in elderly/frail patients); monitor blood pressure at baseline and then hourly:
  - ➢ if necessary, repeat daily for up to 5 days
  - ➢ if *no* analgesic response to an infusion, increase the dose of the next one by 30%
  - ➢ further dose titrate according to response and/or undesirable effects
  - ➢ repeat the above if the pain subsequently recurs.[53]

Or

- start with 50–150microgram/kg/h (typically 50–100mg/24h) and titrate as necessary (typical increments 25–50mg/24h)
- in one series of 46 patients with cancer:
  - ➢ 20% responded to ≤100mg/24h
  - ➢ typical dose 100–300mg/24h
  - ➢ no psychotomimetic effects were seen with doses <300mg/24h.

Supply

Ketamine (generic)

Injection 10mg/mL, 20mL vial = $18; 50mg/mL, 10mL vial = $6; 100mg/mL, 5mL vial = $10, 10mL vial = $14.

Ketalar® (JHP Pharmaceuticals)

Injection 10mg/mL, 20mL vial = $18; 50mg/mL, 10mL vial = $6; 100mg/mL, 5mL vial = $10, 10mL vial = $14.

Although use as an analgesic is off-label, ketamine injection can be prescribed both in hospitals and in the community.

Abbreviations/Key

*	Specialist use only
†	Off-label indication
AMPA	α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid
ATP	Adenosine triphosphate
b.i.d.	Bis in die, twice daily
CIVI	Continuous intravenous infusion
CSCI	Continuous subcutaneous infusion
CSF	Cerebrospinal fluid
CT	Computerized tomography
CVA	Cerebrovascular accident
CYP	Cytochrome P450
ED	Epidural
HCN	Hyperpolarization-activated cyclic nucleotide-gated
LFTs	Liver function tests
MRI	Magnetic resonance imaging
NMDA	N-methyl-D-aspartate
IM	Intramuscular
IV	Intravenous
PO	Per os, by mouth
PR	Per rectum
p.r.n.	Pro re nata, as required
q.i.d.	Quarta in die, four times daily
RCT	Randomized controlled trial
SC	Subcutaneous
SL	Sublingual
t.i.d.	Ter in die, three times daily
WFI	Water for injection

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