

## Therapeutic Reviews

**Series Co-Editors: Andrew Wilcock, DM, FRCP, and Robert Twycross, DM, FRCP**

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### **Ketamine\***

**AHFS 28:04**

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**Class:** General anesthetic.

**Indications:** Induction and maintenance of anesthesia; †pain unresponsive to standard treatments (post-operative, neuropathic, inflammatory, ischemic limb, myofascial and procedure-related).<sup>1–3</sup>

**Contraindications:** Any situation in which an increase in blood pressure or intracranial pressure would constitute a hazard. Acute intermittent porphyria.

### **Pharmacology**

The NMDA-glutamate receptor is a calcium channel closely involved in the development of central sensitization of dorsal horn neurons, which transmit pain signals (Figure).<sup>4</sup> At normal resting membrane potentials, the channel is blocked by magnesium and is inactive.<sup>5</sup> When the resting membrane potential is changed as a result of prolonged excitation, the channel unblocks and calcium moves into the cell. This results in neuronal hyperexcitability and consequently a reduction in opioid-responsiveness, hyperalgesia and allodynia. These effects are probably mediated by the intracellular formation of nitric oxide.<sup>6</sup>

Ketamine is a dissociative anesthetic that has analgesic properties in subanesthetic doses.<sup>3,7</sup> Ketamine is the most potent NMDA-receptor-channel blocker available for clinical use, binding to the phencyclidine site when the channels are in the open activated state.<sup>8</sup> It also may bind to a second membrane-associated site, which decreases the frequency of channel opening.<sup>9</sup>

In some countries, both the racemic mixture and the S-enantiomer are commercially 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 (parenterally) is about 4 times more potent an analgesic than the R-enantiomer, and twice as potent as the racemic mixture.<sup>10–12</sup> When equianalgesic doses are compared,

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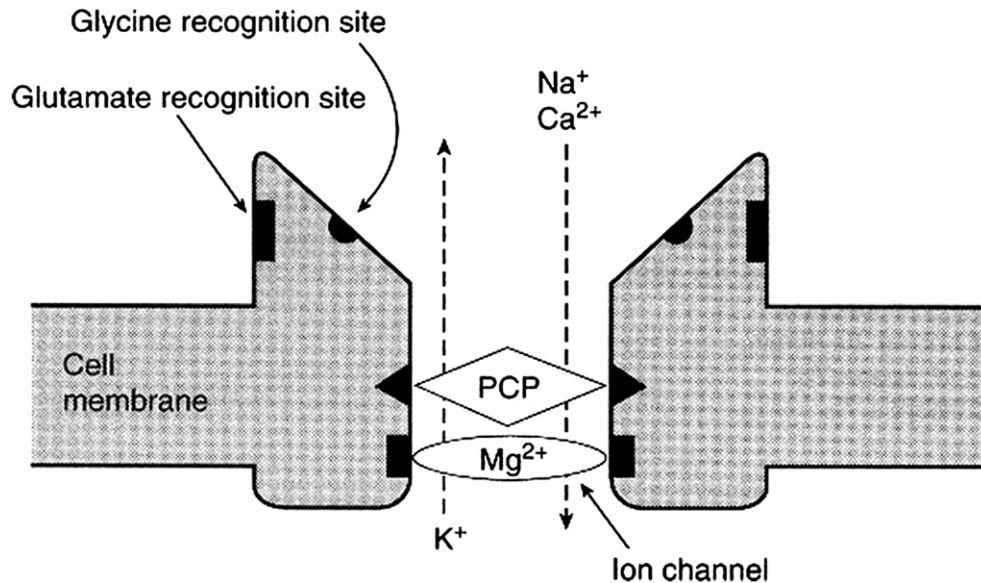


Figure. Diagram of NMDA (excitatory) receptor-channel complex. The channel is blocked by  $Mg^{2+}$  when the membrane potential is at its resting level (voltage-dependent block) and by drugs that act at the phencyclidine (PCP) binding site in the glutamate-activated channel, e.g., dextromethorphan, ketamine, methadone (use-dependent block).<sup>4</sup> Figure reproduced by permission of [palliativedrugs.com](http://palliativedrugs.com) Ltd.

the S-enantiomer is also associated with lower levels of undesirable effects, e.g., anxiety, tiredness, cognitive impairment.<sup>11,13</sup> However, no significant differences in efficacy or tolerability were found between the PO racemic mixture (median dose 320 mg/24 h), the S-enantiomer, or placebo in patients with cancer-related neuropathic pain.<sup>14</sup>

Ketamine has other actions, some of which also may contribute to its analgesic effect. These include interactions with other calcium and sodium channels, dopamine receptors, cholinergic transmission, and noradrenergic and serotonergic re-uptake (intact descending inhibitory pathways are necessary for analgesia), together with opioid-like and anti-inflammatory effects.<sup>15,16</sup> Ketamine also appears to have a rapid antidepressant effect in patients with major depression.<sup>17</sup>

The analgesic effects of ketamine have been utilized in a wide range of clinical settings using various regimens and routes of administration.

**Postoperative analgesia:** Two systematic reviews of 37 RCTs of subanesthetic doses of ketamine as an adjunct to opioid-based postoperative analgesia concluded that:

- IV and ED ketamine reduce opioid requirements and possibly chronic post-surgical pain
- CIVI (typically 120–600 microgram/kg/h) is best for surgery associated with high opioid requirements, although a single IV dose (typically 150 microgram–1 mg/kg) may suffice for minor surgery
- adding ketamine to IV patient-controlled analgesia (PCA) is *not* effective.<sup>18,19</sup>

**Chronic non-cancer pain:** A review of subanesthetic 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
- because of a lack of data, long-term use should be restricted to a controlled trial.<sup>20</sup>

There is RCT evidence of benefit in complex regional pain syndrome type 1.<sup>21,22</sup>

**Cancer pain:** A systematic review of ketamine as an adjunct to opioids in cancer pain found only two studies of sufficient quality,<sup>23,24</sup> and concluded that there was insufficient robust evidence to reach a conclusion.<sup>20</sup> Thus, in patients with cancer, evidence of ketamine's efficacy as an analgesic is mainly from case reports, retrospective surveys or uncontrolled studies in patients with refractory neuropathic, bone and mucositis-related pain.<sup>23–39</sup> Generally, ketamine is used in addition to morphine or an alternative strong opioid when further opioid increments have been ineffective or precluded by unacceptable

undesirable effects. When used in this way, ketamine is generally administered PO or SC/CSCI.<sup>27,33</sup> It also can be administered IM, IV, SL, intranasally, PR and spinally (preservative-free formulation).<sup>24,40–45</sup> However, for spinal routes, concerns have been raised about the potential for neurotoxicity with long-term use.<sup>46</sup> Ketamine has been given by CIVI in adults and children in combination with opioids (fentanyl, morphine) ± midazolam to control intractable cancer pain and agitation.<sup>47–49</sup>

**Miscellaneous:** Ketamine can provide analgesia during painful procedures, e.g., change of burns dressings.<sup>50</sup> Topical ketamine has been applied to the skin in various non-cancer pains,<sup>51,52</sup> and used as an oral rinse in radiation-induced mucositis.<sup>53</sup>

**“Burst” ketamine:** There is some evidence that short-term “burst” treatment with ketamine may have relatively long-term benefit in both cancer and non-cancer pain. For example, in patients taking regular strong opioids for ischemic limb pain, a single 4 h IV infusion of ketamine 600 microgram/kg reduced opioid requirements during a week of observation.<sup>54</sup> Ketamine 100 mg/24 h by CIVI for 2 days in a cancer patient, repeated a month later, reduced opioid requirements by 70%.<sup>55</sup> In several case series of cancer patients with severe intractable pain from various causes, “burst” ketamine 100–500 mg/24 h by CSCI for 3–5 days relieved pain in about 50% of patients.<sup>35,37,56</sup> Relief lasted from several days to one month, and occasionally for two months. In one study using this regimen, although there were no withdrawals, 1/4 of the patients experienced severe undesirable effects, such as sedation and confusion.<sup>35</sup>

There is increasing concern about the potential for urinary tract toxicity with ketamine (see **Box A**). Thus, in patients with a prognosis of months to years, it is probably best to first try a “burst” approach and limit the long-term regular use of ketamine to situations where this fails. Even then, after 2–3 weeks of satisfactory analgesia with regular ketamine, an attempt can be made to tail off the ketamine over several weeks. Although this may fail and the dose may need to be increased again, for some patients benefit persists without ketamine for weeks to months, or with a smaller maintenance dose.<sup>57</sup>

PO ketamine undergoes extensive first-pass hepatic metabolism mainly to norketamine (via CYP3A4).<sup>58</sup> As an *anesthetic*, norketamine is about 1/3 as potent as parenteral ketamine. However, as an *analgesic*, it is equipotent. The maximum blood concentration of norketamine is greater after PO administration than after an injection,<sup>59</sup> and in chronic use norketamine may be the main analgesic agent.

Ketamine causes tachycardia and intracranial hypertension. After anesthetic use, most 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. These occur to a lesser extent

#### **Box A. Ketamine and urinary tract toxicity**

The use of ketamine can cause urinary tract symptoms, e.g., frequency, urgency, urge incontinence, dysuria, and hematuria.<sup>69,70</sup> The causal agent has not been determined, but direct irritation by ketamine and/or its metabolites is a possibility.

Investigations have revealed interstitial cystitis, detrusor overactivity, decreased bladder capacity, vesico-ureteric reflux, hydronephrosis, papillary necrosis, and renal impairment. Irreversible damage leading to renal failure has occurred.

The largest case series involved 59 people who had used “street” ketamine over a prolonged period (6 months–several years).<sup>69</sup>

A small series of three chronic pain patients developed urinary symptoms after receiving ketamine PO 650–800 mg/24 h for 5–18 months.<sup>71</sup> However, urinary symptoms developed after only 9 days in a 16 year-old receiving ketamine PO 8 mg/kg/24 h.<sup>72</sup>

Thus, when patients on ketamine experience urinary symptoms with no evidence of bacterial infection, practitioners should consider discontinuing the ketamine and seeking the advice of a urologist.

Symptoms generally settle several weeks after stopping ketamine; ideally this should be done gradually to avoid worsening pain (see Dose and Use).<sup>73</sup>

with the subanesthetic analgesic doses given PO or CSCI, and generally can be controlled by concurrent administration of a benzodiazepine (e.g., diazepam, midazolam) or haloperidol.<sup>24,60,61</sup> Subanesthetic doses of ketamine are associated with impaired attention, memory and judgement, and it is used as a pharmacological model for acute schizophrenia.<sup>3</sup>

Less than 10% of ketamine is excreted unchanged, half in the feces and half renally. Norketamine is excreted renally. Long-term use of ketamine leads to hepatic enzyme induction and enhanced ketamine metabolism.

**Bioavailability:** 93% IM; 45% nasal; 30% SL; 30% PR; and 20% PO.<sup>62,63</sup>

**Onset of action:** 5 min IM; 15–30 min SC; 30 min PO.

**Time to peak plasma concentration:** no data SC; 30 min PO; 1 h norketamine.<sup>64</sup>

**Plasma half-life:** 1–3 h IM; 3 h PO; 12 h norketamine.<sup>65</sup>

**Duration of action:** 30min–2 h IM; 4–6 h PO, sometimes longer.<sup>66</sup>

### Cautions

Current or past history of psychiatric disorder; epilepsy, glaucoma, hypertension, heart failure, ischemic heart disease and a history of cerebrovascular accidents.<sup>67</sup> Severe hepatic impairment (consider dose reduction).

Plasma concentration increased by diazepam. CYP3A4 inhibitors, e.g., clarithromycin, ketoconazole, increase plasma concentrations of ketamine and reduce those of norketamine, but the clinical relevance of this is unclear.<sup>68</sup>

### Undesirable Effects

For full list, see manufacturers' PI.

Generally dose-related. Occur in about 40% of patients when given CSCI; less PO: psychotomimetic phenomena (euphoria, dysphasia, blunted affect, psychomotor retardation, vivid dreams, nightmares, impaired attention, memory and judgement, illusions, hallucinations, altered body image), delirium, dizziness, diplopia, blurred vision, nystagmus, altered hearing, hypertension, tachycardia, hypersalivation, nausea and vomiting, erythema and pain at injection site. Urinary tract toxicity (see Box A).

When used at higher doses in anesthesia, tonic-clonic movements are very common (>10%); however, these have not been reported after PO use or with the lower parenteral doses used for analgesia.

Ketamine can be abused (or diverted) and careful monitoring is essential.

### Dose and Use

Because of concerns around urinary tract toxicity (see Box A), consider using ketamine long-term only if a "burst" approach has failed (see Pharmacology).

Dose recommendations vary considerably but ketamine is often started in a low dose PO (see below). An oral solution can be compounded by a local pharmacy (Box B). Alternatively, patients can be supplied with vials of ketamine and 1 mL graduated syringes. Two needles (one as an air vent) should be inserted in the stopper of the vial to facilitate withdrawing the ketamine; sterility is not necessary for PO administration.

#### Box B. Preparation of ketamine oral solution: pharmacy guidelines

Use generic ketamine 50 mg/mL 10 mL 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 100 mL of 50 mg/5mL oral solution:

- 2 × 10 mL vials of ketamine 50 mg/mL for injection
- 80 mL purified water.

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

In some centers, 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 centers, 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%.<sup>31,41,42,74</sup>

#### **By mouth**<sup>27,33,75–77</sup>

Use direct from vial or dilute for convenience to 50 mg/5 mL (patient adds flavoring of choice, e.g., fruit cordial, to mask the bitter taste):

- start with 10–25 mg t.i.d.–q.i.d. and p.r.n.
- if necessary, increase dose in steps of 10–25 mg up to 100 mg q.i.d.
- maximum reported dose 200 mg q.i.d.<sup>75,77</sup>
- give a smaller dose more frequently if psychotomimetic phenomena or drowsiness occur, which do not respond to a reduction in opioid
- after analgesia is achieved, some centers try withdrawing the ketamine over several weeks; benefit can persist without ketamine for weeks to months
- if the pain recurs, a further course of ketamine can be given.

#### **Sublingual**<sup>45</sup>

- start with 10–25 mg
- place SL and ask patient not to swallow for 2 min
- use a high concentration to minimize dose volume; retaining >2 mL is difficult.

#### **Subcutaneous**<sup>33</sup>

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

#### **CSCI**<sup>25–27,29,60,78</sup>

Because ketamine is an irritant, dilute to the largest volume possible (e.g., for a Graseby syringe driver, 18 mL in a 30 mL luerlock syringe given over 12–24 h), preferably using 0.9% saline:

- start with 1–2.5 mg/kg/24 h
  - if necessary, increase by 50–100 mg/24 h
  - maximum reported dose 3.6 g/24 h
- Alternatively, give as short-term “burst” therapy:<sup>35,37,56</sup>

- start with 100 mg/24 h
- if 100 mg not effective, increase after 24 h to 300 mg/24 h
- if 300 mg not effective, increase after further 24 h to 500 mg/24 h
- stop 3 days after last dose increment.

Half of patients respond and the regimen can be repeated p.r.n.; the duration of benefit varies and undesirable effects are common. The use of prophylactic diazepam, lorazepam, midazolam or haloperidol is recommended (see text).

#### **Intravenous**<sup>33,79</sup>

For cancer pain:

- typically 2.5–5 mg p.r.n.

For procedures which may cause severe pain:

- 500 microgram–1 mg/kg (typically 25–50 mg; some start with 5–10 mg), given over 1–2 min preceded by, e.g., lorazepam 1 mg or midazolam 100 microgram/kg (typically 5–10 mg; some start with 1–2 mg) to reduce emergent phenomena.

The right dose should provide analgesia within 1–5 min that lasts for 10–20 min. Note: there is a risk of marked sedation when ketamine and a benzodiazepine are combined in this way; use only if competent in airway management and when the patient can be adequately monitored. Procedures of longer duration may require ketamine CIVI; obtain advice from an anesthesiologist.

**CIVI**<sup>47,80</sup>

- start with 50–200 microgram/kg/h and titrate as necessary *or*
- give a single “burst” of 600microgram/kg up to a maximum of 60 mg over 4 h (reduce dose by 30–50% in elderly/frail patients); monitor blood pressure at baseline and then hourly:
  - if necessary, repeat daily for up to 5 days
  - if no response to an infusion, increase the next dose by 30%
  - continue to titrate according to response and/or occurrence of undesirable effects
  - repeat the above if the pain subsequently recurs.<sup>57</sup>

When given by CSCI, ketamine is often mixed with morphine ± other drugs. Most likely mixtures are known to be compatible in 0.9% saline (Box C). For further compatibility data, including in WFI, see [www.palliativecare.com](http://www.palliativecare.com) Syringe Driver Survey Database.

In some centers, the regular opioid dose is routinely reduced 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 5 mg PO stat and at bedtime, lorazepam 1 mg PO stat and b.i.d., midazolam 5 mg SC stat and 5–10 mg CSCI, or haloperidol, e.g., 2–5 mg PO stat and at bedtime, or 2–5 mg SC stat and 2–5 mg CSCI.<sup>61</sup> In patients at greatest risk of dysphoria, i.e., those with high anxiety levels, these measures may be more effective if given before starting ketamine.<sup>8</sup>

When switching from CSCI to PO after just a few days of use, a conversion ratio of 1:1 should be used.<sup>32,81</sup> However, after weeks to 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 400 mg/24 h → PO 150 mg/24 h.<sup>30</sup> 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.

Withdrawal phenomena do not generally occur when stopping ketamine. However, after long-term use it is preferable to discontinue ketamine gradually; whole body hyperalgesia and allodynia have been reported after sudden cessation of ketamine after 3 weeks of use.<sup>73</sup>

**Supply**

Ketamine (generic)

**Injection** 50 mg/mL, 10 mL vial = \$7; 100 mg/mL, 5 mL vial = \$11.

Ketalar<sup>®</sup> (Pfizer)

**Injection** 10 mg/mL, 20 mL vial = \$18; 50 mg/mL, 10 mL vial = \$33; 100 mg/mL, 5 mL vial = \$33.

**Box C. Compatibility data for drug mixtures containing ketamine****2-drug compatibility data for ketamine in 0.9% saline**

Alfentanil, clonazepam, dexamethasone (low-dose), diamorphine, haloperidol, levomepromazine, midazolam, morphine sulfate, oxycodone.

**3-drug compatibility data for ketamine in 0.9% saline**

Haloperidol or midazolam with either diamorphine or morphine sulfate.

**Incompatibility**

Ketamine forms precipitates with barbiturates and diazepam (manufacturer’s data on file); *do not mix*.

Mixing lorazepam with ketamine is also not recommended; compatibility data is lacking and there is a risk of adsorption of lorazepam to the tubing.

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
CIVI	Continuous intravenous infusion
CSCI	Continuous subcutaneous infusion
CYP	Cytochrome P450
ED	Epidural
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
SL	Sublingual
t.i.d.	ter in die, three times daily
WFI	Water for injection

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