***KETAMINE BNF 15.1.1**

Class: General anaesthetic.
Indications: Induction and maintenance of anaesthesia; †pain unresponsive to standard therapies (neuropathic, inflammatory, ischaemic limb, myofascial and procedure-related).[1,2]

Contra-indications: Raised intracranial pressure, epilepsy.

Pharmacology
The NMDA-glutamate receptor is a calcium channel closely involved in the development of central (dorsal horn) sensitisation (Figure 13.1).[3] At normal resting membrane potentials, the channel is blocked by magnesium and inactive.[4] When the resting membrane potential is changed as a result of prolonged excitation, the channel unblocks with a reduction in opioid-responsiveness and the development of allodynia and hyperalgesia. These effects are probably mediated by the intracellular formation of nitric oxide.[5]

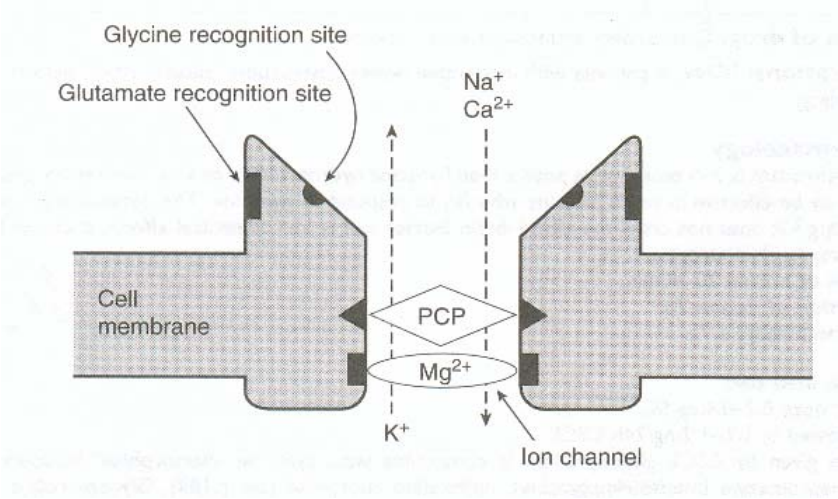

Figure 13.1 Diagram of NMDA (excitatory) receptor-channel complex. The channel is blocked by Mg^{2+} when the membrane potential is at its resting level (voltage-dependent block) and by drugs which act at the phencyclidine (PCP) binding site in the glutamate-activated channel, e.g. dextromethorphan, ketamine, methadone (use-dependent block).[3]

Ketamine is a dissociative anaesthetic which has analgesic properties in sub-anaesthetic doses.[6] 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.[7] It also binds to a second membrane-associated site which does not require the channel to be open and thereby decreases the frequency of channel opening.[8] A racemic mixture and the S-enantiomer (not UK) are available commercially for clinical use. Compared to the R-enantiomer, the S-enantiomer has greater affinity and selectivity for the NMDA receptor; it is 3–4 times more potent an analgesic and less likely to cause undesirable effects.[9,10] Ketamine has other actions

which may also contribute to its analgesic effect, including interactions with other calcium and sodium channels, cholinergic transmission, noradrenergic and serotoninergic re-uptake inhibition (intact descending inhibitory pathways are necessary for analgesia) and μ, δ and κ opioid-like effects.[11] Ketamine also appears to have an antidepressant effect in patients with major depression.[12]

Evidence of ketamine's efficacy as an analgesic is mainly from case reports, retrospective surveys or uncontrolled studies in patients with neuropathic pain.[13–20] A few prospective studies or randomized controlled trials have been published in severe ischaemic limb pain and refractory pain in cancer.[21-26] However, a recent systematic review of ketamine as an adjuvant to opioids for cancer pain found insufficient robust evidence to reach a conclusion.[27] Ketamine may be less effective in neuropathic pain of long duration (≥3 years).[28,29] Generally, ketamine is used in addition to **morphine** or 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.[16] It can also be administered IM, IV, SL, intranasally, PR and spinally (preservative-free formulation).[25, 29-32] There is some evidence that short-term 'burst' treatment with ketamine may have long-term benefit.[23,24,33] For example, in patients taking regular strong opioids for ischaemic limb pain, a single 4h IV infusion of ketamine 0.6mg/kg reduced opioid requirements during a week-long period of observation.[24] In cancer, ketamine 100–500mg/24h by CSCI for 3–5 days relieved pain in 67% of patients and, in over 80% of these, the relief lasted for several weeks or more.[23] In one case report, ketamine 100mg/24h by CIVI for 2 days, repeated a month later, reduced opioid requirements by 70%.[33]

Oral ketamine undergoes extensive first-pass hepatic metabolism to norketamine which is CYP3A4 dependent. As an anaesthetic, 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 oral administration than after injection;[34] in chronic use norketamine may be the main analgesic agent and possibly explains why an equianalgesic PO dose is approximately 25–50% of the previous parenteral dose.[18] Less than 10% of ketamine is excreted unchanged, half in the faeces and half renally. Long-term use of ketamine leads to hepatic enzyme induction and enhanced ketamine metabolism.

Ketamine causes tachycardia and intracranial hypertension. Most patients experience vivid dreams, misperceptions, hallucinations and alterations in body image and mood as emergent phenomena after anaesthetic use, i.e. as the effects of a bolus dose wears off. These occur to a lesser extent with the sub-anaesthetic analgesic doses given PO or CSCI, and generally can be controlled by **diazepam**, **midazolam** or **haloperidol**.[25,35,36]

Bio-availability 93% IM; 20% PO.
Onset of action 5min IM; 15–30min SC; 30min PO.
Time to peak plasma concentration no data SC; 30min PO; 1h norketamine.[37]
Plasma halflife 1–3h IM; 3h PO; 12h norketamine.[38]
Duration of action 30min–2h IM; generally given by CSCI; 4–6h, sometimes longer PO.[39]

Cautions

Hypertension, cardiac failure, ischaemic heart disease and history of cerebrovascular accidents.[40] Plasma concentration increased by **diazepam**.

Undesirable effects
For full list, see manufacturer's SPC.
Occur in about 40% of patients when given CSCI; less PO. Hypertension, tachycardia; psychotomimetic phenomena (euphoria, dsyphoria, blunted affect, psychomotor retardation, vivid dreams, nightmares, poor concentration, illusions, hallucinations, altered body image), delirium, dizziness, diplopia, blurred vision, nystagmus, altered hearing. Erythema and pain at injection site.

Dose and use
Dose recommendations vary considerably but ketamine is often started in a low dose PO (Box 13.A).[41] An oral solution is now available (see Supply) or can be extemporaneously prepared by the pharmacy (Box 13.B). Alternatively, patients can be supplied with vials of ketamine and 1ml graduated syringes. Two needles (one as an air vent) should be inserted in the bung of the vial to facilitate withdrawing the ketamine; sterility is not necessary for PO administration. Use 10mg/ml or 50mg/ml; 100mg/ml is too bitter. Long-term success, i.e. both pain relief and tolerable undesirable effects, varies from <20% to about 50%.[20,29,31,42]

Box 13.A Dose recommendations for ketamine

PO[16,46]
Use direct from vial or dilute for convenience to 50mg/5ml (patient adds flavouring of choice, e.g. fruit cordial, to mask the bitter taste):
• starting dose 10–25mg t.d.s.–q.d.s and p.r.n.[47]
• increase dose in steps of 10–25mg up to 50mg q.d.s.
• maximum reported dose 200mg q.d.s.[48,49]
• give a smaller dose more frequently if psychotomimetic phenomena or drowsiness occurs which does not respond to a reduction in opioid.

SC[16]
≤500microgram/kg, typically 10–25mg p.r.n.

CSCI[13,16,35]
Because ketamine is irritant, dilute with sodium chloride 0.9% to the largest volume possible (i.e. for a Graseby syringe driver, 18ml in a 30ml luerlock syringe given over 12–24h):
• starting dose 1–2.5mg/kg/24h[14,15]
• increase by 50–100mg/24h; maximum reported dose 3.6g/24h.[50]
Alternatively, give as short-term 'burst' therapy:
• starting dose 100mg/24h
• increase after 24h to 300mg/24h if 100mg not effective
• increase after further 24h to 500mg/24h if 300mg not effective
• stop 3 days after last dose increment.[23]
Ketamine is miscible with dexamethasone (low-dose), diamorphine, haloperidol, levomepromazine (methotrimeprazine), metoclopramide, midazolam, morphine. Inflammation at infusion site may be helped by hydrocortisone 1% cream or by adding dexamethasone 0.5–1mg to the infusion (dilute in 5–10ml sodium chloride and then add ketamine).

Box 13.A Continued

IV
To cover procedures that may cause severe pain:[51]
• 0.5–1mg/kg (typically 25–50mg), usually combined with
• midazolam 0.1mg/kg (typically 5–10mg) IV to reduce psychotomimetic emergence reactions.
Give over 1–2min. An effective dose of ketamine should provide analgesia within 1–5min that lasts for 10–20min. Procedures of longer duration may require ketamine CIVI; seek advice of an anaesthetist.

Box 13.B Preparation of ketamine oral solution: pharmacy guidelines

Use ketamine 100mg/ml 10ml vials because this is the cheapest concentration. Raspberry Syrup BP 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.

With higher doses by CSCI, the dose of **morphine** should be reduced if the patient becomes drowsy. If a patient experiences dysphoria or hallucinations, the dose of ketamine should be reduced and a benzodiazepine prescribed, e.g. **diazepam** 5mg PO stat & o.n., **midazolam** 5mg SC stat and 5–10mg CSCI, or **haloperidol**, e.g. 2–5mg PO stat & o.n., 2–5mg SC stat and 2–5mg CSCI.[36] 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.[7] When switching from CSCI to PO, after weeks to months of use, a total daily dose that is equivalent to 25–50% of the total parenteral dose provides a similar level of analgesia.[18] However, others report that when switching from CSCI to PO after only a few days of use, a conversion ratio of 1:1 is required.[19] Ketamine has been used IV with **fentanyl** and **midazolam** to control intractable pain and agitation.[43,44]

Ketamine is used less in centres where spinal analgesia is readily available or where **methadone** is used as the NMDA-receptor-channel blocker of choice; the affinity of **methadone** and ketamine for the NMDA-receptor-channel binding site is approximately the same.[45]

Supply
Oral solution 50mg/5ml, 28 days @ 50mg q.d.s. = £58.78. (Unlicensed, available as a special order from Martindale 01708 386660; see Special orders and named patient supplies).

Ketalar® (Pfizer 01304 616161)
Injection 10mg/ml, 20ml vial = £3.52; 50mg/ml, 10ml vial = £7.31; 100mg/ml, 10ml vial = £13.42. *Although use as an analgesic is unlicensed, ketamine injection can be prescribed both in hospitals and in the community. The procedure varies with the wholesaler the community pharmacist uses:*
• if Unichem, the pharmacist should telephone their local Unichem customer services to receive a faxed form. This requires the patient's name, dose of ketamine prescribed, quantity required, GP and pharmacist's details and wholesaler branch and account number. It should be faxed directly to Pfizer (Fax: 01304 655885) who will then authorize Unichem to initiate the supply.
• for all other wholesalers, the pharmacist should contact Pfizer customer services (Tel: 01304 645262, Fax: 01304 655885) and provide the same information as above. Pfizer will then supply the pharmacy directly, but will bill via the wholesaler.

Ketanest S®
Injection **ketamine (S-) hydrochloride** (esketamine hydrochloride) *equivalent to ketamine (S-) base* 5mg/ml, 20ml vial = £12.06; 25mg/ml, 10ml vial = £18.96. (Unlicensed, available as a named patient supply from IDIS 020 8410 0700; see Special orders and named patient supplies).

Injection (preservative free) **ketamine (S-) hydrochloride** (esketamine hydrochloride) *equivalent to ketamine (S-) base* 5mg/ml, 5ml amp = £3.86; 25mg/ml, 2ml amp = £5.23. (Unlicensed, available as a named patient supply from IDIS 020 8410 0700; see Special orders and named patient supplies).

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