Class: General anaesthetic.

Indications: Induction and maintenance of anaesthesia; †pain unresponsive to standard therapies (postoperative, neuropathic, inflammatory, ischaemic limb, myofascial and procedure-related).[1-3]

Contra-indications: 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 (dorsal horn) sensitization (Figure 13.1).[4] At normal resting membrane potentials, the channel is blocked by magnesium and inactive.[5] 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.[6]

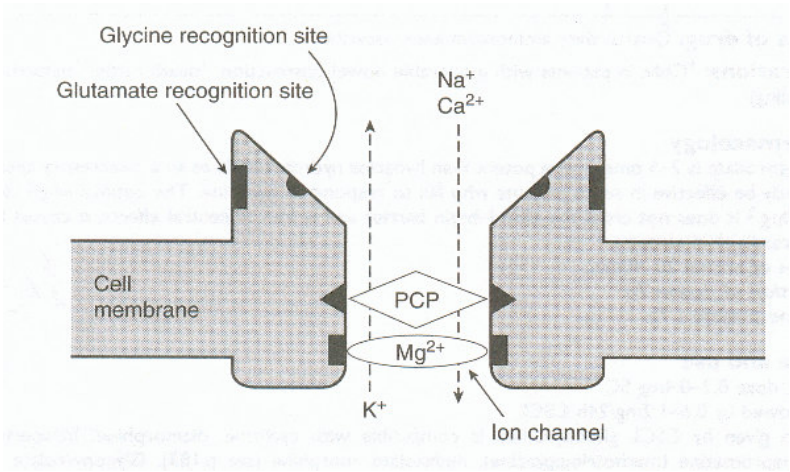

Figure 13.1 Diagram of NMDA (excitatory) receptor-channel complex. The channel is blocked by Mg^{2+} when the membrane potential is at its resting level (voltage-dependent block) and by drugs which act at the phencyclidine (PCP) binding site in the glutamate-activated channel, e.g. **dextromethorphan**, ketamine, **methadone** (use-dependent block).[4]

Ketamine is a dissociative anaesthetic which has analgesic properties in sub-anaesthetic doses.[3,7] 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.[8] 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.[9] A racemic mixture and the S-enantiomer (not UK) are available commercially for clinical use. 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.[10-12] When equianalgesic doses are compared, the S-enantiomer is also associated with

lower levels of undesirable effects, e.g. anxiety, tiredness, cognitive impairment.[11,13] However, no significant differences in efficacy or tolerability were found between PO racemic mixture (median dose 320mg/day), the S-enantiomer or placebo in patients with cancer-related neuropathic pain.[14] Ketamine has other actions which may also contribute to its analgesic effect, including interactions with other calcium and sodium channels, dopamine receptors, cholinergic transmission, noradrenergic and serotoninergic re-uptake inhibition (intact descending inhibitory pathways are necessary for analgesia) μ, δ and κ opioid-like effects and an anti-inflammatory effect.[15,16] Ketamine also appears to have an antidepressant effect in patients with major depression.[17,18]

A systematic review of sub-anaesthetic doses of ketamine as an adjunct to opioid-based postoperative analgesia identified 37 double-blind RCTs, and concluded that IV or ED ketamine is effective and did not increase undesirable effects. CIVI (generally 0.12–0.6mg/kg/h) was best for surgery associated with high opioid requirements, although a single IV dose (generally 0.15–1mg/kg) may suffice for minor surgery. Adding ketamine to IV patient-controlled analgesia was *not* effective. Ketamine reduced the incidence of chronic post-surgical pain, e.g. post-thoracotomy pain.[19] Conversely, a systematic review of ketamine as an adjuvant to opioids for cancer pain found only two studies and concluded that there was insufficient robust evidence to reach a conclusion.[20] 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 neuropathic pain.[21-30] A few prospective studies or randomized controlled trials have been published in refractory pain in cancer, including neuropathic, bone and mucositis-related.[31-36] In chronic non-cancer pain, evidence of benefit is mixed and undesirable effects occur in about half of patients.[3,37] Ketamine may be less effective in neuropathic pain of long duration (≥3 years).[12,38] 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.[23,29] It can also be administered IM, IV, SL, intranasally, PR and spinally (preservative-free formulation).[33,38-43]

There is some evidence that short-term 'burst' treatment with ketamine may have relatively long-term benefit. 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 of observation.[44] Ketamine 100mg/24h by CIVI for 2 days in a cancer patient, repeated a month later, reduced opioid requirements by 70%.[45] In several case series of cancer patients with severe intractable pain from various causes, 'burst' ketamine 100–500mg/24h by CSCI for 3–5 days relieved pain in about 50% of patients. [34,36,46] Relief lasted from several days to 4 weeks, and occasionally for 2 months. In one study using this regimen, although there were no withdrawals, 1/4 of patients experienced severe undesirable effects, such as sedation and confusion.[36]

PO ketamine undergoes extensive first-pass hepatic metabolism to norketamine (via CYP3A4). 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 PO administration than after injection,[47] and in chronic use norketamine may be the main analgesic agent. This possibly explains why, when switching from CSCI to PO after weeks–months, an equi-analgesic PO dose is *smaller* than the parenteral dose. It can be as little as 25–50% of the previous parenteral dose.[26] 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 (psychotomimetic) phenomena after anaesthetic use, i.e. as the effects of a bolus dose wear 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**.[33,48,49] 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]

Bio-availability 93% IM; 30% SL; 20% PO.[50]

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

Time to peak plasma concentration no data SC; 30min PO; 1h norketamine.[51]

Plasma halflife 1–3h IM; 3h PO; 12h norketamine.[52]

Duration of action 30min–2h IM; generally given by CSCI; 4–6h, sometimes longer PO.[53]

Cautions

Epilepsy, hypertension, heart failure, ischaemic heart disease and a history of cerebrovascular accidents.[54] 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: psychotomimetic phenomena (euphoria, dysphasia, blunted affect, psychomotor retardation, vivid dreams, nightmares, poor concentration, illusions, hallucinations, altered body image), delirium, dizziness, diplopia, blurred vision, nystagmus, altered hearing, hypertension, tachycardia, erythema and pain at injection site.

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

Dose and use

Dose recommendations vary considerably but ketamine is often started in a low dose PO (Box 13.A). An oral solution can be obtained as a special order or 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 stopper 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%.[27,38,40,55]

Box 13.A Dose recommendations for ketamine

PO[23,29,56-58]

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):

- start with 10–25mg t.d.s.–q.d.s and p.r.n.
- if necessary, increase dose in steps of 10–25mg up to 50mg q.d.s.
- maximum reported dose 200mg q.d.s.[56,58]
- give a smaller dose more frequently if psychotomimetic phenomena or drowsiness occurs which does not respond to a reduction in opioid.

SL[43]

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

SC[29]

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

CSCI[21-23,25,48,59]

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

- start with 1–2.5mg/kg/24h
- if necessary, increase by 50–100mg/24h
- maximum reported dose 3.6g/24h.
- Alternatively, give as short-term 'burst' therapy:[34,36,46]
- start with 100mg/24h
- if 100mg not effective, increase after 24h to 300mg/24h
- if 300mg not effective, increase after further 24h to 500mg/24h
- stop 3 days after last dose increment.

50% 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, midazolam or haloperidol is recommended (see text).

IV[29,60]

For cancer pain:
2.5–5mg.
To cover procedures which may cause severe pain:
0.5–1mg/kg (typically 25–50mg; some start with 5–10mg), given over 1–2min with

- midazolam 0.1mg/kg (typically 5–10mg; some start with 1–2mg) to reduce emergent phenomena.

The right dose should provide analgesia within 1–5min lasting for 10–20min.
Procedures of longer duration may require ketamine CIVI; obtain advice from an anaesthestist.

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.

When given by CSCI, ketamine is often mixed with morphine ± other drugs. Most likely mixtures are known to be compatibile in 0.9% saline (**Box 13.C**). Further details can be found on www.palliativedrugs.com syringe driver survey database.

Box 13.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 sulphate, oxycodone.

3-drug compatibility data for ketamine in 0.9% saline
haloperidol or midazolam with either diamorphine or morphine sulphate.

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

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.[49] 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.[8]

After weeks–months of use, when switching from CSCI to PO, a *smaller* total daily dose (25–50% of the parenteral dose) maintains a similar level of analgesia, e.g. CSCI 400mg/day → PO 150mg/day (see Pharmacology).[26] However, when switching from CSCI to PO after just a few days, a conversion ratio of 1:1 should be used. [28]

After long-term use it may be preferable to discontinue ketamine gradually; whole body hyperalgesia and allodynia have been reported after the sudden cessation of ketamine after 3 weeks of use.[61]

Ketamine has been used IV with **midazolam** for procedure-related pain, and with **fentanyl** and **midazolam** to control intractable pain and agitation.[62,63]

Supply

Oral solution (sugar-free) 50mg/5ml, 28 days @ 50mg q.d.s. = £108; *aniseed, lemon and ginger flavour*. (Unlicensed, available as a special order from Martindale; see Special orders and named patient supplies).

Ketalar® (Pfizer)

Injection 10mg/ml, 20ml vial = £4; 50mg/ml, 10ml vial = £9; 100mg/ml, 10ml vial = £16.

Although use as an analgesic is unlicensed, ketamine injection can be prescribed both in hospitals and in the community. The procedure for community pharmacies is as follows:

- contact Pfizer customer services (Tel: 01304 645262, Fax: 01304 655885) to request a supply
- to initiate the supply, Pfizer require the following details to be faxed to them on headed notepaper:
  - patient's name
  - dose of ketamine prescribed
  - quantity required
  - GP and pharmacist's details
  - details of the pharmacist's local wholesaler (branch and account number)
- depending on the quickest and most convenient arrangement for the pharmacy, Pfizer will then either:
  - supply via the local wholesaler or
  - supply the pharmacy directly but bill via the wholesaler.

Ketanest S®

Injection **ketamine (S-) hydrochloride** (esketamine hydrochloride) *equivalent to ketamine (S-) base* 5mg/ml, 20ml vial = £15; 25mg/ml, 10ml vial = £24. (Unlicensed, available as a named patient supply from IDIS; see Special orders and named patient supplies).

Injection (preservative-free) **ketamine (S-) hydrochloride** (esketamine hydrochloride) *equivalent to ketamine (S-) base* 5mg/ml, 5ml amp = £4; 25mg/ml, 2ml amp = £6. (Unlicensed, available as a named patient supply from IDIS; see Special orders and named patient supplies).

1 Persson J *et al.* (1998) The analgesic effect of racemic ketamine in patients with chronic ischemic pain due to lower extremity arteriosclerosis obliterans. *Acta Anaesthesiologica Scandinavica.* **42**: 750–758.

2 Graven-Nielsen T *et al.* (2000) Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. *Pain.* **85**: 483–491.

3 Visser E and Schug SA (2006) The role of ketamine in pain management. *Biomedicine and Pharmacotherapy.* **60**: 341–348.

4 Richens A (1991) The basis of the treatment of epilepsy: neuropharmacology. In: M Dam (ed.) *A Practical Approach to Epilepsy.* Pergamon Press, Oxford, pp.75–85.

5 Mayer M *et al.* (1984) Voltage-dependent block for Mg^{2+} of NMDA responses in spinal cord neurones. *Nature.* **309**: 261–263.

6 Elliott K *et al.* (1994) The NMDA receptor antagonists, LY274614 and MK-801, and the nitric oxide synthase inhibitor, NG-nitro-L-arginine, attenuate analgesic tolerance to the mu-opioid morphine but not to kappa opioids. *Pain.* **56**: 69–75.
7 Fallon MT and Welsh J (1996) The role of ketamine in pain control. *European Journal of Palliative Care.* **3**: 143–146.
8 Oye I (1998) Ketamine analgesia, NMDA receptors and the gates perception. *Acta Anaesthesiologica Scandinavica.* **42**: 747–749.
9 Orser B *et al.* (1997) Multiple mechanisms of ketamine blockade of N-methyl-D-aspartate receptors. *Anesthesiology.* **86**: 903–917.
10 Oye I *et al.* (1991) The chiral forms of ketamine as probes for NMDA receptor function in humans. In: T Kameyama (ed.) *NMDA receptor Related Agents: biochemistry, pharmacology and behavior.* NPP, Ann Arbor, Michigan, pp.381–389.
11 White PF *et al.* (1980) Pharmacology of ketamine isomers in surgical patients. *Anesthesiology.* **52**: 231–239.
12 Mathisen L *et al.* (1995) Effect of ketamine, an NMDA receptor inhibitor, in acute and chronic orofacial pain. *Pain.* **61**: 215–220.
13 Pfenninger EG *et al.* (2002) Cognitive impairment after small-dose ketamine isomers in comparison to equianalgesic racemic ketamine in human volunteers. *Anesthesiology.* **96**: 357–366.
14 Fallon M *et al.* (in press) A randomized, double-blind, placebo-controlled study comparing oral racemic ketamine and S-ketamine in the treatment of cancer-related neuropathic pain. *Journal of Clinical Oncology.*
15 Meller S (1996) Ketamine: relief from chronic pain through actions at the NMDA receptor? *Pain.* **68**: 435–436.
16 Kawasaki C *et al.* (2001) Ketamine isomers suppress superantigen-induced proinflammatory cytokine production in human whole blood. *Canadian Journal of Anaesthesia.* **48**: 819–823.
17 Berman R *et al.* (2000) Antidepressant effects of ketamine in depressed patients. *Biological Psychiatry.* **47**: 351–354.
18 Zarate CA, Jr. *et al.* (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry.* **63**: 856–864.
19 Subramaniam K *et al.* (2004) Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. *Anesthesia and Analgesia.* **99**: 482–495, table of contents.
20 Bell RF *et al.* (2003) Ketamine as adjuvant to opioids for cancer pain. A qualitative systematic review. *Journal of Pain and Symptom Management.* **26**: 867–875.
21 Oshima E *et al.* (1990) Continuous subcutaneous injection of ketamine for cancer pain. *Canadian Journal of Anaesthetics.* **37**: 385–392.
22 Cherry DA *et al.* (1995) Ketamine as an adjunct to morphine in the treatment of pain. *Pain.* **62**: 119–121.
23 Luczak J *et al.* (1995) The role of ketamine, an NMDA receptor antagonist, in the management of pain. *Progress in Palliative Care.* **3**: 127–134.
24 Mercadante S (1996) Ketamine in cancer pain: an update. *Palliative Medicine.* **10**: 225–230.
25 Bell R (1999) Low-dose subcutaneous ketamine infusion and morphine tolerance. *Pain.* **83**: 101–103.
26 Fitzgibbon EJ *et al.* (2002) Low dose ketamine as an analgesic adjuvant in difficult pain syndromes: a strategy for conversion from parenteral to oral ketamine. *Journal of Pain and Symptom Management.* **23**: 165–170.
27 Kannan TR *et al.* (2002) Oral ketamine as an adjuvant to oral morphine for neuropathic pain in cancer patients. *Journal of Pain and Symptom Management.* **23**: 60–65.
28 Benitez-Rosario M *et al.* (2003) A retrospective comparison of the dose ratio between subcutaneous and oral ketamine. *Journal of Pain and Symptom Management.* **25**: 400–402.
29 Kotlinska-Lemieszek A and Luczak J (2004) Subanesthetic ketamine: an essential adjuvant for intractable cancer pain. *Journal of Pain and Symptom Management.* **28**: 100–102.
30 Fitzgibbon EJ and Viola R (2005) Parenteral ketamine as an analgesic adjuvant for severe pain: development and retrospective audit of a protocol for a palliative care unit. *Journal of Palliative Medicine.* **8**: 49–57.
31 Yang CY *et al.* (1996) Intrathecal ketamine reduces morphine requirements in patients with terminal cancer pain. *Canadian Journal of Anaesthesia.* **43**: 379–383.
32 Lauretti G *et al.* (1999) Oral ketamine and transdermal nitroglycerin as analgesic adjuvants to oral morphine therapy and amitriptyline for cancer pain management. *Anesthesiology.* **90**: 1528–1533.

33 Mercadante S *et al.* (2000) Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized , controlled, double-blind, crossover, double-dose study. *Journal of Pain and Symptom Management.* **20**: 246–252.
34 Jackson K *et al.* (2001) 'Burst' ketamine for refractory cancer pain: an open-label audit of 39 patients. *Journal of Pain and Symptom Management.* **22**: 834–842.
35 Lossignol DA *et al.* (2005) Successful use of ketamine for intractable cancer pain. *Supportive Care in Cancer.* **13**: 188–193.
36 Jackson K and Howell D (In press) *A multicentre open phase I/II trial of the efficacy of Ketamine for refractory cancer pain*., The Cancer Council.
37 Hocking G and Cousins MJ (2003) Ketamine in chronic pain management: an evidence-based review. *Anesthesia and Analgesia.* **97**: 1730–1739.
38 Haines D and Gaines S (1999) N of 1 randomised controlled trials of oral ketamine in patients with chronic pain. *Pain.* **83**: 283–287.
39 Lin T *et al.* (1998) Long-term epidural ketamine, morphine and bupivacaine attenuate reflex sympathetic dystrophy neuralgia. *Canadian Journal of Anaesthesia.* **45**: 175–177.
40 Batchelor G (1999) Ketamine in neuropathic pain. *The Pain Society Newsletter.* **1**: 19.
41 Beltrutti D *et al.* (1999) The epidural and intrathecal administration of ketamine. *Current Review of Pain.* **3**: 458–472.
42 Carr DB *et al.* (2004) Safety and efficacy of intranasal ketamine for the treatment of breakthrough pain in patients with chronic pain: a randomized, double-blind, placebo-controlled, crossover study. *Pain.* **108**: 17–27.
43 Mercadante S *et al.* (2005) Alternative treatments of breakthrough pain in patients receiving spinal analgesics for cancer pain. *Journal of Pain and Symptom Management.* **30**: 485–491.
44 Mitchell AC and Fallon MT (2002) A single infusion of intravenous ketamine improves pain relief in patients with critical limb ischaemia: results of a double blind randomised controlled trial. *Pain.* **97**: 275–281.
45 Mercadante S *et al.* (2003) Burst ketamine to reverse opioid tolerance in cancer pain. *Journal of Pain and Symptom Management.* **25**: 302–305.
46 Wilcock A (2005) Burst ketamine in cancer patients. *Data on file*.
47 Clements JA *et al.* (1982) Bio-availability, pharmacokinetics and analgesic activity of ketamine in humans. *Journal of Pharmaceutical Sciences.* **71**: 539–542.
48 Hughes A *et al.* (1999) Ketamine. *CME Bulletin Palliative Medicine.* **1**: 53.
49 Giannini A *et al.* (2000) Acute ketamine intoxication treated by haloperidol: a preliminary study. *American Journal of Therapeutics.* **7**: 389–391.
50 Chong CC *et al.* (2006) Bioavailability of Ketamine After Oral or Sublingual Administration. *Pain Medicine.* **7**: 469–469.
51 Grant IS *et al.* (1981) Pharmacokinetics and analgesic effects of IM and oral ketamine. *British Journal of Anaesthesia.* **53**: 805–810.
52 Domino E *et al.* (1984) Ketamine kinetics in unmedicated and diazepam premedicated subjects. *Clinical Pharmacology and Therapeutics.* **36**: 645–653.
53 Rabben T *et al.* (1999) Prolonged analgesic effect of ketamine, an N-methyl-D-aspartate receptor inhibitor, in patients with chronic pain. *Journal of Pharmacology and Experimental Therapeutics.* **289**: 1060–1066.
54 Ward J and Standage C (2003) Angina pain precipitated by a continuous subcutaneous infusion of ketamine. *Journal of Pain and Symptom Management.* **25**: 6–7.
55 Enarson M *et al.* (1999) Clinical experience with oral ketamine. *Journal of Pain and Symptom Management.* **17**: 384–386.
56 Clark JL and Kalan GE (1995) Effective treatment of severe cancer pain of the head using low-dose ketamine in an opioid-tolerant patient. *Journal of Pain and Symptom Management.* **10**: 310–314.
57 Broadley K *et al.* (1996) Ketamine injection used orally. *Palliative Medicine.* **10**: 247–250.
58 Vielvoye-Kerkmeer A (2000) Clinical experience with ketamine. *Journal of Pain and Symptom Management.* **19**: 3.
59 Lloyd-Williams M (2000) Ketamine for cancer pain. *Journal of Pain and Symptom Management.* **19**: 79–80.
60 Mason KP *et al.* (2002) Evolution of a protocol for ketamine-induced sedation as an alternative to general anesthesia for interventional radiologic procedures in pediatric patients. *Radiology.* **225**: 457–465.
61 Mitchell AC (1999) Generalized hyperalgesia and allodynia following abrupt cessation of subcutaneous ketamine infusion. *Palliative Medicine.* **13**: 427–428.

62 Berger J *et al.* (2000) Ketamine-fentanyl-midazolam infusion for the control of symptoms in terminal life care. *American Journal of Hospice and Palliative Care.* **17**: 127–132.
63 Enck R (2000) A ketamine, fentanyl, and midazolam infusion for uncontrolled terminal pain and agitation. *American Journal of Hospice and Palliative Care.* **17**: 76–77.