

The role of Ketamine in the management of chronic pain

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Abstract

There has been increasing clinical interest in the role of the non-competitive N-methyl-D-aspartate (NMDA) antagonist ketamine for the management of complex pain states. *In vivo* and *in vitro* studies increasingly suggest involvement of the NMDA receptor complex in a variety of chronic pain states associated with the clinical features of allodynia, central hypersensitivity and plasticity. This article explores the evidence for the role of the NMDA receptor complex in acute and chronic pain, and for the therapeutic use of NMDA receptor antagonists such as ketamine. It concludes with a discussion of the adverse effects of ketamine and some recommendations for its clinical use.

The NMDA receptor complex, excitatory neurotransmitters and pain

NMDA Receptor Complex

The N-methyl-D-aspartate (NMDA) receptor is defined by its selectivity for the prototypic agonist NMDA and its recognition of the naturally occurring excitatory amino acids glutamate and aspartate. The NMDA receptor complex is distributed throughout the central nervous system, and is associated with the physiological processes relating to learning and memory, neural development, neural plasticity, as well as some acute and chronic pain states.¹

The NMDA receptor complex is uniquely both ligand and voltage gated, enabling the passage of Ca⁺⁺ into a cell from the extracellular environment.² In its resting state there is a Mg⁺⁺/voltage-dependant sensory block of the NMDA receptor. Release of excitatory neurotransmitters and of neuropeptides such as substance P from primary afferent nerve terminals effectively removes this block, thereby promoting Ca⁺⁺ influx into dorsal horn neurones. This influx of Ca⁺⁺ provides a mechanism by which neuronal activity can be switched from low to high levels, the clinical result of which is a form of central sensitisation to peripheral pain stimuli.^{1,2}

Excitatory Amino Acids

In the last 15 years there has been widespread interest in the role of excitatory amino acids such as glutamate and aspartate in the transmission of nociceptive pain. Neurochemical studies have suggested that excitatory amino acids are present in C-fibre processes and their terminals in the dorsal horn of the spinal cord, and that glutamate coexists in most substance P – containing C-fibres.² Stimulation of C-fibres in the periphery may result in the co-release of a number of peptides together with excitatory amino acids in the spinal cord, leading to activation of the NMDA receptor complex.^{1,2}

Wind-Up

Activation of the NMDA receptor complex is associated with phenomenon of “wind-up”. In animal models, repeated stimulation of a dorsal horn nociceptive neurone by the peripheral electrical stimulation that will activate C-fibres results in a two phase response: the initial “fast” synaptic transmission (A- and C-fibres) which produces a constant response to the first few stimuli followed by a second phase response that increases dramatically and then stabilises at a level many times greater than the original response.^{3,4} This “wind up” is characteristic of the ligand and voltage-gated NMDA receptor, and is reduced or abolished by NMDA receptor antagonists in animal models^{5,10} and man¹¹. The A-fibre and initial C-fibre responses are little or unaffected by NMDA receptor antagonists.^{7,9}

Clinical effects of activation of the NMDA receptor complex

Allodynia (pain evoked by a stimulus that does not normally produce pain) and hyperalgesia (an increased degree of pain provoked by a stimulus that is normally painful) appear to be sensory abnormalities that reflect altered central processing of afferent input. The current evidence from animal models supports activation of the NMDA receptor complex in the development and maintenance of allodynia and hyperalgesia^{1,6,8}, but the involvement of other receptor subtypes has not been excluded.¹²

Pharmacology of Ketamine

Ketamine is a non-selective NMDA antagonist, which has been used as an anaesthetic agent for many years. The commercial preparation contains equal concentrations of the two enantiomers, s (+) and r (-) ketamine. The s (+) enantiomer has been shown to bind to kappa and mu opioid receptors.¹²

Ketamine is extensively metabolised in the liver to norketamine. This is pharmacologically active with the anaesthetic potency approaching one-third of the parent compound. Other metabolites have also been identified, but their anaesthetic properties are not known. The ketamine metabolites are renally excreted, and the elimination half life of parenteral ketamine is 2-3 hours in adults.^{13,14}

Routes of administration

The bioavailability of ketamine following parenteral administration is over 90%.¹⁴ Ketamine is poorly absorbed by the oral or rectal routes, with a bioavailability of only 16%, and peak serum levels of ketamine are only one-fifth as high as following intramuscular injection; times to peak levels are also longer with oral administration, reflecting a delay due to gastrointestinal absorption and hepatic first pass metabolism.¹⁴ Norketamine levels are three times higher following oral compared to intramuscular administration of ketamine, and this appears to contribute significantly to the analgesic effects noted

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with the oral route.¹⁴ Ketamine is also absorbed subcutaneously, but no pharmacokinetic data are available on this.

Evidence for use of ketamine in non-malignant pain

The role of ketamine as an anaesthetic agent is well established. Ketamine has also been found to be effective as an analgesic for post-operative pain in both adult^{15,16,17} and paediatric populations¹⁸. In the management of an acutely painful burn in a three year old girl, Morgan used a 15 mg (1mg/kg) dose of oral ketamine with good effect, and use of this dose twice daily allowed the child's dressings to be changed without pain.¹⁹ There are an increasing number of reports in the literature of the use of ketamine for a variety of chronic pain states: post herpetic neuralgia (PHN),^{20,22} peripheral and central neuropathic pain states²³⁻²⁵, phantom limb pain,²⁶⁻²⁹ osteoporosis,³⁰ orofacial pain³¹ and HIV neuropathy,³² the most important of which are summarised in Table 1. In addition to significant reductions in pain, several authors noted improvement in allodynia^{20,22,25} and hyperalgesia and after-sensation.²³ Nikolajsen and Eide also reported significant inhibition of wind-up pain in the populations studied.^{20,26} Although the numbers of patients in these studies is small, there is consistent evidence for the therapeutic benefit of ketamine in non-malignant chronic neuropathic pain.

Evidence for the use of other NMDA antagonists in chronic pain

Dextromethorphan is a selective NMDA antagonist, commercially available as a cough suppressant. McQuay studied the analgesic effects of oral dextromethorphan in a double-blind randomised cross-over trial with a n-of 1 design of nineteen patients with chronic neuropathic pain. There were no significant differences in pain intensity, pain relief, adverse events, mood, sleep

and a global rating of treatment between dextromethorphan 40.5 and 81mg/day and placebo.³³ Two other trials studying the analgesic effect of oral dextromethorphan in brain ischaemia³⁴ and amyotrophic lateral sclerosis³⁵ have also produced negative results. Price, however, found that doses of dextromethorphan of 30 and 45 mg were effective in relieving the temporal summation of second pain induced by repeated painful electric shocks to normal volunteers¹¹. Memantine, an anti-viral, anti-Parkinsonian drug which is also a potent non-competitive NMDA antagonist, is approved for chronic use in humans. Animal studies suggest that it is effective in reducing neuropathic pain,^{36,37} but to date there are no reported clinical trials in humans. The reasons for the predominantly negative clinical studies with dextromethorphan are not clear, but raises the possibility that the analgesic effects of ketamine may be in addition to its properties as a NMDA receptor antagonist.¹²

Evidence for use of ketamine in cancer pain

There are no published reports of placebo-controlled trials of ketamine in cancer pain, but evidence from open studies suggests that ketamine may have a role in intractable pain in cancer patients. Oshima reported the effectiveness of a subcutaneous (sc) infusion of ketamine (10 mg bolus dose followed by an infusion at 2.5-15 mg/hr) in thirteen of eighteen cancer patients with intractable pain.³⁸ Luczak reported very good or good pain relief in 24 (75%) of 32 cancer patients with ketamine at doses of 50-700 mg/day by subcutaneous infusion (30 patients) or 10-50 mg every 4 hours orally (6 patients).³⁹ Similarly, Shima reported improvement in pain control in 11 out of 14 patients with advanced cancer and neuropathic pain with doses of 48-450 mg/day by continuous iv or sc infusion.⁴⁰ Harvey and Davies treated 7 patients with cancer-related neuropathic pain with oral ketamine in doses ranging from 12.5-50 mg six hourly. Marked improvements in pain were

Author	Diagnosis	No. patients	Study design	Control drug	Dose/route	Pain score	Outcome
Cherry 1995 ³⁰	Osteoporosis	1	double-blind, multi-dose	morphine	0-40mg, i.m., 8 x day	VAS* for pain	fall in pain score with increasing dose p<0.001
Eide 1994 ²⁰	PHN†	8	randomised, double-blind, cross-over	morphine / saline	0.15 mg/kg i.v. single dose	VAS pain relief/pain intensity	improvement in pain in 6/8 patients p<0.03
Backonja 1994 ²³	peripheral neuropathic pain	3	double-blind, placebo-controlled	saline	250 mcg/kg i.v. single dose	VAS pain rating	3/3 peripheral pain reduction in pain VAS
	central pain	3					2/3 central pain reduction in pain VAS
Nikolajsen 1996 ²⁶	stump & phantom limb pain	11	double-blind, placebo-controlled	saline	bolus 0.1 mg/kg/5 min i.v. then infusion 7 mcg/kg/min	pain VAS and McGill pain questionnaire	reduction in mean pain score on VAS p<0.05
							pain rating index reduced for stump and phantom limb pain p=0.006
Oye 1993 ³¹	orofacial pain	7	open	-	i.m/i.v. injections, no dose recorded	pain VAS	3/7 reported pain free period
Felsby 1995 ²⁴	peripheral neuropathic pain	10	double-blind, placebo-controlled	magnesium chloride/placebo	bolus 0.2 mg/kg i.v. the infusion 0.3 mg/kg/hr	pain VAS	reduction in mean VAS score of 57% p=0.006

Table 1: Clinical Trials of Ketamine for Chronic Neuropathic Pain †PHN post herpetic neuralgia *VAS visual analogue scale

Author	Diagnosis	Ketamine dose	Outcome
Broadley ³²	Intramedullary cystic glioma	10-12.5 mg/hr (0.16-0.2 mg/kg/hr) sc then 25-200 mg 6 hourly po	Pain free for 7 months (at time of publication)
Clark ⁴³	Squamous cell carcinoma maxillary sinus	50 mg bolus iv followed by infusion 100-200 mg/hr	Pain controlled for 13 days until death
Wood ⁴⁴	Perisylvia astrocytoma	2 mg/kg/24hr	Pain controlled for 18 days until death
Mercandante ⁴⁵	Malignant lumbosacral infiltration(unknown primary)	150-400 mg/24hr sc	Adequate pain relief for 13 months until death
Laird ⁴⁶	Ca breast - cutaneous infiltration	0.25-0.5 mg/kg/hr sc	Good pain control for 48 days until death

Table 2: Case reports of ketamine in cancer-related neuropathic pain

noted in 4, and only 1 patient did not benefit.⁴¹ In 10 patients with cancer-related neuropathic pain, Edmonds noted marked (4) or moderate (2) improvements in pain after a bolus dose of subcutaneous ketamine of 10 mg followed by an infusion of 10-15 mg/hr.⁴² The five case reports summarised in Table 2 also demonstrate the efficacy of ketamine in complex malignant pain states,^{32,43-46} but further interpretation is hampered by the small number of patients and lack of prospective controlled studies.

Adverse effects of ketamine

In the studies of ketamine in non-malignant pain states, psychomimetic side effects were most commonly reported, such as sedation, dizziness, vivid dreams, visual disturbance and disorientation.²⁰⁻³⁰ These effects appeared more pronounced at higher doses and with continuous infusions,^{23,25} and were only rarely dose-limiting.²⁵ The treatment related toxicity observed in the series of cancer patients is summarised in Table 3.³⁸⁻⁴² Psychomimetic effects

Author	Psychomimetic toxicity (no. patients)	Inflammation at injection site
Oshima ³⁸	2/18	6/8
Luczak ³⁹	9/32	
Shima ⁴⁰	2/14	
Harvey ⁴¹	6/7	
Edmonds ⁴²	5/10	

Table 3: Reported toxicity with the use of ketamine for cancer pain

were again the most commonly observed, and necessitated discontinuation of treatment in 3/7 (Harvey⁴¹) and 4/10 (Edmonds⁴²) patients in two series. In addition, Luczak reports on the administration of ketamine to a terminally ill cancer patient with intractable neuropathic pain requiring large doses of oral morphine, where the administration of ketamine resulted in long-lasting pain relief but excessive sedation and respiratory depression requiring the use of naloxone.³⁹

Recommendations for use of ketamine

Although the numbers of patients reported in the literature are small, there is now a body of evidence supporting the use of ketamine for chronic neuropathic pain. A large variety of dose schedules have been employed, making cast-iron recommendations impossible. When considering the use of ketamine, the following should be considered:

- Ketamine should be used by pain or palliative care physicians who are familiar with its use, or practitioners should receive expert advice prior to commencing treatment
- A test dose of 5-10 mg iv or sc is recommended initially to determine whether the pain is likely to respond

- Ketamine may be given by sc infusion: effective starting doses may be as low as 0.1 mg/kg/hr and should be titrated against effect. Inflammation at the injection site may limit use of this route
- Ketamine is effective orally in doses of 10-200 mg 4-6 hourly - the efficacy of ketamine should initially be determined by a bolus dose, and prior use of subcutaneous ketamine may help in establishing then minimum effective starting dose
- The morphine or alternative opioid dose should be reduced by approximately 50% on starting ketamine to limit opioid toxicity
- If psychomimetic side effects are troublesome, midazolam (5-20mg/24 hour) or haloperidol (2-4 mg/24 hours) may be effective
- There are no reports of the compatibility of ketamine with other drugs in an infusion pump

Conclusions

The evidence suggests that sub-anaesthetic doses of ketamine are effective in relieving some chronic non-malignant and malignant pain states. Ketamine may produce its analgesic effect by antagonism of the NMDA receptor complex, although other modes of action may also be important.¹² Further research is required to establish the optimum dose, schedule and route of administration of ketamine, and in the development of competitive NMDA antagonists with an improved toxicity profile.

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