The role of Ketamine in the management of chronic pain

Polly M. Edmonds

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. Activation of the NMDA receptor complex is uniquely both ligand and voltage gated, enabling the passage of Ca++ into a cell from the extracellular environment. 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.

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 noxious 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. 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.

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. 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 and man. The A-fibre and initial C-fibre responses are little or unaffected by NMDA receptor antagonists.

Clinical effects of activation of the NMDA receptor complex
Alldynia (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, but the involvement of other receptor subtypes has not been excluded.

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.

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.

Routes of administration
The bioavailability of ketamine following parenteral administration is over 90%. 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. 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.
with the oral route. 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 and paediatric populations. 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. 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), peripheral and central neuropathic pain states, phantom limb pain, osteoradionecrosis, orofacial pain and HIV neuropathy, the most important of which are summarised in Table 1. In addition to significant reductions in pain, several authors noted improvement in alldynia and hyperalgesia and after-sensation. Nikolajsen and Eide also reported significant inhibition of wind-up in allodynia and hyperalgesia, and after-sensation.

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 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. Two other trials studying the analgesic effect of oral dextromethorphan in brain ischaemia and amyotrophic lateral sclerosis 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 volunteers. 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, 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.

**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.

Lucaz reported very good or good pain relief in 24 (75%) of 32 cancer patients with ketamine at doses of 50-700 mg/day by continuous iv or sc infusion. Similarly, Shimura reported improvement in pain control in 11 out of 14 patients with advanced cancer and neuropathic pain with doses of 48-430 mg/day by continuous iv or sc infusion.

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

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

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

Good pain control for 48 days until 2/18
5/10
150-400 mg/24hr sc

Squamous cell carcinoma maxillary sinus

Pain controlled for 13 days until death

Ca breast - cutaneous infiltration

Adequate pain relief for 13 months until 6/7

Psychomimetic toxicity

Intramedullary cystic glioma

Outcome

Pain free for 7 months (at time of publication)

Intratumoral cystic glioma

Malignant lumbosacral infiltration (unknown primary)

Adequate pain relief for 13 months until death

Ca breast - cutaneous infiltration

Good pain control for 48 days until death

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Psychomimetic toxicity (no. patients)</th>
<th>Inflammation at injection site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oshima</td>
<td>2/18</td>
<td>6/8</td>
</tr>
<tr>
<td>Luczak</td>
<td>9/32</td>
<td></td>
</tr>
<tr>
<td>Shima</td>
<td>2/14</td>
<td></td>
</tr>
<tr>
<td>Harvey</td>
<td>6/7</td>
<td></td>
</tr>
<tr>
<td>Edmonds</td>
<td>5/10</td>
<td></td>
</tr>
</tbody>
</table>

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

The treatment related toxicity observed in the series of cancer patients is summarised in Table 3. Psychomimetic effects noted in 4, and only 1 patient did not benefit. 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. The five case reports summarised in Table 2 also demonstrate the efficacy of ketamine in complex malignant pain states, 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. These effects appeared more pronounced at higher doses and with continuous infusions, and were only rarely dose-limiting. The treatment related toxicity observed in the series of cancer patients is summarised in Table 3. Psychomimetic effects were again the most commonly observed, and necessitated dis-continuation of treatment in 3/7 (Harvey) and 4/10 (Edmonds) 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.

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.

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

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

References:
3. Woolf CJ; Central mechanisms of acute pain. Pain 1990, supplement 5, S218
7. Dickenson AH and Sullivan AF; Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurones following C-fibre stimulation. Neuropharmacology 1997, 26 (8), 1235-1238.
8. Woolf CJ and Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation: implications for the treat-
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