Ketamine's second life : Treatment of acute and chronic pain

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Section I

Introduction

Chapter 1

Introduction

1.1 Prevalence and impact on daily life of chronic pain

A large survey in Europe investigating chronic pain revealed that 19% of the more than 45.000 participants suffered pain for more than 6 months, had experienced pain in the last month and several times during the last week, seriously affecting the quality of their social and working lives. Their pain intensity was ≥ 5 on a 10-point Numeric Rating Scale (1= no pain, 10 = worst pain imaginable). 66% had moderate pain (NRS = 5-7), 34% had severe pain (NRS = 8 – 10), 46% had constant pain, 54% had intermittent pain. 59% had suffered with pain for two to 15 years, 21% had been diagnosed with depression because of their pain, 61% were less able or unable to work outside the home, 19% had lost their job and 13% had changed jobs because of their pain. 60% visited their doctor about their pain 2 – 9 times in the last six months. Only 2% were currently treated by a pain management specialist. One-third of the chronic pain sufferers were currently not being treated and nearly half received inadequate pain management.[1]

1.2 Ketamine

Rationale on the use of ketamine in pain

Recent research has focused on new clinical uses of ketamine, often in low doses as a supplement to conventional anesthetic and analgesic techniques in an attempt to improve the efficacy of these techniques while minimizing ketamine related side effects[2,3]. A number of randomized controlled trials (RCT's) suggest that ketamine has pre-emptive analgesic and opioid sparing effects in doses as low as 0.15 mg/kg[4]. Additionally, there are few RCT's of long-term administration of ketamine for neuropathic pain. These studies demonstrated the efficacy and safety of ketamine in the treatment of different causes of neuropathic pain.[5–12] Several studies have been published about the use of ketamine as an adjuvant analgetic drug to opioids or as a sole analgetic drug. These studies concluded that ketamine might play an important role in pain management,[2,13–16], although one RCT did not reported a difference in pain reduction postoperatively between the use of ketamine and a placebo drug.[17]

Mechanism of action

Glutamate is one key excitatory transmitter in the central nervous system and is used in the information transfer between most, if not all, neurones. A large proportion of peripheral sensory fibers, both large and small diameter, including C-fibers, contain glutamate and the related amino-acid, aspartate. In addition to these afferent sources, there is a large pool of glutamate in intrinsic dorsal horn neurones. In chronic pain conditions the post-synaptic activation of dorsal horn nociceptive neurones will include activation of the NMDA receptor amongst others. For a number of reasons, including the fact that the channel is plugged by normal physiological levels of mag-

nesium, the NMDA receptor and its channel does not participated in 'normal activity' in pain circuits but is brought into play under certain conditions. Co-operation between spinally released peptides and glutamate is needed for activation of the NMDA receptor since peptide depolarizations are needed to remove the magnesium block. Once the block is removed and the NMDA complex activated, the ion flow, mainly calcium but also sodium, elicits massive neuronal depolarizations and greatly increases the level of excitability of the neurone. By this means, the NMDA receptor plays a pivotal role in more prolonged pain states to enhance, prolong and alter activity in nociceptive circuitry in the spinal cord where it seems to be responsible for hyperalgesia and allodynia.[18] The analgesic action of ketamine appears therefore to be due to NMDA antagonism. Ketamine acts at the phencyclidine (PCP) site on the NMDA receptor.[19–21]

Pharmacotherapeutic information and pharmacokinetics

Ketamine was introduced in 1965 as an intravenous anesthetic agent. It produces dissociative anesthesia rather than generalized depression of the central nervous system.[22] Ketamine is a racemic mixture of the isomers R(-)-ketamine and S(+)-ketamine.[2,23] The S(+)isomer (Ketanest) is 3-4 times as potent as an analgesic with a faster clearance than R(-) isomer[14,24] The use of the S(+) single isomer form results in a faster recovery of cognitive function and a lower incidence of psychomimetic side effects.[14] Only approximately 12% of ketamine is bound to protein. The initial peak concentration after intravenous injection decreases as the drug is distributed, but this occurs more slowly than with other intravenous anaesthetic agents. The elimination half-life is approximately 2.5 hour. Distribution and elimination are slower if halothane, benzodiazepines or barbiturates are administered concurrently. Ketamine's bioavailability is 93% after parenteral use (intravenous, intramuscular or subcutaneous injection),[14] but less than 20% after oral use. Its low oral bioavailability is due to high first pass metabolism. It is metabolized in the liver predominantly to nor-ketamine, which has some activity (between 20-30%). It is further hydroxylated to hydorxynorketamine, which is conjugated to water-soluble glucuronide derivatives (80%) before being excreted in the urine. Impaired renal function does not prolong the action of ketamine.[25] Only 2.5% is excreted unchanged.

Side effects

Side effects of ketamine intravenous in a subanesthetic dose can be categorized as follows: central nervous system, gastro-intestinal, cardiovascular and hepatic side effects. The appendix 1 of a article of Correll *et al.*[26] mentioned that in rats prolonged NMDA-receptor blockade with high dose phencyclidine and MK-801 results in neurotoxicity in rats. However, the original paper by Jevtovic-Todorovic *et al.*[27] shows that apart from neurotoxicity, NMDA receptor antagonists produce dose dependent neuroprotection. Neurotoxicity has never been shown in humans after intravenous or intramuscular administration of ketamine.

Psychomimetic side effects are the most common side effect of intravenous ketamine and include: feeling of inebriation, vivid dreams, hallucinations, confusion, drowsiness, and dizziness. Infusion rates up to 50 mg/hr (mean 23.4 ± 9.6 mg/hr) were given before these side effects occurred.[26] They can be prevented, at least partly, by benzodiazepines (*e.g.* midazolam). One study reported headaches in 4 patients (10%). However treatment was not necessary.[28] Nausea was reported relatively common. Increased blood pressure and heart rate appears to be transient[12] and mostly does not require any treatment. In one retrospective study[26] the liver functions test were elevated in few patients, which had the consequence of premature discontinuation of the infusion, resulting in liver function test returned to normal.

1.3 Complex Regional Pain Syndrome

Complex Regional Pain Syndrome type 1 (CRPS 1) is a syndrome that frequently follows a trauma or operation and predominantly affects females. In the initial phase the syndrome is characterized by pain, paraesthesias, oedema, changes in skin temperature and colour, and hyperhidrosis. In CRPS type 2 there is a clinical evident of nerve laesion.[29] The similarities between the classical symptoms of inflammation and the clinical features of CRPS have led several investigators to suggest an inflammatory origin of the disease. Evidence pointing towards involvement of C and A -fibers of sensory nerves in the generation of the inflammatory response (neurogenic inflammation) in CRPS is compelling.[29,30]

This inflammation leads, among others, to selective upregulation of the glutamate receptor 2 subunits (GluR2) of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor. The presence of the GluR2 subunit determines the permeability of the AMPA receptor channel for Ca^{2+}. If the AMPA receptor consists of GluR2 it is not permeable for Ca2+ and therefore leads to a decreased Ca^{2+}-influx. Since the Ca^{2+}-permeable AMPA channels inhibit adjacent N-methyl D-aspartate (NMDA) receptors, the upregulation of the GluR2 subunits may suppress Ca^{2+}-permeability of the AMPA receptor assembly, thus releasing Ca^{2+}-dependent inhibition of the NMDA receptor. This will in turn facilitate NMDA receptor activation leading to central sensitisation.[31–33]

This process of central sensitisation is considered a leading factor in the development of chronic pain, and is associated with the release of excitatory amino acids such as aspartate and glutamate.[34] These changes lead toward an increased excitability of neurons, such that spontaneous pain, allodynia, hyperalgesia, and movement disorders occur.[24,33,35] At least for dystonia, neurophysiological and therapeutic data have highlighted the important role of impaired GABA-ergic inhibitory neurotransmission in central sensitization in CRPS 1.[36] At this stage it is unknown if in CRPS the molecular pathways that underlie pain and motor features are different.

Ketamine is a non-competitive antagonist of the NMDA receptor channel and therefore it inhibits significantly the function of the NMDA receptor.[19] Ketamine may thus play an important role in the treatment of central sensitisation of CRPS. Hitherto, two open studies[26,37] have used ketamine i.v. in both acute and chronic patients with

CRPS. One study on continuous ketamine in 33 CRPS patients (disease duration 0.25 – 240 months), found an almost total pain relief in 92% of the patients.[38] There is an impression that compared to patients with a short disease duration, patients with a long disease duration more frequently experience a relapse, but this has not formally been studied.

1.4 Aim of thesis.

The experiments and studies described in this thesis were designed to investigate:

1. The analgesic effect of ketamine in chronic pain patients (CRPS-1).
2. The dynamic effect of ketamine on acute pain and cardiac output.
3. The difference between the effect of ketamine on acute pain versus chronic pain.

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