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Commentary

Ketamine and chronic pain – Going the distance

Ketamine is a dissociative anesthetic and its primary mechanism of action is considered to be through antagonism of the *N*-methyl-D-aspartate (NMDA) receptor. For many years it has been used in the treatment of chronic pain, but not fully entrenched in pain treatment, perhaps because of its potential addictive and psychomimetic qualities and lack of controlled clinical trials. From a pain perspective the primary role of ketamine in low doses is as "an 'anti-hyperalgesic', 'anti-allodynic' or 'tolerance-protective' agent" (see [18]). A number of groups have reported the prolonged analgesic effects on pain following ketamine dosing via oral, intranasal, topical or intravenous routes and single doses vs. multi-day [3] or continuous administration over days [7] in open-label studies.

Our current therapeutic armamentarium for chronic pain is quite limited in terms of analgesic efficacy in controlled trials. Some would argue that the small efficacy (at both a population level and the magnitude of change in VAS score) is related to the fact that we need to consider mechanistic approaches to chronic pain subgroups. However, patients and clinicians find themselves in a position of "what to do now". In the paper published in this issue by Sigtermans et al. [15] the authors report on the effects of a prolonged infusion (4.2 days) of low dose ketamine group ($n = 30$) vs. placebo group ($n = 30$) and followed their pain scores over 12 weeks. Pain scores were lower initially but still significantly different at 12 weeks post-infusion. Significantly there was no functional improvement that accompanied the decrease in their pain. This study provides one of the first placebo-controlled trials in CRPS patients on the use of ketamine for chronic pain.

1. Ketamine, brain function and therapeutic effect – neuroprotecive or neurotoxic?

With the onset of chronic pain (including CRPS) a number of changes in brain function occur in the human brain including but not limited to: (1) central sensitization [13]; (2) functional plasticity in chronic pain and in CRPS [1,11]; (3) gray matter volume loss in CRPS [2]; (4) chemical alterations [4]; and (5) altered modulatory controls [14]. Such changes are thought to be in part a result of excitatory amino acid release in chronic pain. Excitatory amino acids are present throughout the brain and are normally involved in neural transmission but may contribute to altered function with excessive release producing increased influx of calcium and potentially neural death. Here lies the conundrum the use of an agent that potentially deleteriously affect neurons that may already be compromised (see [19]) but may also have neuroprotective properties by mechanisms that include reducing phosphorylation of glutamate receptors resulting in decreased glutamatergic synaptic transmission and reduced potential excitotoxicity (see [16]). Alternatively, ketamine may affect glia regulation of glutamate and inhibit glutamate release within glia [17]. However, by whatever mechanism ketamine acts on CRPS pain, there does seem to be a dose/duration effect in that longer doses at levels tolerated by patients seem to prove more effective in terms of the duration of effects (Fig. 1). Intravenous ketamine treatment in anesthetic dose reportedly produced months of pain relief and quality of life and ability to work [6].

So what could be happening in the brain and what is required to alter brain systems and reverse the symptomatic state? Ketamine may diminish glutamate transmission and "resets" brain circuits, but it seems that a minimal dose and/or duration of treatment is required. Alternatively, ketamine may produce neurotoxicity and damage or produce a chemical lesion of affected neurons. These two issues are important to be understood in future trials. Reports from patients who have had anesthetic doses have included prolonged pain relief for many months [6]. While the authors did not address issues such as the effect of dosing duration or repetitive dosing at say 6 weeks, they did show a level of efficacy based on NNT that equals or betters most drug trials for this condition.

2. Lack of effect on functional activity – lessons from other disease states

Although the authors did not find an improvement in functional activity, such changes may be more difficult to be discerned in a short period where maximal pain relief was observed. In other reports following anesthetic doses of ketamine, improvement in pain and other neuropsychologial evaluation at 6 weeks post treatment were reported, albeit these were not controlled trials [8]. Nevertheless there may be lessons from other diseases that affect the brain; it is noteworthy that acute ketamine doses seem to reverse depression [10] and ketamine decreased prevalence of post-traumatic stress disorder (PTSD) in soldiers receiving ketamine during their surgery for treatment of their burns [12]. In addition ketamine attenuates post-operative cognitive dysfunction following cardiac surgery that has been known to produce significant changes in cognition [5]. The data suggest that the drug can alter or prevent other conditions based on its NMDAR activity where other drugs NMDA receptor antagonists are perhaps not as effective in these or pain conditions. Lastly, NMDA antagonists have been used in degenerative disease (and pain may be considered a degenerative disease as defined by loss of gray matter volume, see above) with mixed effects perhaps relating to how they act on specific NMDA subtypes [9]. Taken together, ketamine may act not only on sensory systems affecting pain intensity, but also on a constellation of brain regions that are involved in the pain phentype.

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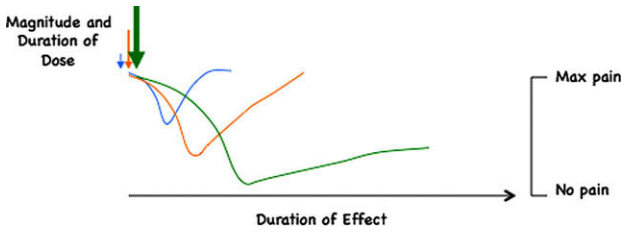

Fig. 1. Short-term vs. long-term circuit stability following ketamine. Magnitude and duration of ketamine dosing in CRPS may define the clinical outcome. Single doses seem to provide short-term relief and larger doses (usually administered over time, e.g., repeatedly over days) may provide increased duration of pain relief.

3. Conclusions

As a community we have a major opportunity to define the efficacy and use of a drug that may offer more to CRPS (and perhaps other) patients than is currently available. This is clearly an opportunity that needs urgent attention and a number of questions remain to be answered. For example, is ketamine more effective in early stage disease? How does ketamine provide long-term effects? Further controlled trials evaluating dose, duration, anesthetic vs. non-anesthetic dosing are needed. Few of us really understand what it is like to suffer from a chronic pain condition such as CRPS. Ketamine therapy may be a way forward that can be brought into our clinical practice through further controlled studies that will allow for appropriate standards for use in patients.

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