Dextromethorphan in Chronic Pain: A Disappointing Update

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Chronic pain syndromes have traditionally been treated by various regimens of opioids, non-steroidal anti-inflammatory drugs, and regional blocks. However, opioids-related respiratory depression and NSAID-associated bleeding tendency or renal impairment can sometimes limit the use of these medications, while the efficacy of regional block fades over time. Recently, the N-methyl-D-aspartate receptor antagonists were shown to alleviate somatic and neuropathic pain sensation in both animal and human models [1–5]. NMDA receptors are located in the posterior column of the spinal cord where pain generated by peripheral nociceptive stimuli and conveyed via sensory fibers is relayed centrally [6]. One of the antagonistic compounds is dextromethorphan, which possesses low affinity to the receptor and acts non-competitively. DM is reputed for its clinical safety as a cough suppressant [7].

NMDA receptor modulation

Immediately after acute tissue injury, action potentials generated at the nerve endings are conveyed along the A_δ and C fibers to the synapses at the dorsal part of the spinal cord. The incoming neuronal arousal causes the induction of mass release of various peptides and excitatory amino acids. The EAA activate the NMDA receptors that are located within the synapses, thus amplifying and facilitating pain transmission upwards towards the central nervous system [8,9]. This state of hyperexcitability or "wind-up" is described as an amplification of the duration and magnitude of the nervous system response to the initial peripheral pain stimulus. The state of hyperexcitability is also responsible for pain sensation long after the initial painful stimulus has stopped [10]. This phenomenon is considered to be the main cause of various pain syndromes such as allodynia (an intense sensation of pain following a relatively minor stimulus) or hyperpathia (a sensation of pain that persists long after the initial nociceptive stimulus has subsided) [9,11,12]. Moreover, NMDA receptors have other neurophysiological functions in the brain. These include learning and memory processing [1]. Thus, their antagonization can sometimes lead to side effects like agitation, hallucinations, somnolence, nausea and vomiting [13–15]. This is one of the reasons why at the present time the clinical use of NMDA-receptor antagonists is limited to the FDA-approved DM, ketamine or amantadine. However, since ketamine affinity to the NMDA receptors is high, its administration – even with the newly tested oral form [16] – is frequently accompanied by unbearable dysphoric effects. In addition, the need to administer it intravenously or even subcutaneously makes it less attractive as a potential antinociceptive agent for patients who suffer from chronic pain. DM, which was originally synthesized as a pharmacological alternative to morphine, was later used as an anti-tussive (in syrup preparations at adult doses of 10 to 30 mg three to six times daily) with an established safety record [7]. In humans, as in animals, DM was also shown to ameliorate discomfort associated with excitotoxicity-related neuralgic disorders such as intractable seizures and Parkinson's disease [17–19]. DM is rapidly metabolized in the liver to dextrorphan, which is, however, a potent NMDA antagonist [20].

DM use in chronic pain syndromes

The neuropharmacological role of NMDA antagonists in modulating chronic pain is still under clinical research, with controversial results. The reason is that although they were shown to block NMDA receptors in animal models of chronic pain [21,22] and proved useful in a few clinical trials (e.g., ketamine) [23,24], on the whole they did not provide clear-cut salutary effects; and some (ketamine or amantadine) even induced untoward neurological manifestations such as dysphoria and dissociative episodes [25,26]. By comparison, DM initially appeared much more promising than the previously mentioned antagonists. Owing to its ability to reduce the "wind-up" state that is responsible for the transformation of acute pain into chronic pain, its availability in oral form that made it an attractive drug in the management of chronic pain syndromes [2,27], and its higher therapeutic ratio as compared to ketamine, even if administered for prolonged periods [7], DM was the preferred drug. In various laboratory studies DM suppressed formalin-induced nociceptive rat behavior in a dose-dependent manner [28]. Chronic pain caused by sciatic

NSAID = non-steroidal anti-inflammatory drug
NMDA = N-methyl-D-aspartate
DM = dextromethorphan
EAA = excitatory amino acids

nerve ligation in the rat was attenuated by intrathecal administration of DM, which also reduced secondary heat-evoked hyperalgesia [29]. When compared with other experimental NMDA receptor antagonists in a rat model of chronic pain after ischemic spinal injury, the use of DM was associated with lesser side effects such as motor impairment and sedation than those caused by the other compounds [30].

However, the first doubts were raised when clinical experimental studies on volunteers pronounced unsatisfactory effects of DM when used alone for the treatment of secondary pain. A single dose of 30 or 45 mg of DM only partially attenuated the secondary temporal summation of pain induced by thermal stimuli in volunteers [31], whereas a dose of 100 mg did not attenuate pain intensity induced by tourniquet ischemia to the hand [32]. When these volunteers were subsequently treated with 200 mg DM in a double-blind crossover fashion, substantial side effects such as diarrhea or dizziness were observed, but pain was not relieved adequately. In another study, volunteers given 90 mg DM before the induction of pain by capsaicin (an experimental nociceptive agent) reported side effects of dizziness and nausea and only minimal pain relief [4]. In a study on a burn injury model where a single DM dose of 60 or 90 mg was given to volunteers, only a slight inhibitory effect on the development of pinprick-induced hyperalgesia was observed, while drowsiness and nausea were frequent [33].

An analysis of the few double-blind human studies where DM was administered in order to alleviate chronic or neuropathic pain revealed that this drug was of limited effectiveness. Wong et al. [34] suggested that in view of the low oral availability of DM, the above mentioned oral doses were too low to produce analgesia. Nevertheless, a careful examination of the relevant literature leads to the conclusion that low dosages are not the only cause for the marginal effectiveness of DM in cases of chronic pain. Other reasons may well be the small number of patients enrolled in most studies or the appearance of significant side effects that caused patients to withdraw from the studies. One double-blind crossover study on chronic neuropathic pain compared the effect of DM (40–80 mg/day) to placebo. The authors found no difference in pain perception during two phases of 10 day surveillance periods in the 19 patients [35]. Neither was a beneficial effect demonstrated when 30 mg DM tid was added to the pre-existent multi-drug cancer therapy in an open fashion study in 30 patients with cancer pain [36]. DM at higher doses (ranging between 45 and 125 mg/day) for 7–14 days in 26 post-herpetic patients [2,27] alleviated pain in only 10 patients, but evoked gastrointestinal side effects. A still higher regimen of DM – starting at 152 mg/day in the first week of treatment and reaching a maximal dose of 381 mg/day 6 weeks later, which was added to the previous analgesics given to 18 patients to alleviate diabetic neuropathy – decreased pain in only 24% of the patients [37]. The same incremental dose trial, however, had no beneficial effect in a second group of 14 patients suffering from post-herpetic neuralgia. Six patients were withdrawn from this two-phase study because of intolerable pain, while the rest of the patients suffered disturbing untoward effects such as ataxia or sedation. The different results in these two phases could be explained by the different pain pathologies, i.e., the ability of NMDA antagonists to attenuate the ongoing painful stimulus due to persistent damage, as occurs in diabetic neuropathy, compared to the "fixed" painful stimuli in post-herpetic neuralgia, where the effect of DM is less than acceptable.

The appearance of side effects is a disturbing aspect of DM treatment in chronic pain patients. While animal studies have demonstrated that DM induces fewer side effects than other NMDA antagonists [7], this is not the case in humans. It seems, but is not yet proved, that the rate of side effects is higher when DM is administered as part of a multi-modal drug therapy whose components can cause side effects by themselves. In addition to the gastrointestinal and neurological side effects in patients with neuropathic pain, there were few cases of respiratory depression [37], intolerable pain, or onset of new pain [27,32,35,36]. These latter rare events occur when DM is added to a pre-existing analgesic treatment. It was hypothesized to be the result of DM sensitizing the central neurons or increasing the state of excitation in the spinal inter-neuronal transmission, causing amplification rather than attenuation of pain perception, as was shown earlier in rats [38]. However, for obvious ethical reasons, DM cannot be used by itself while withholding daily chronic analgesic treatment in patients with chronic pain.

The clinical results of DM for the attenuation of various chronic pain syndromes are far from satisfactory. A better understanding of the neuropharmacological mechanisms that function in maintaining active chronic pain and the ability to interfere with them, thus alleviating central perception of pain by this agent and its receptors, is mandatory. Choosing a protocol that will not induce unacceptable rates and severity of pain will benefit patients and will enhance the future implementation of DM in various treatment protocols in chronic pain syndromes.

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Move those ten thousand horses a trifle to the right. And that mob out there, three feet forward.

D.W. Griffith, American epic film director (1874–1948)