KJP The Korean Journal of Pain
| Letters to Editor |
Korean J Pain 2014 July; Vol. 27, No. 3: 301-302
pISSN 2005-9159 eISSN 2093-0569
http://dx.doi.org/10.3344/kjp.2014.27.3.301

The Potential Role of Intrathecal Nefopam in the Management of Neuropathic Pain

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LETTERS TO EDITORS

We have read with curiosity a recently published article in *The Korean Journal of Pain* by Kim and Abdi [1], entitled "Rediscovery of nefopam for the treatment of neuropathic pain". The authors skillfully reviewed the literature on nefopam's clinical applications, its mechanisms of action, associated adverse reactions, and they offered future directions for research. The present review is a helpful article that highlights the following recently detected dual-analgesic mechanisms of action: a) the prevention of long-term potentiation mediated by N-Methyl-D-aspartic acid (NMDA) from the inhibition of voltage-sensitive sodium channels such as carbamazepine or a blockade of calcium influx similar to that by gabapentinoid anticonvulsants; and b) decreasing pain modulation by means of triple neurotransmitter reuptake inhibition, like antidepressants, enabling nefopam to be used as a therapeutic agent for treating neuropathic pain. The authors are to be congratulated for their focus on the potential role of intrathecal nefopam as part of the management strategy for neuropathic pain according to the results gleaned from the following studies:

Nefopam is a cyclic analog of orphenadrine, though its pharmacological properties differ from those of anti-inflammatory drugs and opioids. Previous animal experiments demonstrated the antinociceptive effects of nefopam on inflammatory, incisional, and thermal pain. The antinociceptive effects of nefopam on neuropathic pain have been reported by several studies [2,3]. Additionally, the central nervous system is the site of action of nefopam, including the spinal cord. The findings of some studies suggest that nefopam reduces neuropathic pain by means of spinal nerve ligation at the spinal level [3,4]. Recently, the role of the 5-HT_7 (5-hydroxytryptamine$_7$) receptor has been highlighted in nociceptive modulation. Intrathecal and intraperitoneal 5-HT_7 receptor agonists decrease diabetic- and nerve-injury-deduced neuropathic pain [5]. Accordingly, the antinociceptive action of nefopam may be exerted in the spinal cord through the 5-HT_7 receptor. A recent animal experiment by Dam et al. [6] revealed that 5-HT synthesis is decreased in the spinal cord during neuropathic pain. In contrast, the synthesis of 5-HT during neuropathic pain is stimulated by nefopam. Consequently, through the activation of the 5-HT_7 receptor at the spinal cord, nefopam reduces neuropathic pain.

As is obvious from the above discussion, intrathecal nefopam may play a significant role in the management

Received April 22, 2014. Accepted May 10, 2014.
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of neuropathic pain. Thus, human studies are required for a deeper understanding of this topic.

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