# Role of gabapentin in postoperative pain

Alparslan Turan, MD

Postoperative pain is a major factor that affects recovery from anesthesia and surgery. Different classes of analgesics have been used alone or in combination for the treatment of postoperative pain. Opioids, although highly effective in managing pain, have a range of side effects such as respiratory depression, central nervous system depression/sedation, and nausea/vomiting.[1] These side effects are common and can limit the use of opioids, despite their analgesic efficacy, in postoperative analgesia. However, a multimodal analgesic concept in which opioids are combined with nonopioids could enhance analgesia, reduce opioid requirements, and decrease opioid-related side effects.

Pain signals from the nociceptors may result in sensitization of secondary nociceptive neurons in the dorsal horn. This is mediated by a decrease in inhibitory input or an increase in synaptic efficacy or membrane excitability, triggered by windup, neurokinin, and N-methyl-d-aspartic acid (NMDA) receptor mechanisms.[2,3] Subsequent activity in nociceptors and non-nociceptive A-β fibers will be amplified, leading to increased pain, hyperalgesia and allodynia.[4]

Gabapentin is a structural analog of γ-aminobutyric acid (GABA), which is an anticonvulsant drug. Gabapentin has been shown to be effective in neuropathic pain,[5] diabetic neuropathy,[6] postherpetic neuralgia,[7] and reflex sympathetic dystrophy.[8] Pretreatment with gabapentin blocked the development of hyperalgesia, suggesting a preventive effect of gabapentin.[9] Recent studies suggest that gabapentin may be useful in the perioperative setting as an adjuvant to parenteral opioid analgesics in the postoperative period.[4,11-13] Different pain models have been used, demonstrating significant analgesic properties and a decrease in opioid consumption in these studies.

A possible mechanism for gabapentin-mediated analgesia is the modulation of glutamate receptors NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate. Gabapentin seems to decrease both NMDA- and non-NMDA-mediated glutamate currents in the superficial lamina of the rat spinal cord,[14] and also inhibits nociceptive responses to intrathecal NMDA and AMPA in vivo.[15] Furthermore, the analgesic effects of gabapentin are antagonized by the NMDA/glycine receptor agonist serine.[16,17] The findings of Suarez et al.[18] suggest that sodium entry through presynaptic NMDA-R channels facilitates axon excitability, and the interaction of gabapentin with this mechanism might contribute to its analgesic benefits. Gabapentin has no direct GABAergic action, and does not block GABA uptake or metabolism.[19] Another suggested mechanism for gabapentin is that it binds to the voltage-dependent calcium channels.[20] All of the suggested mechanisms can be responsible for the analgesic action of gabapentin; however, no consensus has been made. An animal experiment done by Shimoyama et al.[21] showed that intrathecal gabapentin significantly enhanced the effect of an intrathecal subanalgesic dose of morphine in the rat. A recent study[22] also revealed that combined spinal administration of gabapentin and low doses of morphine significantly reduced pain-related behaviors in this acute rat pancreatitis model, whereas these agents were ineffective when used alone in the selected dose range. Regional techniques combined with gabapentin must be the main aim for future studies; interaction with opioids and local anesthetics in different models also needs to be investigated.

Gilron et al.,[23] in a placebo-controlled randomized clinical trial, compared gabapentin individually with rofecoxib, and their combination, on postoperative hysterectomy pain. The combination was superior to the individual agents in pain control, opioid consumption, and accelerated pulmonary recovery. This study is a perfect example of combining different types of drugs in a postoperative pain model setting. Another study by Gilron combining gabapentin with morphine for neuropathic pain also achieved better analgesia with lower doses of a combination of the drugs than either as a single agent.[24]

The main aim in combining different analgesic drugs and techniques is to obtain synergistic or additive analgesia, allowing a lower dose of each agent with an improved safety profile. This can be achieved by combining analgesics acting at different locations, such as centrally and peripherally acting analgesics. Future studies should focus on combining gabapentin with different

NSAIDs and determining the most effective dose to reduce postoperative pain and the potential side effects of opioids.

*Alparslan Turan, MD, Assistant Professor, Department of Anaesthesiology, Trakya University, Edirne, Turkey, and the Department of Anesthesiology and Perioperative Medicine and the Outcomes Research Institute™, University of Louisville, Louisville, Kentucky.*

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