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Pain and Pain-associated Sleep Disturbances: Maximizing Treatment Outcomes

Istanbul - According to the International Association for the Study of Pain, a minimum of 50% of Europe's older citizens suffer from chronic pain. Post-herpetic neuralgia, diabetic peripheral neuropathy and fibromyalgia are among the debilitating painful conditions affecting sleep and quality of life. Encouraging therapeutic results may be obtained by combining pharmacologic treatment with non-pharmacologic methods. Tricyclic antidepressants, controlled-release opioids, topical lignocaine and the GABA (gamma-aminobutyric acid) analogues are among the most widely used compounds in the treatment of pain. With a greater understanding of the mechanisms of pain, more effective treatment can be elaborated. Antiepileptic drugs have also been shown to reduce pain in controlled trials: pooled analyses presented here have confirmed pregabalin's potential role in safely and effectively reducing pain and pain-related sleep disturbances, either alone or with concomitant therapy.

Dr. Stephen Gibson, Director of Research, Caulfield Pain Management and Research Centre, Victoria, Australia, noted that in the elderly there is a decline in the sensitivity to pain, but there is also a reduced tolerance to severe pain. Most national guidelines on the management of such patients emphasize that pharmacologic therapy is most effective when combined with non-pharmacological methods, including transcutaneous electrical nerve stimulation, psychological therapy and, in the case of diabetes, tight glycemic control.

Mechanisms of Chronic Pain

According to Dr. Anthony Dickenson, Professor of Pharmacology, University College, London, UK, the mechanism by which the effects of damage to tissues and/or nerves at the periphery are augmented to produce chronic pain—not only at the site of damage but also centrally—is the key to understanding neuropathic and inflammatory pain. He explained, “Within the spinal cord, these changes underlie central sensitization, whereby the response to a given input is increased by central spinal mechanisms. A first stage in this process seems to involve calcium channels that are essential for transmitter release onto spinal neurons and agents such as pregabalin may act on these changed channels.”

Although pregabalin's mechanism of action is not clear, it has high affinity for a subunit ($\alpha_2\text{-}\delta$ protein) of voltage-gated calcium channels and may modulate the presynaptic release of neurotransmitters such as glutamate and noradrenaline.

Treat the Pain First: Trial Evidence

Several studies of this agent for diabetic peripheral neuropathy (DPN), post-herpetic neuralgia (PHN) and other chronic pain syndromes have demonstrated efficacy in pain relief.

Findings from a study of pooled data from seven randomized controlled trials of pregabalin for PHN or painful DPN led by Dr. Russell K. Portenoy, Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, New York, demonstrated significant reduction in pain scores seen by day 2 with use of the agent. According to four long-term, open-label studies extending over two years analyzed by the same group, tolerance did not develop, indicating a durable therapeutic effect, with no clinically meaningful variations in mean dosage during the extended phase.

Using novel “activity region finder” software, responders to pregabalin for PHN have been identified from another exploration of five randomized controlled trials by Dr. Tanya Murphy, Department of Psychiatry, University of Florida, Gainesville, and colleagues. Overall, 37% of all patients (n=995) responded, with a higher rate of 51% for those receiving pregabalin 300 or 600 mg/day.

Recent data reviewed here at the meeting have shown that the agent has linear pharmacokinetics and can be given b.i.d. or t.i.d. and enables the optimum dose to be found quickly, usually three to seven days after a starting dose.

Rapid and significant improvement in the sleep patterns of these patients, more than half of whom are known to suffer from pain-related sleep deprivation, was demonstrated, following further analysis of such data.

Pain-related Sleep Disturbance

According to Dr. Robert van Seventer, Department of Anaesthesiology, *Amphia Ziekenhuis*, Breda, The Netherlands, and colleagues, people with neuropathic pain spend more time in shallow sleep (stage I) than in the deeper stages of sleep (stages II to IV and REM) and are prone to nighttime awakenings. Investigators presented pooled data from 13 randomized clinical trials of patients with chronic pain syndromes that include DPN, PHN, fibromyalgia, spinal cord injury or osteoarthritis and one trial in healthy volunteers.

The analysis demonstrated the efficacy of pregabalin in improving both pain and sleep interference at the three dose levels used, 150, 300 and 600 mg/day ($P < 0.001$), for all conditions except osteoarthritis. In the review of the study for this condition, pain relief did not attain significance; however, it did provide significant improvements in sleep.

Measures of sleep disturbance were evaluated through patient sleep diaries and the seven-item Medical Outcomes Study-Sleep scale. Treatment significantly improved three items of the scale.

The investigators reported that results from individual studies were consistent with those from pooled analyses and demonstrated onset of significant effect as early as week 1, the first time point measured, and were sustained throughout the studies. There were no significant differences in sleep improvement between patients experiencing somnolence as an adverse event and those who did not.

According to polysomnography readings in healthy volunteers, time spent in stages III to IV increased significantly while nighttime awakenings decreased with pregabalin.

Findings confirmed that the agent reduces pain-related sleep disturbances significantly and improves multiple sleep-quality parameters. It appears that the agent's beneficial effects on sleep are partly independent of pain relief.

Combination Therapies and Sleep

Established pharmacologic treatments for PHN and DPN include tricyclic antidepressants (TCAs), controlled-release opioids, topical lignocaine and the GABA (gamma-aminobutyric acid) analogues.

According to a new study by Dr. Philip J. Siddall, Pain Management Research Institute, University of Sydney at Royal North Shore Hospital, Australia, and colleagues,

the efficacy of pregabalin in reducing pain and improving the sleep of patients with non-progressive, traumatic spinal cord injury is unaffected by commonly prescribed co-medications. They observed that use of the compound was associated with rapid (by week 1) improvement of central neuropathic pain and related sleep interference that persisted to end point regardless of concomitant use of TCAs, opioids, muscle relaxants (MRs) or benzodiazepines (BZDs).

Participants who received placebo plus TCAs or opioids showed worsening of pain and sleep behaviour, while those on placebo plus MRs or BZDs showed improvements no better than on placebo alone. With concomitant pregabalin and antiepileptic drugs, there were improvements in both pain and sleep, but they were not statistically significant. In the study, patients were randomized to placebo ($n=67$) or active treatment flexibly dosed from 150 to 600 mg/day ($n=70$) and studied for 12 weeks.

Similarly, with fibromyalgia, which is a difficult condition to treat, adding pregabalin to the atypical antipsychotic quetiapine improved pain control and quality of life, according to a small trial ($n=19$) presented by Dr. Rodriguez-Lopez, Institute of Neurosciences, University of Granada, Spain.

Generalized anxiety disorder is often a feature of spinal cord injury. In the same cohort of patients as in the Pain Management Research Institute mentioned above, Dr. Teresa Griesing and colleagues, New York, demonstrated that pregabalin effectively treated patients with central neuropathic pain associated with spinal cord injury, regardless of the presence of anxiety symptoms. Active treatment was associated with a significant decrease in the Hospital Anxiety and Depression Scale-Anxiety Subscale score from baseline to end point, suggesting an improvement in anxiety associated with spinal cord injury.

Summary

With the advent of functional dimensions of diagnostic techniques such as nuclear magnetic resonance, positron emission tomography and electro-encephalograms, never before has so much been known of the effects of agents on the brain and nervous system, while the complex sensory response that is pain can now be dissected into its constituents by means of quantitative sensory testing. Taken together, many clinicians believe that these advances are helping to design emerging compounds and may mean more effective treatment of neuropathic pain in the future by individualizing treatment. □

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