High-Dose Opioids May Manage Neuropathic Pain

I was pleased to see the Clinical Challenges feature in the April issue of Oncology Nursing Forum (Vol. 29, pp. 457–459) devote a case study to neuropathic pain. The case study nicely highlighted many of the typical findings associated with postherpetic neuralgia (PHN), a neuropathic pain syndrome likely to increase as the population ages.

However, two points require comment. Amitriptyline (Elavil®, AstraZeneca Pharmaceuticals, Wilmington, DE) no longer is considered a first-line adjuvant analgesic in the management of neuropathic pain syndromes such as PHN. Although more widely studied than other tricyclic antidepressants, amitriptyline has significant anticholinergic effects, including dry mouth, drowsiness, constipation, and urinary retention. Its use should be avoided in people with a history of narrow angle glaucoma, arrhythmias, and orthostasis. Thus, if a tricyclic antidepressant is selected, alternative agents are now recommended, such as nortriptyline (Pamelor®, Novartis Pharmaceuticals, East Hanover, NJ) and desipramine (Norpramin®, Aventis Pharmaceuticals, Parsippany, NJ). Furthermore, gabapentin (Neurontin®, Parke-Davis, Morris Plains, NJ) may be a more effective, better-tolerated choice. Some limitations may be the cost and frequency of administration; therefore, all variables must be considered when devising a treatment plan.

Second, oxycodone is a potent mu opioid agonist (not antagonist), and although it also binds to the kappa receptor, the clinical significance of kappa activity is unknown. In the case of the patient with PHN, upward dose titration might have provided improved analgesia, as opioids are known to be effective in the relief of neuropathic pain, particularly at higher doses. Thank you for devoting this feature to a significant clinical problem.

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The Author Responds

Neuropathic pain, as described in the feature on postherpetic neuralgia (PHN), is challenging to manage. A myriad of adjuvant analgesics have been proposed to treat this and other neuropathic pain syndromes.

The use of tricyclic antidepressants in the management of PHN is widely accepted. The use of tertiary versus secondary amine tricyclic antidepressants has been evaluated in several randomized, controlled clinical trials in patients with PHN and other neuropathic pain syndromes. The secondary amines, nortriptyline and desipramine, are metabolites of the tertiary amines amitriptyline and imipramine, respectively. Tricyclic antidepressants’ mechanisms of action are postulated to be through the inhibition of uptake of norepinephrine (NE) and serotonin (5HT). The tertiary amines broadly inhibit reuptake of NE and 5HT; the secondary amines are more selective NE reuptake inhibitors. Both tertiary and secondary amines have established efficacy in managing neuropathic pain; however, a study evaluating the efficacy of tricyclic antidepressants in the management of neuropathic pain syndromes in 282 patients demonstrated response rates for tertiary amines amitriptyline and doxepin ranging from 51%–59% and response rates for secondary amines desipramine and nortriptyline ranging from 29%–34% (Richeimer, Bajwa, Kahrman, Ransil, & Warfield, 1997). Additionally, in a study by Watson, Vernich, Chipman, and Reed (1998), amitriptyline demonstrated slightly superior clinical effectiveness and improved categorical pain scores over nortriptyline although, overall, visual analog scale scores for pain, depression, sleep, and disability did not differ between the group treated with amitriptyline or nortriptyline. Both studies concurred that side effect profiles of tertiary amines had higher rates of dose limitation and discontinuation than secondary amines. Richeimer et al. concluded that tertiary amines may be most appropriate for younger patients, especially if they suffer from insomnia. Secondary tricyclic antidepressants are preferred for elderly or frail patients who cannot tolerate the anticholinergic effects of tertiary amines. Nortriptyline has the lowest propensity for causing hypotensive and desipramine is the least likely to cause somnolence. However, in the case example presented in the Clinical Challenges feature, amitriptyline was selected for dual management of neuropathic pain and insomnia in a young woman without cardiac disease, glaucoma, or orthostatic changes and whose constipation was being managed.

Gabapentin (Neurontin) and amitriptyline have been evaluated in two randomized clinical trials for the management of neuropathic pain. Morello, Leckhand, Stoner, Moorhouse, and Shagian (1999) found equal efficacy between gabapentin and amitriptyline in the reduction of pain. Dallocchio, Buffa, Mazzarello, and Chirolli (2000) reported that gabapentin was significantly more effective than amitriptyline in reducing pain. In addition, more adverse events occurred in the amitriptyline group. The research design in the study by Dallocchio et al. was unblinded, the dose delivery and titration schedules were inconsistent with clinical recommendations, and benzodiazepines were administered concurrently (a known P450 competition between amitriptyline and benzodiazepines exists). Further studies are needed to evaluate the efficacy and safety of tricyclics and gabapentin in the management of neuropathic pain syndromes. Gabapentin appears to be an effective and safe agent in managing neuropathic pain but needs to be administered three times a day, which potentially can affect compliance. In addition, the cost of gabapentin therapy is significantly higher than tricyclic antidepressants.

Neuropathic pain was once purported to be opioid resistant; however, more recent studies have demonstrated the efficacy of opioids in managing neuropathic pain (Grond et al., 1999; Waton & Bubul, 1998). Oxycodone is an opioid agonist with mu and kappa receptor specificity. Although the efficacy of kappa receptor agonism is not fully established, several studies have defined a benefit specific to opioid affinity for the kappa receptor. Caudle et al. (1998) defined antihyperalgesic and antiallodynic properties inherent in kappa agonist activity. Side effect profiles of kappa

Digital Object Identifier: 10.1188/02.ONF.900-901