Opioids

Formerly referred to as "opioid-nonresponsive pain", analysis of existing studies suggests that opioids are effective in relieving neuropathic pain.[15] In general higher doses of opioids are needed. Scheduled dosing is preferred over as needed administration, beginning with a low dose and gradually titrating upward. Failure to respond to one opioid should result in rotation to another, due to the wide variability in response to individual opioid agonists. Additionally, attention must be given to prevention and management of potential side effects, particularly constipation.

Adjuvants

Cortiocosteroids

Although there are no randomized clinical trials, corticosteroids have long been used to treat a variety of neuropathic pain states, particularly those related to cancer.[11] Dexamethasone has the least mineralocorticoid effect and due to the long duration of effect, dosing can be scheduled once per day. Unfortunately, immunosuppressant and endocrine effects limit long-term use.

Tricyclic antidepressants

T ricyclic antidepressants block the reuptake of biogenic amines, including serotonin and norepinephrine.[16] The anticholinergic effects of agents such as amitriptyline may not be well tolerated, particularly in the elderly. Alternative agents, with fewer adverse effects, include nortriptyline or desipramine. Patients with preexisting conduction abnormalities should have a baseline electrocardiogram, as the tricyclic antidepressants can alter cardiac conduction. In all patients, a low dose should be started, usually at bedtime, and titrated every three to seven days based upon the patient's response. Newer serotonin selective reuptake inhibitors, such as fluoxetine, appear to have little efficacy in relieving neuropathic pain.[17]

Anticonvulsants

Older anticonvulsants, particularly carbamazepine, phenytoin, or valproate, were used extensively to treat neuropathic pain. Potential adverse effects required screening, particularly for neutropenia, megaloblastic anemia, and others. A newer anticonvulsant, gabapentin, approved for treatment of complex partial seizures, has been shown to demonstrate analgesic properties in both animal and human models of neuropathic pain. Two well designed, randomized controlled multicenter studies evaluated the efficacy of gabapentin in postherpetic neuropathy and diabetic neuropathy.[18,19] Using doses of up to 3600 mg/day, mean daily pain intensity scores decreased significantly and other secondary outcome measures, such as sleep and mood, improved when compared to the placebo groups. The most common side effects, dizziness and somnolence, appear to be reduced with slower upward dose titration. As a result of gabapentin's efficacy and limited adverse effects, it has become the first line therapy in most neuropathic pain states.

Local anesthetics

Lidocaine (5%) patches have been found to reduce pain related to postherpetic neuropathy without any significant plasma levels of drug found with application of up to three patches.[20] Oral lidocaine analogues, such as mexiletine, have been shown to be effective in some patients. Intravenous lidocaine infusions are gaining acceptance in a variety of pain management settings, from pain clinics to hospices. A bolus intravenous dose lidocaine of 1-2 mg/kg is given over 15-30 minutes. If this is effective, it may be followed by a continuous infusion of 1-2 mg/kg/hour. In some patients, the effects can be as prolonged as weeks of relief. An early warning sign of potential toxicity is perioral numbness. Hepatic dysfunction and significant cardiac conduction abnormalities are contraindications to the treatment. Epidural or intrathecal administration of a local anesthetic, alone or in conjunction with an opioid, may allow relief in patients who are not candidates for systemic delivery.

NMDA antagonists

Ketamine and dextromethorphan are N-methyl-D-aspartate (NMDA) receptor antagonists that are being explored for their use in neuropathic pain. Particularly regarding ketamine, despite promising case reports, adverse effects (including hallucinations) have