a potent stimulant of electrolyte and water movement in pancreatic and biliary epithelium via activation of secretin receptors. Secretin receptors are also present in human lung, and activation of these receptors by secretin potently stimulates Cl efflux from bronchial epithelial cells. One possible mechanism by which octreotide may have reduced sputum production is by lowering plasma levels of secretin, and hence reducing Cl efflux from bronchial epithelial cells.

The benefit of octreotide in reducing excess sputum production has not previously been reported. Octreotide may be a useful agent in the management of bronchorrhea due to invasive adenocarcinoma of the lung, and may merit investigation in other lung diseases, including BAC.

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Ketorolac in Neuropathic Pain

To the Editor:

Neuropathic pain is the result of damage or dysfunction to the nervous system along afferent sensory pathways. The lesion may be within the central nervous system or at the level of the dorsal root ganglion or peripheral nerve. Neuropathic pain often is described by the patient as shooting or burning pain, numbness, paresthesias, or sensitivity to normal touch. Sensory or motor loss is evident on examination within the area of pain, and often there is a paradoxically altered sensation such as allodynia and hyperalgesia. The prevalence of neuropathic pain in cancer is 25%–50% according to a survey of those visiting pain clinics.1

Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) with greater systemic analgesic than anti-inflammatory potency. Unlike other NSAIDs in the United States, ketorolac can be administered parenterally.2 There are reports of responses to subcutaneous ketorolac in the management of cancer-related bone, visceral, and neuropathic pain.1,3 Ketorolac is not commonly used to treat neuropathic pain, as NSAIDs have limited evidence in the management of neuropathic pain.4

Despite advances in the understanding of the mechanisms that generate neuropathic pain, treatment remains a challenge and empirical. We describe a patient with recurrent metastatic breast cancer and refractory neuropathic pain from a brachial plexopathy who
responded to ketorolac after failing to achieve relief with first-line analgesics.

Case Report

A 52-year-old woman was diagnosed with a poorly differentiated infiltrating adenosquamous carcinoma in October 2002. She underwent a modified radical mastectomy and received adjuvant chemotherapy with Adriamycin and cyclophosphamide. One year after diagnosis, she developed left axillary recurrence and underwent an axillary dissection followed by chemotherapy with taxotere and radiation. In August 2004, she developed a second left axillary recurrence and had a second excision performed. She was then placed on gemcitabine and cisplatin followed by further radiation to the axilla.

After her second recurrence, she developed progressive left upper extremity pain, sensory changes, and loss of motor function in the ipsilateral arm. Her pain was “burning,” “tingling,” and “shooting” and radiated to the left anterior chest wall and left scapula. On examination, she had limited left arm movement with lymphedema and an open axillary wound.

She was initially started on gabapentin 400 mg three times daily with oxycodone as needed. Sustained-release oxycodone 20 mg three times daily was started later, and ibuprofen and tramadol were periodically added. Sustained-release oxycodone was titrated to 40 mg three times daily, and subsequently to 60 mg three times daily by late December 2004, with no improvement. Amitriptyline 25 mg was added at bedtime.

Due to intractable pain and poor response, she was referred to the palliative medicine program in January 2005. Her prior opioids were discontinued, and methadone 30 mg every 3 hours as needed for pain was initiated. Gabapentin and amitriptyline were continued. Methadone was titrated several times before she noted some improvement. Analgesia diminished over time with cancer progression, and methadone was increased to 160 mg twice daily with 120 mg every 4 hours as needed.

She was hospitalized in November 2005 for intractable pain. Rotation to morphine failed to improve her pain, and she was switched back to methadone. She underwent epidural catheter placement with fentanyl infusion and was sent home on epidural fentanyl infusion plus fentanyl patient-controlled analgesia, methadone 80 mg three times daily with 120 mg every 3 hours as needed, transdermal lidocaine, and gabapentin 600 mg four times daily.

The pain in the left arm worsened despite an increase in the methadone dose, and in December 2005, she was started on oral ketorolac 10 mg four times daily. She had a dramatic improvement in pain. Methadone was tapered to 80 mg three times daily with no breakthrough doses. Although her axilla and left arm exhibited new tumor nodules, her pain remained well controlled. Epidural fentanyl was discontinued and transdermal fentanyl 50 μg/h was substituted. She remains on ketorolac with stable pain control.

Comment

Neuropathic pain mechanisms may involve N-methyl-D-aspartate (NMDA) receptors. The activity of these receptors is mediated by prostaglandins and nitric oxide, both of which are inhibited by ketorolac. Peripheral nerve injury also recruits inflammatory cells from the circulation to the site of nerve injury, which leads in turn to perineural proinflammatory cytokines, such as interleukin-1 or tumor necrosis factor. Cytokines stimulate nociceptors and trigger hypersensitivity. Prostaglandins, particularly prostaglandin E2, upregulate certain cytokines and may be inhibited by NSAIDs. NSAIDs blunt NMDA receptor responses through inhibition of prostaglandin and relieve the hyperalgesia caused by neuropathic injury in animal models. Local and systemic administration of ketorolac reverses tactile hypersensitivity in these models.

NSAIDs have traditionally not been considered in neuropathic pain. However, Namaka et al. have suggested that NSAIDs can be used as adjunctive therapy for breakthrough neuropathic pain, in combination with other first-line agents. When coadministered with opioids, NSAIDs have an “opioid-sparing” effect. Ktorolac has moderate anti-inflammatory actions and more pronounced analgesic activity. It has up to 800 times the analgesic potency of aspirin in animal models.
In a study done by Myers and Trotman, ketorolac by continuous subcutaneous infusion resulted in symptomatic improvement in 80% of patients with cancer-related pain, some of whom had neuropathic pain. Advanced cancer patients who receive ketorolac in addition to morphine exhibit better pain control and relief of constipation than those who receive morphine alone.

Ketorolac generally should be limited to a 5- to 7-day treatment course. However, in advanced cancer, longer treatment courses may be justified in those who respond and do not maintain response when crossed over to other NSAIDs. This case suggests that ketorolac can improve neuropathic cancer pain. A trial of ketorolac in neuropathic cancer pain failing to respond to usual drug management is reasonable in light of our experience.

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References


Neostigmine for Refractory Constipation in Advanced Cancer Patients

To the Editor:

Neostigmine is an acetylcholinesterase inhibitor that induces a prompt response in acute colonic pseudo-obstruction. It has manageable toxicity (abdominal pain, excess salivation, vomiting, and not severe bradycardia) when administered as a single intravenous dose of 2 mg1 and can be easily administered subcutaneously.2 This drug is licensed in Spain for the treatment of gastrointestinal atony, a clinical process that also may include opioid-induced constipation, a common problem in advanced cancer patients.3,4 No previous studies have tested neostigmine in advanced cancer patients, and this drug is not included among the recommended treatments of constipation in cancer patients.5

We present our experience with low-dose subcutaneous neostigmine for refractory constipation in eight advanced cancer patients, four inpatients and four outpatients. In all of them, standard therapy (oral laxatives in eight and enemas in six) did not achieve an adequate response and constipation lasted for at least 2 days. The initial dose of neostigmine was lower than the dose recommended in previous studies in order to avoid severe...