Letters

Ultra-Low Dose Oral Naltrexone Decreases Side Effects and Potentiates the Effect of Methadone

To the Editor:

The use of N-methyl-D-aspartate (NMDA) receptor antagonists to decrease opioid side effects, potentiate opioid actions, and decrease the development of tolerance has been a topic of substantial interest over the last decade. The pioneering work by Trujillo and Akil suggested that tolerance to opioids could be prevented by the non-competitive NMDA receptor antagonist MK-801.[1] Subsequent studies indicated that competitive NMDA receptor antagonists could prevent the development of opioid tolerance and reverse it once established.[2] To determine the clinical significance of these observations, numerous clinical trials have been performed with the widely used NMDA receptor antagonists ketamine and dextromethorphan. These studies suggest that both antagonists can improve pain scores in patients with certain types of pain, but, in general, the doses must be high, which predisposes to significant side effects.[3] The addition of dextromethorphan to morphine has been studied in both animals and humans. Mao et al. conducted animal studies to determine the optimal ratio and concluded that a 1:1 ratio was the most efficacious.[4] More recently, clinical trials performed to study this combination yielded inconclusive results, and more studies are needed to determine the correct ratio in humans. In view of the limited benefit obtained by this approach, other strategies to potentiate, decrease side effects, and prevent the development of tolerance to opioids are being explored.

One novel strategy was suggested by work performed by Crain and Shen[5,6] about a decade ago. They proposed a different model to explain hyperalgesia and tolerance. They noted that nanomolar opioid doses, what they called "ultra-low" doses, caused prolongation of the action potential duration (APD).[6] This excitatory opioid effect was blocked by "ultra-low" doses of naltrexone or naloxone.[6] The effects were opposite to those associated with doses equivalent to therapeutic doses, which produce shortening of APD when tested on dorsal root ganglion (DRG) and other structures, an inhibitory effect that correlates with analgesia.

These data suggest that the combination of an opioid and ultra-low dose of an opioid antagonist may potentiate analgesic effects. We present a patient with painful diabetic peripheral neuropathy who experienced significant improvement after the addition of an "ultra-low" dose of oral naltrexone (1 microgram twice daily) to his opioid regimen. This observation suggests that an "ultra-low" dose of oral naltrexone can be utilized safely and may be another strategy to increase the potency of an opioid agonist.

Case Report

A 61-year-old diabetic man developed painful polyneuropathy two years prior to presentation. His chief complaint was pain and paresthesias in the feet, distal legs, and fingers. The pain was very intense, burning in quality, and constant. Pinprick, light touch, temperature sensation, and vibration sense were decreased in the same distribution. His mood had been affected by the pain, and at the point of his visit, he was not complying with the medications indicated for the treatment of the diabetes; finger stick glucose measurements were in the 250 range. His pain medications included methadone 80 mg per day in divided doses

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and oxycodone 5 mg tablets every 6 hours for breakthrough pain. Both medications had been reduced by 50% a week before presentation due to concerns about medication-seeking behavior.

His drug regimen was adjusted, and at the time of a follow-up visit, his pain was better controlled (about a 6/10) and he was complying with the other medications. During the following months, however, his pain worsened and he was evaluated frequently. He underwent numerous dose adjustments, after which he was comfortable for a few weeks before pain would return with the same intensity. Although he was better overall, there were times of the day when the pain was intolerable. He also reported chronic nausea, which he attributed to his medications.

Eight months after presentation, the patient was taking 60 mg of methadone four times a day and methylphenidate 30 mg twice daily for opioid-induced sedation. He had trials with gabapentin, amitriptyline, bupropion, and topiramate. All but gabapentin could not be tolerated. Gabapentin was titrated to up to 3,600 mg a day with minimal relief.

He was offered a trial of "ultra-low" dose naltrexone in an effort to identify an adjuvant analgesic that could be tolerated. A compounding pharmacy prepared a solution of 1 mg of naltrexone (from powder) in 1 liter of sterile water. A total of 100 cc of the solution was stored in a caramel container, delivered to the patient, and kept out of the light in the refrigerator. We instructed the patient to take 1 cc twice daily (Arbuck et al., unpublished observations). We performed daily assessment of potential symptoms of withdrawal as well as of his pain status.

Less than 24 hours after the initiation of oral naltrexone, the patient reported improvement. He had no symptoms of withdrawal and his pain decreased from a score of 9/10 the night prior to the initiation of the naltrexone to a 3/10 the morning after. In addition, his chronic nausea resolved. The methadone dose was decreased to 50 mg four times daily and the methylphenidate dose was kept unchanged. His fatigue improved and the pain remained at the same level. One month later the patient remained with the same degree of pain relief, the same dose of methadone after the dose reduction and utilizing 50% of the short-acting opioid for rescues.

Comment

The administration of naltrexone at "ultra-low" doses raises concerns about side effects. Although the dose is very low, the minimal dose capable of inducing withdrawal is unknown and the potential for abstinence cannot be discounted. Moreover, the theoretical potential of ultra-low dose antagonist to reverse tolerance raises concerns about the emergence of severe side effects, such as respiratory depression or somnolence. No problems with abstinence or emerging nonanalgesic effects occurred in this case. This patient's results suggest that this approach can be safely utilized and may be a potential application of a novel strategy developed by Crain and Shen to potentiate the analgesic effect of opioids.[5,6] Supported by strong pre-clinical data, our observation indicates the need for systematic clinical research focused on the potential benefits of ultra-low dose antagonist therapy.

Previous studies of this potential effect have been limited. In one, patients were treated with intravenous patient-controlled administration (IV PCA) of morphine and were randomized in double-blind fashion to 1 μg/kg or 0.25 μg/kg IV naloxone or placebo. Patients treated with 0.25 mg/kg had a decreased requirement for morphine. A subsequent study that utilized variable doses of naloxone did not confirm this effect.[8] The different results reported in these studies may be due to methodological differences, including different naloxone doses (the dose was higher in the latter study).

The underlying mechanism that may account for the enhancement of opioid analgesia by ultra-low doses of an antagonist has been studied in DRG neurons in culture. As noted, therapeutic micromolar doses of opioids result in shortening of the APD in DRG neurons, an effect that correlates with the analgesia. This inhibitory effect, which can be blocked with naloxone and, therefore, defined as opioid receptor-mediated, is pertusis toxin (PTX)-sensitive, suggesting that the second messenger that mediates the response is a Gi/Go protein type. In contrast, the prolongation of the APD by "ultra-low" doses (nanomolar) of opioids is cholera toxin sensitive and, therefore, believed to have $G_s\alpha$ for second messenger. The prolongation of the action potential, also known as an excitatory effect (observed with agonists that

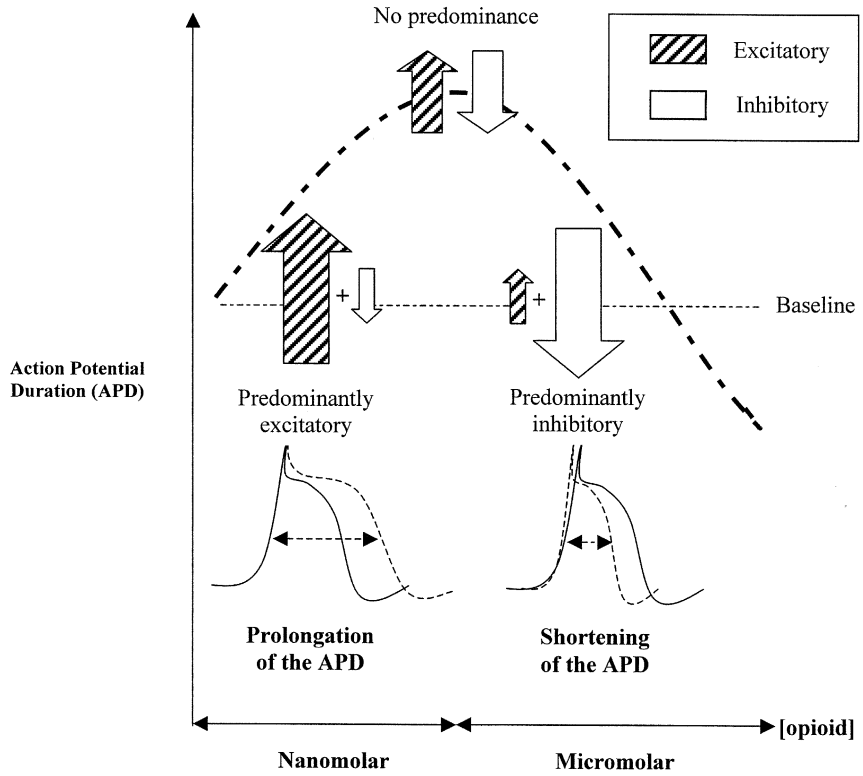

Fig. 1. Bimodal effect of opioids in DRG neurons. When DRG neurons are exposed to picomolar concentrations of an opioid, the action potential duration starts to increase. When the dose is incremented but remains within the low nanomolar range, the prolongation of the action potential continues to increase. However, when approaching micromolar concentrations, the inhibitory responses are also activated and the action potential starts to shorten. Further increment of the dose results in progressive shortening of the action potential.

bind μ, δ and κ receptors), is sensitive to "ultra-low" dose naloxone and, for that reason, also is believed to be mediated by the activation of opioid receptors.

In addition to the potentiation of opioid-induced analgesia, "ultra-low" doses of naloxone have been shown to prevent withdrawal symptoms upon opioid discontinuation in mice exposed to opioids chronically. Cruciani et al. also have reported that intrathecal administration of antisense oligodeoxynucleotide (ODN) to $G_s\alpha$ protein prevented the development of, and reversed, tolerance to morphine. Together, these findings support the notion that a $G_s\alpha$ protein, which may be involved in the opioid excitatory effect, is involved in the development of tolerance to opioids.[9,10]

The coexistence of Gi/Go and Gs second-messenger mediated responses activated by the same agonist has been proposed previously in other systems, including the adrenergic and dopaminergic. Crain and Shen described it as "bimodal effect" for opioid-mediated responses[5] (Figure 1). In view of the numerous μ-opioid receptor spliced variants,[11] it is conceivable that a μ agonist may mediate both excitatory and inhibitory effects.

To our knowledge, this is the first report to illustrate the potential clinical use of ultra-low dose naltrexone. Further studies to validate this approach are needed.

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Flushing and Sweating in an Advanced Breast Cancer Patient Relieved By Olanzapine

To the Editor:

The true incidence of flushing and sweating in advanced cancer is unknown, but on the occasions when it does occur, this symptom is the most troublesome and exhausting to the terminally ill patient. In breast cancer patients, it may be caused by estrogen deficiency and in prostate cancer can be caused by androgen ablation therapy. Hot flushes and sweating probably affect 75% of male patients suffering from prostate cancer. Sweating also may be a part of the paraneoplastic tumor-induced fever syndrome. Drugs, like opioids, may be the cause of flushing and sweating, but in a robust elaboration on this subject in the *Oxford Textbook of Palliative Medicine*, opioids were not specifically mentioned.[1]

Treatment of sweating depends on the cause. Hormone manipulations may be tried.[2,3] In paraneoplastic tumor-induced fever, nonsteroidal anti-inflammatory drugs (NSAIDs) may be effective.[4]

Opioid-induced sweating usually does not respond to opioid rotation. Adding NSAIDs may be effective, but can be nephrotoxic in dehydrated patients. Antimuscarinic drugs like hyoscine may be effective,[5] but may cause dry mouth or even anticholinergic delirium in susceptible patients. Thioridazine, a phenothiazine antipsychotic equipotent to chlorpromazine, has a more balanced antimuscarinic effect and had been used frequently in low doses for this purpose.[6] We describe here a patient with persistent and distressing sweating that responded to olanzapine.

Case Report

A 56-year-old woman had her breast amputated 4 years earlier because of cancer (T1 N1b, estrogen and progesterone receptor negative). Consequently, she was treated with regional radiotherapy. After this, primary hypothyroidism was diagnosed and she was treated with levothyroxine. Three years later, multiple bone metastases were diagnosed and treated with standard cyclophosphamide-methotrexate-5-fluorouracil chemotherapy and radiotherapy to the spine and pelvis. Because of increasing pain, she was prescribed morphine slow-release tablets 30 mg twice daily. This dose was gradually increased to 60 mg twice daily. Her pain was readily under control. She could not tolerate NSAIDs, including rofecoxib, because of esophageal reflux complaints. The progression of the bone metastases was very slow and her functional status was preserved. Her Karnofsky score was 70%.