area. Because of the autonomic signs, EF could resemble SUNCT (Shortlasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing) or SUNA (Shortlasting Unilateral Neuralgiform headache attacks with cranial Autonomic Features). Both consist in paroxysms of neuralgiform periorbital pain with prominent lacrimation or conjunctival injection. Several cases of EF with autonomic signs have been reported, but they are not present in our patient.

In conclusion, our patient fulfills essential features of EF, but it is the first case with sagittal localization so far. This topography does not fit well with other known headaches or neuralgias. The pain may be attributed to terminal sensitive branches instead of a nerve trunk. The dynamic component of the pain from the onset to the end may be explained by aberrant ephatic transmission through different nerve fibers, or either by transdiploic transmission. Central mechanisms can also explain the spreading of pain, through anatomical convergence of cervical and trigeminal afferents at the trigeminal nucleus caudalis.

CAROLINA DE LA CRUZ, MD,* SONIA HERRERO-VELÁZQUEZ, MD, PhD,* MARINA RUIZ, MD,* MARÍA I. PEDRAZA, MD,* PATRICIA MULERO, MD,* ÁNGEL L. GUERRERO, MD,* and MARÍA L. CUADRADO,† MD, PhD

*Neurology Department, Hospital Clínico Universitario, Valladolid, Spain; †Neurology Department, Hospital Clínico San Carlos, Universidad Complutense, Madrid, Spain

Conflict of interest: There are no conflicts of interest to report. There is no financial support.

References

Low-Dose Naltrexone to Prevent Intolerable Morphine Adverse Events: A Forgotten Remedy for a Neglected, Global Clinical Need

Dear Editor,

Opioids are the mainstay of treatment for moderate-severe pain but their use is dramatically limited by intolerable adverse events (AEs), such as constipation, nausea, vomiting, somnolence, dizziness, pruritus, and urinary retention [1,2]. Although opioid AEs constitute a long-standing clinical problem, effective treatment strategies are still not available. Thus, to date opioid AEs continue to represent an insurmountable barrier to therapy for millions of sufferers, who are denied the chance to receive an adequate pain relief.

Even though symptomatic drugs are used to treat opioid AEs, evidence supporting their efficacy is very low and, moreover, the management of several AEs with multiple adjuvant agents increases the risk of harmful drug interactions and diminishes compliance [2]. Although the opioid rotation method proved some efficacy in reducing AEs, this approach requires highly specialized

Letters to the Editor
competences and outcomes are variable [2]. Furthermore, the use of low opioid doses does not prevent the occurrence of AEs, such as nausea, vomiting, and pruritus [3], and attempts from pharmaceutical industries to design more tolerable opioids have been unsuccessful. Therefore, there is an urgent need for new agents able to counteract simultaneously different AEs.

Understanding the mechanisms underlying the onset of opioid AEs is essential to develop more rational treatments. It has been demonstrated that opioids can induce not only inhibitory effects, which are mediated by Gi/Go-coupled receptors and are responsible for the opioid analgesic action, but also Gs-coupled receptor-mediated excitatory effects, which can account for the development of AEs. Interestingly, opioid antagonists at low doses selectively antagonize the opioid excitatory effects without affecting the inhibitory action [4]. We previously observed that AEs (pruritus, nausea, and vomiting) occurred even with very low doses of morphine and were not dose-dependent [3]. This suggests that the excitatory component of the opioid activity is a specific

Figure 1. Dot plots showing, for each AE, the median score values with ranges calculated on patient with nonmalignant pain (A) and on patients with cancer pain (B) after treatment with morphine alone and after treatment with morphine plus NTX. Statistical analysis was performed using the two-tailed Wilcoxon matched-pairs signed-rank test. One asterisk (*) indicates a significant difference ($P < 0.05$) and two asterisks (**) indicates a very significant difference ($P < 0.01$). Actual $P$ values are also reported for all significant differences. + indicates a P value approaching statistical significance ($P = 0.0568$). NTX treatment did not significantly reduce morphine analgesic efficacy, as evaluated by Student $t$-test.
primary effect of the drug that does not depend on the dose. The model that emerges from all these observations predicts that very low doses of opioid would be responsible for the induction of AEs by acting on Gs-coupled receptors and that equivalent low doses of opioid antagonists would be able to selectively antagonize these Gs-coupled receptor-mediated excitatory effects, without affecting the inhibitory action mediated by Gs/Go-coupled receptors. Therefore, the use of opioid antagonists at low doses represents a promising strategy to counteract opioid AEs without impairing analgesia.

We explored the possibility of preventing morphine AEs using a low dose of the opioid antagonist naltrexone (NTX), because of its very advantageous profile, which is unique among opioid antagonists. Indeed, NTX can be administered orally, is inexpensive and has a long-lasting action. This last property is crucial since, to counteract opioid AEs, the duration of the antagonist action should be comparable to that of the agonist opioids. Conversely, the use of opioid antagonists with a short-lasting action (e.g., naloxone) is not indicated, especially when long-acting opioid formulations are used. Moreover, NTX safety profile has been proved during over two decades of clinical use for treatment of opioid and alcohol dependence.

Fourteen patients with chronic nonmalignant pain were treated with intrathecal morphine (0.03 ± 0.012 mg) and 15 patients with cancer pain received oral morphine (62.5 ± 22.8 mg). All the patients subjectively rated the intensity of AEs, on a 0–4 scale, and pain, using a 10 cm visual analog scale (VAS). On a different day, they all received 1 mg of NTX 1 hour before being identically treated with morphine and were monitored for AEs and analgesic efficacy at the same times as with morphine alone. Written informed consent by each patient and approval by Ethics Committee were obtained.

Pretreatment with NTX significantly reduced the intensity of nausea, vomiting, and pruritus in patients with nonmalignant pain and of nausea, vomiting, pruritus, and somnolence in patients with cancer pain (Figure 1). A trend of reduction in dizziness, urinary retention (both patient groups), and lack of appetite (cancer patients) was also observed, which for urinary retention closely approached statistical significance in patients with nonmalignant pain. Although comprehensive data on analgesia were not available for many patients, the analysis performed on the accessible data did not show significant differences in analgesia (Figure 1C). Consistently, our previous preliminary studies showed a reduction in morphine-induced analgesia in only 5 out of 33 patients treated with 1 mg of NTX (unpublished data). Moreover, NTX at low doses (up to 6 mg) was previously observed not to reduce significantly opioid analgesic effects [5,6].

Owing to its exploratory nature, our study presents methodological limitations. Nevertheless, our data suggest that low-dose NTX might be an effective and well-tolerated treatment for several morphine AEs and could represent the best practice for their management. However, despite the strong theoretical basis and the potential advantages of the use of a single opioid antagonist at low doses, such as NTX, to prevent multiple AEs, so far this approach has not been intensively pursued. Conversely, particular interest has been dedicated to opioid antagonists (e.g., intravenous/subcutaneous methylprednisolone, oral alvimopan, and oral naloxone combined with the opioid oxycodone in prolonged-release tablets) that show local effects on the gastrointestinal tract and, thus, guarantee the preservation of the centrally mediated analgesia, but that have the limitation of providing a therapeutic benefit only for peripheral opioid AEs. Indeed, their efficacy has been extensively demonstrated for constipation [7], whereas only limited data suggest that peripheral opioid antagonists, such as oral methylprednisolone and alvimopan, could also counteract other AEs (i.e., pruritus and nausea/vomiting) [8]. The concentration of many studies on opioid-induced constipation is surprising, considering that other AEs are much more critical [9].

An explanation for this wider focus on drugs with more limited action and higher costs might be related to the lack of interest from pharmaceutical companies to inexpensive drugs, such as low-dose NTX, which do not promise profits. Indeed, although we previously obtained a patent (Valducci R, Alighieri T, Avanesian S, Raffaelli W. Use of the opioid antagonist naltrexone to prevent and control side effects caused by opioids: WO Patent 2,002,087,582) demonstrating the feasibility of the idea, we were unable to draw interest from pharmaceutical companies to produce the drug on a large scale and expand our research to successfully translating it into clinical practice.

Overall, considering its safety profile and possible use as a galenic preparation, our data argue for the off-label and compassionate use of NTX to prevent morphine and possibly other opioid AEs. All the stakeholders involved should be encouraged to cooperate to achieve what should be the common goal, which is to reduce pain and prioritize patient health and quality of life over profit.

Acknowledgments

We are thankful to Dr. Francesca Pentimalli for helpful discussion.

William Raffaelli, MD* and Paola Inovyna, PhD†
*ISAL Foundation, Institute for Research on Pain, Rimini, Italy;
†Sbarro Institute for Cancer Research and Molecular Medicine, Center for Biotechnology, College of Science and Technology, Temple University, Philadelphia, Pennsylvania, USA.
Conflict of interest: The authors declare no conflict of interest.

Funding sources: ISAL Foundation (http://www.fondazioneisal.it). PI is the recipient of an ISAL Foundation fellowship.

References

Development of Tactile Allodynia Immediately After Spinal Anesthesia

Dear Editor,

The mechanisms of allodynia are ascribed to crosstalk and impaired inhibitory interneurons [1]. A-beta fibers are indirectly linked to lamina I output neurons via a polysynaptic pathway, and this link is normally repressed by inhibitory interneurons. If these inhibitory interneurons are impaired, allodynia can develop. Lowered nociceptive threshold, phenotypic switch and reorganization of dorsal horn are also mechanisms of allodynia [2]. Concern over exacerbation of pre-existing neurologic disease after spinal anesthesia has been recognized for some time [3]. However, there are few case reports of paradoxical response immediately after spinal anesthesia in the operating room. Kato et al. have reported a case that a burning abdominal pain appeared in a patient with complex regional pain syndrome after spinal anesthesia prior to a cesarean section [4]. We experienced a patient who complained of sudden tactile allodynia immediately after spinal anesthesia despite spinal blockade.

A 20-year-old male patient was scheduled for arthroscopic meniscus repair of both knees under spinal anesthesia. He had a history of previous arthroscopic meniscectomy of both knees 5 years prior due to a fall during wrestling training. He had been experiencing dysesthesia and mild allodynia in both knees when he stretched or scratched his knees since the operation. However, he was not treated for neuropathic pain because it was mild and tolerable with respect to daily activities. He had no history of any other underlying disease.

After the patient was admitted to the operating room, spinal anesthesia was performed with 14 milligrams of 0.5% hyperbaric bupivacaine. A short time later (5 min) after spinal anesthesia, the patient suddenly complained of pain in his lower extremities caused by accidental contact between a theater staff member and the operating table. We assessed his sensory blockade with alcohol swabs. Strangely, the patient complained of a stabbing pain when he received an alcohol swab. However, he did not complain of pain following a pinprick test, which indicated that the blockade level had reached the eighth thoracic (T8) vertebra. He had motor weakness in his lower extremities due to the motor blockade. To test the possibility of malingering we touched his lower extremity when the patient was unaware, but he complained of pain that occurred simultaneously with this stimulus.

Fifteen minutes after spinal anesthesia we injected seventy milligrams of propofol for sedation because the patient explained that he could not bear the sensation of continuous dysesthesia and allodynia in his lower extremities even from the tiny vibrations of the table, and he became agitated. When he awoke a short time later, he seemed to be more comfortable. The tactile numeric...