

Serotonin, Morphine, and Neuropathic Pain

Not a Simple Story

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NEUROPATHIC pain has long been described in the medical literature, from Paré's (Ambroise Paré, France, 1510–1590) description of phantom limb pain in the 1564 to Silas Mitchell's (1829–1914) description of complex regional pain syndrome during the American Civil War. However, a unifying theory of causation of these neuropathic pain syndromes and more importantly efficacious treatment remains elusive. Kimura *et al.*,¹ in this issue of *ANESTHESIOLOGY*, add some further basic science knowledge to the underlying changes that occur in the central nervous system with nerve injury. Importantly, they also show in a rat model of neuropathic pain that the efficacy of morphine as an analgesic agent is reduced. This adds to the controversial debate over whether opioids are effective in neuropathic pain.

A recent meta-analysis by the Cochrane collaboration looking at opioids in neuropathic pain added only eight further studies to its 2006 meta-analysis indicating little progress in this area during the past 7 yr.² Of the 31 studies identified, 17 looked at outcomes in using opioids for short periods (<24 h) and 14 looked at using opioids over longer periods (up to 12 weeks). Only half of the short-term studies showed a benefit of opioids over placebo, whereas all the longer-term studies showed a benefit for opioids over placebo, with a number needed to treat of 5.9 for a 50% reduction in pain. However, as pointed out by the Cochrane reviewers “these results are likely to be subject to significant bias because of small size, short duration, and potentially inadequate handling of drop-outs.” Leading them to conclude that “Analgesic efficacy of opioids in chronic neuropathic pain is subject to considerable uncertainty,” a statement that most chronic pain practitioners are likely to agree with.



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serotonin reduce the efficacy of morphine in normal subjects, and could ondansetron be used to treat patients with neuropathic pain?

In an attempt to answer the latter question, there have been two small studies^{3,4} in the literature using ondansetron for the treatment of neuropathic pain. They showed conflicting results, and a large randomized, placebo, controlled trial is probably required to answer the question definitively.

There are no trials in the literature specifically looking at the former question in actual patients experiencing pain. A small trial in volunteers seems to indicate no difference in the analgesic effects of morphine using an ondansetron dose of 16 mg.⁵ From the literature on postoperative nausea and vomiting, there seems to be no increase in analgesic requirements

Although the evidence provided by this article broadly concurs with the conclusion of the Cochrane review, it is hard to know whether ligating the L5 spinal nerve of a rat provides a valid model for all types of neuropathic pain. This model of neuropathic pain is likely to provide a realistic replication of certain types of neuropathic pain in humans, such as phantom limb pain, or other situations where nerves have been badly injured, not mimic neuropathic pain caused by longstanding insidious causes such as diabetes.

The other obvious area of interest generated by this study is the differing effects of serotonin at the dorsal horn in normal and neuropathic pain. In one instance, it facilitates the analgesic effects of morphine in normal subjects; but in subjects with damaged nerves, it has the opposite effect and blunts the analgesic effect of morphine.

The manner in which they elucidated these differential effects, through the use of intrathecal ondansetron, raises two interesting clinical questions: does ondansetron

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when ondansetron is added to a patient-controlled analgesia agent for controlling nausea and vomiting.^{6,7} Therefore, if there is an effect of ondansetron reducing the efficacy of morphine in clinical practice, it is probably small.

Ondansetron has relatively poor penetration of the central nervous system, and it may be that levels achieved in the dorsal horn after systemic administration are not high enough to cause any effect, and Kimura *et al.*¹ were unable to show the same effect with a smaller dose of ondansetron.

In addition to measuring the effect of serotonin in the spinal cord, Kimura *et al.* also considered the effect of systemic morphine on noradrenaline levels in the spinal cord. Although this same group have shown clearly that spinal noradrenaline release is responsible for some of the analgesic effects of both tramadol and antidepressants,^{8,9} they were unable to show any increase in spinal cord noradrenaline with a systemic morphine dose.

Perhaps, a future direction would be to consider the neurotransmitter changes that occur using other clinically relevant opioids; are the results produced in this study true of fentanyl which is a much more specific μ -receptor agonist, and of methadone which effects a host of different receptors to produce analgesia? Would this provide a laboratory basis for one opioid being more effective than another in neuropathic pain? A clinically important question which is as yet unanswered.

There are promising developments that seem to indicate that targeting the μ - and δ -receptors provides efficacious treatments for neuropathic pain,^{10,11} time will tell whether this translates to clinically effective treatments. The *N*-methyl-D-aspartate and γ -aminobutyric acid B receptors are also implicated in the efficacy of methadone and oxycodone, respectively,^{12,13} suggesting that these drugs may be better choices in the setting of neuropathic pain.

In summary, this study adds knowledge to the complex web of neurotransmitter function in neuropathic pain, and it provides some evidence to the clinical observation that opioids are not very effective in neuropathic pain states. Laboratory studies will continue to progress the pathophysiological understanding of neuropathic pain, whereas the acid test will be the clinical application of this knowledge to the treatment of patients in pain with the medications that we have currently available to us.

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Competing Interests

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