

## Brief Commentary



## Carbamazepine Withdrawal-induced Hyperalgesia in Chronic Neuropathic Pain

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Disclaimer: This work was supported in part by the National Natural Science Foundation of China (No. 81300948), Research Fund for the Doctoral Program of Higher Education by Ministry of Education, China (No. 20120001120072), and Foundation of Peking University Third Hospital, China (2013-BYSY-FUND).

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Combined pharmacological treatments are the most used approach for neuropathic pain. Carbamazepine, an antiepileptic agent, is generally used as a third-line treatment for neuropathic pain and can be considered an option only when patients have not responded to the first- and second-line medications. In the case presented herein, a patient with neuropathic pain was treated using a combined pharmacological regimen. The patient's pain deteriorated, despite increasing the doses of opioids, when carbamazepine was discontinued, potentially because carbamazepine withdrawal disrupted the balance that was achieved by the multifaceted pharmacological regimen, thus inducing hyperalgesia. Interestingly, when carbamazepine was prescribed again, the patient's pain was successfully managed. Animal research has reported that carbamazepine can potentiate the analgesic effectiveness of morphine in rodent models of neuropathic pain and postoperative pain. This clinical case demonstrates that carbamazepine may have a synergistic effect on the analgesic effectiveness of morphine and may inhibit or postpone opioid-induced hyperalgesia. We postulate that a probable mechanism of action of carbamazepine may involve  $\gamma$ -aminobutyric acid-ergic potentiation and the interruption of glutamatergic function via N-methyl-D-aspartate receptors. Further research is warranted to clarify the analgesic action of carbamazepine and its potential use for the prevention of opioid-induced hyperalgesia in chronic neuropathic pain patients.

**Key words:** Analgesia, hyperalgesia, carbamazepine, opioids, neuropathic pain, pharmacologic treatment

**C**arbamazepine is an antiepileptic agent that is generally used as a third-line treatment for neuropathic pain and may be considered an option only when patients have not responded to the first- and second-line medications (1,2). Although it is effective for trigeminal neuralgia, data on painful peripheral neuropathy are limited and inconsistent (3-6). In practice, intolerance to the side effects of carbamazepine limits its use, especially in the elderly. Carbamazepine stabilizes membranes by inhibiting sodium channels. The ability of carbamazepine to interfere with  $\gamma$ -aminobutyric acid (GABA)-ergic

and somatostatinergic mechanisms enhances its antinociceptive effects. Carbamazepine also has other less well-studied mechanisms, including those that block calcium channels and excitatory amino acids (7).

Previous research has reported that carbamazepine potentiated the analgesic effectiveness of morphine in animal models of neuropathic pain (8) and postoperative pain (9). Here we describe a clinical case in which carbamazepine withdrawal appeared to evoke chronic opioid-induced hyperalgesia, and the re-prescription of carbamazepine reversed hyperalgesia, which has not been previously reported.

### Case Report

A 48-year-old man with a history of cervical spondylosis (CSM) presented with a pain syndrome that had lasted over 4 months. The patient had undergone cervical 3-5 (C3-5) anterior cervical decompression and fusion in another hospital 4 months previously, but the pain was not relieved and even became worse. Morphine (10 mg) was injected intraperitoneally 4 times daily but was minimally effective.

The patient was admitted with exacerbation of nucha, shoulder, and upper limb pain and diagnosed with multiple radiculoneuropathy (C2, C4, C6, C8, T1). During this admission, he underwent radiofrequency ablation twice for pain relief, the first time on November 18, 2014, for the bilateral C5 nerve root and the second time on November 27, 2014, for the right C6 and C7 nerve roots, but this treatment was also minimally effective. Initially, the pain medication included tramadol sustained-release tablets (100 mg) twice daily, oxycodone + acetaminophen tablets, morphine injection (10 mg) intraperitoneally 4 times daily, pregabalin, and carbamazepine tablets (0.2 g) twice daily. However, the pain management was unsatisfactory. Gradually, a fentanyl transdermal patch (100  $\mu$ g/h) was used, in addition to carbamazepine tablets (0.2 g) twice daily, duloxetine enteric capsule (120 mg) once each night, gabapentin (0.3 g) 3 times daily, and morphine (20 mg) orally every 4 hours for breakthrough pain. The patient reported control of the pain with a numerical rating scale (NRS) pain score < 3.

On January 10, 2015, hepatic function deteriorated, presenting as a dramatic increase in alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, and  $\gamma$ -glutamyl transferase. To preserve and protect hepatic function, medications that may influence hepatic function (2 gastrointestinal medications, mosapride citrate tablets, famotidine tablets, and carbamazepine) were discontinued. As expected, a great improvement in hepatic functional enzymes was observed 5 days later.

On the day that carbamazepine was discontinued, the patient reported the worsening of pain at night and attempted to alleviate the discomfort with 30 mg and even 40 mg morphine orally or 10 mg morphine intraperitoneally every 1–2 hours. The fentanyl transdermal patch was titrated to 150  $\mu$ g/h. Unfortunately, the burning pain was still unbearable to the patient and diffused over the back, with an NRS pain score of 9–10 and not less than 5. The 24-hour cumulative morphine

dose for breakthrough pain was exceeding a 200 mg oral equivalent, but the pain was still intolerable.

Interestingly, when carbamazepine was prescribed again, the patient reported good pain management one day later, with an NRS score < 2. On the subsequent days, he reported a significant decrease in overall pain, and 30 mg morphine orally was sufficient to manage his breakthrough pain, the frequency of which was also reduced to not more than 2 times over a 24 hour period. He then reported being almost virtually pain-free and was discharged home with adequate pain control. Discharge pain medications included fentanyl transdermal patch (150  $\mu$ g/h), carbamazepine (0.2 g) twice daily, duloxetine enteric capsule (120 mg) each night, gabapentin (0.3 g) every 8 hours, and morphine (30 mg) every 12 hours as needed. Two weeks after discharge, the pain management was satisfactory based on our follow-up.

### Discussion

Carbamazepine is an antiepileptic agent that is generally used as a third-line treatment for neuropathic pain and can also be considered an option only when patients have not responded to the first- and second-line medications (1,2). Although it is effective for trigeminal neuralgia, data on its effectiveness for painful peripheral neuropathy are limited and inconsistent (3-6). In practice, intolerance to the side effects of carbamazepine limits its use, especially in the elderly. Side effects mainly involve dizziness, drowsiness, ataxia, nausea, vomiting, blurred vision, confusion, weakness, fatigue, nystagmus, aplastic anemia, abnormalities in liver function tests, and very rare cases of hepatic failure. Worsening pain with increasing doses of opioids in the absence of other comorbidities is a hallmark of opioid-induced hyperalgesia. In the case presented herein, the patient reported the deterioration of pain after carbamazepine withdrawal and no improvements despite an increase in opioid analgesics, indicating carbamazepine withdrawal-evoked opioid-induced hyperalgesia. Some features of opioid-induced hyperalgesia may help distinguish it from pre-existing pain. With opioid-induced hyperalgesia, the pain intensity may increase above the level of the pre-existing pain, and the pain distribution tends to go beyond the pre-existing pain and become more diffuse. All of these features were seen in this patient, indicating opioid-induced hyperalgesia. One challenge that clinicians face is distinguishing between inadequate pain relief that is caused by

opioid-induced hyperalgesia and inadequate pain relief that is caused by opioid tolerance. A trial of higher opioid doses would be helpful (10). If the pain improves, then this would suggest that the inadequate analgesia resulted from tolerance; if the pain worsens or fails to respond to dose escalation, then this would indicate opioid-induced hyperalgesia (10).

One interesting issue is the way in which carbamazepine withdrawal can promote opioid-induced hyperalgesia. Carbamazepine stabilizes presynaptic neuronal membranes by inhibiting sodium channels, resulting in a reduction of neurotransmitter release (11) and action potential conductance in nociceptive fibers. Carbamazepine can also potentiate GABA receptors (7,12), interrupt glutamatergic function via N-methyl-D-aspartate receptors, and block calcium channel-modulated central sensitization, which is related to its antinociceptive but not anticonvulsant effects (13,14). Carbamazepine was recently reported to potentiate the analgesic effectiveness of morphine in animal models of neuropathic pain (8) and postoperative pain (9), suggesting a synergistic effect on analgesia between carbamazepine and opioids. A double-blinded randomized human study revealed that carbamazepine induced analgesia in all types of peripheral neuropathic pain (15).

The dynamic and plastic nature of the pain system suggests the participation of several mechanisms in the generation and maintenance of chronic pain. In neuropathic pain, the pain-signaling system is distorted,

and the plastic changes become increasingly complex. Hence, the multifaceted treatment of pain is a reasonable approach. Combinations of the actions of tricyclic antidepressants, gabapentin, carbamazepine, and opioids add an additional facet to pain modulation. Thus, the discontinuation of carbamazepine may break the balance that is achieved by the combined pharmacology regimen, resulting in the absence of GABAergic potentiation and interruption of glutamatergic function, which may ultimately evoke hyperalgesia.

The present clinical case demonstrates that carbamazepine can potentially improve the analgesic effects of opioids on neuropathic pain and may have potential for the prevention of opioid-induced hyperalgesia in chronic neuropathic pain patients. The ability of carbamazepine to interfere with GABAergic and somatostatinergic mechanisms and block calcium channels and excitatory amino acids enhances its antinociceptive effects. More research is warranted to clarify the analgesic role of carbamazepine in the treatment of chronic neuropathic pain patients.

### Acknowledgments

This work was supported in part by the National Natural Science Foundation of China (No. 81300948), Research Fund for the Doctoral Program of Higher Education by Ministry of Education, China (No. 20120001120072), and Foundation of Peking University Third Hospital, China (2013-BYSY-FUND).

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