

Opioid-induced hyperalgesia: What to do when it occurs?

Stephan A. Schug

Pharmacology, Pharmacy and Anaesthesiology Unit, The University of Western Australia, Perth, Australia

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While treating cancer pain with opioids, we can sometimes observe a decline in analgesic efficacy of a given opioid dose, in particular with disease progression. If this phenomenon occurs whilst there is no obvious disease progression, this has been traditionally attributed to development of pharmacological tolerance. However, there is now increasing evidence for the phenomenon of opioid-induced hyperalgesia as another mechanism to explain the loss of effectiveness of opioids. Opioid-induced hyperalgesia has been defined as increasing pain sensitivity in patients chronically exposed to opioids without any evidence for new causes of pain. Opioid-induced hyperalgesia has been described in a large number of animal studies, since a first publication of this phenomenon in 1971, which reported that repeated injection of morphine produced hyperalgesia in rats (1). While the phenomenon has been well studied in many animal experiments subsequent to this first description, there is ongoing debate about the clinical relevance of this phenomenon, exemplified by the title of a most recent review "Opioid-induced hyperalgesia: Clinically relevant or extraneous research phenomenon?" (2).

In this issue of The Annals of Palliative Medicine, Mercadante *et al.* describe their observation of opioid-induced hyperalgesia after rapid titration with intravenous morphine in cancer patients (3). Furthermore, they describe successful treatment of this phenomenon by opioid rotation to intravenous methadone. The authors show consistently that cancer patients who show a

worsening of pain, despite increasing doses of morphine, respond to switching the morphine to methadone. Under methadone nearly all patients experienced stable analgesia; the methadone could be continued orally and patients discharged.

Thereby, this paper shows a clinically useful approach to cancer pain in patients poorly responsive to morphine. This is a further study, which supports the concept of opioid rotation, i.e. the switching of patients from one opioid to another in cases of poor responsiveness or severe adverse effects (4). The excellent results achieved here with a switch to methadone are in line with our own and the published experience and confirm the value of methadone in the setting of cancer pain (5). Reasons for the usefulness of methadone might well be its properties as an NMDA receptor antagonist, but could also be by its effect on monoaminergic neurotransmitters.

However, this paper also makes obvious the difficulty in diagnosing opioid-induced hyperalgesia in the clinical setting, in particular in cancer patients.

When observing decreasing efficacy of opioids in the setting of cancer pain, this could be withdrawal-associated hyperalgesia, newly developing allodynia, opioid tolerance or opioid-induced hyperalgesia (2). All these phenomena can show similar symptoms of increasing pain, but are caused by different mechanisms and might require different approaches. In the here presented study, "patients who did not respond favourably or showing a worsening pain despite increasing doses of morphine" were clinically diagnosed as presenting with opioid-induced hyperalgesia and switched to intravenous methadone (3). Basing the diagnosis of opioid-induced hyperalgesia on such weak clinical parameters increases the risk of not separating this from the differential diagnoses mentioned above. The ideal diagnostic tool for opioid-induced hyperalgesia would be the measurement of pain thresholds by the use of quantitative sensory testing (QST). Another practical test would be demonstration of improved analgesia when opioid doses are reduced, as tolerance would show an increased pain with reducing opioid doses. Therefore, there are concerns that, in the paper presented here, diagnostic criteria for opioid-induced hyperalgesia were weak

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Corresponding to: Professor Stephan A. Schug, MD. School of Medicine and Pharmacology, The University of Western Australia, Level 2, MRF Building G Block, Royal Perth Hospital, GPO Box X2213, PERTH WA 6847, Australia. Tel: +61-8-9224 0201; Fax: +61-8-9224 0279. Email: stephan.schug@uwa.edu.au.

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leading to a potential overestimation of this phenomenon.

These limitations do not reduce the clinical relevance of the presented results. The authors show successfully, that opioid rotation from morphine to methadone in patients with poor response to morphine is a clinically useful and highly successful strategy. Although we cannot be sure that all patients treated in this way truly had opioid-induced hyperalgesia, the treatment options for this phenomenon would include opioid switching, in particular to a drug with proven NMDA antagonist activity. The usefulness of methadone as a drug to reduce opioid requirements, possibly by its specific mechanism of action, have been recently shown in a very interesting study on peri-operative administration of a single methadone dose (6). Another approach to opioid-induced hyperalgesia could clearly be a dose reduction in an attempt to reduce the hyperalgesic response. Other approaches, which have been suggested, are the use of NMDA receptor antagonists such as ketamine or the use of alpha-2-delta modulators such as gabapentin and pregabalin (2).

In conclusion, while this study illustrates again the great difficulties in diagnosing opioid-induced hyperalgesia in the clinical setting, it offers evidence for the effectiveness of an

opioid rotation to methadone in cancer pain patients poorly responsive to increasing doses of morphine.

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