

When Similar Is Not Alike: Decreased Sensory Thresholds After Intravenous Infusion of Remifentanyl May Not Be Remifentanyl-Induced Hyperalgesia

To the Editor

Recently, Ishida et al.¹ reported decreased sensory thresholds after 120-minute, but not after 30-minute remifentanyl infusions in rats. Although these data seem to support the existence of opioid-induced hyperalgesia, a closer look at the methodology points to other factors that must be considered before ascribing the observed hypersensitivity to a direct pronociceptive effect of remifentanyl.

First, the authors used 2 stimulation modalities, thermal and mechanical, to determine pain thresholds. Application of heat may result in burns when protective responses are abolished by opioids. This is usually avoided by establishing cutoff points,² but there is always a risk of cumulative injury with repeated stimulation. During the 30-minute remifentanyl infusions, thermal thresholds were taken at 0, 5, 10, 20, and 30 minutes. It seems that in the case of the 120-minute infusions, measurements at every 30 minutes were preceded with measurements at 0, 5, 10, and 20 minutes, although only the first (0-minute) data from the latter 4 were presented on their graph. With the greater number of heat exposures during 120-minute infusions, there is a possibility of burn injury emerging as hyperalgesia after the infusion.

Second, the authors did not describe how and which parts of the tail were stimulated. In rats, the reaction time decreases when the stimulus is applied to increasingly distal parts of the tail.³ If, to avoid cumulative injury, the authors altered the stimulation sites from more proximal to more distal, such testing would appear as false hyperalgesia on their graph.

Third, the rat tail is a richly vascularized thermoregulatory organ and vasodilators can increase tail skin temperature.² This results in decreased tail withdrawal latencies, which again can be falsely interpreted as hyperalgesia.^{4,5} Because the ability of remifentanyl to cause vasodilatation is well known,^{6,7} the longer exposure to remifentanyl could be responsible for decreased thresholds in the 120-minute groups.

Fourth, the authors also reported decreased mechanical thresholds after remifentanyl infusion. Their baseline von Frey thresholds are equal to or in the vicinity of the cutoff value of 15 g. This is evidence of animal stress and anxiety or of an inadequately chosen testing method. Also, saline controls seemed to be better responders than any of the remifentanyl-treated groups, suggesting some differences in animal handling between the groups.

Finally, if mechanical and thermal thresholds were measured simultaneously in the same animals, it is possible that tail skin sensitized by repeated thermal stimulation also became sensitive to mechanical stimulation that manifested as decreased von Frey thresholds. Also, if mechanical thresholds were measured not on the tail as we are

presuming but on the rat hindpaws, there is still a possibility that the observed hypersensitivity was due to thermal injury of the tail, because the injury to the tail can cause hyperalgesia in the hindpaws.^{8,9}

Opioid-induced hyperalgesia is a topic about which there is some disagreement in the analgesia research community.¹⁰ Most evidence supporting its existence comes from behavioral studies in rodents. To have any clinical implications, these studies must be based on reliable methodology.

Andrey B. Petrenko, MD, PhD

Hideaki Ishii, MD, PhD

Tatsuro Kohno, MD, PhD

Hiroshi Baba, MD, PhD

Division of Anesthesiology

Niigata University Graduate School of Medical and

Dental Sciences

Niigata, Japan

abpetr@med.niigata-u.ac.jp

REFERENCES

1. Ishida R, Nikai T, Hashimoto T, Tsumori T, Saito Y. Intravenous infusion of remifentanyl induces transient withdrawal hyperalgesia depending on administration duration in rats. *Anesth Analg* 2012;114:224–9
2. Le Bars D, Gozariu M, Cadden SW. Animal models of nociception. *Pharmacol Rev* 2001;53:597–652
3. Ness TJ, Jones SL, Gebhart GF. Contribution of the site of heating to variability in the latency of the rat tail flick reflex. *Brain Res* 1987;426:169–72
4. Eide PK, Tjolsen A. Effects of serotonin receptor antagonists and agonists on the tail-flick response in mice involve altered tail-skin temperature. *Neuropharmacology* 1988;27:889–93
5. Tjolsen A, Lund A, Berge OG, Hole K. An improved method for tail-flick testing with adjustment for tail-skin temperature. *J Neurosci Methods* 1989;26:259–65
6. Unlugenc H, Itegin M, Ocal I, Ozalevli M, Guler T, Isik G. Remifentanyl produces vasorelaxation in isolated rat thoracic aorta strips. *Acta Anaesthesiol Scand* 2003;47:65–9
7. Kaye AD, Baluch A, Phelps J, Baber SR, Ibrahim IN, Hoover JM, Zhang C, Fields A. An analysis of remifentanyl in the pulmonary vascular bed of the cat. *Anesth Analg* 2006;102:118–23
8. Bianchi M, Panerai AE. Effects of lornoxicam, piroxicam, and meloxicam in a model of thermal hindpaw hyperalgesia induced by formalin injection in rat tail. *Pharmacol Res* 2002;45:101–5
9. Zhuo M. NMDA receptor-dependent long term hyperalgesia after tail amputation in mice. *Eur J Pharmacol* 1998;349:211–20
10. Tompkins DA, Campbell CM. Opioid-induced hyperalgesia: clinically relevant or extraneous research phenomenon? *Curr Pain Headache Rep* 2011;15:129–36

DOI: 10.1213/ANE.0b013e318263ca5c

Immediate and Delayed Remifentanyl-Induced Hypersensitivity

To the Editor

Recently, Ishida et al.¹ reported that IV infusions of remifentanyl induced transient withdrawal hyperalgesia in uninjured rats, its magnitude dependent on duration but not on the dose of the opioid administered. In

their model, 120-minute remifentanyl infusions (0.1, 1, or 3 $\mu\text{g}/\text{kg}/\text{min}$) induced hyperalgesia from 5 to 60 minutes after infusion. They did not detect hyperalgesia after 10-minute (30 $\mu\text{g}/\text{kg}/\text{min}$) or 30-minute infusions (0.1, 1, or 10 $\mu\text{g}/\text{kg}/\text{min}$). The authors compare their findings with those from previously published reports including results reported in mice by our group,²⁻⁴ consistently showing delayed remifentanyl-induced hypersensitivity after 30-minute infusions, lasting up to 7 days, its extent and duration depending on the dose administered. These factors, together with the rapid onset and short duration of remifentanyl-induced hypersensitivity observed by Ishida et al. suggest that 2 different phenomena are being investigated.

The different time(s) of nociceptive evaluation after the remifentanyl infusions in the study by Ishida et al. makes the comparison with other results difficult. In our work, we consider that the first time-point regarded sufficiently reliable to determine opioid-induced hyperalgesia is 4 hours after infusion; we think that it is important to avoid potential residual effects of the opioid such as antinociception, sedation, motor impairment, and especially opiate withdrawal. Thus, it is not known from the results by Ishida et al. whether delayed opioid-induced hyperalgesia might have been present. Numerous publications support the development of long-lasting remifentanyl-induced hypersensitivity after a single dose or infusion. We have recently reported in rats with incisional injury⁵ that similar doses of IV remifentanyl (6.67 $\mu\text{g}/\text{kg}/\text{min}$) as those used by Ishida et al., induce significant mechanical hypersensitivity 4 hours, 1 and 2 days after a 30-minute infusion. Heintz et al.⁶ also demonstrated protracted mechanical hyperalgesia from 4 hours to >7 days with similar doses (7.5 $\mu\text{g}/\text{kg}/\text{min}$, 60 minutes). Remifentanyl long-lasting hyperalgesia was also observed after single intraperitoneal injections in a different rat model of postoperative pain.⁷ It could be claimed that transient withdrawal remifentanyl hyperalgesia is not dose-dependent, even if Kiss et al.⁸ reported dose-dependent remifentanyl-induced acute and short-lived hyperalgesia in the rat; in humans, the clinical effect of this phenomenon is small and is probably masked/prevented by the administration of analgesia on emergence from general anesthesia. Collectively, preclinical data are supported by clinical studies reporting that remifentanyl hyperalgesia is (a) dose-dependent and long-lasting, and (b) significant particularly in the setting of incisional injury.^{9,10} Thus, based both on preclinical and clinical data, it can be concluded that a reduction in the doses of intraoperative remifentanyl must be considered to decrease postoperative pain hypersensitivity in humans.

David Cabañero, DVM, PhD

Department of Anesthesiology

Columbia University College of Physicians and Surgeons

New York, New York

Margarita M. Puig, MD, PhD

Department of Anaesthesiology

Hospital del Mar

Universitat Autònoma de Barcelona

Barcelona, Spain

MPuigR@hospitaldelmar.cat

REFERENCES

1. Ishida R, Nikai T, Hashimoto T, Tsumori T, Saito Y. Intravenous infusion of remifentanyl induces transient withdrawal hyperalgesia depending on administration duration in rats. *Anesth Analg* 2012;114:224-9
2. Cabanero D, Campillo A, Celerier E, Romero A, Puig MM. Pronociceptive effects of remifentanyl in a mouse model of postsurgical pain: effect of a second surgery. *Anesthesiology* 2009;111:1334-45
3. Cabanero D, Celerier E, Garcia-Nogales P, Mata M, Roques BP, Maldonado R, Puig MM. The pro-nociceptive effects of remifentanyl or surgical injury in mice are associated with a decrease in delta-opioid receptor mRNA levels: prevention of the nociceptive response by on-site delivery of enkephalins. *Pain* 2009;141:88-96
4. Celerier E, Gonzalez JR, Maldonado R, Cabanero D, Puig MM. Opioid-induced hyperalgesia in a murine model of postoperative pain: role of nitric oxide generated from the inducible nitric oxide synthase. *Anesthesiology* 2006;104:546-55
5. Romero A, Rojas S, Cabanero D, Gispert JD, Herance JR, Campillo A, Puig MM. A 18F-fluorodeoxyglucose MicroPET imaging study to assess changes in brain glucose metabolism in a rat model of surgery-induced latent pain sensitization. *Anesthesiology* 2011;115:1072-83
6. Heintz C, Drdla-Schutting R, Xanthos DN, Sandkuhler J. Distinct mechanisms underlying pronociceptive effects of opioids. *J Neurosci* 2011;31:16748-56
7. Gu X, Wu X, Liu Y, Cui S, Ma Z. Tyrosine phosphorylation of the N-methyl-D-aspartate receptor 2B subunit in spinal cord contributes to remifentanyl-induced postoperative hyperalgesia: the preventive effect of ketamine. *Mol Pain* 2009;5:76
8. Kiss I, Degryse AD, Bardin L, Gomez de Segura IA, Colpaert FC. The novel analgesic, F 13640, produces intra- and postoperative analgesia in a rat model of surgical pain. *Eur J Pharmacol* 2005;523:29-39
9. Mao J. Opioid-Induced Hyperalgesia. 1st ed. New York: Informa Healthcare USA, Inc., 2010
10. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* 2006;104:570-87

DOI: 10.1213/ANE.0b013e318263ca82

In Response

Petrenko et al.¹ mention the possibility of a burn injury induced by the tail-flick test. However, both the 120-minute and 30-minute groups received the same number of heat stimulations.² In the 30-minute group, the measurements were taken at 0, 5, 10, 20, and 30 minutes during drug infusion. Similarly, in the 120-minute group, the measurements were taken at 0, 30, 60, 90, and 120 minutes. The experiments were performed under equivalent conditions. Additionally, the control group, saline 120, received the same heat stimulation for measurements as did the other 120-minute groups. However, we did not observe any changes in the pain thresholds in the control group. If pain hypersensitivity caused by heat injury was observed only in the remifentanyl groups, as suggested by Petrenko et al., it would imply that pain hypersensitivity is induced by remifentanyl. Furthermore, the decrease in tail-flick latency recovered to baseline within 30 minutes, an observation that cannot be accounted for by a thermal injury.

We performed the tail-flick test with great care to prevent heat injury. At each measurement point, heat was applied 3 times and the values were averaged. The testing location was limited to an area 4 cm from the tip of the tail. We divided the area into 3 regions—the proximal, middle, and distal—and heat was applied to each area sequentially,