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Opioid-free anesthesia opioid side effects: Tolerance and hyperalgesia

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Opioids are the most potent drugs used to control severe pain. However, neuroadaptation prevents opioids' ability to provide long-term analgesia and produces opposite effects, i.e., enhancement of existent pain and facilitation of chronic pain development. Neuroadaptation to opioids use results in the development of two interrelated phenomena: tolerance and "opioid-induced hyperalgesia" (OIH). Tolerance, a pharmacologic concept, and OIH, a clinical syndrome, have been mostly observed under experimental conditions in animals and in human volunteers. In contrast, their occurrence and relevance in clinical practice remain debated. In perioperative setting, intraoperative administration of high doses of opioids increases postoperative opioid requirements and worsens pain scores (acute tolerance or perioperative OIH). Further, preoperative chronic opioid intake and postoperative long-term use of opioid analgesics beyond the normal healing period have a negative effect on surgical outcome. Conversely, observations of improved patient's recovery after opioid-sparing anesthesia techniques stand as an indirect evidence that perioperative opioid administration deserves caution. To date, perioperative OIH has rarely been objectively assessed by psychophysics tests in patients. A direct relationship between the presence of perioperative OIH and patient outcome is missing and certainly deserves further studies.

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Introduction

A major increase in the use of opioids analgesics for pain control has emerged during the last 20 years [1]. The widespread use of opioids to relieve acute pain (after surgery and trauma)—now considered as "the fifth vital sign"—and the more liberal use of opioids to relieve chronic non-cancer pain have unmasked the perverse effects of these analgesics. In acute pain setting, well-known adverse effects (nausea-vomiting, dizziness, and pruritus) may delay recovery and even harm the patients (deep sedation and respiratory depression). In the context of chronic use, major social issues (abuse, misuse, and unintentional deaths from overdoses) have appeared [1]. Despite that, opioids remain the most potent drugs used to control severe pain. However, neuroadaptation prevents opioids' ability to provide long-term analgesia and produces opposite effects, i.e., enhancement of existent pain and facilitation of chronic pain development [2]. Neuroadaptation to opioids use yields to the development of tolerance and to a phenomenon called "opioid-induced hyperalgesia."

Opioid tolerance and opioid-induced hyperalgesia: rethinking definition, context and perioperative implications

Opioid tolerance and opioid-induced hyperalgesia (OIH) are interrelated phenomena that contribute to pain worsening during opioid administration. Confusion between them may lead to inadequate treatment of the patients [2,3]. While opioid tolerance may be solved by increasing the doses of opioid, OIH is be controlled by tapering the doses of opioid administered.

Tolerance is described as a pharmacological effect, a state of adaptation, in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time [4]. Opioid tolerance is a multidimensional phenomenon as tolerance occurs not only to analgesia but also to nausea, sedation, respiratory depression, and other central nervous system depressive effects of opioids. The progressive lack of response to opioid administration can be explained by a "*within-system adaptation process,*" where the drug elicits an opposite reaction within the same system in which the drug elicits its primary action [2]. This neuroadaptative response will progressively neutralize the drug's effect [Table 1].

OIH refers to increased pain sensitivity due to opioid use. "Hyperalgesia" has been, for a long time, referred to as an increased response to a stimulus that was normally painful. According to a more recent view, hyperalgesia, i.e., increased pain sensitivity, refers to an umbrella term including allodynia, decreased pain threshold, and increased response to suprathreshold stimulation [5]. Moreover, it is mandatory that the paradoxical phenomenon of OIH develops during opioid administration [6]. In practice, the main problem that remains is the definition of OIH and its detection [Table 2]. OIH has often been observed after the administration of opioids (most of the time, after the termination of ultra-short-acting opioid remifentanil infusion), questioning the cause of hyperalgesia: acute tolerance

Table 1
Mechanisms underlying neuroadaptation to opioid use.

Opioid intake simultaneously induces a potent analgesic effect, which masks the concomitant development of the phenomena of	
Opioid Tolerance explained by "Within-system" adaptation theory	**Opioid-induced Hyperalgesia** explained by "Between-system" adaptation theory
Opioid receptors desensitization - internalization - down-regulation - phosphorylation or heterodimerization with other receptors (e.g., chemokine receptors)	Recruitment of opponent neuronal circuits - NMDA - Dynorphins and BDNF - CCK - Neuro-inflammation (interleukin, TOLL-R4)
Opioid tolerance may occur first [45]	OIH might occur after longer time use and higher doses of opioids [45] OIH is a contributor to the development of opioid tolerance [10]

From Rivat and Ballantyne [2] and Simonnet and Rivat [10].