Research Article
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Nalbuphine and addiction: from the basic science to clinical set

Abstract

The use of opioid analgesics, especially in the postoperative period, is commonly used, with morphine being the drug of choice. Nalbuphine (C21H27NO4) is a synthetic kappa receptor agonist and partial Mu receptor antagonist opioid drug, available and approved in our middle, which has been synthesized in an attempt to provide analgesia without the undesirable side effects of pure agonists such as Mu-opioids whose main representative is Morphine. The possibility of using Nalbuphine as an alternative drug in view of the increasing worldwide addiction/dependence rates and therefore alarming rates of opioid overdose deaths may be realized due to its favourable pharmacological profile in terms of adverse effects and its equivalent analgesic potential. Thus, it was decided to perform a literature review of studies published in the last 10 years in the main databases "PubMed" and "MedLine" to evaluate the basic and clinical scientific evidence about Nalbuphine addiction and its potential role in the current scenario of addiction and dependence to opiates.

Keywords: Nalbuphine, Opioid, Kappa Opioid, Addiction, Dependence, Opioid epidemic

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Abbreviations: CDC, centers for disease control; USA, united states of america; GPCRs, protein G-coupled receptors; MORs, Mu receptors; DORs, delta receptors; KOR, kappa receptors; CSN, central nervous system; KOPR, kappa opioid receptors; NAc, nucleo accumbens; MAC, monitored anesthesia care; PNS, peripheral nervous system.

Introduction

Opioid drugs are currently the main treatment for acute and chronic pain control. Over the past three decades, misuse of opioids has led to rising worldwide addiction/dependence rates and overdose deaths. In the United States of America, this opiate crisis scenario, which in 2016 alone resulted in the estimated death of over 64,000 people, was characterized as the Opioid Epidemic and declared as a national public health emergency.[1] Nalbuphine (C21H27NO4) is a synthetic kappa receptor agonist opioid and partial Mu receptor antagonist,[2,3] which has been synthesized in an attempt to provide analgesia without the undesirable side effects of pure agonists.[4] Thus, the central analgesic action and lower Nalbuphine addiction/dependence potential would be exerted by the agonist action on kappa receptors, while its Mu-opioid agonist action would be responsible for its analgesic potential, equivalent to morphine and its lower respiratory depression.[5]

To assess opioid addiction/dependence, analysis of a representative sample of cancer-free adults who received prescription opioid analgesics showed that the likelihood of chronic use increased with each additional day of medication provided from the third day and that the risk of continuing doubled after the second prescription and varied according to the pharmacological profile of the opioid used. In a recent report on morbidity and mortality, the CDC/USA reported a total of 2.6% (33,548 patients out of 1,294,247 patients) who continued opioid use for more than one year after prescription. Nalbuphine would be in the group with the lowest rates in both one year (5%) and 3 years (2.2%) when compared to morphine (27.3% in 1 year; 20.3% in 3 years) or even at Tramadol (13.7% and 6.8%, respectively).[6] This study aims to review in the literature the basic and clinical evidence on nalbuphine addiction, to elucidate the neurobiology of opioid addiction in particular related to the Kappa pathway and to contextualize the clinical aspects of opioid addiction especially Nalbuphine.

Material and methods

For this Literature Review, studies available in the PubMed and Medline databases with the search words "Nalbuphine", "Kappa Opioid", "Addiction" and "Opioid epidemic" in the last 10 years were selected. A selective search was performed in the previous period as relevant in the references. Among the exclusion criteria for article selection are studies that do not contain the search words in the title and that after reading the abstracts do not agree with the proposed of this review of literature. After selection and full reading, articles that were not relevant to this study were excluded.

Discussion

Recently, an "opioid epidemic" has emerged in western countries, particularly in North America.[7] The use of opioids for pain relief over the past 20 years has led to a rapid increase in non-medical use of prescribed opioids, with overdose deaths and transition to heroin abuse growing at alarming rates.[8–11] The increasing availability of low-cost synthetic opioids, such as non-pharmaceutical fentanyl, further fuels the epidemic.[12] This opioid crisis has initiate new public policy and much interest in developing better opioids for pain management. For medical purposes, the ideal opiate would relieve pain with high and sustained efficacy (ie, without tolerance), without the threats of respiratory depression (the leading cause of overdose death) and without drug addiction (contributing to addiction).[13]

The opioid system comprises three homologous protein G-coupled receptors (GPCRs) known as mu, delta and kappa-opioid receptors (MORs, DORs and KORs, respectively). Under physiological conditions, opioid receptors are stimulated by endogenous opioid peptides, forming a family of peptides that include β-endorphin, encephalins and dynorphins. These receptors are distributed throughout the nervous system, opioid peptides act on receptors and reduce responses to painful stimuli, stress and influence the dopaminergic

reinforcement and reward system; Endogenous opioid system activity is extremely broad and encompasses many other aspects of physiology and behaviour, but these are less related to addiction.[14] Addiction is a complex and recurring disorder in which drugs of abuse sequester, overstimulate, and compromise the dopaminergic pathway and reward system, leading to dysregulation of opioid neurotransmission. Together, positive and negative changes contribute to the development and maintenance of addiction. All three opioid receptors are involved in the process, although with very different contributions: MORs promote recreational drug use (including opioids and others) and adapt to chronic activation (leading to tolerance and dependence); KORs enable and sustain aversive withdrawal and abstinence states; PAINs improve moods and facilitate contextual learning; and all three receptors modulate motivation. That MOR and KOR activities drive the onset, progression and maintenance of addiction are well recognized, while the contribution of DORs remains less clear.[15,16]

The use of opioid analgesics, especially in the postoperative period, is commonly used, with morphine being the first choice. The option to use Nalbuphine, an alternative drug available and approved in our country, may be made due to its favourable pharmacological profile in terms of adverse effects, especially regarding respiratory depression,[17] nausea, vomiting, pruritus[18] and lower potential for addiction/dependence, maintaining analgesia similar to Morphine[19] and being a quarter as potent as nalorphine and 10 times that of pentazocine.[20]

Nalbuphine, a synthetic opioid, is an opiate kappa receptor agonist and a partial antagonist of mu opioid receptors in the CNS, causing inhibition of upward pain pathways, altering pain perception and response, and producing generalized CNS depression. When the opioid receptor-K subtype was first distinguished, there was a strong interest in developing analgesics that would provide pain relief without activating Mu-opioid-stimulated reward pathways such as morphine.[21,22] Thus, selective k-agonists were developed, although different complications, including dysphoria and constipation, as well as maximum ceiling analgesic effect limited the greater diffuse of its use.[23]

A κ receptor agonist-antagonist, nalbuphine can activate κ receptor to achieve the analgesic effect and antagonize the μ receptor to reduce the adverse effects. Several preclinical studies provided evidence that Kappa opioid receptors (KOPR) in DRG may control visceral pain and have suggested the use of peripherally restricted kappa agonists for these types of pain.[24–26] Activation of Kappa opioid receptors (KOPR) in the dorsal raphe nucleus mediates descending antinociception. Additionally, the KOPR system transmits affective information related to stress and anxiety from the basolateral amygdala to the bed nucleus of the striaterminalis, as well as from inputs from the locus coeruleus. Although it is not yet fully understood for pain perception, it is known that the KOPR system is well positioned in the NAc (NucleoAccumbens) circuitry to modify the hedonic value of nociceptive events and shape motivational behaviours in response to painful experiences. The dynorphin-kappa system regulates stress, aversion, mood and relapse in drug-seeking for all major classes of drug abuse and may also contributes to shaping the negative effect pain-induced, driving comorbid depression and addiction.

Nalbuphine has as pharmacological characteristics onset of action <15 min if administered intramuscularly and 2-3min if intravenous; its plasma half-life is 5 hours, ranging from 3 to 6 hours and varying proportionally with increasing age, especially due to its binding to carrier proteins which is close to 50%, while drug clearance decreases inversely. The most common adverse reaction in 1066 Nalbuphine-treated patients was sedation 381 (36%), less frequent: cold and damp skin 99 (9%), nausea and vomiting 68 (6%), dizziness/vertigo 58 (5%), xerostomia 44 (4%), headache 27 (3%).[27] For pruritus, it was also effective, although the variety of regimens tested makes it difficult to provide clear treatment recommendations. There is scientific evidence for lower pain intensity, but increased sleepiness with nalbuphine.[28]

Nalbuphine addiction is poorly described in the literature. The first three cases were described in 1984 but without much detail.[29] In 1985 Industry made 4 more inaccurate reports of dependence on Nalbufina, but never in street use, always in a hospital environment. In 1996, there was the first report with 3 cases of injecting anabolic drug users concomitantly using Nalbuphine illegally obtained outdoors.[30] There are findings from studies in rats suggesting that nalbuphine may be used as an effective pharmacological adjunct in the treatment of opioid dependence[31] and that the use of nalbuphine with morphine in the treatment of chronic pain may be one of the therapies to reduce the development of opioids tolerance and dependence of morphine.[32] The neurobiological basis of the potential addiction to nalbuphine is controversial. While the role of dynorphin (the main endogenous kappa receptor ligand) in dopaminergic reinforcement and reward circuits in the ventral tegmental area and nucleus accumbens is responsible for the dysphoric effects related to recurrence of misuse in experimental studies, the few clinical studies of nalbuphine show a lower potential for abuse or addiction. Some reasons for this may be necessarily parenteral use, low availability in both hospital and illegal settings, short postoperative use (24-72h) and also its possible lower pharmacological probability of exogenous induction of epigenetic alterations than facilitate the installation of addiction.[33,34]

Conclusion

Parenteral opioids are commonly used to provide analgesia and supplement sedation during general anesthesia or MAC, and are the most commonly used agents in the treatment of acute pain in the immediate postoperative period. Opioids indicated for perioperative use mainly bind to mu receptors in the CNS to produce analgesia, having as main para-effects dependence/addiction, respiratory depression, nausea/vomiting, pruritus and urinary retention. Opioid binding to mu receptors in the peripheral nervous system (PNS) in addition to contributing to its analgesic efficacy produces effects such as cough suppression and constipation. Despite the controversy between experimental studies of the endogenous role of the dynorphin/KOR system and experimental and clinical studies of the use of exogenous agonists (Nalbuphine) in opioid addiction, evidence points to a lower risk of addiction with opioids compared to other available opioids, especially agonists One, but also in relation to tramadol.

Conflicts of interest

The authors declare no conflicts of interest.

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