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Nalbuphine and Addiction: From the Basic Science to Clinical Set

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Abstract

The use of opioids, especially morphine, have been the main choice for analgesia in moderate to severe pain. Nalbuphine (C21H27NO4) is a synthetic kappa-receptor agonist and partial mu-receptor antagonist opioid drug, available and approved to use, designated in an attempt to provide analgesia without the undesirable side effects of pure mu-opioids agonists like 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 seems the rational option due to its favourable pharmacological profile in terms of adverse effects and its equivalent analgesic potential. Thus, we performed a literature review of the last 10 years to evaluate the basic and clinical scientific evidence about nalbuphin[potential role in the current scenario of addiction and dependence to opioids.

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

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 Anaesthesia 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 led to rising worldwide addiction / dependence rates and overdose deaths. In the United States of America, this opioid 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 (KOR) agonist opioid and partial mu-receptor (MOR) antagonist [2,3] which has been synthesized in an attempt to provide analgesia without the undesirable side effects of pure agonists [4]. The central and peripheral analgesic action and the lower risk of addiction/ dependence potential seems to be related to the agonist action on KOR, while its MOR antagonist action would be responsible for its lower risk of respiratory depression [5].

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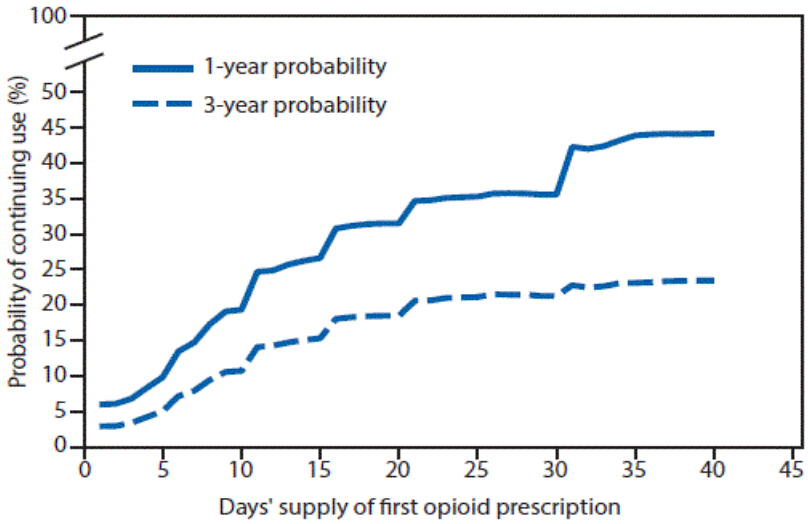
In a recent report on morbidity and mortality, the CDC / USA reported 2.6% (33,548 patients out of 1,294,247 patients) who continued opioid use for more than one year after prescription. To assess opioid addiction/ dependence, analysis of a representative sample of cancer-free adults who received prescription 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 continued use doubled after the second prescription and varied according to the pharmacological profile of the opioid used (figure 1).



Data are from the Centres of Disease Control and Prevention (6).
* Days' supply of the first prescription is expressed in days (1–40) in 1-day increments. If a patient had multiple prescriptions on the first day, the prescription with the longest days' supply was considered the first prescription.
Figure1**:** 1- and 3-year probabilities of continued opioid use among opioid-naïve patients, by number of days' supply* of the first opioid prescription — United States, 2006–2015.

Nalbuphine was in the group with the lowest rates in both one year (5%) and 3 years (2.2%) continued use when compared to morphine (27.3% in 1 year; 20.3% in 3 years) or even to Tramadol (13.7% and 6.8%, respectively) (Table 1) [6].

Choice of first prescription	Number (%) of patients	One year probability of continued use, %	Three year probability of continued use, %	Median days to discontinuation
Long Acting Opioids	6,588 (0.5)	27.3	20.5	63
Tramadol	120,781 (9.33	13	6.8	
Hydrocodone Short Acting	742,112 (57.3)	5.1	2.4	5
Oxcodone Short Acting	219,224 (16.9)	4.7	2.3	6
Schedule II Short Acting	14,877 (1.2)	8.9	5.3	8
Schedule III -I V and Nalbuphine	190,665 (14.7)	5	2.2	5

Data are from the Centers of Disease Control and Prevention [6].
* The first prescription was categorized into six mutually exclusive categories, and in case of multiple prescriptions on the index date, the following hierarchy was used to assign category: Long Acting; Other Schedule II Short Acting; Oxycodone Short Acting; Hydrocodone Short Acting; Schedule III - IV and Nalbuphine; Tramadol
Table1**:** One and Three year probabilities of continued use, and median time to discontinuation of opioid use, by choice of first opioid prescription*

This study aims to review the literature of 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

Studies available in the PubMed database 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. The exclusion criteria for article selection are studies published in languages other than English, Portuguese and Spanish, and that do not contain the search words in the title or abstract and that after analysis of the abstracts do not attend to the subject. 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 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 opioid must 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 extensive 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, over stimulate, and compromise the dopaminergic pathway and reward system, leading to deregulation 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; DORs improve moods and facilitate contextual learning; and all three receptors modulate motivation. The 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 KOR-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 KOR agonist activity is responsible the analgesic effect while the MOR antagonist activity 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].

The KOR system transmits affective information related to stress and anxiety from the basolateral amygdala to the

bed nucleus of the strain terminal is, as well as from inputs from the locus coeruleus. Although it is not yet fully understood for pain perception, it is known that the KOR system is well positioned in the NAc (Nucleo Accumbens) circuitry to modify the hedonic value of nociceptive events and shape motivational behaviours in response to painful experiences. (figure2). 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.

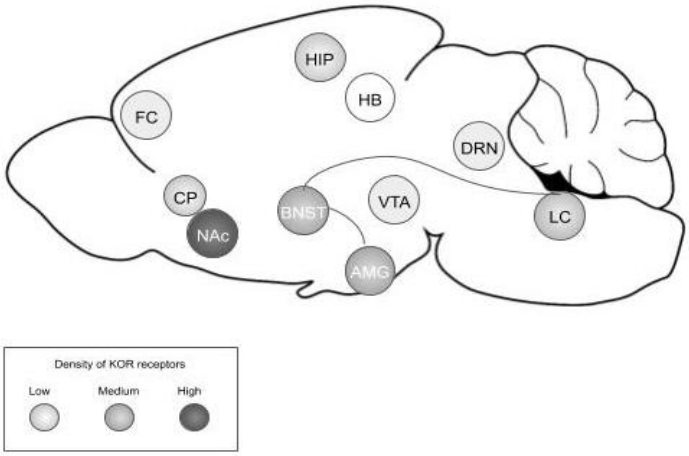


Figure 2: KOR function in neurocircuits of addiction. This simplified scheme represents a sagittal section of a rodent brain illustrating brain regions involved in drug abuse (Circles). Receptor density is indicated for each region, and the opioid-receptor-regulated pathways identified in the studies discussed in this Review are shown by black lines [27]. KORs in excitatory amygdala (AMG) neurons projecting to the bed nucleus of strain terminal is (BNST) promote stress and anxiety. KORs in NAc inputs negatively regulate motivational processes and modify the hedonic value of nociceptive events and shape motivational behaviours in response to painful experiences. KORs in AMG are related to induce the affective state of addiction [15-27].

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]. It was also effective treating pruritus, 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 nalbuphine, but never in street use, always in a hospital environment. In 1996, there was the first report of 3 cases of injecting anabolic drug users concomitantly using Nalbuphine illegally obtained [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 to 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 [33-35].

Conclusion

Parenteral opioids are commonly used to provide analgesia and supplement sedation during general anaesthesia 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 nalbuphine than other opioids, especially Morphine.

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