Nefopam and its Role in Modulating Acute and Chronic Pain

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Pain is a very important issue to take into account during hospitalization. Nefopam, a centrally acting analgesic, has a relative safety pharmacological profile with few and well-tolerated side effects, being used to treat acute or chronic pain. It inhibits the central reuptake of serotonin, norepinephrine and dopamine and modulates the sodium and calcium channels having only few contraindications. Nefopam can be part of balanced analgesia along with others non-opioids agents in order to reduce the opioid consumption and their complications, to control postoperative pain and to reduce the risk of neuropathic pain appearance. In order to avoid its adverse reactions, a slow infusion is always recommended. Nefopam has its role in preventing the shivering appearance during neuraxial or general anesthesia, can modulate the emergence agitation after nasal and maxillofacial surgery and can inhibit the sever hiccup during mechanical ventilation. Some cases about fatal overdoses are reported in the literature.

Key words: nefopam, acute or chronic pain, balanced analgesia, slow injection.

Analgesia is one of the most important aspect of daily medical practice because pain interfere with the patient outcome and it can delay the patients' recovery and their rehabilitation. Liebeskind and Melzack were saying in 1987 that *by any reasonable code, freedom from pain should be a basic human right limited only by our knowledge of achieving it* [1].

Nefopam (© Acupan) is used to treat acute or chronic mild and moderate pain since the mid-1970s [2] and has a distinct analgesic profile being a centrally acting molecule, non-narcotic and non-steroidal analgesic drug with supra-spinal and spinal sites of action [3]. In 1976 it was used for the first time in Europe in oral or intravenous form [4]. There are only few classes of non-opioid analgesics and, together with non-selective non-steroidal anti-inflammatory drugs, selective inhibitors of cyclooxygenase 2 and acetaminophen, Nefopam provides the management of acute or chronic pain in order to avoid the multitude of side effects produced by opioid drugs and reducing their consumption with 30-40% [2]. This combination is known as balanced analgesia, with different pharmacological classes of analgesics having synergistic effects, and permitting a reduction in each drug dose and therefore decreasing the risk of side effects [3]. Some studies have shown the efficacity of Nefopam in modulating perioperative pain [2], decrease the shivering threshold and treat postanesthetic shivering with minimal adverse effects by mediating the thermoregulatory responses [5] and seemed to reduce the hiccup frequency in mechanical-ventilated patients [6].

There are some side effects than need to be taken into account when Nefopam is used, like nausea, vomiting and sweating, dizziness, somnolence, light-headache, asthenia, confusion and tachycardia which are corelated with its central mechanism of action [7]. Some patients described pain at the injection site [4]. To avoid the appearance of these adverse effects, the manufacturer recommended that the drug should be slowly injected. But it does not cause tolerance or physical dependence, has no hemodynamic effects, does not induce respiratory depression and has no sedative effect with a safety profile regarding coagulopathy (no effect on platelet function) [8]. All of this should be put in balance with the side effects of the other pharmacologic classes of analgesics in pain management.

The present study aims to take into agenda the analgesic potency of this drug according to the studies published in literature and reported cases, its role in opioid-free balanced analgesia, the risk of adverse effects and their impact on the body, the secure dose and route of administration and the new approaches regarding other clinical properties of Nefopam.

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Pharmacological properties

Nefopam is a racemic mixture of two enantiomers: (+)nefopam and (-)nefopam [9]. It inhibit the central synaptosomal reuptake of serotonin (5-hydroxytryptamine, 5-HT), norepinephrine and dopamine, it interacts directly with á2 -adrenoreceptors and modulate the calcium and sodium channels of the glutamatergic pathway and therefore decreasing the activation of postsynaptic glutamatergic receptors, like N-methyl-D-aspartate (NMDA), which has a specific role in hyperalgesia appearance [9]. In the first place, it was used as an anti-depressant and as an antispasmodic drug due to its myorelaxant properties [10] but studies have shown its effectiveness in preventing acute postsurgical hyperalgesia [11] and modulation of non-surgical neuropathic pain [12]. It is a benzoxazocine known as 5-methyl-1-phenyl-1,3,4,6-tetrahydro-2,5-benzoxazocine ($C_{17}H_{19}NO$) obtained from a non-sedative benzoxazocine and is a cyclized analogue of an antihistamine (diphenhydramine -$C_{17}H_{21}NO$) [13]. It has been demonstrated that Nefopam is unstable under acidic condition and can be easily oxidized [14]. Nefopam has a chemical structure close to orphenadrine (an antimuscarinic). It is synthesized from O-benzoyl benzoic acid in four steps and has a half-life of 3 to 5 hours. The plasma peak concentration is obtained in 15-20 minutes after intravenous administration and after approximately 30 min during a continuous infusion [15]. Its oral bioavailability is 40% and go through extensive hepatic transformation to its almost 31 human metabolites, especially Desmethylnefopam (with biological activity) and N-oxide-nefopam [16]. It is metabolized by recombinant human Cytochrome P450 1A2 (CYP2C19) and 2D6 (CYP2D6). Nefopam binds to protein in a proportion of 75%. The main route of elimination (approximately 87%) is via kidney and the rest is excreted in the faeces [4]. Only 5% of a dose is excreted in urine as the unchanged molecules [16] but it has no interaction with antidiuretic drugs [17]. In patients with impaired renal function, especially patients with chronic dialysis and in elderly patients the elimination of Nefopam is altered [18-20].

Intravenous administered Nefopam determines a strong inhibition of the nociceptive flexion reflex in humans [21]. Studies has shown that it has opioid-sparing effects (it reduces de opioid consumption after cholecystectomy [22], cardiac surgery [11], upper and lower abdominal surgery [23, 24], hysterectomy [25], palliative interventions [26, 27], breast cancer surgery [28], nasal surgery, orthopedic interventions [29, 30], by 30-40% [2] and that 20 mg of Nefopam is equipotent with almost 6-12 mg Morphine and 50 mg of Meperidine [31] having the same analgesic potency as nonsteroidal anti-inflammatory drugs.

There are no studies regarding the efficacy of Nefopam in children.

Adverse effects and contraindications

Nefopam is usually well tolerated, with minor and not long lasting adverse reactions according to data reported having only few relative contraindications. If it is not infused in a slow manner, Nefopam can produce pain at the injection site [16]. Other known side effects are profuse sweating, nausea and vomiting, dizziness, dry mouth [7], tachycardia and cutaneous reactions (pruritus and erythema) [7]. In critically ill patients, Nefopam produces an increase in heart rate about 15% in almost 25% of patients [32]. In a study from 2001, Mimoz *et al.* [23] has shown that the risk of tachycardia appearance is less in case of continuous infusion over 30 min. There are about 7 reported cases regarding convulsive seizure produced by Nefopam infusion [7, 33]. Some extremely rare neuropsychiatric adverse reaction are confusion, disorientation, sedation, restlessness, delirium and hallucinations [7, 34]. A number of six-reported case were found with anaphylactic reactions produced by Nefopam with angioedema and anaphylactic shock [7].

Nefopam is better to be left aside for those patients with severe cardiac pathology, especially limited coronary reserve, patients with glaucoma or prostate affection because of its sympathomimetic effects [35] and should be avoided in patients with impaired kidney function [18, 36, 37], especially patients that are chronically dialyzed and have systemic complications [38, 39].

There are some cases reported in literature of Nefopam fatal overdoses characterized by disorientation, aggressive convulsions, cardiac arrhythmia and respiratory depression [40]. Important cerebral edema was found postmortem in these patients [41].

Route of administration and effective dose

For oral administration, the usual dose is between 30-90 mg three times per day. Nefopam can be delivered by slow intravenous injection or intramuscular in a dose of 20 mg that can be repeated at 4-6 h . Maximum oral dose is 200 mg/24 h and maximum intravenous dose is 120 mg/24 hours [4]. It can be converted from parenteral to enteral administration without any consequences.

Djerada *et al.* [42] published in 2013 the first study about the pharmacokinetics of Nefopam in elderly patients. They had concluded that it should be used in a single 20 mg dose administered over more than 45 min in a patient with or without renal dysfunction.

For patients with end-stage renal disease, the Nefopam distribution and elimination is modified, while the risk of over dosage is high. In this group of patients, the usual dose should be decreased by 50%. Mimoz *et al.* had demonstrated in 2010 that a reduced dose with 50 % but keeping an administration of 10 mg every 4 hours (6 times per day) lead to a peak plasma concentration equivalent with patients with normal kidney function [43].

The role of nefopam in multimodal analgesia

Nefopam is a drug of choice in balanced analgesia to control acute or chronic pain caused by different diseases [44, 45] because of its safety profile, with few and relative well-tolerated side effects and with small interaction with respiratory, hemodynamic and neurologic systems. Contrary to opioid analgesics, Nefopam does not produce addiction or respiratory depression, somnolence, urinary retention or ileus. It has no action on platelet function, being used in patients with hemorrhagic diathesis, unlike non-steroidal anti-inflammatory agents [8]. A meta-analysis made by Evans *et al.* in 2008 had shown that the use of Nefopam in postoperative period lead to lowering of the opioid drug dose with almost 30% in the first 24 h after surgery (*postoperative morphine-sparing*) [15]. Studies has shown a statistically significant decrease in pain intensity both at rest and on moving at 24 hours (lower pain scores) after short or long-term surgery [46, 47] suggesting that Nefopam has more analgesic effect than acetaminophen [34, 35] and was equianalgesic with ketamine and non-steroidal anti-inflammatory drugs (diclofenac) [15, 48].

Kim KH *et al.* had suggested that Nefopam can reduce the incidence of exaggerated postoperative pain induced by using fentanyl in perioperative period and can prevent the appearance of long-term postoperative hyperalgesia [49]. So, it can be used to treat neuropathic pain because its effect in modulating (by inhibition) the reuptake of

serotonin, norepinephrine and dopamine (similar to tricyclic antidepressants), by blocking the sodium channels and sympathetic blockage, the NMDA glutamate receptors antagonism and because of its effects on the visceral mechanosensitive afferent nerve fibers [50].

The combination of paracetamol and Nefopam was used in some studies and they have produced effective analgesia with a more potent nociceptive action [51] due to their synergistic interaction, with a dose reduction of each analgesic [52]. In addition, Maaliki *et al.* demonstrated the synergistic action between Nefopam and ketoprofen with their ability to ensure a qualitative analgesia [53].

Nefopam is a good alternative to opioids agents in critically ill patients, a single dose being effective to control moderate-to-severe pain in this specific group of patients [30]. It also can be used in combination with botulinum neurotoxins to control the acute and chronic pain [54] or for controlling the pain during intraoperative time without interacting with the others anesthetic drugs [55].

Nam JS et al. tried to demonstrate the protective effect of Nefopam in preventing the appearance of neuropathic pain in diabetic rats [56], but this experimental study has some limitations, therefore further research should be made [57].

Other clinical properties

Studies had shown that Nefopam could be used for the prevention of shivering after general anesthesia, spinal anesthesia or sedation for different minimally invasive interventions [58, 59]. Bilotta *et al.* has shown, in a study from 2005, that Nefopam, in comparison with Clonidine, has the benefit of lowering the need for vasoactive agents [60]. In addition, Kim YA *et al.* demonstrated that Nefopam has the same effect over shivering like Meperidine in case of neuraxial anesthesia and maintain a stable arterial pressure compared with this one, being so, a good replacement for hemodynamically unstable patients [61].

Severe hiccup is a serious problem during mechanical ventilation and obtaining a rapid pharmacological control can be hard to deal with. There are some cases reported about the use of Nefopam to inhibit severe hiccup during weaning from mechanical ventilation with a dose of 40 mg [62, 63].

Jess YS *et al.* [64] presented a study about the efficacity of Nefopam in preventing and even reducing the frequency and severity of emergence agitation in case of nasal surgery, without any effect on the extubation time. Emergence agitation is frequent in surgery of the ear, nose or throat and can occur even after minimal procedures [65].

In 2002, Fernandez-Sanchez *et al.* made an experimental study about the neuroprotective effect of Nefopam in reducing the neuronal death by activating the voltage-operated sodium channels in cultured rat neurons. It seems that Nefopam can reduce the release of endogenous glutamate and may have a positive role in some neurodegenerative disease [66].

Conclusions

Nefopam is a centrally acting molecule, with a mechanism of action not well known. It can inhibit the central reuptake of serotonin, dopamine and norepinephrine and modulate the calcium and sodium channels. It has a safety pharmacological profile and can be used to modulate acute or chronic pain. Some experimental studies have shown its neuroprotective efficacity. As part of balanced analgesia, along with non-selective non-steroidal anti-inflammatory drugs, selective inhibitors of cyclooxygenase 2 and acetaminophen, Nefopam reduces pain intensity in the first 24 hours after surgery and can prevent the appearance of neuropathic pain. In order to avoid its side effects, a slow infusion is recommended. It is better to adapt the Nefopam dose in patients in renal impairment function and in elderly.

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