Journal of Pharmacy and Pharmaceutical Sciences

Open Access Research Article

Nalbuphine Nasal Spray: Analgesic Efficacy and Safety

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ABSTRACT

Opioids are used for the treatment of moderate to severe pain that is not responsive to other analgesics. Powerful opioid analgesics (full mu-agonists), such as morphine and fentanyl, are highly effective but have multiple harmful side effects, including abuse and dependence. The decades-long search for an 'ideal analgesic' that provides fast pain relief for various types of pain, has long-lasting effects, is well-tolerated and can be taken orally has led to the development of biased opioid agonists providing potent pain relief with reduced side effects. These promising new medications still need extensive clinical investigation, while the potential for pharmacokinetic improvements of well-studied and long-used opioid medications remains.

Nalbuphine, a mixed partial mu-receptor antagonist and kappa-receptor agonist, is as effective as morphine in relieving moderate to severe pain and has no serious side effects. It could be considered close to an 'ideal analgesic', with one exception of being administered solely through parenteral routes due to extensive pre-systemic metabolism and poor oral bioavailability.

Intranasal nalbuphine delivery represents a safe and non-invasive alternative to parenteral routes of administration. Although nalbuphine has been used clinically for 40 years, the first results of clinical trials on nasal administration of the injectable solution were published in 2019. Certain progress has been made in the pharmaceutical development of nasal forms of nalbuphine, leading to the recent development of a nasal spray. Retrospective analysis of the issue and recently published data from clinical investigations of the newly developed nalbuphine nasal spray, are briefly reviewed.

Keywords: Nalbuphine nasal spray; Pain management; Non inferiority clinical trial; Patient-controlled analgesia

INTRODUCTION

Pain is not only a common symptom of a range of etiologies but also a pathogenetic factor in the transition from acute to chronic pain [1,2].

A variety of clinical protocols and guidelines have been developed for effective pain management in speci ic patient populations, taking into consideration the origin, character and topology of pain, as well as possible side effects and complications.

Received:	24-June-2024	**Manuscript No:**	IPIPR-23-20492
Editor assigned:	27-June-2024	**PreQC No:**	IPIPR-23-20492 (PQ)
Reviewed:	11-July-2024	**QC No:**	IPIPR-23-20492
Revised:	18-July-2024	**Manuscript No:**	IPIPR-23-20492 (R)
Published:	15-August-2024	**DOI:**	10.21767/ipipr.8.02.011

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Citation: Kuznetsov IE, Tymko VG (2024) Nalbuphine Nasal Spray: Analgesic Efficacy and Safety. J Pharm Pharm Res. 8:011.

A common feature of these recommendations is the use of opioid analgesics to cope with moderate or severe pain that is resistant to non-opioid and adjuvant analgesics. For many patients with severe pain, opioids are the only avenue for analgesia [3-5]. Historically, the opium poppy was used as an analgesic back in ancient Greece and opium alkaloid morphine has been used as a pain reliever since the early 1800's. More than 150 years later, binding sites for opioids were identified using radiolabeled ligands and based on physiological and pharmacological data; these structures were classified into four main types, namely mu, delta, kappa and nociception opioid receptors [5,6].

The era of synthetic opioids began parallel to the differentiation of opioid receptor types and led to the development of the majority of opioid medications currently used. In the past decade, a variety of biased opioid agonists have been designed using structure based methodology. These next generation medicines are highly promising but still need extensive clinical investigations. The purpose of this brief review is to highlight the potential of improving the pharmacokinetic properties and changing the route of administration of currently used opioid drugs, which could enhance pain management in a wide range of patients in outpatient and home settings shortly.

Opioid Receptors' Origin and Effects

Mu, delta and kappa Opioid Receptors (ORs) mediate analgesia but have differing side effects, likely due to the variable regional expression, plasticity and functional activity of receptors in different parts of central and peripheral organ systems. Opioid drugs such as morphine, codeine, methadone, fentanyl and their derivatives are primarily mu-agonists that have the most potent analgesic effect and the highest side effects. Kapa-agonists also have high analgesic efficacy but less expressed adverse reactions that raised hopes that selective kappa-agonists would provide analgesia without the side effects of morphine-like mu-opioids such as addiction, respiratory depression, constipation and urinary retention. Therefore, selective kappa-agonists came into the focus of efforts, but soon it was found they cause psychotomimetic, dysphoria, sedation, diuresis and constipation with weaker analgesic effects than mu-opioids. The strategy of increasing the selectivity of ligands for ORs to maximize therapeutic over side effects has proven elusive [7].

The ORs that mediate the analgesic effects of endogenous and exogenous opioid agents belong to the seven-transmembrane type A (rhodopsin-like) Guanine nucleotide-binding Protein-Coupled Receptor (GPCR) family. These receptors are encoded by individual genes located on separate chromosomes and exhibit 50%-70% sequence homology in extant vertebrates. ORs encoding genes originated from a duplication of the ancestral opioid unireceptor gene and subsequent divergent adaptive evolution. Each type of ORs shares similar composition and properties and activates the inhibitory G-protein cascade but is distributed differently in central and peripheral nervous structures and other tissues demonstrating slightly different qualities and variability in the opioid response [8-10].

Effector Mechanism and Signal Transmission

Ligand binding in the pocket formed by transmembrane domain of the receptor leads to conformational changes of the intracellular C-terminus of the receptor that allows GPCR coupling to the heterotrimeric G-protein that activates intracellular signal transduction *via* GDP to GTP substitution at the Gα subunit and dissociation of Gα and Gβγ subunits to launch G-protein intracellular signaling cascades. The opioid receptors are almost exclusively inhibitory, interacting primarily through the Giα and Goα proteins of Gi/o family. The Gα subunit inhibits adenylyl cyclases and cAMP production, whereas Gβγ complex directly interacts with different ion channels. Mu, Delta and Kappa Opioid Receptors (MOR, DOR and KOR) can modulate pre-and postsynaptic Ca^{2+} channels, suppress Ca^{2+} influx, activate G-protein-coupled Inwardly Rectifying K^+ (GIRK) channels, inhibits Na^+ channels in the dorsal root ganglia neurons and glutamate excitatory postsynaptic currents in the spinal cord neurons. These processes cause attenuation of neurons excitability and transmission of nociceptive impulses at all neuraxis levels and the suppression of pronociceptive neuropeptides release resulting in reduced pain perception [11,12].

ORs interact with such intracellular signal transducers as G-proteins, arrestins and/or GPCR kinases, functioning as part of a three component system of receptor-transducer effector where each component poses a range of genetic variants with different functional performances. The activation of these transducers triggers non-overlapping signaling pathways that determine the ligand-specific responses. Given the four major types of ORs, the eight isoforms of Gi/o transducers and the pools of their splice variants, it still is unclear how an extracellular ligand exerts a specific intracellular effect by coupling the receptor with a proper transducer [13-15]. One OR can couple to more than one Gi/o protein isoforms due to their high structural similarity, resulting in different coupling efficiencies in certain GPCR-G protein pairs. Such pairs are characterized by higher or lower binding kinetics and take specific conformations that determine the preferential coupling of certain transducers. The type of selected transducer determines the signaling cascade to launch inside the cell. The concept of functional selectivity (biased agonism) the ligand dependent selection of certain signal transduction pathways resulting in specific cellular effects is the basis for structure-based drug design [16,17].

Biased Agonism

The recognition that different agonists binding to the same receptor can produce varying effects has led to a revision of the two state model of receptor signaling as on/off switches and to the promotion of the concept of "biased agonism", implying functional selectivity and ligand-directed signaling. Compared to endogenous "balanced" agonists, which activate different G-proteins and β-arrestins equally, functionally selective "biased" agonists can selectively activate G-proteins while blocking β-arrestins or vice versa [18]. β-arrestins represent a family of multifunctional cytoplasmic proteins that not only regulate nearly all aspects of GPCR activity, including desensitization, downregulation, trafficking and signaling *via*

binding to the activated receptors, but also couple to numerous members of signaling cascades, including the mitogen activated protein kinases, the serine/threonine and the tyrosine kinases, nuclear factor-κB and phosphoinositide 3-kinase, acting as adaptors and scaffolds.

The commonly used opioid drugs, such as morphine, codeine, methadone and fentanyl are MOR agonists that induce analgesia through Gαi pathway signaling. However, their side effects are mediated *via* β-arrestin pathway signaling downstream of MOR activation. The analgesic action of the KOR agonists is mediated by Gβγ subunit, while the adverse effects are related to β-arrestin mediated activation of p38 MAPK, which regulates serotonin transporter and inward rectifying potassium channel function in neurons of reward processing centers (the dorsal raphe nucleus and ventral tegmental area). Recently developed G-protein-biased MOR and KOR agonists (Oliceridine, TRV734, PZM21) and (Triazole 1.1, RB-64), which display limited β-arrestin recruitment and provide analgesia with fewer side effects compared with morphine, is considered the therapeutic promising as optimal opioid analgesics. On the other hand, it was shown that most of the therapeutic and adverse effects of agonist-induced OR activation are mediated by the G protein-dependent signaling pathway and that many drugs described as G-protein-biased agonists are actually low-intrinsic-efficacy agonists, which are correlated with partial agonism rather than biased signaling perse.

Functional parallelism between newly developed G-protein-biased ligands and partial opioid agonists or mixed agonists/antagonists conceptually aligns with a recent trend in clinical practice to utilize partial instead of full opioid agonists. The mixed partial opioid agonists/antagonists must occupy a greater fraction of the available pool of functional receptors than full agonists to induce the equivalent analgesic response, whereas acting as antagonists of the same or another type of ORs; they typically exhibit reduced harmful adverse reactions due to ceiling effect.

The Mixed Partial Opioid Agonists/Antagonists

The mixed partial agonists/antagonists comprise a chemically heterogeneous group of synthetic and semi-synthetic opioids that are widely used in clinical practice. Just three members of this group buprenorphine (a partial MOR/NOR agonist and a KOR/DOR antagonist), nalbuphine and similarly butorphanol, which are combined MOR antagonists and KOR partial agonists, are commonly used medications today. The clinical advantages and limitations of mixed agonists/antagonists are determined by three general features: (i) they target multiple types of opioid receptors, (ii) produce low intrinsic activity of opioid receptors after binding, resulting in dose response curves exhibiting a ceiling effect at less than the maximal effect produced by a full agonist and (iii) they undergo extensive first pass metabolism. Poor oral bioavailability (5%-17%) due to extensive pre-systemic elimination determines the primarily injectable routes of administration and hampers their application in oral dosage forms needed for outpatient use.

Clinical availability of only injectable solutions significantly limits the use of mixed agonists/antagonists outside of hospital settings with few exemptions of transdermal and buccal forms of buprenorphine and nasal forms of butorphanol.

MATERIAL AND METHODS

Nalbuphine

Nalbuphine, a phenanthrene opioid derivative, structurally close to naloxone (competitive ORs antagonist) and oxymorphone (strong mu-agonist), has unique pharmacological properties compared to other members of the mixed agonists/antagonists group. In clinical practice, nalbuphine is considered equianalgesic to morphine, demonstrating an analgesic potency of 0.8-0.9 compared to equimolar doses of morphine. Nalbuphine is a partial KOR agonist that produces potent analgesic effects without the harmful side effects associated with MOR activation and has low addiction potential, making it the only opioid analgesic not included in the controlled substances act.

As a weak MOR antagonist rather than an inverse agonist, it is less likely to cause withdrawal when combined with other opioids in acute pain management. In the general population, withdrawal symptoms from nalbuphine are almost nonexistent and its abuse potential is lower than the mu-agonists, however, nalbuphine can be abused in certain patient populations who are tolerant to potent opioids. The ceiling effect of nalbuphine for respiratory depression provides an important safety factor. Its depressive effects on respiration plateau at a low dose and breathing is not further compromised with higher doses of the drug. In low doses, nalbuphine can reverse opioid related respiratory depression, urinary retention and opioid induced pruritus caused by mu-agonists without reversing analgesia. In contrast to mu-agonists, nalbuphine does not cause pruritis even at high doses because of its MOR antagonistic activity and lack of histamine release. Nalbuphine at high doses does not affect hemodynamics, cause hypotension, reduce cardiac output or prolong the QTc interval, providing satisfactory analgesia for most patients with acute myocardial infarction. Nalbuphine is applied in patients with myocardial ischemia, especially in the course of cardioprotective therapies. It is considered the preferred opioid for patients with cardiovascular disease and an excellent analgesic for intensive care patients receiving vasopressor medications. Compared to mu-opioids, nalbuphine exerts a less pronounced effect on the gastrointestinal tract, where ORs are widely distributed. It does not cause biliary spasms or colic and blocks the harmful effects of potent opioids on gastrointestinal mobility, resulting in reduced ileus. Nalbuphine therapy is associated with a significantly lower incidence of constipation compared to morphine. Since the sensation of bladder fullness is decreased by MOR and DOR agonists (but not KOR) through the inhibition of parasympathetic nerves, nalbuphine administration was shown to improve urine output in patients with opioid associated urinary retention.

In comparison to potent opioids like morphine, nalbuphine itself causes little to no urinary retention.

Nalbuphine Pharmacokinetics

In addition to its pharmacological characteristics, nalbuphine exhibits specific physicochemical and pharmacokinetic properties that distinguish it from other mixed agonist/antagonist opioids. The bioavailability of oral nalbuphine is 12%-17% due to extensive first pass metabolism, resulting in the exclusive clinical use of injectable forms. In this regard, physicochemical parameters such as the dissociation constant (pKa), lipid solubility and protein binding, which determine intestinal absorption, seem clinically less important than drug metabolism and the pharmacological activity of the metabolites. In contrast to buprenorphine and butorphanol, which undergo cytochrome P_{450} oxidation, nalbuphine is metabolized mainly by UDP glucuronosyltransferases (UGT2B7, UGT1A3, UGT1A9) to inactive glucuronide conjugates, resulting in fewer drug interactions and less variable pharmacodynamics. Recent publications have reported that nalbuphine glucuronides, especially nalbuphine-6-glucuronide, have analgesic effects. The major route of elimination is fecal, with little renal elimination. The elimination half-life of nalbuphine is 2 to 5 hours, which correlates with a duration of analgesic effect ranging from 3 to 6 hours. Systemic clearance of nalbuphine is reduced in neonates (due to an immature enzyme system), elderly individuals and patients with hepatic or renal insufficiency. As a lipophilic small molecule, nalbuphine has a large volume of distribution and readily crosses the blood brain barrier.

Nalbuphine Medical Use

Nalbuphine was first introduced into clinical practice in June 1979. Naturally, the following clinical trials aimed to compare nalbuphine with other opioid analgesics, primarily morphine (considered the gold standard), to determine its applicability, efficacy and safety in controlling pain of different origins. In 1983, the first review of such studies discussed the results of nine double blind clinical trials comparing morphine and nalbuphine. Thirty years later, a meta-analysis of 15 randomized controlled trials, comparing nalbuphine with morphine for analgesic effect and safety, showed no significant difference between the two drugs in pain relief with the pooled relative risk of 1.01 (95% CI, 0.91 to 1.11; P=0.90). The incidence of opioid-associated side effects (pruritus, nausea and vomiting, respiratory depression) was significantly lower in patients receiving nalbuphine compared with the morphine group. The conclusion of comparable analgesic efficacy of morphine and nalbuphine with a better safety profile of the latter was based on clinical data of 820 patients from North America, Europe and Asia who experienced severe pain syndrome associated with arthroscopic and otolaryngology surgery, hip replacement, gynecology-related conditions and burn debridement pain. Nalbuphine has been one of the most commonly used analgesics for children since the 1980s due to its potent pain relieving properties and favorable side effects profile (ceiling effect for respiratory depression, minor urinary retention and minimal impact on hemodynamics) making it a safe option for pediatric pain management.

Conceptually, nalbuphine seems to be a compound with the qualities of an "ideal analgesic." It retains the analgesic potency of morphine (the gold standard) while reducing side effects. However, it still causes tolerance and addiction development associated with chronic intake, although nalbuphine has lower abuse potential compared to its counterparts. Nalbuphine may induce opioid withdrawal symptoms if administered to individuals tolerant to potent opioids. In practical terms, the main limitation of nalbuphine is its poor oral bioavailability, which necessitates administration *via* injectable solutions intravenously, intramuscularly, subcutaneously or rarely intrathecally.

Rectal Nalbuphine Administration

The availability of only injectable solutions greatly limits the use of this effective and safe pain reliever outside of hospital settings due to the lack of trained medical personnel. It is even more disappointing since nalbuphine is a non-scheduled medication that is easily accessible to patients with chronic pain who are in home settings. This limitation became evident over 40 years before, coinciding with the onset of clinical use of nalbuphine. Animal and clinical studies have evaluated the potential of bypassing hepatic first pass metabolism through rectal and nasal administration of nalbuphine since the early 1980's. Several groups of French researchers presented the results of studies evaluating the analgesic efficacy, safety and pharmacokinetics of rectally administered nalbuphine solution in children undergoing general anesthesia for surgery. A commercially available solution of nalbuphine hydrochloride (10 mg/mL) was diluted with saline to a concentration of 2 mg/mL and administered rectally via a catheter at a dosage of 0.3 mg/kg (2.1 ml-3.2 ml based on body weight). It was shown that rectal nalbuphine is rapidly absorbed (mean T_{max}=25 ± 11 min) and provides adequate analgesia but is characterized by highly variable pharmacokinetics (CV for C_{max} and AUC equaled 62% and 68%, respectively). The absolute bioavailability of rectal nalbuphine has not been experimentally determined due to the study design; however, the authors inferred that it is "better" when compared with published data on oral nalbuphine.

Nasal Nalbuphine Administration

The intranasal route has garnered more attention due to its potential to achieve bioavailability comparable to injectable forms and provide convenient administration. In 1985, the first monograph on the fundamentals and developmental concepts of these medications was published summarizing the advantages of intranasal drug delivery as: (i) bypassing "first-pass" metabolism, (ii) efficient absorption into the bloodstream through the highly vascularized microvillus structured nasal mucosa and (iii) similar kinetics of systemic delivery compared to parenteral administration for some compounds. The first reports of therapeutic and Pharmacokinetic (PK) studies of intranasally administered opioids, buprenorphine to healthy volunteers and sufentanil

to surgery patients, were presented by independent research teams four years later, in 1989. It was reported that both compounds were rapidly and effectively absorbed from the nasal mucosa. The absolute bioavailability was 48.2% for buprenorphine and 78.0% for sufentanil. There were no significant differences in sedation between patients receiving sufentanil intravenously and intranasally. Both medications did not cause clinically important adverse reactions. The authors concluded that the intranasal route of buprenorphine and sufentanil administration may be an attractive alternative to intravenous or intramuscular injection. In the following two decades, a range of complementary strategies were developed to enhance the bioavailability of intranasally administered drugs, which included facilitating permeability, preventing enzymatic degradation, inhibiting efflux transporters and reducing mucociliary clearance. Plenty of clinical trials have been conducted on the intranasal administration of almost all opiate compounds used in medical practice. The obtained results significantly expanded the understanding of the impact of physicochemical properties, physiological factors and pharmaceutical procedures on the observed variations in absorption and disposition of intranasal formulations. Finally, several innovative nasal opioid medications have been developed and approved for clinical use.

Despite decades of nalbuphine use in pain management and the clear need for a nasal nalbuphine medication, the results of the first human study on intranasal nalbuphine were only published in 2019, while a brief mention of nasal nalbuphine administration to children for perioperative analgesia appeared in 2014. The first study reporting clinical usage of intranasal nalbuphine was performed in the university children's hospital Zurich emergency department between 2017 and 2018. Infants aged 1-3 months with fever, not requiring a partial or full sepsis work-up, were included in the study. The study aims to evaluate the pharmacokinetics, pain control and tolerability of a single intravenous (0.05 mg/kg) and intranasal (0.1 mg/kg) administration of 10 mg/ml nalbuphine solution for injection (OrPha Swiss, Switzerland). The intranasal dosage was doubled because the expected bioavailability of intranasal nalbuphine, calculated based on lipophilicity and molecular weight, was anticipated to be between 50%-80%. One milliliter syringe was utilized to administer 25-200 microliters of nalbuphine solution through the porous nozzle (MAD 300 Teleflex, USA). Patients were assigned to two parallel groups using the open procedure, which involved alternating to balance the bias in the numbers of patients receiving nalbuphine solution either intranasally or intravenously before each painful intervention (such as establishing venous access, urinary catheterization and lumbar puncture). Pain control and tolerability were assessed using the Neonatal Infant Pain Scale (NIPS) for each intervention. Adverse Events (AEs) and vital signs (oxygen saturation, heart rate and blood pressure) were recorded at baseline and during each intervention. In total, data from 52 infants, who received nalbuphine (26 intravenously and 26 intranasally), were collected for analysis of pain control, safety and tolerability.

The analgesic effect of intranasal nalbuphine was found to be similar to intravenous administration, with 67% and 71% of cases reporting mild to no pain (NIPS<3), respectively. PK analysis revealed similar exposure coverage following a single administration of 0.1 mg/kg of nalbuphine intranasally and 0.05 mg/kg intravenously, suggesting an intranasal bioavailability is close to 50% (41% (95% CI: 26%-56%)). The authors mentioned that between 45% and 82% of patient's experienced severe pain during urinary catheterization and lumbar puncture. Based on the exposure pain response simulation, they suggested that increasing the intranasal nalbuphine doses to 0.4 mg/kg may be necessary to achieve pain control similar to that of an intravenous dose of 0.1 mg/kg-0.2 mg/kg. The results of the first clinical study comparing nalbuphine pharmacokinetics, analgesic efficacy, safety and tolerability after intranasal and intravenous administration led the authors to conclude that intranasal administration of nalbuphine solution is a safe, non-invasive alternative approach to the parenteral administration of nalbuphine. The authors concluded that this approach can reduce pain for pediatric patients and alleviate stress for parents and medical staff.

The first clinical observation of intranasal nalbuphine administration to adults was also conducted in Switzerland in 2017-2020. This observational cohort study aimed to analyze data from trauma victims receiving analgesia by intranasal nalbuphine administration in the prehospital phase. Trained first responders enrolled patients according to the study instructions; the inclusion of patients was non-consecutive and there was no reference group in this study. Administration of nalbuphine according to an algorithm was required to assure patient safety and improve overall treatment. Nalbuphine hydrochloride solution for injection 10 mg/ml (OrPha Swiss, Switzerland) was administered intranasally using a syringe equipped with the porous nozzle (MAD 300, Teleflex, USA) as described above. The dosage was based on the patient's body weight, with 5 mg for adolescents weighing 20 kg-44 kg and a maximum of 20 mg for adults weighing over 75 kg with severe pain. The volume of the solution administered in each nostril did not exceed 1 ml. The risk of respiratory depression was monitored by pulse oximetry and respiratory. Pain intensity was defined as a score of 5 or higher on a Numeric Rating Scale (NRS), with 0 indicating no pain and 10 indicating the worst imaginable pain. Nalbuphine should not be administered in cases of altered consciousness, head trauma, alcohol consumption or abnormal vital signs. Also, contraindications included known allergy to the drug or its additives, patient refusal or body weight less than 20 kg.

Data from 267 patients with extremity injuries and traumas to the shoulder, knee, lower leg, trunk, thorax and abdomen were analyzed statistically. The mean baseline pain intensity in trauma victims assessed by first responders was 8 NRS points (IQR 7 to 9).

After intranasal administration of nalbuphine solution, most patients experienced pain relief without any major adverse events. Intranasal nalbuphine administration resulted in a statistically significant and clinically relevant reduction in pain levels, with a median decrease of 3 NRS units, being more effective in adolescents than in patients aged 20 to 60 years. Referring to the literature, obtained pain reduction of more than 2 NRS points was deemed good pain relief. An average pain reduction of 3 points on the NRS was also observed after nasal administration of fentanyl in the pre-hospital phase. Of the 267 trauma victims who received intranasal nalbuphine solution, 145 (54.3%) experienced clinically relevant pain reduction and 41 (15.3%) expressed dissatisfaction with the treatment. The authors concluded that administering nalbuphine nasally to acutely injured patients in the prehospital setting is a potentially safe and effective noninvasive pain management approach and a viable alternative to parenteral administration.

Both research teams reached similar conclusions about the clinical prospects of intranasal nalbuphine, despite substantial differences between these clinical trials and specific limitations associated with the study protocols. They also encountered the same difficulties related to the nasal administration of the injection solution. The point is the low nalbuphine concentration of the licensed solution for injection (10 mg/ml) and the limited volume of the nasal cavity. The latter is the reason for the recommendations to reduce the delivered unit volume to 100 mcl per nostril. An oversized unit volume applied in the nasal cavity leads to greater surface area deposition, causing swallowing or leakage of the administered solution. Thus, to deliver a single therapeutic dose of nalbuphine (10 mg-20 mg, *i.e.,* 1.0 ml-2.0 ml of 10 mg/ml solution), some consecutive units should be administered at several minutes intervals. An effective approach is to use a highly concentrated solution near the water solubility limit of nalbuphine hydrochloride (35.5 mg/ml). However, this approach presents challenges due to the poor stability of the concentrated nalbuphine solution caused by rapid oxidation following contact with atmospheric air and impurity formation. Furthermore, nalbuphine tends to precipitate in concentrated solutions at low temperatures. Early pharmaceutical development of a metered nasal form of nalbuphine was supposedly hindered by the poor stability of the finished product.

Nalbuphine Nasal Spray

The pharmaceutical company Microkhim (Kyiv, Ukraine) has recently realized a practical solution to the poor stability issue and has developed a nalbuphine nasal spray Apain®. The developers utilized the so called binary approach to neutralize nalbuphine oxidation in an aqueous solution by separating the dry formulation from the solvent. For this purpose, an innovative spray bottle containing two chambers separated by a destructible membrane and equipped with a precise dosing pump has been developed. A ready to use solution of nalbuphine hydrochloride forms within two minutes after cranking the safety ring on the spray bottle before the first use of the nasal spray. Changing the position of the safety ring ruptures the membrane between chambers, allowing dry ingredients to dissolve.

The spray composition is ready for application when it turns light blue. A pink color appears over time, indicating impurities formation due to prolonged exposure of the spray composition to atmospheric oxygen, making the medication unusable. The stability of the freshly prepared spray composition at room temperature is maintained for at least 28 days, significantly exceeding the recommended duration of nalbuphine administration for pain relief in the majority of clinical applications. The pharmaceutical company Microkhim conducted a series of preclinical studies using cell cultures and animal experiments to obtain approval from the national regulatory agency for a phase I pharmacokinetic study on healthy volunteers in 2021. Positive results of the phase I PK study enabled the company to conduct a phase II clinical trial on postoperative patients one year later.

Comparative Pharmacokinetic Study

Phase I clinical trial is the first randomized, cross over study to compare the PK parameters and safety of nalbuphine solution administered intravenously and intramuscularly with intranasal administration of the nalbuphine nasal spray Apain® in healthy volunteers. The study was carried out in the inpatient therapeutic unit of the clinical and diagnostic center pharmbiotest (Kyiv, Ukraine). Twenty four healthy volunteers, 15 men and 9 women, aged 18-50 years, with a body mass index of 18 kg/m^2-30 kg/m^2, were enrolled in this randomized, open label, cross over study consisting of three periods and six sequences. In each period, the study participants received one of the following drugs: 7.0 mg nasal spray (3.5 mg in each nostril), nalbuphine hydrochloride solution for injection, 10 mg/ml, 1 ml intravenously and the same solution, 1 ml intramuscularly. The nasal spray dose was selected based on published data of a tolerable 0.1 mg/kg dose, recalculated for the average adult body mass of 70 kg. Study participants were closely monitored for potential respiratory depression within 24-72 hours after dosing.

A comparison of the PK profiles for Intravenous (IV), Intramuscular (IM) and Intranasal (IN) routes of nalbuphine administration revealed a close similarity in the absorption phases between nasal spray and IM injection. Differences between the mean T_{max} and dose-adjusted C_{max} values for the nasal spray and IM injection were not statistically significant. The elimination rate constants and the terminal elimination half-life following IV, IM and IN nalbuphine administration had similar median values. The mean absolute bioavailability of the nasal spray Apain® equaled 65.04%. Since the nasal spray is a hybrid medication on authorized nalbuphine solution, a bioequivalence principle was applied to compare systemic exposure after IM and IN administration at consecutive time intervals corresponding to blood sampling points for PK measurements. It was found that within 30 minutes post-dose, the difference in systemic nalbuphine exposure between nasal spray and IM injection was clinically insignificant (≤ 20%) and gradually elevated reaching 37% by the fourth hour after dosing. The study drugs were well tolerated; only non-serious adverse reactions related to the routes of administration were reported. PK parameters obtained for injectable routes closely match the published data, whereas PK parameters for intranasal nalbuphine significantly differ.

The differences could be explained by variations in the designs, ages and conditions of the subjects enrolled in the study, as well as the quantity and timing of blood samples taken for PK analysis. However, the main factor contributing to these differences was the use of different intranasal pharmaceutical forms, *i.e.,* specially designed spray and injection solution. The same bodyweight dose of 0.1 mg/kg was introduced intranasally in both studies, resulting in a significant disparity in average bioavailability: 65% versus 41%. The similarity in the PK parameters between IM-injected nalbuphine solution and nasal spray administration raised the question of comparing the efficacy and safety of these medications.

RESULTS AND DISCUSSION

Non-Inferiority Clinical Trial

Results of the non-inferiority clinical trial establishing the relative effectiveness and safety of the nalbuphine nasal spray versus IM injection in postoperative patients have been recently published. This comparative study was conducted to assess the effectiveness and tolerance of nalbuphine nasal spray Apain® (Microkhim, Ukraine) and nalbuphine hydrochloride solution for injection (Hospira Inc., USA) in patients following orthopedic and traumatological procedures. This double blind, randomized, parallel group study was conducted at two specialized medical centers in Kharkiv (Ukraine) in 2021-2022. The statistical phase of the trial was performed by CDC Pharmbiotest (Kyiv, Ukraine). It was the first clinical trial to evaluate a specially designed nasal form of nalbuphine.

90 postoperative male and female patients were randomly assigned to parallel groups of 45 subjects receiving alternative nalbuphine forms. A double dummy technique was used to retain blinding. Patients of the test (nasal) group received the nalbuphine nasal spray in a dose of 10.5 mg (three sprays of 3.5 mg/100 mcl) and 1 ml of placebo saline injected intramuscularly. Subjects of the reference (IM) group received a placebo spray of the same composition, but without the active ingredient and 1 ml intramuscular injection of nalbuphine hydrochloride solution (10 mg dose). Unblinded pharmacists prepared injections before dosing under the supervision of the study coordinator to maintain the double-blinding of the investigator and study participants. The main criteria for inclusion were as follows: Age 18-70 years, body mass index 18.5 kg/m^2-35.0 kg/m^2, written informed consent, negative COVID-19 test, postoperative pain intensity measured by a Visual Analog Scale (VAS) score ≥ 4 cm after recovering from anesthesia. To compare the pain relieving effectiveness of the nalbuphine medications, the VAS score was assessed before administration and at seven consecutive time points up to 6 hours after dosing to analyze the dynamics of the pain relief response and to calculate the Summed Pain Intensity Differences (SPID0-6) over the 6 hours as a comprehensive measure of efficacy. The primary endpoint of the study was the SPID0-6 values; the secondary endpoints were time to onset of meaningful pain relief, duration of analgesic effect, rescue medication rate; the number of patients in study groups who demonstrated sufficient analgesia without remedication, the area under the curve of pain intensity versus time for 6-hour observation and RASS score values. The pre-specified non-inferiority margin (representing the clinically meaningful difference in SPID0-6 means between study groups) was set at -13 mm, based on published data regarding the validated Minimum Clinically Important Difference (MCID) of VAS scores in patients experiencing severe pain. Due to the potential risk of respiratory depression following administration of the study drug, patients were closely monitored within the first 24-72 hours after dosing.

95 people were screened and 90 patients were enrolled in the study and completed the trial. 11 patients (5 from the nasal and 6 from the IM group) did not complete the observation schedule because of unsatisfactory pain relief and use of rescue medication. Thus, the ITT safety population comprised 90 and the PP efficacy population-79 patients. Patients in the IM and nasal groups were well matched for age, gender and BMI and baseline pain intensity at randomization. Baseline vas scores varied from 40 mm to 91 mm in the IM group and from 42 mm to 95 mm in the nasal group. The homogeneity analysis did not reveal statistically significant differences between the study groups in demographic/anthropometric characteristics and for the "type of intervention" indicator.

No statistically significant differences were found in the VAS scores between postoperative patients receiving nalbuphine nasal spray and intramuscular injections (**Figure 1**). However, two trends were observed: (i) slightly lower mean VAS scores in the NASAL group compared to the IM group, especially at the 15-minute mark and 3-6 hours after administration and (ii) a higher interquartile range of VAS scores in the IM group 3-6 hours post-dose, indicating greater dispersion.

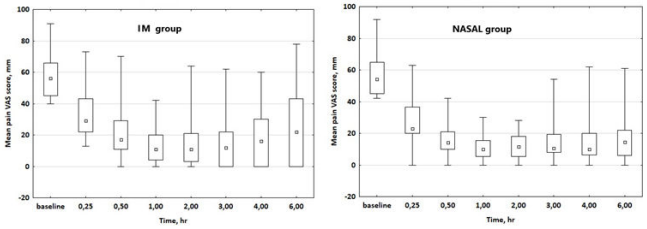

Figure 1: Summary statistics for pain intensity VAS scores measured before (baseline) and after intramuscular injection of nalbuphine hydrochloride solution (IM group, reference) and administration of nalbuphine nasal spray (nasal group, test) to patients after orthopedic interventions and traumatological procedures.

In a box plot, the bottom and top of the box represent the 25th and 75th percentiles, the square dot inside the rectangle is the median (50th percentile) and the bars (whiskers) represent the minimum and maximum values. The Interquartile Range (IQR), depicting the central portion of the data set spread, was calculated by subtracting Q1 (25th percentile) from Q3 (75th percentile), IQR=Q3-Q1.

The primary endpoint value (the mean SPID0-6) for patients of the nasal group, receiving nalbuphine intranasally, proved to be slightly higher as compared to the patients of the IM group, receiving nalbuphine intramuscularly; the difference did not reach the statistically significant level. A comparison of additional efficacy measures did not reveal statistically significant differences as well, indicating a close coincidence of the secondary endpoints' mean values between groups (**Table 1**). RASS scores were not analyzed statistically due to the single occurrence of baseline and study drug-related agitation/ sedation effects and insufficient data. It has been claimed that nalbuphine nasal spray is not inferior to intramuscular injection since a 95% Confidence Interval (CI) for the difference of SPID0-6 mean values included zero and the lower limit of the 95% CI equaled -11.88 mm, which exceeded the margin of non-inferiority.

The study participants tolerated nalbuphine well regardless of the route of administration, but there was a greater incidence of discomfort in the nasopharynx following nasal spray administration (**Table 2**). A total of 66 adverse events were reported in 42 patients; 23 AEs were reported in 17 patients of the IM group and 43 AE's in 25 patients of the NASAL group. The severity of all AEs registered was assessed as mild or moderate; concomitant therapy for coping with AEs was not used and AEs did not lead to study discontinuation. Patients of the nasal group experienced more AEs related to the nasal route of administration, however, the difference in the number of patients experiencing AEs did not reach the statistically significant level (p=0.091, Pearson's *chi-square* test).

The results of reviewed here clinical studies examining the use of intranasal nalbuphine are consistent with each other, demonstrating effective pain relief and safety in both infants and adult patients. The specially designed nasal spray expectedly has a higher bioavailability and pain relief potency than injection solution administered intranasally. In this regard, the claimed non-inferiority of nalbuphine nasal spray 'Apain' to intramuscular nalbuphine administration has proven the hypothesis of the previous studies that nasal nalbuphine administration can be an adequate noninvasive alternative to the injectable form of nalbuphine.

Table 1: The average values of the treatment effectiveness metrics in patients receiving nalbuphine nasal spray and intramuscular injection.

Efficiency variables	Study groups		Total	P value
	IM	Nasal		
The sum of pain intensity difference ($SPID_{0-6}$), VAS score				
N (PP population)*	39	40	79	
Mean (SD)	228.08 (71.21)	248.73 (73.90)	238.53 (72.86)	0.211#
Time to onset of analgesia, h				
N**	44	45	89	
Mean (SD)	0.28 (0.09)	0.27 (0.07)	0.28 (0.08)	0.703##
Duration of effective analgesia, h				
N**	44	45	89	
Mean (SD)	5.55 (1.30)	5.51 (1.41)	5.53 (1.35)	0.993##
The number of patients who received rescue medications				
N (ITT population)	45	45	90	
n (%)	6 (13.3)	5 (11.1)	11 (12.2)	0.748###
The number of patients who achieved adequate pain relief				
N (ITT population)	45	45	90	
n (%)	39 (86.7)	40 (88.9)	79 (87.8)	0.748###

Note: *: Data from 11 patients were excluded due to rescue medication intake for 6-hour observation, **: Data from one patient was excluded due to the insufficient analgesic effect achieved (less than 10 mm VAS score) after study medication intake. In 10 of 11 patients, the duration of analgesia was measured as the difference between the time of rescue medication intake and the time of analgesia onset, #-Student t-test for independent samples. Datasets distribution normality was confirmed using the Shapiro-Wilk test (p>0.01), ##-Mann-Whitney U-test, ###-Pearson's *chi-square* test

Table 2: Types and incidence of adverse events experienced by patients of the IM (reference) and nasal (test) groups after receiving a single dose of study medications

Number of subjects	Study groups	
	IM n (%)	Nasal n (%)
Discomfort in nasopharynx	12 (52.2)	16 (37.2)
Burning sensation	4 (17.4)	8 (18.6)
Bitter taste	5 (21.7)	18 (41.9)
Drowsiness	1 (4.3)	-
Dizziness	1 (4.3)	-
Nausea	-	1 (2.3)
In total	23	43

Since the absolute bioavailability of the nasal spray is 65%, resulting in less systemic exposure compared to intramuscular administration of injectable solutions in the same dose, the absence of statistically significant differences in the rate, extent and durations of pain relief effect does not match direct exposure response relationship. Referring to PK data of equivalent systemic nalbuphine exposure for at least thirty minutes after the nasal spray administration and intramuscular injection, it could be assumed that the peripheral nociceptive system is influenced equipotently at this time interval. Thus, the non-inferior analgesic efficacy of the nasal spray could be attributed to heightened action on the central nociceptive structures. Direct nose to brain delivery by circumventing the blood-brain barrier is the initial consideration in this regard. This assumption is supported by the results of numerous animal studies that demonstrate the possibility of reaching brain targets through neural connections of the olfactory bulb and trigeminal nerve for many pharmacological agents, including nalbuphine nanoparticles. In the future, it may be possible to explain these findings by comparing nalbuphine concentration profiles in the brain tissue and/or cerebrospinal fluids after both nasal and injectable administration, but the protocol for such clinical study is difficult to imagine.

CONCLUSION

The clinical prospects of the developed nasal spray are related to the expanding capabilities of Patient-Controlled Analgesia (PCA), as in postoperative and acute in-hospital pain management, as in long-term care of chronic pain in ambulatory or home settings. Nalbuphine, the only non-scheduled potent opioid analgesic with a wide therapeutic window and favorable side-effect profile, has been used for PCA since the early 80s. Nalbuphine nasal spray Apain®, developed to be easy to use and convenient for self-administration and dose-adjusting by patients themselves, has a great potential to extend PCA availability in homes and other settings without the need for medical personnel to administer parenteral drugs.

The nasal spray can also be used in field conditions, emergencies, accidents and battlefields because of the packaging in a damage-resistant plastic bottle and the long-term stability of the medication at ambient temperatures. Implementing nalbuphine nasal spray-based PCA in routine medical practice will require a lot of effort.

DECLARATION

None.

AVAILABILITY OF DATA AND MATERIAL

All data needed to evaluate the conclusions in the paper are presented in the paper. Data related to this manuscript may be requested from the authors.

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

No external funding was obtained for the study.

AUTHORS CONTRIBUTIONS

The study was jointly conceived, IK wrote the manuscript and VT revised it to ensure intellectual content and exposition.

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