REVIEW ARTICLE

Nalbuphine Nasal Spray: Proven Medication and New Capabilities

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ABSTRACT

Nalbuphine is a potent opioid analgesic that is not under the Controlled Substance Act (CSA). It exhibits agonistic effects on kappa and antagonistic on mu-receptors, which explains its unique pharmacodynamic properties of combining equal to morphine analgesic efficacy with favourable side effects profile. Nalbuphine has been widely used to treat acute, perioperative, and chronic pain since the 1980. Nalbuphine is available as a parenteral solution only; oral forms do not use due to poor oral bioavailability (about 15%) caused by extensive presystemic metabolism. The sole availability of injectable nalbuphine medications drastically limits the utilization of this non-scheduled potent opioid analgesic with a wide therapeutic window and low incidence of side effects outside the clinical settings. Considering the need for practical medicine in non-injectable nalbuphine preparations bypassing the hepatic first-pass effect, several clinical trials with rectal and nasal nalbuphine administration were conducted for the present day. Here we review the results of relevant pharmacokinetic and clinical studies, focusing on recently published data comparing the pharmacokinetic parameters of developed nalbuphine nasal spray with intravenous and intramuscular injections of nalbuphine solution in healthy volunteers. Challenges in nalbuphine nasal form development are briefly discussed as well.

Key Words: Nalbuphine nasal spray; First-pass effect bypassing; Pharmacokinetics; Bioavailability; Drug delivery's

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INTRODUCTION

Nalbuphine is a synthetic phenanthrene derivative opioid agent exerting agonistic action on kappa and antagonistic influence on mu-receptors [1]. Being equianalgesic to morphine (the gold standard of opioid analgesics), nalbuphine has a more favourable side effects profile, since kappa-receptors activation (*via* G-protein and β-arrestin 2 signalling pathways) reduces opioid-specific side effects like nausea or pruritus [2]. Antagonistic action upon mu-receptor results in the "ceiling" (plateau) effect attenuating sedation, euphoria, impact on the psycho-emotional state, addiction potential, and respiratory depression, which prevents the risk of overdose death. Nalbuphine in low doses (2.5-5.0 mg) reverses opioid pruritus, urinary retention, and respiratory depression without a reversing analgesia [1-3]. Nalbuphine is a particular value in balanced anesthesia in adults, children and infants providing haemodynamic stability, a ceiling effect on respiratory depression, rapid recovery of wakefulness and a low incidence of nausea and vomiting after surgery. These properties underlie its wide usage for severe pain management in different fields of medicine [4-6].

The oral bioavailability of nalbuphine equaled 15%-20% due to extensive first-pass metabolism and high systemic clearance, thence only injectable forms (ampoules of 1 ml, 10% or 20%) are available. The latter substantially limit usage of this non-scheduled potent opioid analgesic with a wide therapeutic window and low incidence of side effects outside the clinical settings. Interest in bypassing the first pass nalbuphine metabolism emerged with the start of its clinical use in early 1980 [2,4,7]. For the past 40 years, only two administration methods (rectal and intranasal) have been clinically studied, but a Finished Pharmaceutical Product (FFP) alternative to solution for injection has not been developed.

The reason to refer to this issue was the recent publication presenting a specially designed nalbuphine nasal spray and pharmacokinetic data of its comparison with intravenous and intramuscular injections in healthy volunteers.

LITERATURE REVIEW

The disposition and bioavailability of injectable solution and variety of oral nalbuphine forms were extensively studied in late 1980 [8-10]. The pharmacokinetic parameters for nalbuphine hydrochloride solution administered intravenously, intramuscularly, and subcutaneously in 10 mg and 20 mg doses were found to be quite similar: T_{max}=0.44-0.63 h, t1/2=2.23-2.55 h, CL=1,5-1.6 l/min, and the absolute bioavailability ranged from 75%-82% for subcutaneous and intramuscular routes, respectively [8]. The oral forms, besides very low bioavailability of 16.4%-17.4%, demonstrated a prolonged elimination half-life (6.9-7.7 h) due to extensive first-pass metabolism and enterohepatic circulation [9,10]. The very high volume of distribution (270-310 l), which is greater than that of morphine, indicates considerable tissue uptake of nalbuphine [10]. As a rule, healthy volunteers were enrolled in these crossover design pharmacokinetic studies, and the clinical phases for blood sample collection were of short duration, resulting in less variable data. Even in such conditions, the pharmacokinetic parameters exhibited CV=40-60%, characterizing nalbuphine as having significant intersubject variability [8,11].

In contrast, a few available pharmacokinetic studies bypassing hepatic metabolism *via* rectal and intranasal nalbuphine administration involved patients (mainly children and infants) [12-15]. Expectedly, investigators focused on perioperative analgesia and surgery; nalbuphine was administered as a component of complex anesthesia, and a limited number of blood sampling time points for pharmacokinetic analysis were available. As to the rectal administration, the exact value of nalbuphine bioavailability was not determined, whereas comparing Cmax and AUC values obtained for rectal administration with published data for the oral route allowed authors to deduct a better rectal bioavailability [12].

The first brief report comparing nalbuphine pharmacokinetics after intranasal and intravenous administration to humans was published in 2019 and was followed by two publications by the same investigators' team from Switzerland [13-15]. Infants 1-3 months old undergoing sepsis workup in the emergency unit were included in this prospective, single centre, open-label, and parallel-group pharmacokinetic study. The objective of this study was to characterize population pharmacokinetics and exposure-pain response associations following intranasal or intravenous administration of nalbuphine to

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optimize dosing and timing of painful interventions. Infants received commercially available nalbuphine hydrochloride solution of either 0.05 mg/kg intravenously or 0.1 mg/kg intranasally; alternation was switched to balance the number of patients in the two groups. A nasal atomization device (MAD 300, Teleflex, USA) was applied to spray the solution. Blood samples for pharmacokinetic analysis were taken at 3 predefined time points (15, 30, and 120 to 180 min post-dose). A comparison of pharmacokinetic data obtained in 20 infants after intranasal and 11 infants after intravenous administration confirmed that the bioavailability of intranasal nalbuphine was close to 50% (point estimate: 41%, 95%CI: 26-56%). Considering Tmax occurred 37 (32-65) min after intranasal administration, the authors concluded that the optimal time window for painful procedures scheduling is 30 min after an intranasal dose of 0.4 mg/kg nalbuphine [13-15].

An observational cohort study conducted also in Switzerland between 2017 and 2020 summarized the practical experience of intranasal nalbuphine analgesia of adolescents and adults in prehospital trauma management at ski resorts [16]. The commercially available nalbuphine hydrochloride solution was administered based on body weight in a range of 5mg for patients weighing 20-44 kg and 20 mg for adults weighing over 75 kg experiencing severe pain. The maximal volume of solution administered in each nostril was 1 ml. The Numeric Rating Scale (NRS) was used to evaluate the levels of pain before and after taking nalbuphine. A median pain level reported by 267 trauma victims before nalbuphine administration equaled 8 NRS points. Nalbuphine caused clinically relevant and statistically significant decrease in pain level by a median of 3 NRS points. Nalbuphine was more effective in adolescents than in patients aged 20 to 60 years. 41 patients (15.3%) expressed dissatisfaction with the treatment. No major adverse events to be reversed by naloxone were observed. The authors concluded that non-invasive pain management by nasal nalbuphine provided effective and safe analgesia for acutely injured patients during prehospital care in field settings [16].

A common feature of these studies was the intranasal or rectal administration of a licensed injectable solution of nalbuphine hydrochloride (10 mg/ml) [13-16]. Administering 1-2 ml of the solution into the rectum to achieve the desired systemic exposure seems adequate; however, such volume is excessive for intranasal administration, which should be limited to 100-200 mcl per nostril [17].

One of the significant challenges in developing the nasal form for systemic absorption is the retaining long-term stability of highly concentrated solutions of active ingredients. The water solubility of nalbuphine hydrochloride equals 35.5 mg/ml [18]. To prepare an aqueous nasal formulation for delivering a recommended single dose of 10 mg (5 mg/200 mcl/nostril), 25 mg of the substance needs to be dissolved in 1ml of water. Reduction of sprayed volume to decrease the run-off loss and enhance nasal absorption requires preparing a more concentrated solution, which is inherently unstable due to prompt impurities formation. As an example, may be considered results of stability evaluation of newly developed nalbuphine nasal drops (0.5%, 5 mg/ml) revealed a 4% change in assay from its initial value after storage in closed glass vials for 6 months [19]. Said changes passed the 5% ICH (Q1A(R2)) acceptance criterion for FFP stability but look excessive in a practical view. Supposedly, nalbuphine degradation with parallel impurities formation in concentrated solutions exposed to atmospheric oxygen hampered the development of the nasal nalbuphine forms demanded by medical practice.

DISCUSSION

The good news is that the mentioned difficulties have been overcome-nalbuphine nasal spray as FFP has been developed; its comparative pharmacokinetics has been studied in man [20]. Pharmaceutical company Microkhim (Kyiv, Ukraine), the developer of nalbuphine nasal spray Apain®, applied a binary approach elaborating a container with two independent chambers separated by a soft membrane and equipped with a precision medical pump. Nalbuphine spray composition is prepared before the first use by cranking the safety ring at the container that destroys the membrane separating aqueous solvent and dry ingredients, allowing its dissolution. Ready-to-use spray composition formed two minutes later and can be sprayed *via* a 100 mcl precision pump delivering 3.5 mg of nalbuphine hydrochloride in each actuation. The stability of ready-to-use nalbuphine spray composition at room temperature is retained for at least 28 days, which significantly exceeds the duration of nalbuphine use for severe pain management [20].

Biopharmaceutical penetrability, pharmacokinetics, analgesic efficacy, and local irritant action of this spray composition were evaluated in cell models and animal experiments. Based on the results of pre-clinical studies, the national regulator-the State Expert Center of the Ministry of Health of Ukraine, permitted conducting a clinical trial to study the pharmacokinetics of nalbuphine nasal spray Apain® in healthy volunteers. The purposes of this study were the comparison of pharmacokinetic profiles after intranasal, intravenous, and intramuscular nalbuphine administration, the determination of the absolute and relative bioavailability of the nasal spray, assessment the variability of basic pharmacokinetic parameters, and estimation of safety and tolerability. Clinical and bioanalytical phases of the study, pharmacokinetic parameters calculation, and statistical analysis were conducted by the Clinical and Diagnostic Center Pharmbiotest (Kyiv, Ukraine) accordingly to the Guideline on the Investigation of Bioequivalence of Medicinal Products 42-7.3:2020 (MoH of Ukraine) and CPMP/QWP/EWP/1401/98 Rev.1/Corr** «Guideline on the Investigation of Bioequivalence» EMA 2010.

The study was designed as a randomized, open-label, cross-over study with three periods and six sequences (ABC, ACB, BAC, BCA, CAB, CBA) with blinding the bioanalytical phase. In each period, the subjects were administered one of the drugs: A-the nasal spray 7.0 mg/dose (3.5 mg in each nostril); B-Nalbuphine hydrochloride, solution for injection, 10 mg/ml, and 1ml intravenously; C-Nalbuphine hydrochloride, solution for injection, 10 mg/ml, and 1ml intramuscularly. Twenty-four healthy Caucasian volunteers (15 men, 9 women) aged 18-50 years with a body mass index 18-30 kg/m^2 were enrolled in this study. The dose of the nalbuphine nasal spray was selected considering data from the sole pharmacokinetic study in humans -0.1 mg/kg [13-15]. This dose extrapolation to subjects with an average body weight of 70 kg gives a 7mg dose, administered intranasally to the study participants [20].

After overnight fasting, total of a 21 blood samples of 6 ml were collected within 24h after dosing in EDTA-containing vacuum tubes. Blood samples were centrifuged; the plasma was stored at -78°C ± 10°C until analysis. Plasma concentrations of nalbuphine were analyzed with a LC-MS/MS method using direct liquid-liquid extraction with acetonitrile Internal Standard (IS) solution. Chromatographic separation was performed using a Shimadzu HPLC system with ZORBAX Eclipse XDB-C18 column (Agilent Technologies Inc., USA). API 4000 triple-quadrupole mass spectrometer (Applied Biosystems, USA) was used as a detector. MRM transitions were measured at positive ion mode m/z 358-240 for nalbuphine and 361-243 for nalbuphine-d3 (IS). A calibration curve was established for concentrations of 0.50-199.72 ng/ml, and the lower limit of quantification for nalbuphine was 0.50 ng/ml. The bioanalytical method was validated by the Guideline of the SEC/MoH of Ukraine (2013) and the EMA Guideline on Bioanalytical Method Validation, 2011. Pharmacokinetic parameters were estimated using non-compartmental methods in WinNonLin 8.3 software (Pharsight Corp., USA); the area under the plasma concentration-time

curve was calculated by the linear log trapezoidal rule. The research results were also processed using MS Excel and R-Studio software packages.

All 24 volunteers completed the study nobody dropped out. Totally 1512 blood samples were analyzed; nalbuphine concentrations obtained were used for pharmacokinetic and statistical analysis (Table 1).

Table 1: The mean values of basic pharmacokinetic parameters after nalbuphine nasal spray and injectable solution administration to healthy volunteers (n=24).

Parameters	Route of administration		
	Intravenous 10.0 mg	Intramuscular 10.0 mg	Intranasal 7.0 mg
Cmax/dose (ng × h/ml)/mg	7.10 ± 1.84	5.53 ± 1.99	4.66 ± 1.76
AUC(0-t)/dose (ng × h/ml)/mg	12.21 ± 2.10	12.23 ± 2.02	7.68 ± 1.87
AUC(0-∞)/dose (ng × h/ml)/mg	12.72 ± 2.24	12.80 ± 2.10	8.17 ± 1.85
AUCres (%)	3.97 ± 2.04	4.44 ± 1.79	6.23 ± 5.00
Tmax (h)	0.083 (0.083-0.250)	0.25 (0.083-0.750)	0.167 (0.083-0.750)
kel (h-1)	0.264 ± 0.068	0.256 ± 0.049	0.245 ± 0.062
T1/2 (h)	2.48 (2.003-6.043)	2.7 (1.876-4.262)	2.7 (2.068-11.904)
F abs. (%)	-	-	65.04
F rel. (%)	-	-	64.03

Note: Values are expressed as Mean ± Standard Deviation (SD) and Median (min-max) for Tmax and T1/2. Values of Cmax and AUC were dose normalized and recalculated to 1mg of nalbuphine.

Comparison of nalbuphine pharmacokinetic profiles for the mentioned routes of administration revealed similarity not only in dynamics of absorption and Cmax values after intramuscular and intranasal administration but the similarity of SD values, as in individual points of pharmacokinetic curves, as in mean values. A comparable variability of plasma nalbuphine concentrations for principally different routes of administration was indicative of a similar overall impact of factors influencing nalbuphine absorption *via* multilayer nasal mucosa barrier and muscle tissue capillaries.

Kruskal-Wallis test for median values of Tmax and dose-adjusted Cmax after nasal intake and intramuscular injection resulted in significance levels of p=0.1349 and p=0.8366 respectively (both p>0.05), which confirmed the hypothesis of its equality for nasal and intramuscular routes. The coincidence of the kel and t1/2 values following intravenous, intramuscular, and intranasal administration indicated the absence of differences in the nalbuphine biotransformation and excretion after its absorption into the blood, regardless of the route of administration. As expected, notable differences were found between the Areas Under the concentration-time Curve (AUC) for intranasal and injectable routes due to unavoidable loss of the active substance during spraying (run-off loss) and penetrating through mucus and epithelial barrier before systemic absorption, overall resulting in 65.04% absolute and 64.03% relative bioavailabilities [20].

Systemic nalbuphine exposures after intranasal and intramuscular administration during 0-4 hours post-dose interval, corresponding to the mean duration of nalbuphine analgesic action, were compared using ± 20% basic bioequivalence rule. It was shown that during half an hour post-dose, the relative differences in segmental $AUC_{(0-t)}$ for intranasal and intramuscular nalbuphine did not exceed 20% limits indicative of clinically insignificant differences in systemic exposure. Practically, the nasal spray works like intramuscular nalbuphine for the first half an hour after administration, i.e., at the peak of absorption and analgesic action development [20].

Nalbuphine was well tolerated by volunteers irrespectively of the administration route. Adverse effects that occurred were expected, had non-serious intensity, and were related to the route of administration. Its severity was assessed as mild or moderate; no therapy was used. The most common adverse effects of nasal spray were burning and bitter taste sensations; the latter is considered an inherent feature of nasal medications and could be hardly attenuated [20].

CONCLUSION

Many papers presenting experimental data on nalbuphine pharmacokinetics, which were reviewed here, bear the phrase 'for the first time' reflecting the progress in developing the patient-oriented medicinal tool to control severe pain. In this regard, the appearance of specially designed FFP to deliver nalbuphine into the systemic circulation by nasal route with efficiency close to intramuscular injection looks like a game-changing event widening the possibility of nalbuphine use in outpatient settings and at home as well as in emergency and tactical medicine. Besides the opportunity of simple dose adjusting, the nasal spray possesses the potential of direct nose-to-brain delivery, which was extensively studied during the last two decades and has been demonstrated for nasal nalbuphine in animal experiments. No doubt that the clinical performance and bioavailability of nalbuphine nasal forms will be improved. The pharmacokinetic data of the nasal nalbuphine spray will be served as a reference point for the following research.

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.

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AUTHORS CONTRIBUTIONS

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

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