Exposure, tolerability and pain control with intranasal or intravenous administration of nalbuphine in infants

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Introduction

Nalbuphine is a mixed agonist-antagonist opioid analgesic agent frequently used in pediatrics, and approved for parenteral use only. Intranasal delivery could be a safe efficacious non-invasive alternative, especially in infants in the acute emergency setting. Pharmacokinetic (PK) data with intranasal dosing of nalbuphine is however lacking.

Aims of this study:

1. **To assess PK of nalbuphine in infants 1-3 months of age following single iv (iv 0.05 mg/kg) and intranasal (0.1 mg/kg) administration, respectively**
2. **To assess tolerability of intranasal application, and compare pain control after single iv (0.05 mg/kg)/intranasal (0.1 mg/kg) nalbuphine**

Conclusion

- This is the first study investigating PK and tolerability of intranasal nalbuphine administration in infants 1-3 months of age.
- Similar median $AUC_{0\text{-}Tlast}$ after single dose of 0.1 mg/kg intranasal vs 0.05 mg/kg iv suggests intranasal bioavailability close to 50%.
- Non-invasive intranasal administration was well tolerated and provided comparable pain control as iv administration.
- Given the relatively high proportion of patients with severe pain during venous access, urinary catheterization and lumbar puncture, we hypothesize that dosages may need to be increased.
- Next step: investigation of optimal dosing and timing of interventions as C_{max} was lower and delayed after intranasal administration.

Patients & Methods

- Design: prospective, single centre, open-label pharmacokinetic study
- Inclusion criteria: infants 1-3 months of age undergoing sepsis workup in the emergency unit
- Exclusion: premature birth, kidney-, liver- or other chronic disease
- Intervention (alternating allocation): nalbuphine 0.05 mg/kg iv bolus or 0.1 mg/kg intranasally
- PK sampling: ≈15, 30 and 120-180 minutes after nalbuphine administration
- Analytical method: LC-MS/MS
- Statistical data analysis:
  1. Noncompartmental analysis (NCA) using package NonCompart in R, including patients with all 3 PK samples; patients with implausible concentration measurements were excluded according to predefined criteria
     - Primary outcomes: Area under the concentration-time curve ($AUC_{0\text{-}Tlast}$) compared by Wilcoxon test
     - Secondary outcomes: $AUC_{0\text{-}infinity}$, maximum concentration (C_{max}) and time of maximum concentration for intranasal (t_{max})
  2. Neonatal Infant Pain Score (NIPS) during nalbuphine administration [tolerability] and each intervention (venous access, urinary catheterization, lumbar puncture) [pain control]

Results

Out of 52 study subjects, 31 (11 iv, 20 intranasal) were eligible for NCA analysis. 9 patients out of 40 registering all 3 concentrations measurements had to be excluded because of implausible serum concentrations. Out of 52 patients (26 iv, 26 intranasal), 21 were eligible for tolerability assessment of intranasal application and 14 for iv administration.

Table 1: Patient characteristics of patients included in the analysis

Categories	Number of patients in iv group, N=11	Number of patients in intranasal group, N=20
male [n (%)]	7 (64%)	13 (65%)
age [days]	42 (37-76)	55 (38-63)
weight [kg]	4.7 (4.3-6.2)	5.0 (4.6-5.6)

N = number of patients. Continuous variables are given as median (interquartile range)

NCA analysis

Table 2: Comparison of pharmakokinetic parameter estimates (NCA)

Variable	iv 0.05 mg/kg	intranasal 0.1 mg/kg	P-value*
$AUC_{0\text{-}Tlast}$ [mcg*h/L] % of $AUC_{0\text{-}infinity}$	8.7 (8.0-18.6) 85% (71-87%)	7.6 (5.4-10.4) NA	0.091
C_{max} [µg/L]	6.5 (5.3-15.9)**	4.5 (3.5-5.6)	0.014
t_{max} [min]	18 (17-19)**	37 (32-65)	<0.001

All variables are given as median (interquartile range).
*Wilcoxon-test. **Cmax after iv dose = first measured concentration (planned at 15 min post-dose) -> tmax,iv ~ 15 min, NA: not available

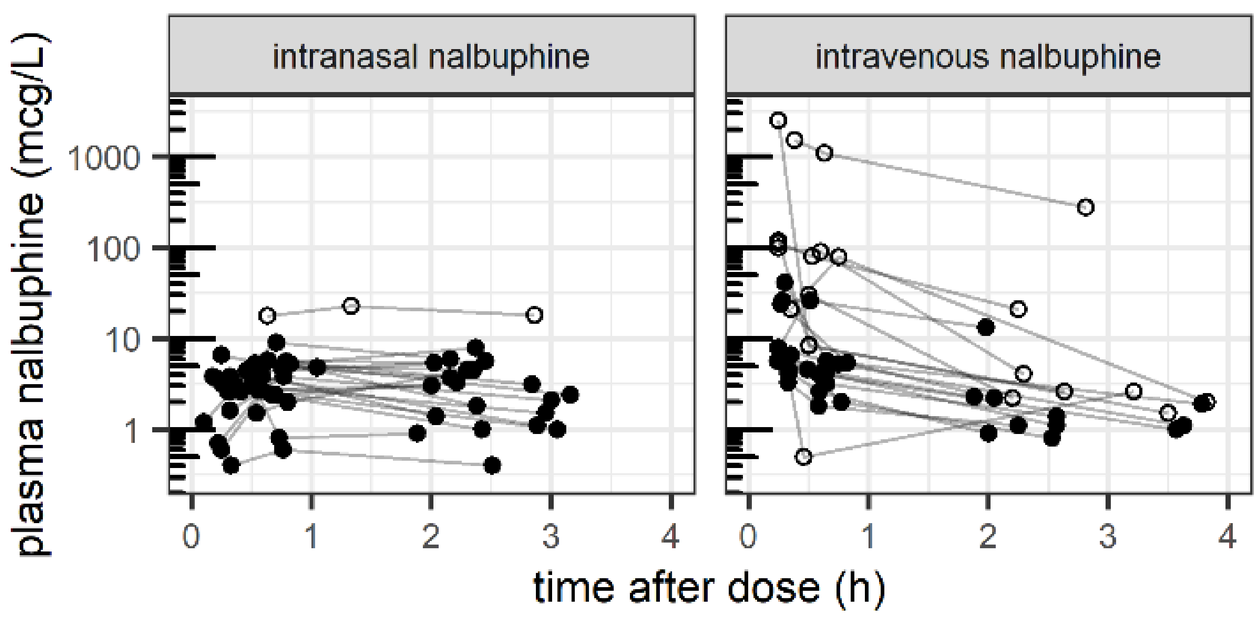

Figure 1: Illustration of measured pharmacokinetic profiles from n = 40 patients with all 3 concentration measurements. *Black dots*: n=31 patients included in PK analysis. *Open circles*: Excluded implausible concentration measurements according to predefined criteria.

Tolerability: During iv (intranasal) nalbuphine administration mild to no pain (NIPS 0-4) was recorded in 71% (67%) of study subjects.
Pain control: Severe pain (NIPS>4) was recorded in the iv (intranasal) study group during venous access in 42% (62%), during urinary catheterization in 45% (50%) and during lumbar puncture in 82% (57%) of patients.