Pharmacometric analysis of intranasal and intravenous nalbuphine to optimize pain management in infants

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Introduction

Nalbuphine is an opioid analgesic agent used for the treatment of moderate to severe pain. As it shows ceiling effect on respiratory depression it is frequently used in paediatric patients, including infants and neonates. We have previously studied intranasal administration of 0.1 mg/kg nalbuphine as a non-invasive, off-label alternative to intravenous (iv) dosing of 0.05 mg/kg nalbuphine for procedural pain management in infants 1-3 months of age.

Aims of this study:

1. **To characterize population pharmacokinetics (PPK) and evaluate achievement of target exposure (efficacy threshold of 12 mcg/L[1])**
2. **To evaluate exposure-pain response associations and strategies for optimized dosing and timing of intranasal nalbuphine in infants**

Conclusion

- Pharmacometric analysis confirmed that bioavailability of intranasal nalbuphine is close to 50%
- PPK and exposure-pain response simulations indicated that an intranasal dose of 0.4 mg/kg may be required to provide a comparable pain control achieved with an iv dose of 0.1- 0.2 mg/kg
- Optimal time window for painful procedures appears to be *within* first 30 min after 0.1 mg/kg iv nalbuphine, whereas such procedures should be scheduled 30 min *after* an intranasal dose of 0.4 mg/kg nalbuphine
- Additional clinical studies are warranted to confirm these recommendations to further optimize pain management in this vulnerable patient population

Patients & Methods

- Patients: infants 1-3 months, having received nalbuphine 0.05 mg/kg iv bolus or 0.1 mg/kg intranasally in a prospective, single centre, open-label PK study
- PK sampling: ≈ 15, 30 and 120-180 minutes after nalbuphine administration
- Analytical method: LC-MS/MS
- Statistical data analysis:
  1. PPK analysis using the software package Monolix, including patients with ≥1 PK sample (excluding patients with implausible concentration measurements according to predefined criteria), followed by PPK model simulations of higher intranasal doses (0.2- 0.4 mg/kg) to evaluate achievement of a previously proposed target concentration (12 mcg/L = efficacy threshold).[1]
  2. Mixed effect (random intercept) logistic regression was used to evaluate the relationship between model-predicted individual drug concentration and the probability of severe pain (defined as NIPS>4, NIPS= Neonatal Infants Pain Score) after pooling all pain assessments under nalbuphine exposure (establishment of iv access, urinary catheterization or lumbar puncture)

Results

Out of 52 study subjects receiving nalbuphine, 38 could be included (median age: 55 days, median weight: 5 kg). 10 patients out of 48 registering at least one serum concentration had to be excluded because of implausible serum concentrations.

PPK analysis and simulations

A two-compartment model with allometric scaling was used to characterize PK data, with intranasal bioavailability estimated to be 47% (95%CI: 28-67%). Median (IQR) individual C_{max} was 3 (3-5) mcg/L after intranasal administration at t_{max} = 50 (39-64) min versus 18 (8-33) mcg/L after intranasal administration at time = 0 min. Model-based simulations showed that proposed efficacy threshold is expected to be exceeded by 50% of patients (median) with an iv dose of 0.05, 0.1, and 0.2 mg/kg for 6, 30 min and 80 min, respectively. This efficacy threshold is not exceeded with intranasal doses of 0.1 and 0.2 mg/kg. An intranasal dose of 0.4 mg/kg is expected to exceed such threshold between 30 to 100 min. (Fig. 1)

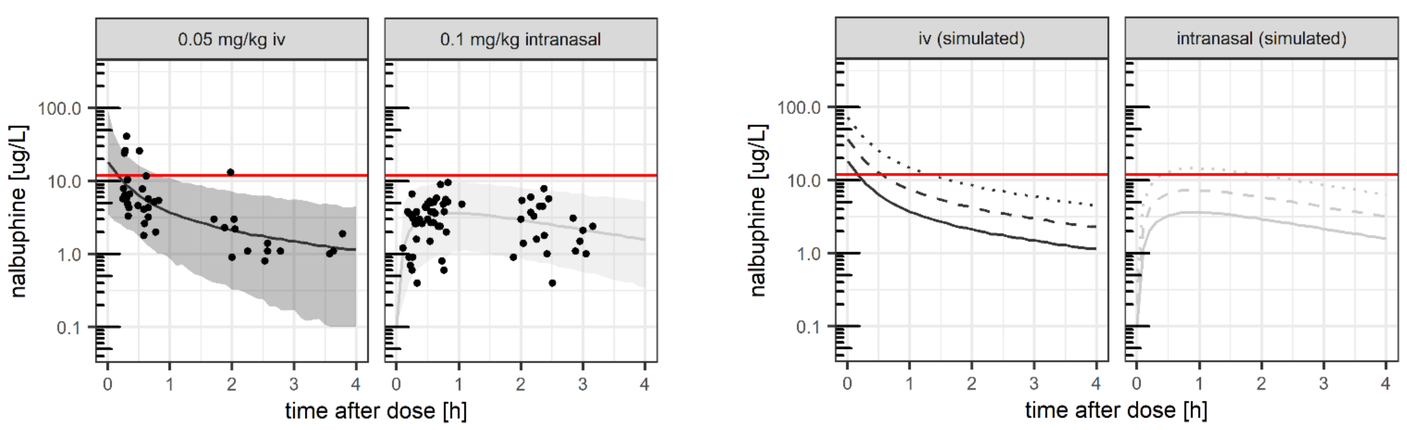

Figure 1: Model-predicted exposure. Left: studied nalbuphine dose of 0.05 mg/kg iv and 0.1 mg/kg intranasal, respectively. Right: studied nalbuphine dose compared with simulated 2-4x higher dose. Lines: model-predicted median (solid: studied dose, dashed: 2x higher dose, dotted: 4x higher dose). Dots: observed exposure. Shaded area: 5th and 95th exposure percentiles.

Exposure-response associations

A significant concentration-pain response relationship could be found (baseline probability of severe pain at 1 mcg/L = 80%, odds ratio for doubling nalbuphine exposure: 0.49 (95%CI: 0.21-0.86)). The corresponding predicted probability of severe pain over time is shown in Fig. 2.

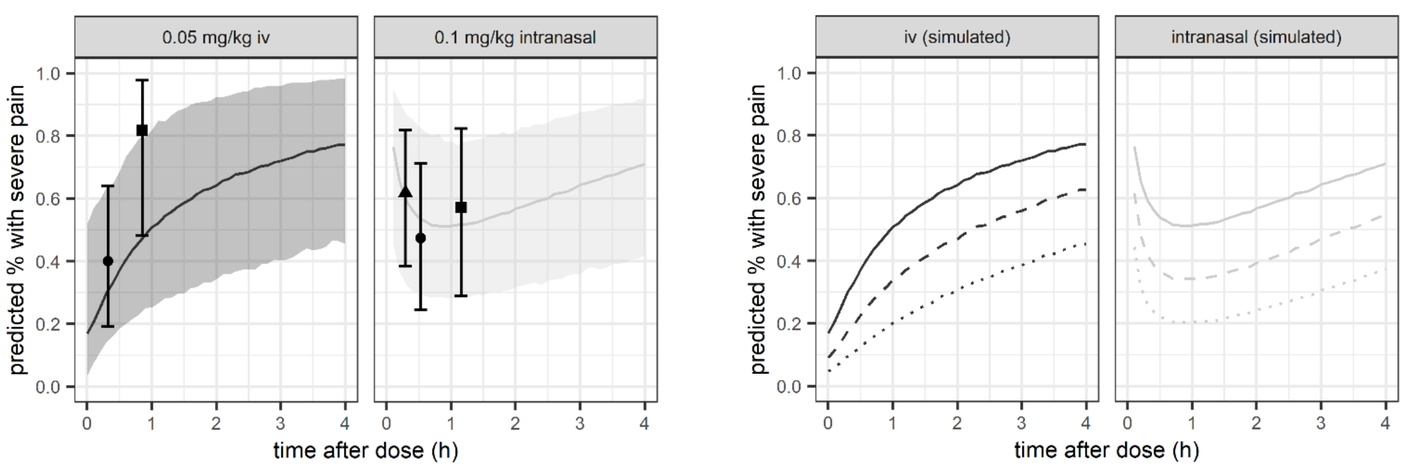

Figure 2: Proportion of patients with severe pain. Left: studied nalbuphine dose of 0.05 mg/kg iv and 0.1 mg/kg intranasal, respectively. Right: studied nalbuphine dose compared with simulated 2-4x higher dose. Lines: model-predicted median (solid: studied dose, dashed: 2x higher dose, dotted: 4x higher dose). Shaded area: 5th and 95th exposure percentiles.
▲: establishment of venous accesses, ●: urinary catherization, ■: lumbar puncture.

[1] Bressolle et al. Br J Anaesth. 2011;106(4):558–65