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ORIGINAL ARTICLE

# Intranasal sufentanil/ketamine analgesia in children

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## Summary

**Background:** The management of procedural pain in children ranges from physical restraint to pharmacological interventions. Pediatric formulations that permit accurate dosing, are accepted by children and a have a rapid onset of analgesia are lacking.
**Objectives:** To investigate a pediatric formulation of intranasal sufentanil 0.5 mcg·kg$^{-1}$ and ketamine 0.5 mg·kg$^{-1}$ for procedural pain and to characterize the pharmacokinetic (PK) profile.
**Methods:** Fifty children (≥10 kg) scheduled for a painful procedure were included in this prospective nonrandomized open-label clinical trial. Thirteen of these children had central venous access for drug assay sampling; enabling a compartmental PK analysis using nonlinear mixed-effects models. Pain intensity before and during the procedure was measured using age-appropriate pain scales. Heart rate, oxygen saturation and sedation were recorded.
**Results:** Children had a mean age of 8.8 (SD 4.9) years and weight 35.2 (SD 20.1) kg. Sufentanil/ketamine nasal spray was effective (procedural pain intensity scores ≤5 (0–10)) in 78% of the painful procedures. The spray was well accepted by 94% of the children. Oxygen saturation and heart rate remained stable, and sedation was minimal. The bioavailability of sufentanil and ketamine was 24.6% and 35.8%, respectively. Maximum plasma concentration ($C_{max}$) of sufentanil was 0.042 mcg·l$^{-1}$ (coefficient of variation (CV) 12.9%) at 13.8 min (CV 12.4%) ($T_{max}$). $C_{max}$ for ketamine was 0.102 mg·l$^{-1}$ (CV 10.8%), and $T_{max}$ was 8.5 min (CV 17.3%).
**Conclusion:** Sufentanil/ketamine nasal spray provided rapid onset of analgesia for a variety of painful procedures with few adverse effects and has promising features for use in pediatric procedural pain management.

## Introduction

Children attending hospital frequently experience painful procedures that can leave lasting negative impressions. Procedures range from a simple venipuncture to the more invasive removal of drainage tubes and burn dressings. Children who have once experienced procedural pain are more likely to have increased pain during future painful procedures (1). Furthermore, procedural pain in the pediatric population is often underestimated and undertreated (1). Pharmacological management includes several drug options, for example, opioids,

nitrous oxide, topical anesthetics. However, pediatric formulations that permit accurate dosing and are accepted by children are often lacking.

Intranasal administration provides direct access to the systemic circulation and may be an acceptable route of administration for children (2,3). In children, intranasal midazolam (4), sufentanil (5–8), and ketamine (7,9–11) have been used for preinduction of anesthesia and combinations of sufentanil/midazolam or ketamine/midazolam for preinduction of anesthesia and postoperative analgesia (12). The analgesic effect of intranasal ketorolac (13), diamorphine (3) and fentanyl (14) has been investigated in children, but clinical trials that investigate the analgesic effect of a mixture of intranasal sufentanil and ketamine are absent (15). The aim of this study was to investigate the analgesic effect of intranasal sufentanil/ketamine in a pediatric formulation for procedural pain and to further characterize the pharmacokinetic (PK) profile.

## Methods

The clinical trial was approved by The Research Ethics Committee for the Capital Region of Denmark (H-2-2009-093) and the Danish Medicines Agency (EudraCT 2009-013801-33). It was registered within the clinical trials registry sponsored by the United States National Library of Medicine (http//:www.clinicaltrials.gov, NCT01047241). The study was conducted from April 2010 to February 2013 and monitored by the Good Clinical Practice unit of the Copenhagen University Hospital. Written informed parental consent and verbal child assent, when possible, were obtained before inclusion into the study.

### Study design

This study was designed as a prospective nonrandomized open-label clinical trial investigating analgesic effect and PKs of a pediatric formulation of a nasal spray containing sufentanil and ketamine. Primary outcome was pain intensity score. A pain intensity score of ≤5/10 during the procedure was considered acceptable analgesia in accordance with hospital guidelines. Secondary outcomes included acceptance of the intranasal route of administration by the child and the degree of sedation until 70 min after administration. Sedation was scored by the University of Michigan Sedation Scale (UMSS), a five-point scale ranging from 1 (awake and alert) to 5 (unrousable) (16). This was an open-label exploratory PK and pharmacodynamic (PD) study and no power calculation determined by a specific end-point was performed to determine sample size. A total of 50 patients were planned for enrollment in the study and of these 15–20 children with a central venous catheter (CVC) would be recruited for PK analysis. The sample size reflected similar studies involving PK and PD of intranasal medication (17–19).

Fifty children (age range 0.8–17 years) who were admitted to Copenhagen University Hospital, Rigshospitalet, and undergoing a painful procedure related to their medical treatment (e.g., removal of a drain, insertion of peripheral venous catheter, burn dressing change, etc.) were included. Exclusion criteria were weight less than 10 kg, an inability of the parents or child to speak or understand Danish, known allergies to ketamine or sufentanil, an abnormal nasal cavity or obstruction, administration of sufentanil or ketamine within the previous 48 h, as well as any clinical contraindications to narcotic analgesia including head injury. No meals were allowed two hours before drug administration. Children with a CVC were eligible for blood sampling for drug assay. The study medication contained aqueous solutions of a preservative-free mixture of sufentanil and ketamine, pH 6 in 2 ml vials (The Capital Region Pharmacy, Herlev, Denmark). Immediately before administration, the study medication was transferred to a nasal spray device (amber glass bottles 5 ml with pediatric actuator, dose volume 0.1 ml (Aptar Pharma, Radolfzell, Germany)). Four different concentrations of the study medication were available, and dosing was weight-based with 5 kg blocks, that is, children with a body weight of 10–15 kg received sufentanil 5 mcg + ketamine 5 mg (dose volume 0.1 ml); corresponding to an administered dose of sufentanil 0.36–0.50 $mcg \cdot kg^{-1}$ and ketamine 0.36–0.50 $mg \cdot kg^{-1}$. One to three doses of 0.1 ml of the study medication was administered to achieve a dose of sufentanil 0.36–0.50 $mcg \cdot kg^{-1}$ and ketamine 0.36–0.50 $mg \cdot kg^{-1}$. The doses of sufentanil and ketamine selected for this study were based on off-label use of sufentanil and ketamine nasal drops in children (15). The spray was administered while the child was sitting in an upright position. The painful procedure was initiated approximately 10 min after administration of the nasal spray.

Regular postoperative analgesic treatment (including paracetamol, nonsteroidal antiinflammatory drugs or opioids) was continued during inclusion in the clinical trial. Topical anesthetics were administered according to hospital guidelines before insertion of peripheral venous catheters.

### Assessment of pain intensity

Preprocedural and procedural pain intensity (assessed immediately after the procedure) was measured using

age-appropriate pain scales. In preverbal and younger children (approximately 4 years of age and below), pain intensity was assessed by the observer-reported FLACC (Face Leg Activity Cry Consolability) scale (0–10) (20), which is validated and recommended for children older than approximately 1 year (21). The visual analog scale (VAS) modified with six faces by Wong and Baker (22) (VAS 0-10) was used for children of 6–8 years of age. In children above 8 years of age, pain intensity was assessed using either the VAS modified with 6 faces by Wong and Baker (22) (VAS 0-10) or the visual analog scale (VAS 0-10). These scales are validated instruments for measuring children's self-reported pain intensity (21) and are known to correlate with each other (23). Pain scores are presented as median and interquartile range (IQR).

### Adverse events and monitoring

The children were monitored by pulse oximetry (heart rate, oxygen saturation). Heart rate, oxygen saturation, and sedation (UMSS) were recorded at baseline and 8, 20, 45, 70 min after dosing. Any adverse events or side effects were recorded up to 24 h after administration of study medication. An adverse event was defined as any untoward medical occurrence in a patient administered study medication as part of the clinical investigation and did not necessarily have to have a causal relationship with this treatment.

### Assay methodology

Blood samples (2 ml in heparin tubes) were drawn from the child's CVC at baseline and after 5, 10, 15, 30, and 60 min. The blood was centrifuged at 1340 ***g*** for 10 min at 4°C (Sigma Laborzentrifugen 2K15; KEBO Lab, Osterode, Germany), and the plasma was divided into two aliquots of approximately 1 ml and frozen at −80°C pending analysis. Plasma concentrations of sufentanil, ketamine, and the metabolite norketamine were determined using validated assays. Sufentanil was extracted from plasma with solid-phase extraction using deuterated sufentanil as internal standard. The plasma samples were analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) (24) and lower limit of quantification was established as 0.25 $pg \cdot ml^{-1}$. Plasma concentrations of ketamine and norketamine were also determined by LC-MS/MS 0.25 (modified from (25)). The lower limit of quantification was 0.1 $ng \cdot ml^{-1}$ for ketamine and norketamine. Accuracy and precision for all assays were within 85% and 115% for all concentrations.

### Pharmacokinetic analysis

*Population parameter estimations*

*Sufentanil* A three-compartment linear disposition model with first order absorption and first order elimination was used to analyze time-concentration profiles. The model was parameterized in terms of clearance (CL), intercompartmental clearances (Q2 and Q3), three volumes of distribution (V1, V2, V3), and an absorption rate constant (Ka). The latter was expressed as an absorption half-life ($Tabs_{1/2}$).

*Ketamine* A two-compartment (central, peripheral) linear disposition model was used to fit the parent drug. An additional metabolite compartment was linked to the central compartment by a series of intermediate compartments to account for norketamine formation time delays. Norketamine volume of distribution ($V_m$) was fixed equivalent to central volume (26).

*The use of priors*

Data were limited and to estimate the relative bioavailability of the nasal formulation ($F_{NASAL}$), we used prior information from a study of intravenous sufentanil in adults (27) and of ketamine in children (26). Adding the prior information to the compartment models enabled us to estimate the bioavailability of each drug ($F_{SUFENTANIL}$, $F_{KETAMINE}$) and absorption half-times ($Tabs_{1/2}$). Pharmacokinetic analysis details are reported in the Appendix.

*Simulation*

A simulation study was performed to investigate ketamine and sufentanil concentrations in a child (10 years, 30 kg) given sufentanil-ketamine intranasally. PK parameter estimates and their variability from this current analysis were used to predict individual time-concentration profiles.

## Results

A total of 50 patients were planned for PD analysis, including 15–20 patients for PK analysis. However, due to logistic reasons, we only enrolled 13 patients for PK analysis. Patient characteristics are listed in Table 1.

### Pharmacokinetic analysis

Blood samples from one patient were not analyzed, and that patient was excluded from PK analysis. In another patient, one blood sample at 15 min was not obtained due to nonfunction of the CVC. Thus, the analysis

**Table 1** Patient characteristics

| Intranasal sufentanil/ketamine | PK analysis | PD analysis |
|---|---|---|
| Number of patients | 13 | 50 |
| Number of patients withdrawn | 0 | 0 |
| Age, years: mean (SD) | 10.6 (4.4) | 8.8 (5.0) |
| Weight, kg: mean (SD) | 31.9 (16.1) | 34.9 (20.1) |
| Height, cm: mean (SD) | 147.3 (29.2) | 138.4 (32.0) |
| Gender, *n* | | |
| Female | 4 | 14 |
| Male | 9 | 36 |
| Diagnose, *n* | | |
| Cardiothoracic surgery | 5 | 11 |
| Other surgery | 1 | 5 |
| Pleural empyema | 1 | 8 |
| Pneumothorax or Hemothorax | 1 | 5 |
| Postoperative complications | 2 | 4 |
| Burn injury | – | 7 |
| Other | 3 | 10 |
| Preprocedural pain: median (IQR) | 0.0 (0.0–1.0) | 0.0 (0.0–2.0) |
| Assessment of pain intensity, number of FLACC/VAS | 3/10 | 14/36 |

comprised 12 patients with 59 drug assay observations in the sufentanil group and 118 drug and metabolite assay observations in the ketamine group. Raw data are shown in Figure 1.

Parameter estimates for the sufentanil 3-compartment analysis are shown in Table 2 and those for the 2-compartment ketamine analysis in Table 3. Figures 2 and 3 show satisfactory prediction-corrected visual predictive check (PC-VPC) plots for these PK data. There were no age-related changes of CL or V. The maximum concentration ($C_{max}$) of sufentanil was 0.042 (CV 12.9%) mcg·l$^{-1}$ at ($T_{max}$) 13.8 (CV 12.4%) min. The $C_{max}$ for ketamine was 0.102 (CV 10.8%) mg·l$^{-1}$ and $T_{max}$ was 8.5 (CV 17.3%) min. Time-concentration profiles and the 90% prediction intervals for a child (age 10 years, weight 30 kg) given a mixture of sufentanil 0.5 mcg·kg$^{-1}$ and ketamine 0.5 mg·kg$^{-1}$ intranasally and repeated dose at 15 min are shown in Figure 4.

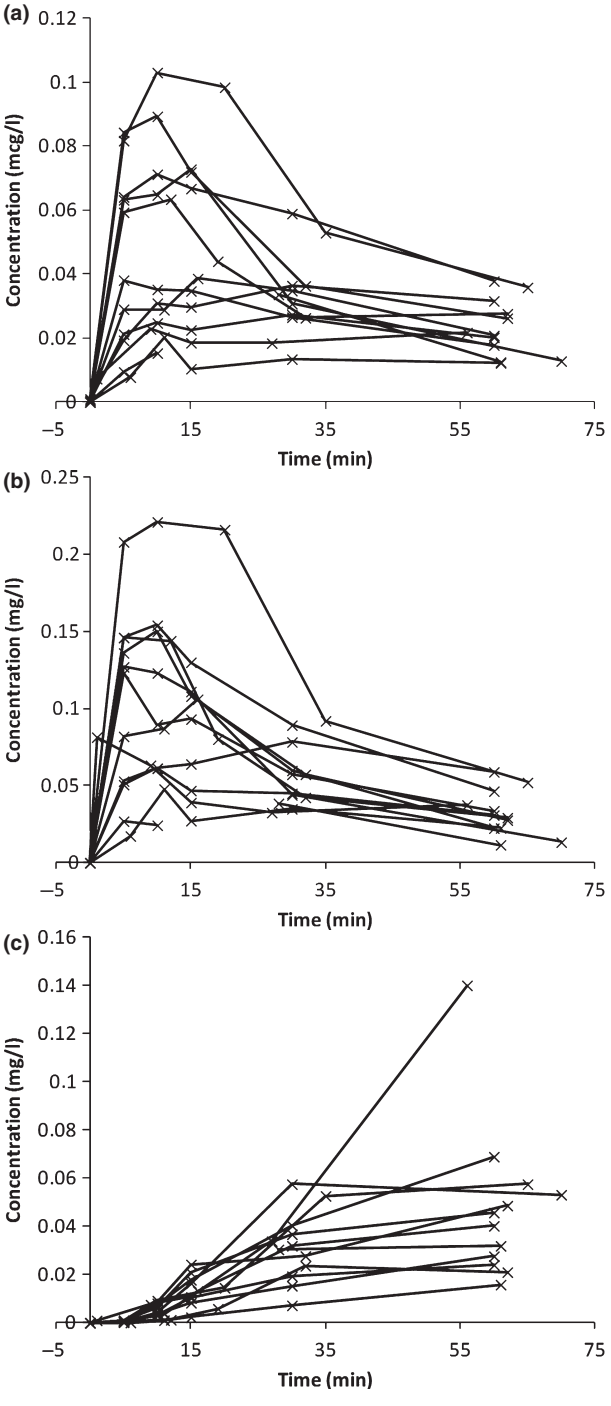


**Figure 1** Individual observed plasma concentrations profiles are shown for (a) sufentanil (upper panel), (b) ketamine (middle panel), and (c) norketamine (lower panel). The administered dose of sufentanil was 0.36–0.50 mcg·kg$^{-1}$ and ketamine 0.36–0.50 mg·kg$^{-1}$.

## Analgesic effect

The study drug was administered for a number of different painful medical procedures (Table 4). Mean time for performance of the painful procedure after administration of the nasal spray was 16 (SD 3) min. Half of the painful procedures involved removal of drains, for example, removal of pleural chest tubes. The median preprocedural pain intensity score was 0.0 (IQR 0.0–2.0). The distribution of procedural pain intensity scores are shown in Figure 5. The median procedural pain intensity score was 3.1 (IQR 2.0–4.9). Acceptable analgesia (pain intensity scores ≤5 during procedures)

**Table 2** Standardized population pharmacokinetic parameter estimates for sufentanil

| Parameter | Estimate | % BSV | % SE | 95% CI |
|---|---|---|---|---|
| CLstd ($l \cdot h^{-1}$ per 70 kg) | 55.1 | 22.9 | 18.9 | 47.6, 58.8 |
| Q2std ($l \cdot h^{-1}$ per 70 kg) | 102 | 46.6 | 14.2 | 93.4, 113 |
| Q3std ($l \cdot h^{-1}$ per 70 kg) | 40.7 | 76.4 | 35.4 | 13.4, 45.7 |
| V1std (l per 70 kg) | 16.5 | 21.8 | 26.6 | 9.75, 26 |
| V2std (l per 70 kg) | 70.7 | 30.8 | 21.8 | 60.5, 76.9 |
| V3std (l per 70 kg) | 608 | 76 | 2.8 | 607, 608 |
| $Tabs_{1/2}$ (h) | 0.442 | 77.5 | 33.9 | 0.215, 0.738 |
| $F_{SUFENTANIL}$ | 0.246 | – | 18.5 | 0.151, 0.277 |
| Err add ($mcg \cdot l^{-1}$) | 0.00514 | – | 15.5 | 0.0001, 0.00652 |
| Err prop (%) | 4.38 | – | 88.4 | 0.05, 14.8 |

BSV, between subject variability; SE, standard error of the structural estimate; CI, confidence interval of the structural estimate. A three-compartment linear disposition model with first order absorption and first order elimination was used to analyze time–concentration profiles. Population estimates of clearance (CL), intercompartmental clearances (Q2 and Q3), three volumes of distribution (V1, V2, V3), respectively, standardized to a 70 kg person using allometric models. $Tabs_{1/2}$ = absorption half-life, F = bioavalability. Residual unidentified variability was described by combined proportional and additive residual error model for each observation prediction (Err pror, Err add).

**Table 3** Standardised ketamine population pharmacokinetic parameter estimates

| Parameters | Estimate | % BSV | % SE | 95% CI |
|---|---|---|---|---|
| Ketamine | | | | |
| CLstd other ($l \cdot h^{-1}$ per 70 kg) | 37.5 | 37.8 | 45.1 | 10.2, 68.9 |
| V1std (l per 70 kg) | 24.2 | 90.7 | 21.9 | 16.9, 29.5 |
| Qstd ($l \cdot h^{-1}$ per 70 kg) | 214 | 62.8 | 7.4 | 205, 222 |
| V2std (l per 70 kg) | 132 | 31.4 | 9.0 | 124, 137 |
| $Tabs_{1/2}$ (h) | 0.121 | 16.4 | 17.9 | 0.084, 0.200 |
| $F_{KETAMINE}$ | 0.358 | | 15.4 | |
| Residual error | | | | |
| Additive ($mg \cdot l^{-1}$) | 0.007 | – | 27.9 | 0.0002, 0.009 |
| Proportional | 10.2% | – | 34.9 | 2.1, 13.1 |
| Norketamine | | | | |
| CL2Mstd ($l \cdot h^{-1}$ per 70 kg) | 25.2 | 123 | 18.6 | 21, 29.4 |
| CLMstd (l per 70 kg) | 8.01 | 132 | 80.4 | 0.08, 29.8 |
| KMIstd ($h^{-1}$) | 24.4 | 57.4 | 20.5 | 16.4, 29.9 |
| $V_m$ = V1 | 24.2 | 90.7 | 21.9 | 16.9, 29.5 |
| Residual error | | | | |
| Additive ($mg \cdot l^{-1}$) | 0.0001 FIX | – | – | – |
| Proportional | 26.9% | – | 16.3 | 15.6, 34.1 |

BSV, between subject variability; SE, standard error of the structural estimate; CI, confidence interval of the structural estimate. A two-compartment (central, peripheral) linear disposition model was used to fit the parent drug. An additional metabolite compartment was linked to the central compartment by a series of intermediate compartments to account for norketamine formation time delays. Population estimates of clearance (CL), intercompartmental clearance (Q), volume of distribution (*V*), respectively, rate constant for intermediate compartment (KMI), standardized to a 70 kg person using allometric models. $Tabs_{1/2}$ = absorption half-life, F = bioavalability. Residual unidentified variability was described by combined proportional and additive residual error model for each observation prediction (Err pror, Err add).

was reported for 39 of 50 children. Procedures for which pain intensity scores >5 included insertion of peripheral venous catheter, removal of chest tube, cleaning of minor burns, and dressing change of (pilonidal or perianal) abscess.

### Adverse events

No serious adverse events were reported. Oxygen saturation and heart rate remained stable during the study period. Sedation scores of 0–2 (UMSS awake and alert – somnolent/arouses to light stimuli) were observed. The reported adverse effects were mild and mostly related to an unpleasant bitter taste (15 out of 50 children) immediately after administration of the nasal spray. Children experiencing an unpleasant taste were offered something to drink, which relieved the taste in minutes. Three events of vomiting occurred and two were considered 'possibly related' to the study drug, whereas one was considered 'probably not related'.

### Acceptability

Almost all (94%) of the children or parents (for preverbal children) stated that they would like to receive this treatment again in a similar situation rather than analgesic suppositories, tablets, oral solutions, or injections.

## Discussion

We have demonstrated that a low-dose combination of intranasal sufentanil ($0.5\ mcg \cdot kg^{-1}$) and ketamine ($0.5\ mg \cdot kg^{-1}$) was effective in 78% of children undergoing painful procedures. Peak plasma concentrations were attained within 15 min, and the spray was well accepted by 94% of the children. Advantages of the nasal route include ease of administration, rapid systemic absorption, and avoidance of hepatic first-pass metabolism. Conversely, the limitations include the physiochemical properties of the drug, between patient variability in absorption and acceptance of the intranasal route by the child (28). Both sufentanil and ketamine are lipophilic, small molecules that are freely soluble in

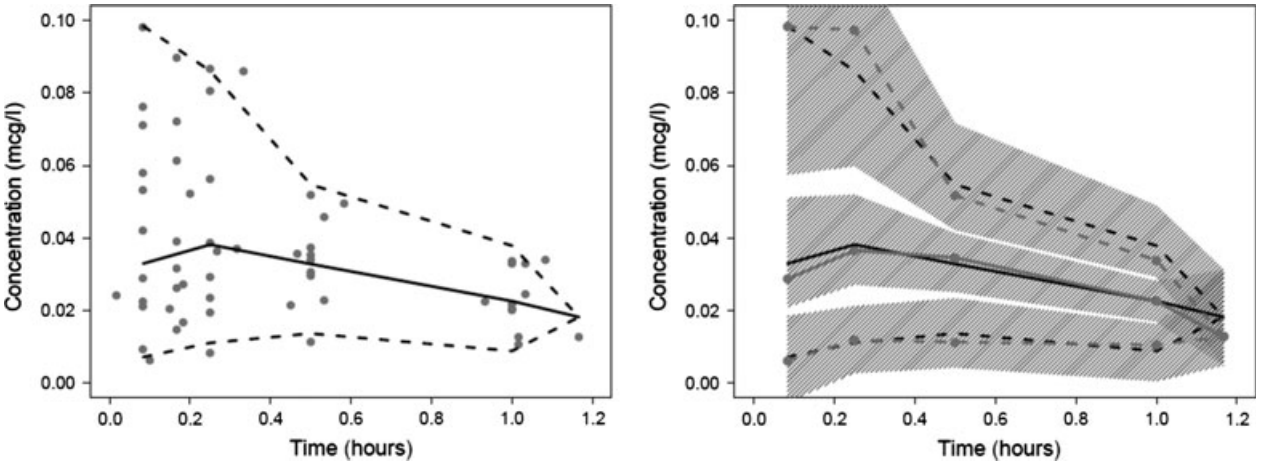


**Figure 2** Visual predictive check for the sufentanil PK model. All plots show median and 90% intervals (solid and dashed lines). (a) left hand plot shows all prediction-corrected observed concentrations. (b) right hand plot shows prediction-corrected percentiles (10%, 50%, and 90%) for observations (lines with symbols) and predictions (lines) with 95% confidence intervals for prediction percentiles (gray shaded areas).

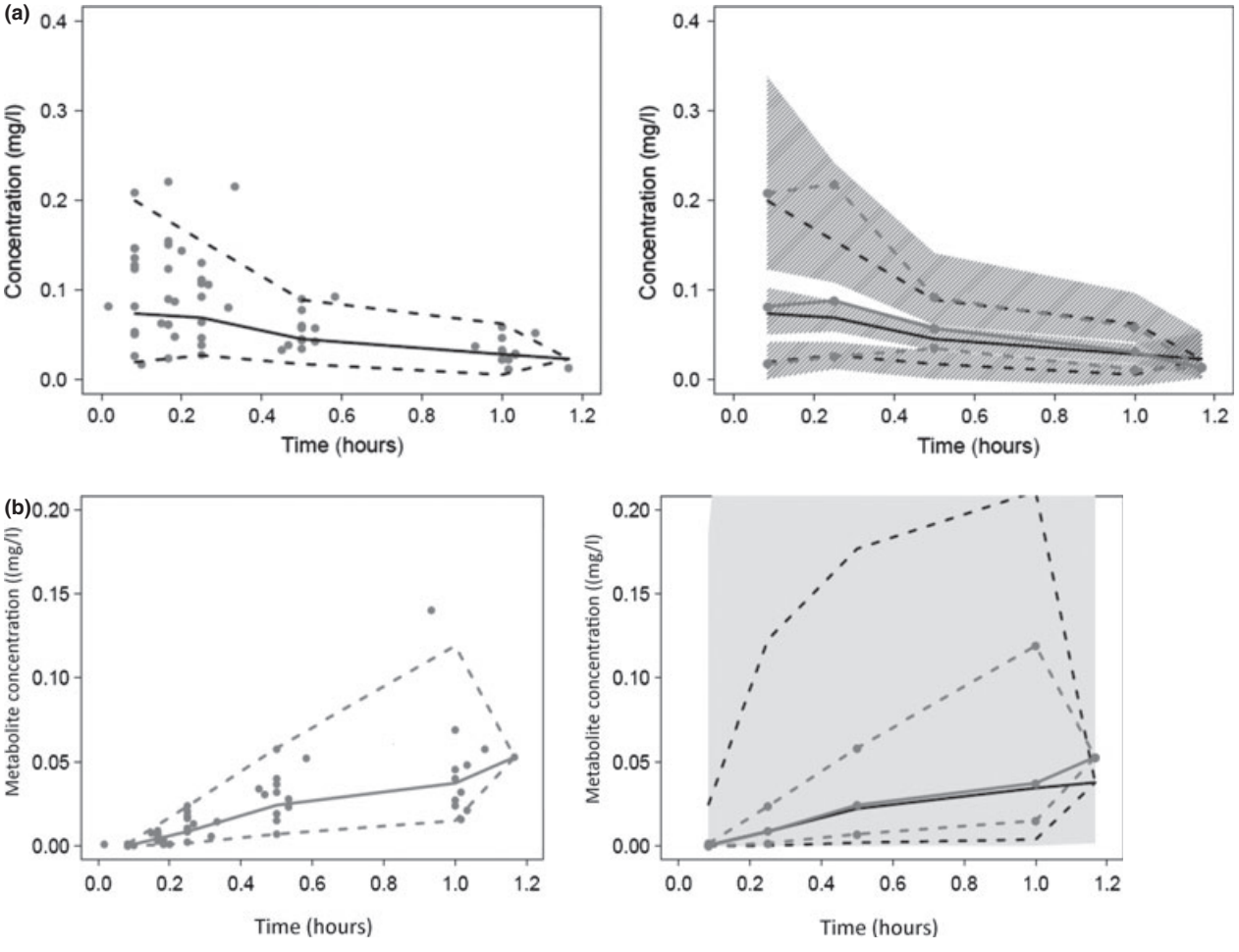


**Figure 3** Visual predictive check for the ketamine PK model. All plots show median and 90% intervals (solid and dashed lines). Left hand plot shows all prediction-corrected observed concentrations. Right hand plot shows prediction-corrected percentiles (10%, 50%, and 90%) for observations (lines with symbols) and predictions (lines) with 95% confidence intervals for prediction percentiles (gray shaded areas). (a) Parent ketamine; (b) Metabolite norketamine.

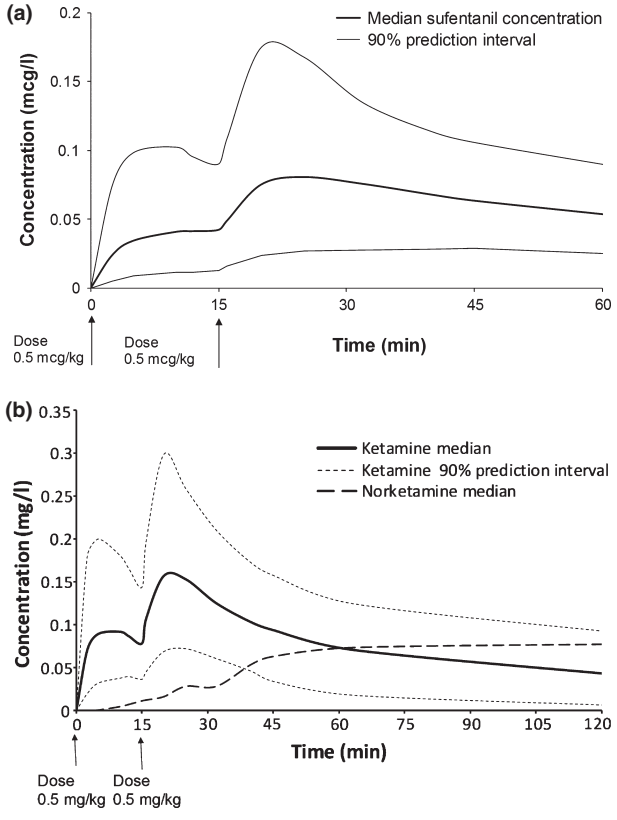


**Figure 4** (a) Time–concentration profile and 90% prediction intervals for a dose of intranasal sufentanil of 0.5 mcg·kg$^{-1}$ and a second dose of 0.5 mcg·kg$^{-1}$ at 15 min. (b) Ketamine time–concentration profile and 90% prediction intervals after a dose of intranasal ketamine 0.5 mg·kg$^{-1}$ and a second dose of 0.5 mg·kg$^{-1}$ at 15 min. The median time–concentration profile of the norketamine metabolite is also shown.

water allowing preparation of a concentrated solution needed to administer a small intranasal volume.

The analgesic dose of intranasal sufentanil and ketamine in the present study was lower than reported in previous pediatric studies with either sufentanil nasal drops 1.0–4.5 mcg·kg$^{-1}$ (5–8), ketamine nasal drops 3–9 mg·kg$^{-1}$ (10,11,29), or s-ketamine nasal drops 1–2 mg·kg$^{-1}$ (9,30) used for preinduction of anesthesia. In addition, combinations of sufentanil approximately 1 mcg·kg or ketamine 5 mg·kg with midazolam 0.3 mg·kg have been used for preinduction of anesthesia/postoperative analgesia (12). However, sufentanil nasal spray 0.5 mcg·kg$^{-1}$ has been investigated for analgesia in adult patients, achieving pain relief after surgery (31) or from limb extremity injuries (19).

Pharmacokinetic parameter estimates were similar to those reported by others for both ketamine (32,33) and sufentanil (34–36). The lack of an observed age-related influence on either sufentanil or ketamine PKs was

**Table 4** Painful procedures and pain intensity score before and during procedure

| Painful procedure | Number of children enrolled | Preprocedural pain intensity, median (IQR) | Procedural pain intensity, median (IQR) |
|---|---|---|---|
| Removal of drains | | | |
| Pleural chest tube | 22 | 1.1 (0.0–3.6) | 2.9 (2.0–5.6) |
| Pericardial drain | 4 | 0.5 (0.0–1.5) | 3.0 (2.0–4.3) |
| Abdominal drain | 1 | 0 | 0 |
| Peripheral venous catheter | 6 | 0 (0.0–0.0) | 2 (0.5–2.75) |
| Burn injury | | | |
| Major burn injury, dressing change | 3 | 0.0 (0.0–0.0) | 3.0 (2.6–3.5) |
| Minor burn injury, cleaning of wounds | 3 | 1.0 (0.5–3.0) | 8.0 (5.5–8.5) |
| Other | | | |
| Abscess (Pilonidal/Perianal) | 2 | 0.0 (0.0–0.0) | 8.0 (7.5–8.5) |
| Wound defects postoperative | 2 | 0 (0.5–1.5) | 3.8 (3.6–3.8) |
| Dressing change, infected wound | 1 | 2 | 4 |
| Nasogastric tube insertion | 1 | 0 | 3 |
| Removal of stitches | 1 | 0 | 2 |
| Mastoiditis, drainage | 1 | 5 | 3.5 |
| Puncture of elbow joint | 1 | 7 | 4 |
| Laceration of gingiva | 1 | 2 | 5 |
| Removal of pacing wires | 1 | 0 | 0 |

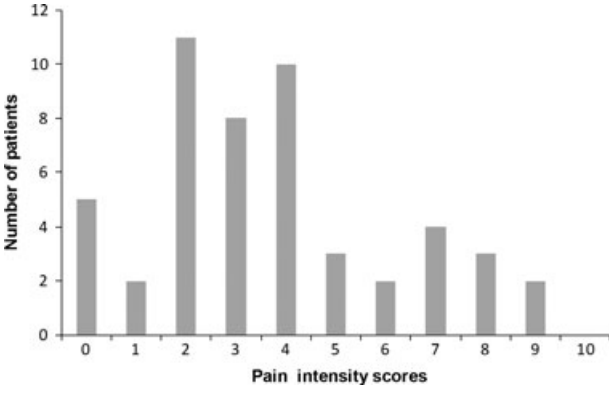


**Figure 5** Distribution of pain intensity scores during the painful procedures.

consistent with allometric theory where maturation processes are anticipated completed before the postnatal age of 2 years (37). Estimates of relative bioavailability were lower than anticipated ($F_{KETAMINE}$ 0.36, $F_{SUFENTANIL}$ 0.25). Others have reported a value of 0.78 for sufentanil

nasal drops in adults (18) and 0.45–0.5 for ketamine nasal spray in healthy volunteers (38) or ketamine nasal drops in anesthetized children (29,38). The absorption of intranasal ketamine in anesthetized children in the supine position may differ from those in children that are awake and sitting up. Furthermore, most drug absorption occurs under the inferior turbinate. Should the spray be directed elsewhere, then reduced absorption may be observed. The administered volume of intranasal sufentanil/ketamine in the current trial was small, however, some children experienced an unpleasant taste and it is possible that the drug may have reached the nasopharynx and then swallowed; resulting in decreased bioavailability. Observed sufentanil plasma concentrations in awake children from an outpatients clinic given sufentanil nasal drops were similar to our observations once scaled to dose (17).

Absorption parameters for nasal sufentanil were similar to those reported by others in adults where $T_{max}$ occurred at 10 min (18). Absorption of intranasal ketamine was more rapid than that reported by others where $T_{max}$ was 18–20 min (30,31), which is considerably longer than $T_{max}$ of 8.5 (CV 17.3%) min in the present study. This may be due to administration of ketamine as nasal drops in previous studies, while intranasal sufentanil/ketamine in the present study was administered as a nasal spray that distributes to a greater surface area of the nasal cavity. The time to intranasal sufentanil analgesia in adults was 10–20 min (19,31), and no data were available for intranasal ketamine analgesia in children. Time to sedation was approximately 10 min in pediatric studies investigating intranasal ketamine for preinduction (11). Intranasally, administered drug enters the central nervous system by the 'nose to systemic circulation to brain' pathway (28). Additionally, a nose–brain pathway has also been mooted and may potentially transport drug directly to the brain via the olfactory mucosa influencing observed analgesia and sedation. However, little is known about this pathway in children.

Considerations of drug administration timing in relation to the painful procedure are important. The $T_{max}$ of sufentanil was 13.8 (CV 12.4%) min while that of ketamine was 8.5 (CV 17.3%) min. However, there will be a further delay before peak concentration in the effect compartment is reached. This delay, characterized by the equilibration half-life parameter ($T_{1/2}$keo) was very small for ketamine ($T_{1/2}$keo 11 s) (39) but was larger for sufentanil ($T_{1/2}$keo 6.2 min) (40). The analgesic effect of sufentanil-ketamine nasal spray will be prolonged by the sufenanil $T_{1/2}$keo and because ketamine retains analgesic effect at low concentrations and also because additional analgesia is contributed by norketamine (41). Consequently, we suggest that the painful procedure should be undertaken 15 min after administration of the nasal spray.

Analgesic plasma concentrations of ketamine 0.1–0.2 $mg{\cdot}l^{-1}$ (41,42) and of sufentanil above 0.03 $mcg{\cdot}l^{-1}$ (43) have been suggested. Our maximum observed concentrations were at the lower end of this therapeutic window for analgesia (ketamine $C_{max}$ 0.1 $mg{\cdot}l^{-1}$, sufentanil $C_{max}$ 0.042 $mcg{\cdot}l^{-1}$). If sufficient analgesia is not achieved with a single dose of sufentanil-ketamine nasal spray, the question of the timing of a second dose may raise. Simulations of a repeated dose administered 10 or 15 min after the first dose showed mean plasma concentrations within the therapeutic window for analgesia (Figure 4).

In the current study, a variety of painful procedures were included but the majority were removal of chest tubes (44%). Pain scores associated with removal of chest tubes in a postoperative cohort of children were reported normally distributed with a median pain score of 5.3 (IQR 3.5–7.1) (0 = no pain, 10 = worst imaginable pain) (44). We report a lower median procedural pain score of 2.9 (IQR 2.0–4.9) for removing of chest tubes postoperatively after administration of intranasal sufentanil/ketamine, suggesting an effective treatment modality. Procedural pain intensity scores >5 were not correlated with plasma concentrations of sufentanil or ketamine but may reflect the nature of the painful procedure.

A nonrandomized open-label study design was chosen for the current study because comparison with pharmacological treatment in a control group was not suitable for a wide range of painful procedures where no standard analgesic treatment exists. The use of a control group who were not given analgesia was considered unethical (45). Both sedation and adverse effects observed in the present study were mild. In our experience, food restrictions before administration are not necessary with a low dose of intranasal sufentanil/ketamine. This qualifies the sufentanil-ketamine nasal spray for use in ambulatory and emergency settings. However, due to the relatively small sample size of the present study, adverse events may not have been adequately studied.

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## Conflict of interest

The authors declare no conflict of interest.

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## Appendix

### Pharmacokinetic modeling

Population parameter estimates were obtained using nonlinear mixed-effects models (NONMEM VII, Globomax LLC, Hanover, MD, USA). The population mean parameters, between subject variance and residual variance were estimated using the first order conditional estimation method using ADVAN 11 TRANS 4 of NONMEM VI. Convergence criterion was three significant digits.

The population parameter variability was modeled in terms of random effect ($\eta$) variables. Each of these variables was assumed to have mean 0 and a variance denoted by $\omega^2$, which was estimated. The population parameter variability in model parameters was modeled with an exponential model. We report the estimate of $\omega$ for each variability component expressed as a percentage because these quantities were approximate coefficients of variation for a log normal distribution. Residual unidentified variability was described using a combined proportional and additive residual error model for each observation prediction ($Err_{PROP}$, $Err_{ADD}$).

#### *Covariate analysis*

The parameter values were estimated standardized for a body weight of 70 kg using an allometric model (37).

$$P_i = P_{\text{std}} \cdot (W_i/W_{\text{std}})^{\text{PWR}}$$

where $P_i$ was the parameter in the $i$th individual, $Wi$ was the weight in the $i$th individual, and $P_{\text{std}}$ was the parameter in an individual with a weight $W_{std}$ of 70 kg. This standardization allows comparison of pediatric parameter estimates with those reported for adults. The PWR exponent was 0.75 for clearance, 0.25 for half-times, and 1 for distribution volumes.

#### *Quality of fit*

The quality of fit of the PK model to the data was sought by NONMEM's objective function and by visual examination of plots of observed versus predicted concentrations. Models were nested and an improvement in the objective function was referred to the chi-squared distribution to assess significance, for example, an objective function change (OBJ) of 3.84 was significant at $\alpha = 0.05$.

Bootstrap methods, incorporated within the Wings for NONMEM program, provided a means to evaluate parameter uncertainty (46). A total of 1000 replications were used to estimate parameter confidence intervals. A visual predictive check (VPC) (47), a modeling tool that estimated the concentration prediction intervals and graphically superimposes these intervals on observed concentrations after a standardized dose, was used to evaluate how well the model predicted the distribution of observed plasma concentrations. Simulation was performed using 1000 subjects with characteristics taken from studied patients. For data such as these where covariates such as dose, weight, and height are different for each patient, we used a prediction-corrected VPC (PC-VPC) (48). Observations and simulations were multiplied by the population baseline value divided by the individual-estimated baseline.

#### *The use of priors*

The principle of using prior information was that previous data could be used to support a PK model under which the current data were being analyzed (49). The parameters (including their uncertainty) of the model

derived from the more informative data were then used to analyze the data in question in the context of prior knowledge. The better the prior knowledge, in other words the lower the prior parameter uncertainty, the more the data under analysis would be constrained to be similar to the prior information. Using prior information was carried out by augmenting the objective function (a measure of fit) derived from the observed data with a penalty function, which was a summary of data from previous (more informative) studies (50).