Propofol Dose-Finding to Reach Optimal Effect for (Semi-)Elective Intubation in Neonates

Anne Smits, MD[1,2], Liesbeth Thewissen, MD[1,2], Alexander Caicedo, PhD[3], Gunnar Naulaers, MD, PhD[1,2], and Karel Allegaert, MD, PhD[1,4]

Objective To define the effective dose for 50% of patients (ED_{50}) of propofol for successful intubation and to determine the rate of successful extubation in those patients with planned intubation, surfactant administration, and immediate extubation (INSURE procedure). In addition, pharmacodynamic effects were assessed.

Study design Neonates (n = 50) treated with propofol for (semi-)elective endotracheal intubation were stratified in 8 strata by postmenstrual and postnatal age. The first patient in each stratum received an intravenous bolus of 1 mg/kg propofol. Dosing for the next patient was determined using the up-and-down method. A propofol ED_{50} dose was calculated in each stratum with an effective sample size of at least 6, via the Dixon-Masey method, with simultaneous assessment of clinical scores and continuous vital sign monitoring.

Results Propofol ED_{50} values for preterm neonates <10 days of age varied between 0.713 and 1.350 mg/kg. Clinical recovery was not attained at the end of the 21-minute scoring period. Mean arterial blood pressure showed a median decrease between 28.5% and 39.1% from baseline with a brief decrease in peripheral and regional cerebral oxygen saturation. Variability in mean arterial blood pressure area under the curve could not be explained by weight or age.

Conclusions Low propofol doses were sufficient to sedate neonates for intubation. Clinical recovery was accompanied by permissive hypotension (no clinical shock and no treatment). The propofol ED_{50} doses can be administered at induction, with subsequent up-titration if needed, while monitoring blood pressure. They can be used for further dosing optimalization and validation studies. *(J Pediatr 2016;179:54-60).*

Trial registration ClinicalTrials.gov: NCT01621373; EudraCT: 2012-002648-26.

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It is standard of care to give premedication before (semi-)elective intubation in neonates.[1] Drug selection and dosing for this procedure is highly variable and not yet evidence-based.[1-3] One of the compounds used is propofol, a short-acting anesthetic. Postmenstrual age (PMA) and postnatal age (PNA) have been shown to affect propofol clearance,[4] but pharmacodynamic (PD) data in neonates are limited. Ghanta et al[5] documented a shorter time until sleep or muscle relaxation and shorter time to intubation when using 2.5 mg/kg propofol compared with a morphine/atropine/suxamethonium regimen in preterm neonates. Vanderhaegen et al[6] reported a short-lasting decrease in heart rate (HR), peripheral oxygen saturation (SaO_2), and cerebral tissue oxygenation index after a 3 mg/kg propofol bolus in neonates; however, a decrease of mean arterial blood pressure (MABP) beyond 60 minutes was observed. Significant hypotension was documented by Welzing et al,[7] resulting in preliminary termination of their study. Although the hypotensive effect of propofol also is described by others,[8-10] absence of a profound impact on mean arterial blood pressure also has been reported.[5,11]

AUC	Area under the curve
cFTOE	Cerebral fractional tissue oxygen extraction
cMABP	Mean arterial blood pressure corrected for postmenstrual age
ED_{50}	Effective dose for 50% of patients
HR	Heart rate
ICS	Intubation condition score
INSURE	Intubation, intratracheal administration of surfactant, and immediate extubation
MABP	Mean arterial blood pressure
PD	Pharmacodynamics
PI	Perfusion index
PMA	Postmenstrual age
PNA	Postnatal age
$rScO_2$	Regional cerebral oxygen saturation
SaO_2	Peripheral oxygen saturation

From the [1]Department of Development and Regeneration, KU Leuven, Leuven, Belgium; [2]Neonatal Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium; [3]Department of Electrical Engineering (ESAT), STADIUS Center for Dynamical Systems, Signal Processing and Data Analytics, KU Leuven, Leuven, Belgium; and [4]Intensive Care and Department of Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands

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Because optimal propofol dosing and its PD effects in newborns are lacking, we combined a prospective dose-finding approach with PD assessment in neonates receiving propofol as intravenous bolus for preintubation sedation (The Exploratory Propofol Dose-Finding Study In Neonates [NEOPROP] study). The primary objective was to define the ED_{50} (ie, effective dose for 50% of patients) for successful intubation and to determine the rate of successful extubation in those patients with planned intubation, surfactant administration, and immediate extubation[12,13] (INSURE procedure). Simultaneously, PD data were explored as a safety analysis and to define PD covariates.

Methods

Neonates of the University Hospitals Leuven needing preintubation sedation were included after consent from their parents was obtained. Patients had to be hemodynamically stable and not receiving sedatives or analgesics (except acetaminophen) in the previous 24 hours. INSURE is performed predominantly in preterm infants with a fraction of inspired oxygen >0.30 on nasal continuous positive airway pressure and respiratory distress syndrome. The study was registered (ClinicalTrials.gov: NCT01621373; EudraCT: 2012-002648-26) and approved by our institutional review board. Clinical characteristics were collected.

Dose Finding Approach

Propofol (Diprivan 1%; AstraZeneca, Brussels, Belgium) as intravenous bolus (followed by NaCl 0.9% 1 mL/kg in 30 seconds) was used as preintubation medication to prevent discomfort. Patients were stratified in 4 groups and 8 strata (**Figure 1**; available at www.jpeds.com) according to PMA and PNA, the major clearance covariates. The first patient in each stratum received 1 mg/kg. If sedation and relaxation perceived by the treating physician were unsatisfactory, additional propofol (1 mg/kg, if unsatisfactory titration up to satisfactory condition) was administered. The decision for additional propofol and initiation of the intubation procedure was made by the treating physician. The initial dose for the next patient in the same stratum was based on the outcome (success/failure) of the previous patient and decreased/increased by 0.5 mg/kg (up-and-down method).[14] Successful outcome was defined as intubation with satisfactory sedation and relaxation (assessed by treating physician) without additional propofol. In patients with planned INSURE, successful extubation within 1 hour was an additional criterion for a successful outcome. The initial dose for the next patient increased if additional propofol was needed but decreased if no extra propofol was needed or if extubation failed in INSURE.

Propofol ED_{50} Calculation

An up-and-down dose-response design was used to calculate ED_{50} (mg/kg) in strata with an effective sampling size (N) of at least 6, by use of the Dixon-Massey method[14] for small samples. N is the number of trials reduced by 1 less than the number of similar responses at the beginning. $ED_{50} = \sum X_i/N + d(A + C)/N$, with X_i: initial dose, d: interval between dose levels (0.5 mg/kg) and A, C: tabulated values provided by Dixon.[14] SAS 9.2 for Windows (SAS Institute, Inc, Cary, North Carolina) was used.

Intubation Procedure

The number of attempts and the physician performing the final intubation (resident, fellow, neonatologist) were recorded. After 2 failed attempts, the neonatologist performed the intubation. In INSURE patients, time to intubation and extubation (expressed as minutes after propofol administration) and the need for reintubation (within 12 hours) were recorded.

Propofol PDs

Relaxation, Sedation, and Intubation Condition Score (ICS). Relaxation and sedation were assessed every 2 minutes, from 5 minutes before until 21 minutes after propofol administration, also at the time of propofol administration, and 1 minute thereafter with the use of predefined scores. Four relaxation grades, adapted from Naulaers et al[15,16] and assessed by clinical evaluation of the tone in arms and legs, were considered (1: hypertonic, 2: normal tone, 3: mildly hypotonic, 4: hypotonic) with effective relaxation defined as a score greater than grade 2. Sedation was assessed as the motor response to heel-rubbing.[17] Four sedation grades were considered (1: moves spontaneously, 2: moves when touched, 3: moves when stimulated, 4: no reaction to stimulus),[15,16] with effective sedation defined as a score greater than grade 2. ICS at final intubation was assessed retrospectively by the intubating physician. ICS of Viby-Mogensen[1,18] was used, with ICS ≤10 defining good intubation condition.

Vital Signs and Cerebral Oxygenation. Vital signs (HR [beats/min], MABP [mmHg], SaO_2 [%], respiration rate [breaths/min], and perfusion index[19] [PI, %]) were measured with IntelliVue MP70 (Philips, Eindhoven, The Netherlands) with a Nellcor Pulse Oximeter from 2 minutes before up to 12 hours after propofol. Data were recorded continuously with a sampling rate of 1 Hertz (Rugloop; Demed, Temse, Belgium). MABP was measured invasively if an arterial line was present. Noninvasive blood pressure was excluded for analysis. Near-infrared spectroscopy was used to evaluate regional cerebral oxygen saturation ($rScO_2$, %) with the INVOS 5100 with a cerebral neonatal OxyAlert NIRSensor (Covidien, Mansfield, Massachusetts).[20] Cerebral fractional tissue oxygen extraction ($cFTOE = SaO_2 - rScO_2/SaO_2$) indicates the balance between oxygen delivery and consumption.[21,22]

Descriptive Statistics and Vital Sign Processing

Clinical characteristics were reported as the median (range) or incidence. For INSURE patients, time until intubation and extubation was compared between "success" vs "failure" by the use of the Mann-Whitney *U* test. A *P* value < .05 was considered to be statistically significant. SPSS version 20.0 (IBM Corp, Armonk, New York) and Medcalc version 13.1.7 (Medcalc, Ostend, Belgium) were used. For vital sign analysis MATLAB Release 2013a (The MathWorks, Natick, Massachusetts) was