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ORIGINAL ARTICLE

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Population pharmacokinetics and pharmacodynamics of dobutamine in neonates on the first days of life

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Aims: To describe the pharmacokinetics (PK) and concentration-related effects of dobutamine in critically ill neonates in the first days of life, using nonlinear mixed effects modelling.

Methods: Dosing, plasma concentration and haemodynamic monitoring data from a dose-escalation study were analysed with a simultaneous population PK and pharmacodynamic model. Neonates receiving continuous infusion of dobutamine 5–20 μg kg^{-1} min^{-1} were included. Left ventricular ejection fraction (LVEF) and cardiac output of right and left ventricle (RVO, LVO) were measured on echocardiography; heart rate (HR), mean arterial pressure (MAP), peripheral arterial oxygen saturation and cerebral regional oxygen saturation were recorded from patient monitors.

Results: Twenty-eight neonates with median (range) gestational age of 30.4 (22.7–41.0) weeks and birth weight (BW) of 1618 (465–4380) g were included. PK data were adequately described by 1-compartmental linear structural model. Dobutamine clearance (CL) was described by allometric scaling on BW with sigmoidal maturation function of postmenstrual age (PMA). The final population PK model parameter mean typical value (standard error) estimates, standardised to median BW of 1618 g, were 41.2 (44.5) L h^{-1} for CL and 5.29 (0.821) L for volume of distribution, which shared a common between subject variability of 29% (17.2%). The relationship between dobutamine concentration and RVO/LVEF was described by linear model, between concentration and LVO/HR/MAP/cerebral fractional tissue oxygen extraction by sigmoidal E_{max} model.

Conclusion: In the postnatal transitional period, PK of dobutamine was described by a 1-compartmental linear model, CL related to BW and PMA. A concentration–response relationship with haemodynamic variables has been established.

The authors confirm that the PI for this paper is Maarja Hallik and that she had direct clinical responsibility for patients.

EU Clinical Trials Register number 2015-004836-36.

KEYWORDS

cardiovascular pharmacology, intensive care, neonatology, NONMEM, pharmacokinetic–pharmacodynamic

1 | INTRODUCTION

Dobutamine is a **β_1-adrenoceptor** (AR) agonist catecholamine, designed to increase cardiac output (CO) without evoking vasoconstriction or tachycardia.[1] In critically ill neonates, inotropic therapy with dobutamine is often used because of low blood pressure (BP), signs of low organ perfusion, or CO measured at echocardiography. [2] Early administration of dobutamine to preterm infants during the first days of life has been found to stabilise transitional circulation. [3-6]

The pharmacokinetics (PK) of dobutamine in the paediatric population is described in children rather than neonates. [7-13] Except for 1, [10] the studies indicate first-order elimination kinetics within the dose range of 2.5–10 μg kg^{-1} min^{-1} for neonates and 2.5–17.5 μg kg^{-1} min^{-1} for infants and children. Plasma clearance (CL) rate is widely variable. [7-13] The only study describing PK of dobutamine in neonates, reported mean (standard deviation) CL of 90 (38) mL min^{-1} kg^{-1} with variability independent of gestation and birth weight (BW). [13] However, the sample size was small and postmenstrual age (PMA), a potentially better marker for maturation of elimination processes, was not explored. [13] In the dose range of 2.5 to 7.5 μg kg^{-1} min^{-1} the elimination of dobutamine was linear[13] but as doses rise above this range the kinetics may become nonlinear. [10]

Studies on pharmacodynamic (PD) effect of cardiac performance have mostly assessed dose–response relationship in doses up to 10 μg kg^{-1} min^{-1}. [13,14] CO increases at low doses, but heart rate (HR) or BP require larger doses to be affected. [13,14] However, such associations have not been consistently found[15] that may be in part due to wide variation in CL, requiring simultaneous analysis of actual plasma concentrations and response. Considering the immaturity of the cardiovascular system in neonates, a plateau of the effect on CO and BP at doses of 7.5–10 μg kg^{-1} min^{-1} in children[9] may not occur in neonates and thus PKPD in larger doses needs to be studied.

We aimed to describe the PK and PD of dobutamine in simultaneous PKPD modelling in critically ill preterm and term neonates treated with dobutamine in doses of 5–20 μg kg^{-1} min^{-1} on clinical indication in the first days of life.

What is already known about this subject

- Dobutamine clearance has high interindividual variability in neonates and children.
- Individual plasma concentrations are linearly related to the doses, with increasing uncertainty at higher levels.
- Concentration–effect relationship is described in neonates with dose range of 2.5–7.5 μg kg^{-1} min^{-1}.

What this study adds

- Describes pharmacokinetics and pharmacodynamics of dobutamine in postnatal transitional period using population nonlinear mixed effects modelling.
- For clearance 62% of between subject variability is related to birth weight and postmenstrual age.
- Dobutamine effects to central haemodynamic parameters and cerebral fractional tissue oxygen extraction are concentration related.

2 | METHODS

The study was approved by the Ethics Committee of the University of Tartu and registered at the EU Clinical Trials Register under number 2015–004836-36.

A prospective 2-centre study was performed in Tallinn Children's Hospital, Tallinn, Estonia and Tartu University Hospital, Tartu, Estonia. All neonates hospitalized to NICU within the first 72 h of life from April 2016 to December 2017 were screened for eligibility. We included neonates who needed inotropic therapy according to the decision of the treating physician (based on echocardiographic assessment, cerebral regional oxygen saturation ($rScO_2$), mean arterial blood pressure (MAP), acid–base balance, serum lactate and capillary refill time), and had arterial catheter and/or central venous catheter in place on clinical indication. Study exclusion criteria were congenital malformations with potential impact on haemodynamic (HD) response to inotropic therapy (congenital heart disease), congenital hydrops, other unresolved cause of low blood flow (air leak), known metabolic disease, situations where the treating physician considered a different vasoactive treatment necessary or dobutamine contraindicated and hypersensitivity to dobutamine or any other component of the study medication. Written informed consent was signed by parents or guardians before study inclusion.

2.1 | Study drug administration and PK sampling

Dobutamine 12.5 mg mL^{-1} concentrate for solution for infusion (Dobutamine Claris, Claris Lifesciences Limited, UK) was diluted with 0.9% NaCl to a concentration of 1.25 mg mL^{-1} within 20 min before administration. Study medication infusion was started immediately

after the first echocardiographic assessment at a dose of 5 μg kg^{-1} min^{-1} and raised by 5 μg kg^{-1} min^{-1} approximately every 30 min to a maximum of 20 μg kg^{-1} min^{-1}. Dose change times were recorded with the precision of the nearest minute. Individual dose escalation maximum was decided based on echocardiographic and clinical findings. Dose-limiting effects of the study medication were (i) persistent tachycardia (HR >200 min^{-1} in preterm and >180 min^{-1} in term neonates) or arrhythmias; (ii) no additional effect of the last dose increase; or (iii) sufficient effect of the last dose. To ensure adequate intravascular volume, all neonates received a bolus of 10 mL kg^{-1} of normal saline over 10 min, unless any fluid bolus was already received within 4 h prior to study inclusion. Further cardiovascular support with volume bolus and inotropes other than study medication was provided on the decision of the treating physician without any restrictions in the study protocol.

Blood samples of 0.3 mL were collected from an indwelling arterial line into Na-heparin vials 15–30 min after every dobutamine dose change and 15 min after termination of dobutamine infusion. It was difficult to predict elimination half-life of dobutamine in the study population, so PK and PD sampling times were balanced against clinical feasibility to reach desired cardiovascular effects within a reasonable time frame. Actual blood collection time was recorded to the nearest minute. Blood was centrifuged immediately, and plasma stored at −80°C (up to 12 h storage at −20°C was accepted). Dobutamine concentrations were measured by ultra-high-performance liquid chromatography coupled to tandem mass spectrometry. The within- and between-run accuracy (coefficient of variability) was 95–99% (4–7%) and 94–102% (3–5%), respectively, lower limit of quantification (LLOQ) 0.97 μg L^{-1}.[16] All concentrations below LLOQ were included into the analysis with the value of 0.5 μg L^{-1}.[17]

2.2 | Patient monitoring

Echocardiography was performed before the start of treatment and approximately 20–30 min after each dose escalation, and left ventricular ejection fraction (LVEF) and CO of right and left ventricle (RVO, LVO) were measured.[18] Patent ductus arteriosus diameter was measured by 2D imaging at the narrowest point. Intra- and interobserver variability was assessed according to a recent recommendation.[19]

HR, BP, peripheral arterial oxygen saturation (SaO_2) and $rScO_2$ were monitored continuously and recorded with 2.5-s intervals by BedBase software (University Medical Center Utrecht, the Netherlands). Demographic data, birth history, Score for Neonatal Acute Physiology Perinatal Extension (SNAPPE II),[20] therapeutic interventions and laboratory data were collected from hospital records. All neonates were monitored for adverse events for 7 days after the end of treatment with study medication.

2.3 | PKPD analysis

PKPD modelling was undertaken with nonlinear mixed-effects software NONMEM version 7.3 (ICON Development Solutions, MD, USA). The first-order conditional estimation method with interaction was used. Dobutamine concentration–time courses were analysed by a 1-compartment PK models with first-order elimination, Michaelis–Menten (M-M) elimination and elimination by parallel first-order and M-M processes was also tested.

CL and volume of distribution (V) were allometrically scaled to population median BW and a maturation function, describing the maturation of dobutamine CL with PMA was applied (Equation 1, Equation 2):

$$CL_i = \theta_{CL} \cdot \left(\frac{BW_i}{W_{st}}\right)^{0.75} \cdot \frac{PMA_i^{Hill}}{PMA_{50}^{Hill} + PMA_i^{Hill}} \quad (1)$$

$$V_i = \theta_V \cdot \left(\frac{BW_i}{W_{st}}\right) \quad (2)$$

where CL_i and V_i are the individual predicted values for CL and V, θ_{CL} and θ_V typical values for CL and V, BW_i and PMA_i are the patient's individual BW and PMA, W_{st} is the population median BW, Hill is the sigmoidicity coefficient and PMA_{50} is the PMA when the maturation of the dobutamine CL reaches 50% of adult values.[21] PMA_{50} and Hill's coefficient for the maturation function of dobutamine CL were estimated from PK data.

In covariate analysis parameterization of PK model with postnatal age, antenatal glucocorticoid hormone administration, coadministration of dopamine, blood haemoglobin and albumin concentration, patent ductus arteriosus diameter, baseline LVEF and baseline RVO was tested.

Models were compared by objective function value (OFV), for a nested model a parameter was added if their inclusion resulted in improvement of OFV value >3.84 ($P < .05$ by likelihood ratio test for 1 degree of freedom).

Simultaneous PKPD modelling was undertaken with HD parameters as PD effect, using the final linear PK structural model with Hill coefficient and PMA_{50} fixed to values estimated from PK data (Table 2). HR, MAP, SaO_2 and $rScO_2$ data recorded during a 15 min period (5 min before and 10 min after each dose change) were selected and averaged over 1 min. Cerebral fractional tissue oxygen extraction (cFTOE) was calculated as a ratio: $(SaO_2 - rScO_2)/SaO_2$.

Adding an effect compartment with a first-order equilibration rate constant (k_{eo}) to the final PK structural model was tested with for HR, MAP and cFTOE PKPD models, assuming that the amount of drug distributing into the effect compartment does not influence the overall PK (Equation 3):

$$\frac{\delta C_e}{\delta t} = k_{eo} \cdot C - k_{eo} \cdot C_e \quad (3)$$

where C is the plasma concentration, C_e is the effect compartment concentration and k_{eo} is the equilibration rate constant between effect and observed (plasma) compartments.

Baseline HD parameter values were estimated. Changes in HD parameter values were explored using linear (Equation 4), E_{max} (Equation 5) and sigmoidal E_{max} (Equation 6) models:

$$E_{ij} = E_{0,i} + SL_i \cdot C_{ij} \quad (4)$$

$$E_{ij} = E_{0,i} + (E_{max,i} - E_{0,i}) \cdot \frac{C_{ij}}{(EC_{50,i} + C_{ij})} \quad (5)$$

$$E_{ij} = E_{0,i} + (E_{max,i} - E_{0,i}) \cdot \frac{C_{ij}^{\gamma}}{\left(EC_{50,i}^{\gamma} + C_{ij}^{\gamma}\right)} \quad (6)$$

where E_{ij} is the j-th observed HD parameter value at the corresponding plasma or effect compartment concentration (C_{ij}) of the i-th individual, $E_{0,i}$ represents the estimated baseline value, SL_i is the slope of the linear relationship between E_{ij} and C_{ij} for the i-th individual, $E_{max,i}$ is the estimated maximum HD parameter value for the i-th individual, and $EC_{50,i}$ represents the concentration at half-maximal effect for the i-th individual, γ describes the steepness of concentration–effect relationship.

Between subject variability (BSV) was estimated for most of the PK and PD model parameters using exponential variance model, assuming log-normal parameter distribution. Individual estimates for BSV for CL and V were highly correlated (r = 1.0), so a shared BSV was used with an estimated scale factor applied for V. The residual unexplained variability was explored to be described by additive, proportional, or combined additive and proportional error models. The residual error was estimated separately for the PK and PD observations.

To assess the goodness of fit (GOF) of the models, population and individual predicted vs. observed dobutamine concentration and PD effect measurements, absolute value of individual weighted residuals *vs* individual predictions, and conditional weighted residual error *vs* time plots were used. A prediction-corrected visual predictive check (VPC) was constructed and a nonparametric bootstrap with 1,000 replicates was undertaken, with software Perl speaks NONMEM[22] and R Version 3.6.0.[23]

2.4 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

Thirty-one neonates were recruited and data from 28 of them were included in the final analysis. The reason for omission was therapeutic hypothermia, considered to possibly affect the PK of dobutamine, in 2, and withdrawal of parental consent in 1 case. Demographic and clinical data of the study patients are presented in Table 1. The main underlying diagnoses were respiratory distress syndrome (14), early onset neonatal sepsis defined as clinical and laboratory signs of infection with antibacterial therapy for more than 3 days (8, none were culture positive), perinatal asphyxia (2), meconium aspiration (2) and foeto-foetal transfusion syndrome (2).

The maximal dobutamine dose was 10, 15 and 20 μg kg^{-1} min^{-1} in 1, 17 and 10 patients, respectively, median (range) infusion duration 3.5 (1.4–17.7) days. A total of 119 dobutamine plasma concentrations were collected, in 2 samples dobutamine was not detected and in 9

TABLE 1 Demographic and clinical data of the study population. Data are presented as median (range) or count (percent of the population), if not stated differently

Patient characteristics (n = 28)	Values
Demographic data	
GA at birth (weeks)	30.4 (22.7–41.0)
GA <28 weeks	7 (25%)
GA 28–32 weeks	9 (32%)
GA 32–37 weeks	7 (25%)
GA >37 weeks	5 (18%)
Sex, male	18 (64%)
Birth weight, g	1618 (465–4380)
Age at recruitment (h)	6 (2–28)
Birth history	
Multiple birth	6 (21%)
Small for GA	2(7%)
Born from caesarean section	22(79%)
SNAPPE II score	16 (3–89)
Apgar score at 5′	7 (1–8)
Antenatal glucocorticoids (% of neonates born <34 weeks of GA)	15 (71%)
Laboratory data at recruitment	
Haemoglobin, g/L	163 (117–203)
Albumin, g/L	27.7 (21.6–41.3)
pH	7.327 (7.137–7.536)
HCO_3, mmol/L	19.1 (15.2–24.9)
Concomitant medications	
Dopamine	5 (18%)
Caffeine	5 (18%)
Opiates	6 (21%)
Sedatives	5 (18%)
Nitric oxide inhalation	1 (4%)
Ventilation support at recruitment	
Invasive ventilation/FiO_2	23 (82%)/0.30(0.21–1)
Noninvasive ventilation or nasal CPAP/FiO_2	5 (18%)/0.25(0.21–0.6)
Circulatory status at recruitment	
RVO (mL/kg/min)	136 (75–306)
LVO (mL/kg/min)	128 (71–338)
LVEF (%)	64 (51–79)

GA, gestational age; SNAPPE II, Score for Neonatal Acute Physiology Perinatal Extension; RVO, right ventricular cardiac output; LVO, left ventricular cardiac output; LVEF, left ventricular ejection fraction

samples dobutamine concentration remained below LLOQ. The maximum measured concentration was 330 μg L^{-1}. The dose–concentration graph is shown in Figure 1.

Intra- and interobserver variability for RVO, LVO and LVEF measurements (mean ± SD) did not exceed 5 ± 5% and 12 ± 10%, respectively.

3.1 | Dobutamine PK and PD

The PK data were described by 1-compartmental linear structural model with proportional error model for residual variability. M-M elimination did not improve fit to the observed data, combining M-M process parallel to linear elimination in PK model resulted only in slightly better fit (ΔOFV = 10). Therefore, to avoid over-parameterization, a linear PK model was carried forward to PKPD modelling. Adding allometric weight scaling and CL maturation function significantly improved model fit (ΔOFV = 26 and 15, respectively) and lowered BSV by 62%, without further improvement by other covariates.

The final linear PK model parameter estimates are presented in Table 2, basic GOF plots in Figure 2 and prediction-corrected VPC in Figure 3.

Concentration-related changes in RVO and LVEF were best described with linear PD models and in LVO with a sigmoidal E_{max} model (Table 3). Continuously measured HD parameters were best described with a sigmoidal E_{max} model with effect compartment equilibration rate constant with mean effect time (k_{eo}^{-1} 60 min) of 9 min for HR and without effect compartment equilibration rate constant for MAP and cFTOE (Table 3). Final PKPD model parameter estimates for RVO, LVO and LVEF are presented in Table 4 and for HR, MAP and cFTOE in Table 5. The observed lower mean EC_{50} estimates (25–53 μg L^{-1}) and steep concentration–effect relationship (γ of 3.4–13.5) for HR, MAP and cFTOE indicate that these changes take place at lower dobutamine concentrations. In contrast, linearity of concentration-effect relationship within the studied concentration range for RVO, LVEF and mean EC_{50} estimate of 117 μg L^{-1} for LVO suggest improvement of cardiac function throughout the studied dose range. Prediction-corrected VPC plots for PD observations are presented in Figure 4, GOF plots of effect predictions in Supporting information Figures S1–S6 and bootstrap analysis results in Supporting information Table S1. Residual variability was best described with proportional error model, remaining >50% in PK observations and between 5–20% in PD observations.

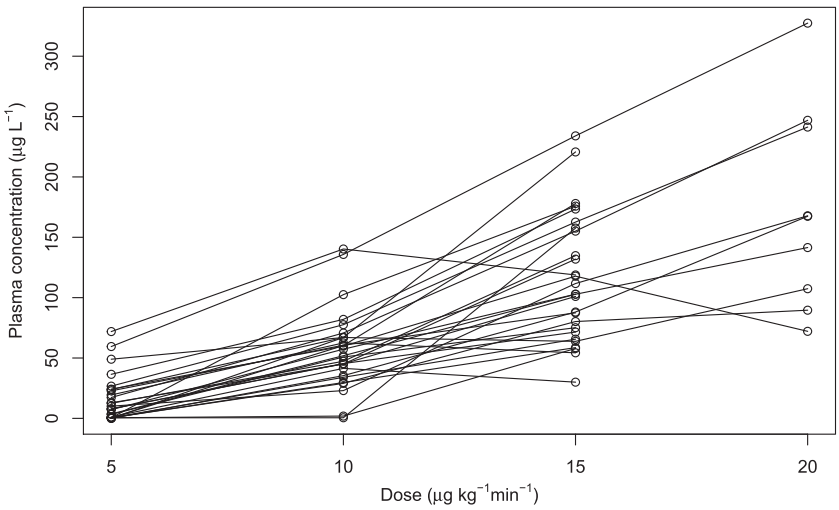

FIGURE 1 Measured dobutamine plasma concentrations at different continuous infusion rates. The connected observation points represent the same patient

TABLE 2 The linear pharmacokinetic model mean (standard error, SE) parameter estimates

Parameters	Fixed effect θ (SE)	BSV (SE)[a]	Shrinkage
CL (L h^{-1} 1618-g $^{-1}$)	41.2 (44.5)	29% (17.2%)	17%
V (L 1618-g $^{-1}$)	5.29 (0.821)	29% (17.2%)	17%
Shared BSV scale factor	1.34 (0.373)	-	-
Hill	2.67 (1.90)	NE	NE
PMA_{50} (weeks)	37.4 (30.6)	NE	NE
Residual error (proportional)	0.581 (0.229)	-	5%

θ, population typical parameter value; NE, not estimated; BSV, between subject variability;
[a]presented as coefficient of variation, calculated as: (square root of ω^2)·100%; CL, clearance; V, volume of distribution; Hill, the sigmoidicity coefficient of maturation of CL; PMA_{50}, the PMA when the maturation of the CL reaches 50% of adult values

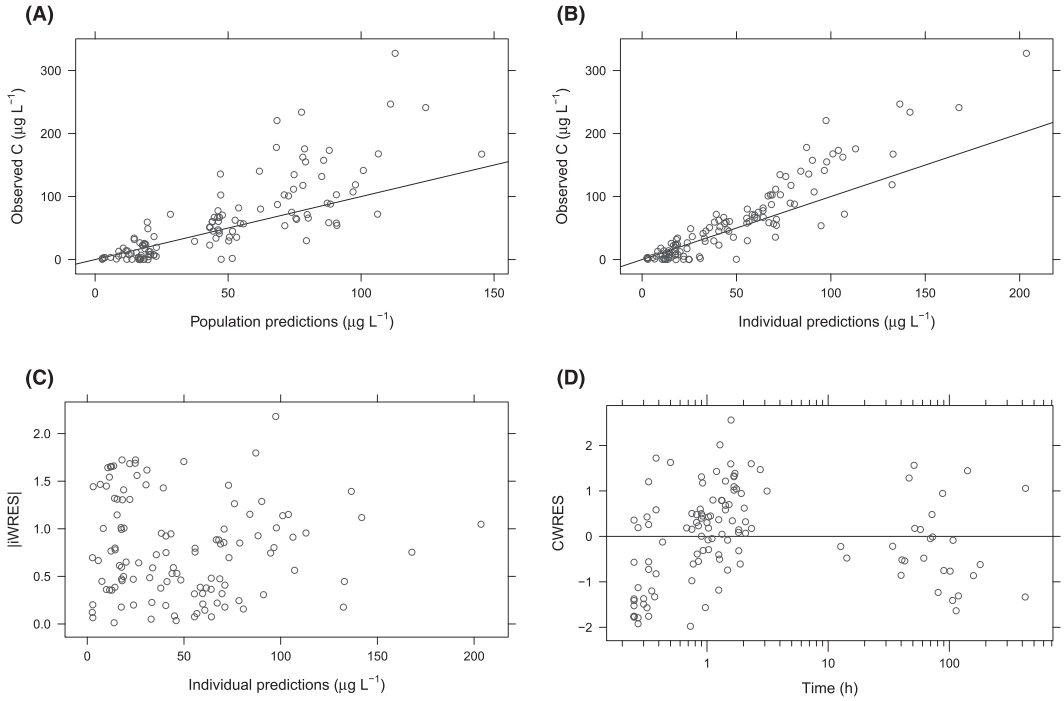

FIGURE 2 Basic goodness-of-fit plots of the final linear pharmacokinetic model: (A) observed *vs* population predicted dobutamine plasma concentrations (C); (B) observed *vs* individual predicted dobutamine plasma concentrations (C); (C) absolute value of individual weighted residuals (|iWRES|) *vs* individual predictions; (D) conditional weighted residuals (CWRES) over time (log-scale)

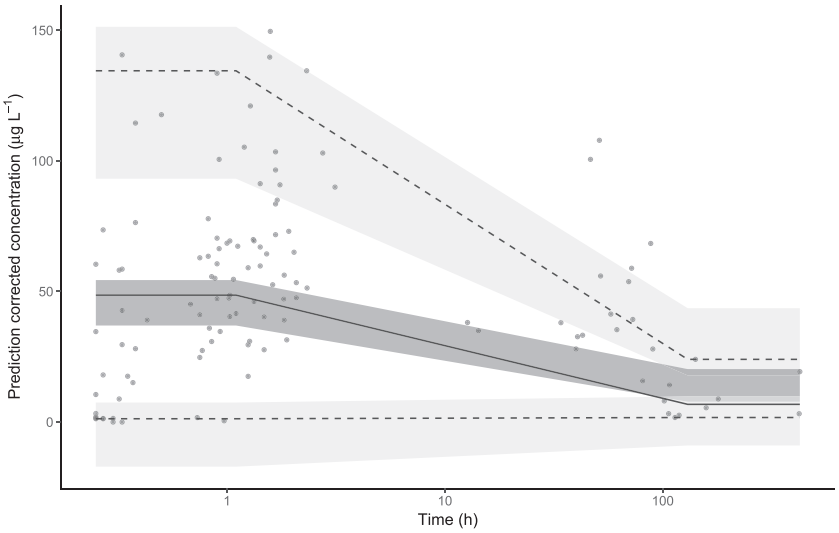

FIGURE 3 Prediction-corrected visual predictive check (VPC) of 1000 simulated concentration–time datasets from the final linear pharmacokinetic model. Open circles represent the observations, solid line the 50th, dashed lines the 2.5th and 97.5th percentiles, shaded areas the 95% confidence intervals of the corresponding predicted dobutamine concentrations

TABLE 3 Objective function values of tested pharmacokinetic–pharmacodynamic models

PD model structure	RVO	LVO	LVEF	HR	HR + K_{EO}	MAP	MAP+K_{EO}	cFTOE	cFTOE+K_{EO}
Linear	1849	1806	1451	7655	7598	5418	5418	−5080	−5108
E_{max}	1847	1801	1451	7654	7513	5240	5145	−5288	−5139
Sigmoidal E_{max}	1847	1797	1451	7457	7411	5076	5101	−5567	−5152

RVO, right ventricular cardiac output; LVO, left ventricular cardiac output; LVEF, left ventricular ejection fraction; HR, heart rate; K_{EO}, equilibration rate constant between effect- and observed (plasma) compartment, indicating that effect compartment was added to the model; MAP, mean arterial blood pressure; cFTOE, cerebral fractional oxygen extraction; underlined objective function values indicate the final models.

TABLE 4 Final pharmacokinetic–pharmacodynamic (PKPD) model mean (standard error, SE) parameter estimates for right and left ventricular cardiac output (RVO; LVO) and left ventricular ejection fraction (LVEF)

Model and parameters	Fixed effect θ (SE)	BSV (SE)[a]	Shrinkage
PKPD model for RVO effect			
CL (L h^{-1} 1618-g $^{-1}$)	41.0 (3.15)	27% (18.7%)	18%
V (L 1618-g $^{-1}$)	5.31 (0.753)	27% (18.7%)	18%
Shared BSV scale factor	1.50 (0.479)	-	-
E_0 (mL kg^{-1} min^{-1})	151 (12.8)	41% (22.2%)	3%
SL	0.214 (0.067)	NE	NE
Pharmacokinetic residual error (proportional)	0.583 (0.052)	-	8%
Pharmacodynamic residual error (proportional)	0.184 (0.014)	-	8%
PKPD model for LVO effect			
CL (L h^{-1} 1618-g $^{-1}$)	40.7 (3.03)	25% (17.5%)	21%
V (L 1618-g $^{-1}$)	5.14 (0.726)	25% (17.5%)	21%
Shared BSV scale factor	1.33(0.490)	-	-
E_0 (mL kg^{-1} min^{-1})	131 (9.64)	36% (19.8%)	3%
γ	2.82 (1.25)	NE	NE
EC_{50} (μg L^{-1})	117 (37.0)	NE	NE
E_{max} (mL kg^{-1} min^{-1})	157 (21.8)	44% (39.7%)	29%
Pharmacokinetic residual error (proportional)	0.589 (0.053)	-	11%
Pharmacodynamic residual error (proportional)	0.167 (0.015)	-	11%
PKPD model for LVEF effect			
CL (L h^{-1} 1618-g $^{-1}$)	41.2(3.22)	28% (19.3%)	17%
V (L 1618-g $^{-1}$)	5.26(0.753)	28% (19.3%)	17%
Shared BSV scale factor	1.38(0.434)	-	-
E_0 (%)	63.5 (1.46)	9% (5.6%)	10%
SL	0.0285 (0.0145)	NE	NE
Pharmacokinetic residual error (proportional)	0.580 (0.051)	-	7%
Pharmacodynamic residual error (proportional)	0.098 (0.007)	-	7%

θ, population typical parameter value; NE, not estimated; BSV, between subject variability;
[a]presented as coefficient of variation, calculated as: (square root of ω^2)·100%; CL, clearance; V, volume of distribution; E_0, estimated baseline value of PD parameter; SL is the slope of the linear relationship between effect and concentration; γ, steepness of concentration–effect relationship; EC_{50}, concentration at half-maximal effect; E_{max}, estimated maximum value of PD parameter

3.2 | Clinical outcome

Twenty-one serious adverse events in 14 patients were observed during the study period. Four patients died of gastric perforation (1), necrotising enterocolitis with intestinal perforation (1) or pulmonary intestinal emphysema (2) combined with haemolysis and pulmonary hypertension in 1 case. Deterioration of respiratory status requiring intubation with invasive ventilation and intestinal perforation occurred in 2 patients each, 1 patient had ileus as a complication of surgery for anal atresia. None of the aforementioned serious adverse events were considered to be related to dobutamine.

Twenty-seven patients had cerebral ultrasonography performed within the follow-up period, intraventricular haemorrhage grade III–IV occurred in 2, grade I-II in 4, periventricular leucomalacia in 3 and other intracranial pathologies in 3 patients.

4 | DISCUSSION

The present study describes for the first time dobutamine population PK and PD in critically ill neonates during the postnatal transitional period. The main findings were that: (i) within the clinically relevant dose range, dobutamine PK was well described by 1-compartment linear model; (ii) PK BSV was related to BW and PMA; (iii) the changes in RVO, LVO, LVEF, HR, MAP and cFTOE were concentration related and described by linear or sigmoidal E_{max} models.

4.1 | Dobutamine PK

Dobutamine is metabolized predominantly through plasma catechol-O-methyltransferase and sulfoconjugation, with renal elimination of inactive metabolites and small extent of unchanged dobutamine.[11,24]

TABLE 5 Final pharmacokinetic–pharmacodynamic (PKPD) model mean (standard error, SE) parameter estimates for heart rate (HR), mean arterial blood pressure (MAP) and cerebral fractional tissue oxygen extraction (cFTOE)

Model and parameters	Fixed effect θ (SE)	BSV (SE)[a]	Shrinkage
PKPD model for HR effect			
CL (L h^{-1} 1618-g $^{-1}$)	42.3 (3.22)	27% (18.0%)	15%
V (L 1618-g $^{-1}$)	5.42 (0.766)	27% (18.0%)	15%
Shared BSV scale factor	1.72 (0.421)	-	-
E_0 (min^{-1})	138 (4.2)	15% (8.1%)	4%
γ	3.36 (0.326)	NE	NE
K_{E0} (h^{-1})	6.59 (2.18)	NE	NE
EC_{50} (μg L^{-1})	39.2 (5.56)	50% (32.2%)	21%
E_{max} (min^{-1})	172 (2.5)	5% (3.1%)	28%
Pharmacokinetic residual error (proportional)	0.590 (0.052)	-	3%
Pharmacodynamic residual error (proportional)	0.051 (0.001)	-	3%
PKPD model for MAP effect			
CL (L h^{-1} 1618-g $^{-1}$)	37.2 (2.88)	24% (16.6%)	4%
V (L 1618-g $^{-1}$)	4.88 (0.958)	24% (16.6%)	4%
Shared BSV scale factor	3.62 (0.760)	-	-
E_0 (mmHg)	39.7 (1.75)	22% (11.8%)	2%
γ	13.5 (2.94)	NE	NE
EC_{50} (μg L^{-1})	25.4 (2.00)	NE	NE
E_{max} (mmHg)	41.9 (2.19)	26% (13.9%)	4%
Pharmacokinetic residual error (proportional)	0.675 (0.062)	-	2%
Pharmacodynamic residual error (proportional)	0.065 (0.001)	-	2%
PKPD model for cFTOE effect			
CL (L h^{-1} 1618-g $^{-1}$)	37.2 (3.61)	35% (21.5%)	9%
V (L 1618-g $^{-1}$)	4.80 (0.993)	35% (21.5%)	9%
Shared BSV scale factor	2.42 (0.333)	-	-
E_0	0.227 (0.023)	50% (26.8%)	2%
γ	3.65 (0.573)	NE	NE
EC_{50} (μg L^{-1})	52.9 (7.26)	NE	NE
E_{max}	0.206 (0.027)	60% (36.2%)	9%
Pharmacokinetic residual error (proportional)	0.653 (0.061)	-	2%
Pharmacodynamic residual error (proportional)	0.181 (0.004)	-	2%

θ, population typical parameter value; NE, not estimated; BSV, between subject variability;
[a]presented as coefficient of variation, calculated as: (square root of ω^2)·100%; CL, clearance; V, volume of distribution; E_0, estimated baseline value of PD parameter; SL is the slope of the linear relationship between effect and concentration; γ, steepness of concentration-effect relationship; K_{E0}, the equilibration rate constant between effect- and observed (plasma) compartments; EC_{50}, concentration at half-maximal effect; E_{max}, the estimated maximum value of PD parameter

In previous paediatric studies an extremely wide BSV in dobutamine plasma CL has been noticed[7,9] and explained by variation in sulfoconjugation and renal function.[11] Maturation of these elimination processes is not well understood. In the present study, the variation in CL was well described with allometric scaling to population median BW with power coefficient of 0.75 and exponential E_{max} maturation function with estimation of PMA_{50} and Hill coefficient from PK data.[21] The estimated mean parameter values of 37.4 weeks for PMA_{50} and 2.67 for Hill coefficient are similar to those identified for CL maturation in other drugs in neonates.[21] This approach yielded a shared BSV coefficient of 29% for CL and V, which is notably smaller than described earlier for dobutamine CL.

There is 1 study reporting highly variable V of dobutamine with a mean (range) of 1.14 (0.09–5.65) L kg^{-1} in paediatric patients aged 1 month to 16 years,[12] the mean value being higher than reported in adults (0.202 L kg^{-1}).[25] The typical value for V of 5.29 L 1618-g $^{-1}$ or 3.27 L kg^{-1} in the present study population is even higher than the paediatric study.[12] Higher V of a water-soluble agents in neonates in their first days of life can be explained by significantly higher total body water content, which undergoes major reduction (accompanied

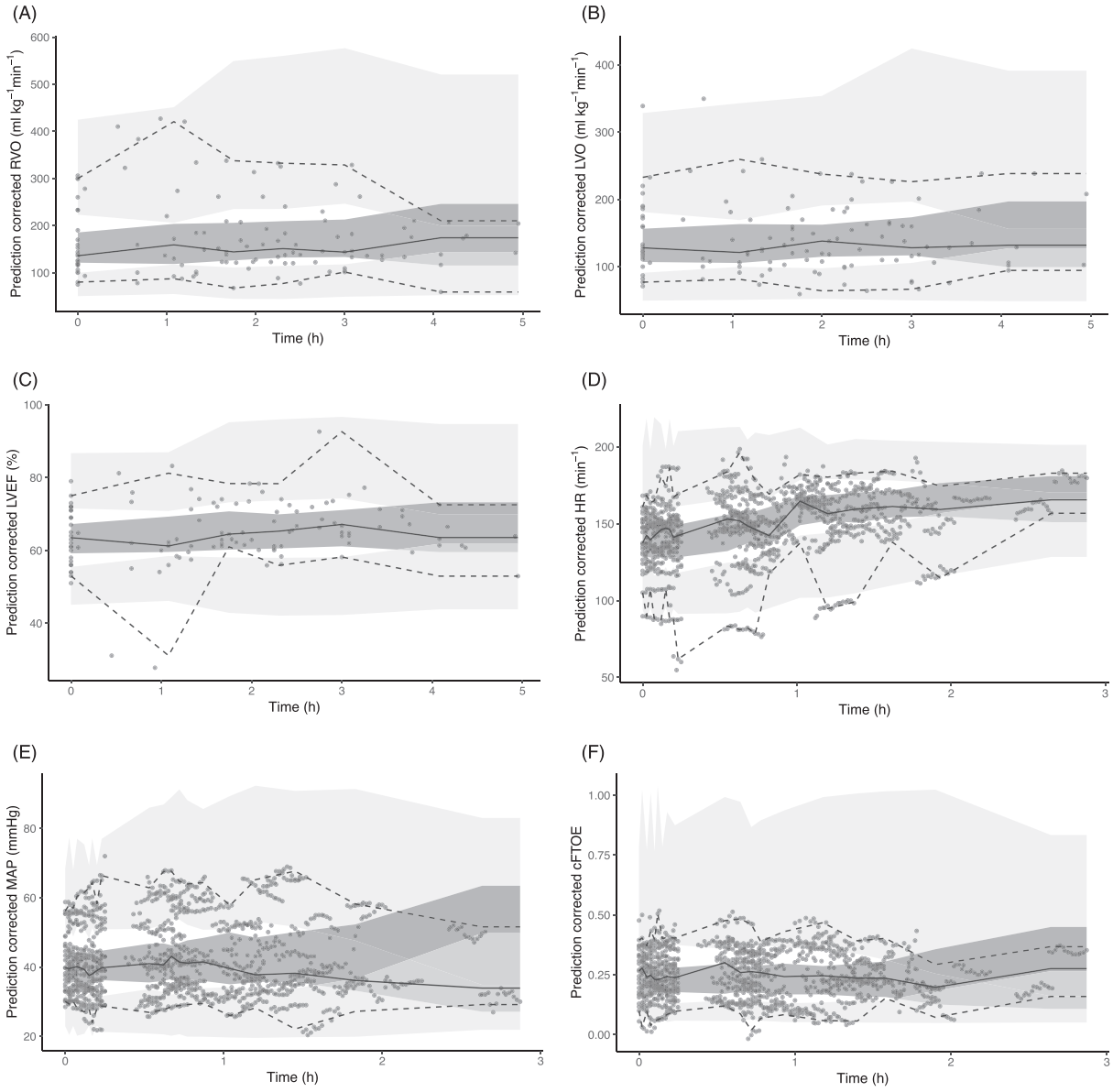

FIGURE 4 Prediction-corrected visual predictive check (VPC) of 1000 simulated effect–time datasets from the final pharmacokinetic–pharmacodynamic models. Circles represent the observations, solid line the 50th, dashed lines the 2.5th and 97.5th percentiles, shaded areas the 95% CIs of the corresponding model predicted haemodynamic parameter values: (A) right ventricular cardiac output (RVO); (B) left ventricular cardiac output (LVO); (C) left ventricular ejection fraction (LVEF); (D) heart rate (HR); (E) mean arterial blood pressure (MAP); (F) cerebral fractional tissue oxygen extraction fraction (cFTOE)

by proportional weight loss) within the first 3–4 days of life,[26,27] as also described for milrinone.[28]

4.2 | Dobutamine PD

Dobutamine is known to increase HR and CO in neonates, whereas the effect of BP varies from no effect to minor increase.[7-9,13,14,29] According to our results, these effects occur at different concentration. The effect on MAP and HR can be observed at relatively low concentrations, with maximum effect reached within concentrations of 50 and 80 μg L^{-1}, respectively. The increase of mean HR from 138 to 172 min^{-1} is in accordance with previous studies.[7-9,13,29] The increase rather than decrease of MAP in response to dobutamine is potentially explained by developmental differences in vascular α- and β- AR expression. During early development cardiovascular α-AR expression is upregulated while maturation of β-AR lags behind,[30] preterm neonates are likely to respond to dobutamine with attenuated decreases in systemic vascular resistance and thus with more pronounced increase in BP.[6]

The additional effect on CO can be achieved with higher doses at least up to concentration of 200 μg L^{-1}. The improvement of CO

beyond maximum HR effect implicates the role of improved myocardial function and/or decreased systemic vascular resistance. Further increase in CO with dobutamine infusion rates 10–20 μg kg^{-1} min^{-1}has also been shown in critically ill children.[8]

Although with limited efficacy, dobutamine has also been shown to increase superior vena cava flow, which is considered to reflect cerebral blood flow.[29,31] The present study describes dobutamine effect to cFTOE, as a surrogate for cerebral blood flow. Decrease in cFTOE with dobutamine may refer to increase in cerebral blood flow.

The aim of neonatal circulatory management is to prevent cerebral hypoperfusion particular in preterm neonates where the cerebral autoregulation may be absent. Although the role of inotropes in prevention of prematurity-related brain injury has been difficult to establish, there is some evidence that early administration of dobutamine may be relatively safe. In a foetal sheep hypoxia-induced brain injury model, dobutamine pretreatment decreased neuroinflammation in the white matter and caudate and did not exacerbate cerebral injury or inflammation in the sham group.[4] In a neonatal study dobutamine was found to be associated with greater increase in systemic blood flow, reduced rates of severe periventricular/intraventricular haemorrhage and fewer disabilities at age 3 years, but combined rates of death or disability similar, compared with infants treated with dopamine.[29,32] The rate of serious cerebral complications in our study patients born before 32 weeks of gestation (2/16 for intraventricular haemorrhage III–IV and 2/16 for periventricular leucomalacia) was comparable to that described in previous studies in extremely and very preterm infants receiving early dobutamine treatment.[29,31]

The present PKPD analysis included most of the well described effects of dobutamine.[33] Describing population HD effect of dobutamine as a function of concentration gives the confidence that at the dose range of 5–20 μg kg^{-1} min^{-1} the medication is effective.

4.3 | Limitations of the study

The limited number of patents, and limited PK sampling, did not yield informative data on V (hence BSV could not be separately estimated for CL and V). As the smallest neonate weighed <500 g, only 3–5 plasma samples could be taken for research purposes, although an analytical micro-method for plasma sample volumes of 20 μL was developed.[16] Having only a few PK samples >200 μg L^{-1} in the dataset, we may not have been able to capture this end sufficiently. The relatively small number of patients limited the covariate analysis. Although adding postnatal age, concomitant medications, severity of illness/status in covariate analysis did not improve PK model fit in our study, a larger and more variable study sample may be needed to draw firm conclusions.[34] In neonatal PK studies, an important limitation/source of residual error is drug administration accuracy. Dilution of the formula, low infusion rates and large dead space may lead to discrepancy between the prescribed and actual infusion rates, resulting in PK observation residual error of >50%. Nevertheless, this considerably homogenous neonatal study population allowed us to model PK of dobutamine, describing the maturation of CL with PMA, and rich PD effect sampling allowed identification of relationships between concentration and HD effects with acceptable accuracy. Moreover, this study was conducted in real-life conditions, e.g. critically ill neonates on their first days of life, with all related challenges.

In conclusion, within the clinically relevant dose range, dobutamine PK in neonates is linear. BSV of dobutamine CL is partly explained by PMA and BW. Dobutamine effects on HD parameters as CO, LVEF, HR, MAP and cFTOE are concentration related during the period of transitional circulation. High BSV of the PD response suggests need for individual dose titration rather than targeting specific dosing regimen in neonates receiving dobutamine for stabilization of transitional circulation.

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The authors have no conflicts of interest to declare.

CONTRIBUTORS

M.H. conceived the study, participated in its design, collected, analysed the data and drafted the manuscript. M.-L.I. conceived the study, collected the data and was involved in revision of the manuscript. J.F.S. supervised the data analysis process and revised the manuscript. H.S. participated in data analysis and revision of the manuscript. T.J., M.R., K.U., K.K. and M.S. collected the data and were involved in revising the manuscript. K.T., R.V. and K.K. supported the work with liquid chromatography–mass spectrometry quantification of dobutamine. J.S. participated in study design process and critically revised the manuscript. T.M. conceived the study, participated in its design and drafted the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILTY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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