

Population pharmacokinetics and dosing of milrinone after patent ductus arteriosus ligation in preterm infants

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ABSTRACT

Objective: The postoperative course of patent ductus arteriosus (PDA) ligation is often complicated by postligation cardiac syndrome (PLCS), occurring in 10-45% of operated infants. Milrinone might prevent profound hemodynamic instability and improve the recovery of cardiac function in this setting. The present study aimed to describe the population pharmacokinetics (PK) of milrinone in premature neonates at risk of PLCS and give dosing recommendations.

Design: A prospective single group open label PK study.

Settings: Two tertiary care NICU-s: Tallinn Children's Hospital and Tartu University Hospital, Estonia.

Patients: 10 neonates with postmenstrual age (PMA) of 24.6 – 30.1 weeks and postnatal age of 5-27 days undergoing PDA ligation and at risk of PLCS, based on echocardiographic assessment of left ventricular output of less than 200 ml/kg/min 1 hour after the surgery.

Interventions: Milrinone at a dose of 0.73 µg/kg/min for 3 hours followed by 0.16 µg/kg/min for 21 hours. Four blood samples from each patient for milrinone plasma concentration measurements were collected.

Measurements and main results: Concentration-time data of milrinone were analyzed with nonlinear mixed-effects software (NONMEM version 7.3). Probability of target attainment (PTA) simulations gave a dosing schedule that maximally attains concentration targets of 150-250 µg/L. Milrinone PK was described by a one-compartmental linear model with allometric scaling to bodyweight and an age maturation function of glomerular filtration rate. Parameter estimates for a patient with the median weight were 0.350 (L/h) for clearance and 0.329 (L) for volume of distribution. The best PTA was achieved with a loading dose of 0.50 µg /kg/min for 3 hours followed by 0.15 µg/kg/min (PMA<27 weeks) or 0.20 µg/kg/min (PMA≥27 weeks).

Conclusions: Population PK modeling and simulations suggest a slow loading dose followed by maintenance infusion to reach therapeutic milrinone plasma concentrations within the timeframe of the PLCS.

INTRODUCTION

Patent ductus arteriosus (PDA) management in preterm infants has been controversial over the decades. Today no consensus exists on the definition of hemodynamically significant PDA and it remains difficult to identify patients most likely to benefit from surgical duct closure. Observational studies show 10-21% incidence of surgical closure (1 – 4).

The postoperative course is complicated by acute cardiorespiratory deterioration or postligation cardiac syndrome (PLCS) in 10-45% of operated infants (5 – 8). The mechanisms behind postligation hemodynamic instability are complex and likely involve both, myocardial dysfunction and vascular tone dysregulation (9, 6). PLCS typically occurs between 6 to 12 hours after surgery (7, 10), providing a window for early (preventive) intervention (11). However, information on pre- and postoperative factors that can predict postligation cardiovascular compromise is scarce. In one retrospective analysis of targeted neonatal echocardiography in 62 infants undergoing PDA ligation, left ventricular output (LVO) <200 ml/kg/min at 1 hour after PDA ligation appeared a sensitive predictor of systemic hypotension and need for inotropes (11).

Milrinone is a selective phosphodiesterase type III inhibitor with positive inotropic and vasodilator ('inodilator') effect. Both effects are independent of beta- adrenergic stimulation (12). Milrinone has been found to prevent respiratory deterioration and hemodynamic instability and improve the recovery of cardiac function after surgical PDA closure (11, 13, 14), although this finding has not been uniformly confirmed (15, 16). Suboptimal dosing has been suggested as possible reason for the variable efficacy (16). This idea is supported

by our previous simulation study, aiming to optimize milrinone dosing regimen for current prospective clinical evaluation (17). Early pharmacokinetic (PK) studies in healthy subjects confirmed that milrinone is predominately eliminated by renal excretion with a fraction excreted unchanged of approximately 80% (12). To the best of our knowledge the PK of milrinone has not been described in preterm neonates undergoing PDA ligation surgery. Data from the first days of life in term (18) and very preterm neonates (19) or pediatric (mostly open heart cardiac surgery) population (20 – 23) may not be directly applicable to older preterm neonates, due to rapid changes in physiology and renal function maturation during the first weeks of life and/or after open heart cardiac surgery (23). Therefore, the prior simulation study (17) and the present study were undertaken to describe the population PK of milrinone in premature neonates at risk of PLCS with the aim to develop dosing recommendations for this specific age group.

MATERIALS AND METHODS

The study was approved by the Ethics Committee of the University of Tartu, and registered at the EU Clinical Trials Register under number 2015-000486-31.

A prospective two-center study was performed in the neonatal intensive care units in Tallinn Children's Hospital, Tallinn, Estonia and Tartu University Hospital, Tartu, Estonia. All neonates and infants up to 90 days of age requiring PDA ligation during the study period (June 2015 to October 2017), who had arterial and/or central venous line in place on clinical indication, were screened

for eligibility. Patients with renal failure (defined as renal replacement therapy or serum creatinine $>100 \mu\text{mol/l}$ or oliguria $<0.5 \text{ ml/kg/min}$ for at least 6 hours), major congenital malformation or known metabolic disease, hypersensitivity or other contraindication to milrinone, expected survival of less than 72 hours, and patients recruited in another clinical trial of medical product, were excluded. Written informed consent was signed by parent(s) or guardian(s) before the study inclusion.

Study drug administration and PK sampling

Milrinone was started in infants at risk of PLCS, based on echocardiographic assessment of LVO of less than 200 ml/kg/min 1 hour after the end of PDA surgery (11). Milrinone (Corotrope 1mg/ml , Sanofi-Aventis France) was diluted with 0.9% NaCl to a concentration of $15 \mu\text{g/ml}$ within 20 min before administration. A loading dose of $0.73 \mu\text{g/kg/min}$ over 3 hours was followed by maintenance infusion of $0.16 \mu\text{g/kg/min}$ for 21 hours, according to the prior simulation study results (17). Milrinone infusion rate could be changed or discontinued at the discretion of the treating physician. To ensure adequate intravascular volume, all infants received a bolus of 9 ml/kg of normal saline over three hours with the milrinone loading dose infusion. Further hemodynamic support with fluid boluses and inotropes was provided according to the routines of the unit.

Blood samples of 0.3 ml were collected from an indwelling arterial line into Na-heparin vials at the end of loading infusion (3h), at the end of maintenance

infusion (24 h) and twice after the end of treatment (28 h, 36 h). Actual blood collection time was recorded with the precision of the nearest minute. Blood was centrifuged immediately and stored at - 80 °C (up to 12 h storage at -20 °C prior to transfer to -80 °C was accepted). Milrinone concentrations were measured by ultra-high performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS; Supplemental digital content 1).

Patient monitoring

All PDA ligation surgeries were performed in NICU by one experienced surgeon, using intravenous anesthesia with ketamine, fentanyl and atracurium.

Echocardiography was done 1 hour before PDA surgery, 1 hour after duct ligation, 3 and 24 hours after the start of study medication infusion. Studies were performed by 4 cardiologists, using the Vivid 7 Dimension or Vivid E9 cardiovascular ultrasound system (GE Healthcare, USA) with 10 or 12 MHz transducers, respectively. LVO was calculated by obtaining the pulsed wave Doppler blood velocity in the aortic root and measuring the diameter of the aortic root (24).

Echocardiography recordings from 3 infants attained by 3 different cardiologists were re-analyzed by one observer (T) for intra- and inter-observer variability, according to a recent recommendation (25).

Heart rate, arterial blood pressure and other vital signs were monitored with IntelliVue MP30, M70 or MX800 patient monitors (Philips Medical Systems, The Netherlands) and recorded with 2.5 sec intervals by BedBase software

(University Medical Center Utrecht, the Netherlands) starting from 1 hour prior to PDA surgery until the end of treatment with study medication. All neonates were monitored for adverse events for 7 days after the end of treatment with study medication.

PK analysis

Concentration-time data were analyzed with nonlinear mixed-effects software NONMEM version 7.3 (ICON Development Solutions, MD, USA). The first-order conditional estimation method with interaction was used. One- and two-compartment linear structural models were considered. An additive residual error model, a proportional residual error model, and a combination of the two were 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 ($P < 0.05$ by likelihood ratio test for 1 degree of freedom). Allometric scaling was used a priori to standardize PK parameters to population mean bodyweight, and a maturation function, describing the maturation of the glomerular filtration rate (GFR) with postmenstrual age (PMA) was applied to scale clearance:

$$\text{maturation function} = \frac{PMA^{Hill}}{PMA_{50}^{Hill} + PMA^{Hill}}$$

where Hill is the sigmoidicity coefficient and PMA_{50} is the PMA when the maturation of the GFR reaches 50% of adult values (26). Fixed parameters from a previous study (27) were used to scale clearance (CL) and volume of

distribution (Vd). As in previous neonatal studies, allometric exponents were fixed to 0.632 for CL and 1 for Vd (28, 29).

Other patient covariates (such as sex, Apgar, albumin level, fluid intake, cardiac output and co-administration with dopamine or dobutamine) were tested for correlation with model parameters.

To evaluate the model, population and individual predicted vs. observed milrinone concentration measurements, and conditional weighted residual error vs. time plots were used. A nonparametric bootstrap with 2000 replicates using the software Perl speaks NONMEM (PsN) was undertaken to assess the robustness of parameter estimates to changes in data. A visual predictive check (VPC) was performed to assess the simulation properties of the final model.

Probability of target attainment (PTA) simulations

PTA simulations aimed to develop a dosing schedule that maximally attains milrinone concentration within the pre-specified target range of 150-250 µg/l by the 6th postoperative hour for the majority of patients (17), as PLCS has been found to occur 6–12 h after ligation (6,7). All simulations were conducted using R software version 3.3.3. (30)

Patient covariate (PMA and weight) data from all PDA ligation patients treated in the study units between 2013-2017 were bootstrapped to 1000 samples. Next, patient PK parameters were simulated using parameter equations and variability estimates from the PK model. Milrinone time-concentration curves were simulated with doses ranging from 0 to 1 µg/kg/min, with a step of 0.05

$\mu\text{g}/\text{kg}/\text{min}$. The dosing scheme consisted of a 3-hour loading dose immediately followed by a 21-hour maintenance infusion, as justified in our prior study (17). An optimal dose maximized the mean of PTA values obtained at 3, 6, 12, 18 and 24 hours of treatment. The PTA estimates targeted within 150 and 250 $\mu\text{g}/\text{l}$ were adjusted with the probability of concentrations above 300 $\mu\text{g}/\text{l}$, to minimize possible side effects.

A second set of analogous simulations additionally assessed the effect of PMA on target attainment. Patient population was divided by a PMA breakpoint into two subgroups of different maintenance doses. The optimization searched for a combination of parameter values yielding maximal PTA. All simulation details are presented in supplemental digital content 2.

RESULTS

During the study period 21 neonates underwent PDA ligation surgery, 14 of them were recruited into the study (Figure 1). The reasons for exclusion were participation in another clinical study (3 patients), absent parental consent (2 patients) and renal failure with creatinine $> 100 \mu\text{mol}/\text{l}$ (2 patients).

Ten out of 14 patients had LVO $< 200 \text{ ml}/\text{kg}/\text{min}$ and were treated with milrinone according to the study protocol. No dose adjustments or preliminary discontinuation of therapy was performed. Mean PMA and weight on the day of PDA ligation were 27.4 weeks and 857.3 g, respectively, and all but three required invasive respiratory support (Table 1).

Milrinone plasma concentrations

In total 40 time-concentration data points, 4 from each patient were available for PK analysis (Supplemental digital content 3). The median (range) plasma concentrations of the drug at 3, 24, 28 and 36 h were 279.7 (213.6 – 366.2), 186.7 (84.3 – 361.0), 105.1 (27.1 -227.3) and 45.4 (3.0 – 113.3) µg/l, respectively.

PK model

A one-compartmental linear structural model with proportional error model was chosen to describe the population PK data (Δ OFV= 1 with two-compartmental model). Adding allometric scaling to bodyweight and maturation function of GFR of the model parameters to the structural model reduced the OFV from 291.9 to 273.1. The final milrinone population PK model parameters are described in equations:

$$CL = \theta_{CL} \cdot \left(\frac{WD1}{857.3}\right)^{0.632} \cdot \frac{PMA^{3.4}}{47.7^{3.4} + PMA^{3.4}}$$

$$Vd = \theta_{Vd} \cdot \left(\frac{WD1}{857.3}\right)^1$$

where CL is clearance, Vd is volume of distribution, θ_{CL} and θ_{Vd} are the population typical values for clearance and volume of distribution, respectively,

WD1 is body weight in grams and PMA the postmenstrual age in weeks on the day of PDA ligation.

Population and individual predicted vs. observed and residual error plots of milrinone plasma concentrations from the final model are shown on Figure 2, VPCs for the model on Figure 3. The final population mean (coefficient of variation) parameter estimates for CL and Vd were 0.350 L/h/857.3g (11.6%) and 0.329 L/857.3g (32.6%), respectively. Comparison with bootstrap results demonstrates that the model is robust to changes in data (Table 2).

Dose optimization and PTA

Demographic data from a total of 52 patients with mean (range) PMA and bodyweight of 27.6 (23.3 – 37.3) weeks and 875.5 (500 – 2351) g, respectively, underwent PDA ligation during the period of 2013-2017 and were included in dose optimization simulations. The best PTA was achieved with a 3-hour loading dose of 0.50 µg/kg/min followed by maintenance infusion rate of 0.15 µg/kg/min (Supplemental digital content 4). Variation of maintenance doses by PMA improved PTA from 0.561 to 0.589 with the PMA threshold of 27 weeks and maintenance doses of 0.15 and 0.20 µg/kg/min, in PMA<27 and PMA≥27 group respectively (Figure 4 and Supplemental digital content 5).

Cardiac output, milrinone side effects and adverse events

None of the study patients developed PLCS. By 24 h of therapy LVO improved in all but two patients by an average (SD) of 54 (64) ml/kg/min (paired Wilcoxon test $p=0.037$; supplemental digital content 6). Intra- and inter-observer variability (mean \pm SD) of LVO measurements were 10 ± 5 ml/kg/min (6 ± 4 %) and 37 ± 43 ml/kg/min ($15\pm 16\%$), respectively (Supplemental digital content 7). Tachycardia ($HR > 200 \text{ min}^{-1}$) registered in 3 patients during milrinone therapy with cumulative time over the threshold of 6, 3 and 37 min, respectively, triggered no change in treatment. Arterial hypotension ($MAP < 30 \text{ mmHg}$) was registered in 6 patients with cumulative time under the threshold of 21, 327, 183, 13, 101 and 30 min, respectively. Vasoactive treatment was started in two cases, one patient was already on dopamine with no increase in dose during milrinone treatment. One patient with thrombocytopenia (platelet count $< 100 \times 10^9 \text{ L}^{-1}$) present prior to PDA ligation was treated with platelet transfusion.

DISCUSSION

The study provides milrinone population PK model and dosing recommendations for preterm neonates to prevent hemodynamic and respiratory deterioration after PDA ligation. The dose recommendations are different from the existing suggestions, derived either from data obtained in preterm neonates in very first days of their life, or from infants undergoing heart surgery.

Consistent with previous data, suggesting the effect of bodyweight and renal function maturation (19, 21 – 23, 31) on the PK of milrinone, a one-compartmental model with allometric scaling to population mean bodyweight and maturation function of elimination described the data best. Scaling PK parameters to size and PMA has been proposed as a standard for describing PK in a range of age groups including preterm neonates (32), and fixing the age and maturation parameters in neonatal studies with limited age and weight ranges is also common (28, 29, 33). Indeed, the principle of delineating size from other potentially important covariates has been applied in many pediatric settings including immunology (34). As milrinone is eliminated primarily by kidneys (35), we chose maturation function of GFR (27) for elimination. In order to compare our results with other similar studies not using this covariate structure, we chose to standardize PK parameters to the population mean weight (857.3 g). Considering the small homogenous population and dosing recommendations for the specific indication, this approach was preferred over the 70 kg standard weight (26). The uncertainty in predicting mature clearance, based on data only from neonatal populations with age below maturation half time (PMA₅₀=47.7 weeks in the model) has been pointed out previously by Anderson and Holford (36).

The lower population mean Vd (0.329 vs. 0.512 L) and higher CL (0.350 vs. 0.035 L/h) found in our study compared to that described previously in preterm infants studied within the first three days of life (19) is probably explained by different postnatal age of the study populations. Significant reduction in total body water (accompanied by proportional weight loss) within the first three to

four days of life (37) results in lower Vd for water soluble agents (38). All but one of our patients were over one week of age, when this reduction in total body water has effectively taken place. Similarly, GFR doubles within the first week of life, while significant maturation of the renal secretion function occurs only over the first 3-4 weeks of life (39). Accordingly, the dosing of milrinone, based on our prior simulation study (17) using milrinone population PK model developed in preterm neonates within the first days of life (19), resulted in higher than expected loading and lower maintenance concentrations in current study population. This underlines the need for prospective validation and further refining of dosing regimens, recommended solely based on simulation studies, especially in populations, where major physiological changes in organ function and maturation take place within weeks, like preterm neonates.

Similar to our approach, a physiology based pharmacokinetic drug-disease model study has suggested the need for milrinone loading infusion to ensure fast achievement of therapeutic plasma concentrations (31). Previously, Jain et al. have found a continuous infusion of 0.33 $\mu\text{g}/\text{kg}/\text{min}$ over 24 h to be effective in the prevention of PCLS (11). However, in a latter retrospective cohort of 86 patients six out of seven, who developed PLCS, were receiving milrinone according to this regimen. The authors suggested insufficient dose of milrinone to offload the LV and prevent late deterioration in myocardial performance as a possible reason for the evolution of low LVO (16). Our results support this idea. With milrinone loading infusion, targeting therapeutic plasma concentrations within 3 h from start of infusion, followed by a 21 h maintenance infusion, none of the 10 patients treated on similar indication (LVO <200 ml/kg/min),

developed PLCS. Yet, this finding should be interpreted with caution, as the study lacks statistical power to draw firm conclusions on clinical efficacy.

In order to minimize the risk of negative hemodynamic effects, we chose a lower target concentration in our *in silico* simulation study (150–200 µg/l) (17) compared to a previous population PK and dosing recommendation study by Paradisis et al. (180-300 µg/l) (19). Nevertheless, measured plasma milrinone concentrations during the treatment period were similar in current study and the randomized placebo controlled study by Paradisis et al. (40), 84 – 366 and 95 – 407 µg/l, respectively. Tachycardia and low blood pressure were the most common hemodynamic side effects in both studies. Paradisis et al. reported significantly higher HR and lower BP, but no difference in the incidence of hypotension, defined as mean BP <24 mm Hg for more than 30 minutes or a drop in mean BP >20% within 2 hours of commencing the infusion or in the number treated with additional inotropes, compared to placebo (40). In our study tachycardia did not trigger dose change or discontinuation of milrinone therapy, low blood pressure was present in 6 cases requiring treatment in two. In both cases 3 h milrinone concentrations exceeded 300 µg/l and the neonates had PMA <27 weeks. According to this scarce data, we adjusted our optimal dose finding simulations to avoid concentrations above 300 µg/l and included maturation of CL with PMA.

The PMA dependent CL of milrinone suggested improved concentration target attainment when differentiating maintenance doses according to PMA. Indeed, application of higher maintenance dose (0.20 instead of 0.15 µg /kg/min) for neonates with PMA ≥ 27 weeks reduced the proportion of patients with

simulated plasma concentrations below the target, however, at the cost of higher proportion exceeding 300 µg/l. According to the PTA simulation results, we would recommend the dosing regimen of 0.5 µg/kg/min 3h loading followed by 0.15 µg/kg/min maintenance infusion for infants PMA < 27 weeks and 0.5 µg/kg/min 3h loading followed by 0.2 µg/kg/min for infants PMA ≥ 27 weeks. The PD effect on blood flow and effectiveness of preventing PLCS of this dosing scheme will be the objective of future studies.

This study has several limitations. First, the small number of patients precluded the exploration of the impact of additional patient characteristics potentially affecting the PK of milrinone, including prior ibuprofen therapy and the status of renal function. Similarly, we cannot provide full PD analysis. However, considering the homogenous population, we believe that the study adds new information to improve the dosing of milrinone for the specific indication of PLCS prevention in preterm neonates without severe renal function impairment.

CONCLUSIONS

Pediatric PK data need to be collected in populations where physiological changes take place over short time periods. Rapid change in total body water content and GFR in the first weeks of a preterm infants life influences significantly the PK of milrinone. Age appropriate PK analysis and dosing recommendations will allow better-targeted efficacy and safety assessments. Slow loading dose of milrinone holds the advantage of reaching adequate plasma concentrations within the therapeutic window prior to the emergence of PLCS.

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FIGURE LEGENDS

Figure 1. Flowchart of the patient recruitment and treatment decision. LVO – left ventricular output.

Figure 2. Basic goodness-of-fit plots of the final PK model: (A) observed versus population predicted milrinone concentrations, (B) observed versus individual predicted milrinone concentrations, (C) absolute value of individual weighted residuals ($|iWRES|$) versus individual predictions, (D) conditional weighted residuals over time.

Figure 3. Visual predictive check (VPC) of 1,000 simulated concentration-time data sets from the final 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 milrinone concentrations.

Figure 4. Simulated concentration-time curves: (A) 3-hour 0.5 $\mu\text{g}/\text{kg}/\text{min}$ loading dose followed by a 21-hour maintenance dose of 0.15 $\mu\text{g}/\text{kg}/\text{min}$, (B) 3-hour 0.5 $\mu\text{g}/\text{kg}/\text{min}$ loading dose followed by a 21-hour maintenance dose of 0.15 $\mu\text{g}/\text{kg}/\text{min}$ in subjects under 27 weeks of PMA and 0.2 $\mu\text{g}/\text{kg}/\text{min}$ in subjects with $\text{PMA} \geq 27$ weeks. The lines show 2.5%, 50% and 97.5% percentiles of the simulated concentrations, shaded areas show bootstrapped 95% confidence intervals.

TABLES

Table 1. Demographics and clinical data of the treated patients

Table 2. Final parameter estimates with uncertainty from NONMEM output file and from the bootstrap analysis

SUPPLEMENTAL DIGITAL CONTENTS

1. Description of milrinone plasma concentration measurement method
2. Detailed description of probability of target attainment (PTA) simulations
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