POPULATION PHARMACOKINETICS OF MILRINONE IN INFANTS AND CHILDREN

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PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development

A project of the Best Pharmaceuticals for Children Act

Disclosures

- Nothing to disclose

Milrinone is a PDE-3 inhibitor with inotropic and vasodilatory properties

- Pharmacokinetics (PK)
  - Highly protein bound (77 – 96%)
  - Volume of distribution approximately 30 – 60 L/70kg
  - 83% of drug eliminated unchanged in the urine
  - Risk of toxic drug accumulation with renal dysfunction

- Pharmacodynamics (PD)
  - Adult therapeutic plasma concentration range 100 – 300 ng/mL
  - In children, hemodynamic effect at peak concentration of 235 ng/mL

- Milrinone is not approved for use in children
  - Routinely used post cardiac surgery
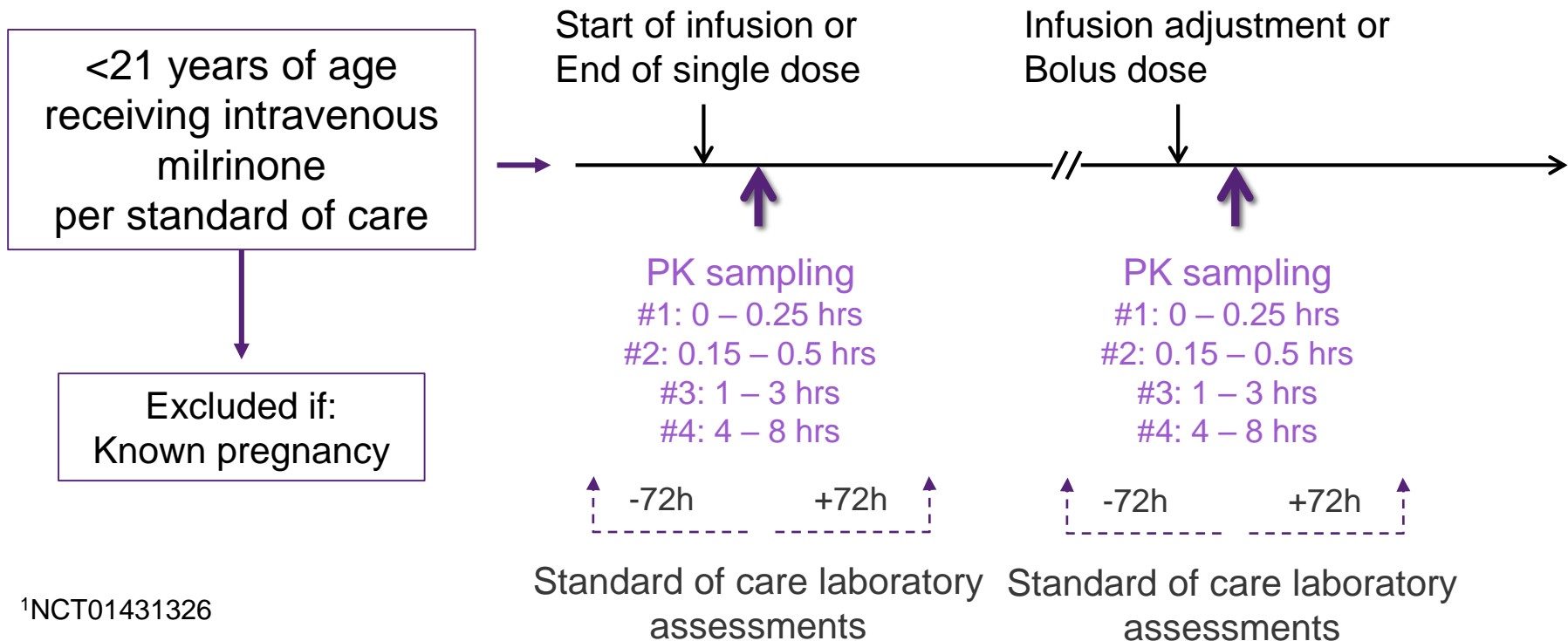 - Commonly used in heart failure conditions

Objective

- Develop a population pharmacokinetic (PopPK) model for milrinone in children ≤18 years of age

- Perform dose-exposure simulations to assess optimal milrinone dosing in children with variable renal function

Methods – POPS trial
Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care

<21 years of age receiving intravenous milrinone per standard of care

Excluded if:
Known pregnancy

Start of infusion or
End of single dose

Infusion adjustment or
Bolus dose

PK sampling
#1: 0 – 0.25 hrs
#2: 0.15 – 0.5 hrs
#3: 1 – 3 hrs
#4: 4 – 8 hrs

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-72h   +72h

-72h   +72h

Standard of care laboratory assessments

Standard of care laboratory assessments

[1]NCT01431326

Methods – PK modeling

- 1-, 2- , and 3- compartment models evaluated
  - Nonlinear mixed effect modeling (NONMEM v.7.4)
  - Estimates of population PK parameters and inter-individual variability
  - Covariate evaluation: gender, race, obesity, PMA and PNA, serum, ECMO, indication, surgery history, creatinine, creatinine clearance

- Milrinone dosing-exposure simulations
  - Surrogate PD target for efficacy: plasma concentration in the 100 – 300 ng/mL range

Results - 74 children contributed 111 PK samples

	Median (range)*
Age (years)	2.9 (0.01, 18)
Weight (kg)	13.1 (2.6-157.7)
Male, n (%)	39 (53%)
Serum creatinine (mg/dL)	0.5 (0.1-3.1)
Creatinine clearance (ml/min/1.73m2)	117.2 (13.1-261.3)
On ECMO, n (%)	17 (23%)
Infusion rate (mcg/kg/min)	0.5 (0.1-41)
PK samples per subject	2 (1 – 11)

*unless otherwise specified

Observed concentrations vs. time after last dose

All
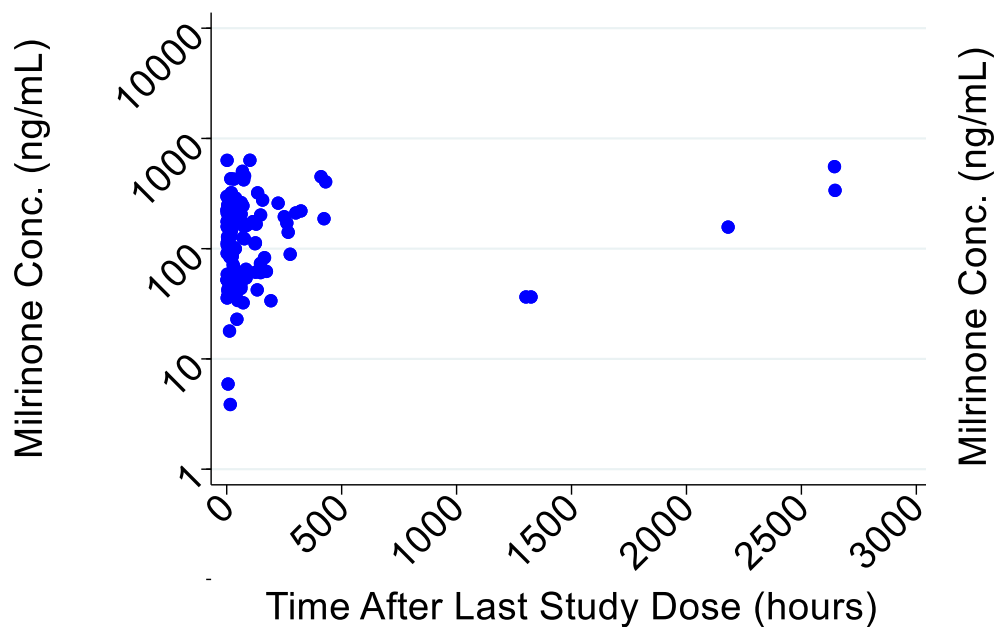
First 500 hours
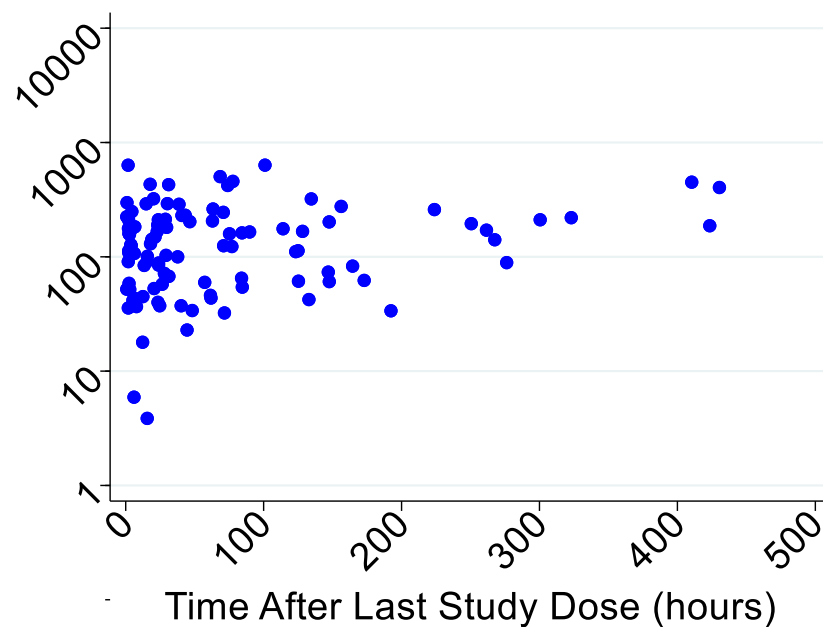
One – compartment population PK model

- $TVCL = 16.7 * (\frac{weight}{70})^{1.05} * (\frac{Creatinine\ clearance}{110})^{0.6}$

Parameters	Estimate (RSE)	Bootstrap Median (5th, 95th percentile)
CL_{70kg} (L/h)	16.7 (14%)	16.6 (13.6, 21.8)
V_{70kg} (L)	31.7 (30%)	32.8 (12.6, 134.6)
Power function for CrCL on CL	0.603 (22%)	0.61 (0.37, 0.85)
Allometric coefficient for weight on CL	1.05 (9%)	1.06 (0.9, 1.23)
IIV CL (CV%)	72 (26%)	70 (56, 85)
Residual proportional error (%)	32 (28%)	28 (19, 37)

RSE: relative standard error (%); IIV: inter-individual variability

Relationship between milrinone elimination and estimated GFR
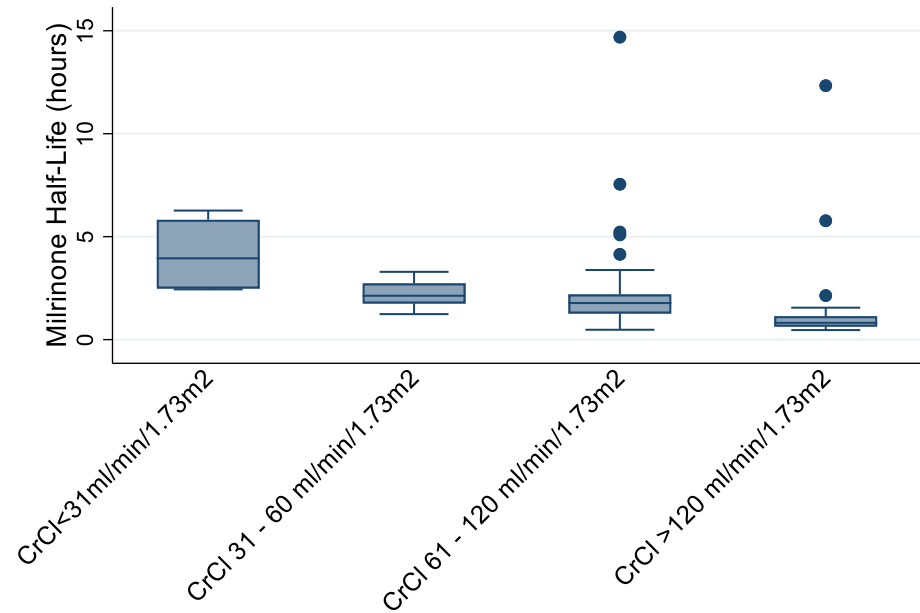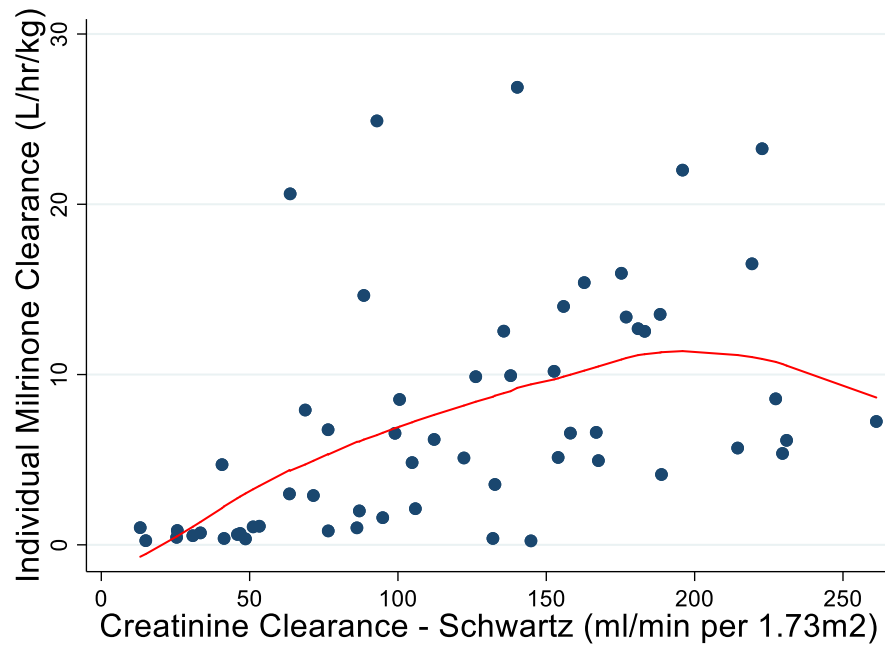
Milrinone dose simulation in 3kg neonate

25 mcg/kg load followed by 0.25 mcg/kg/min infusion
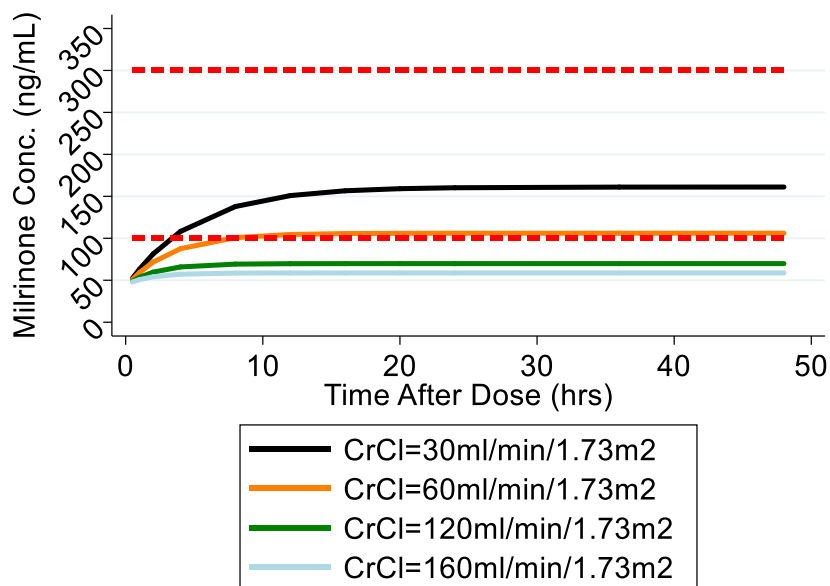
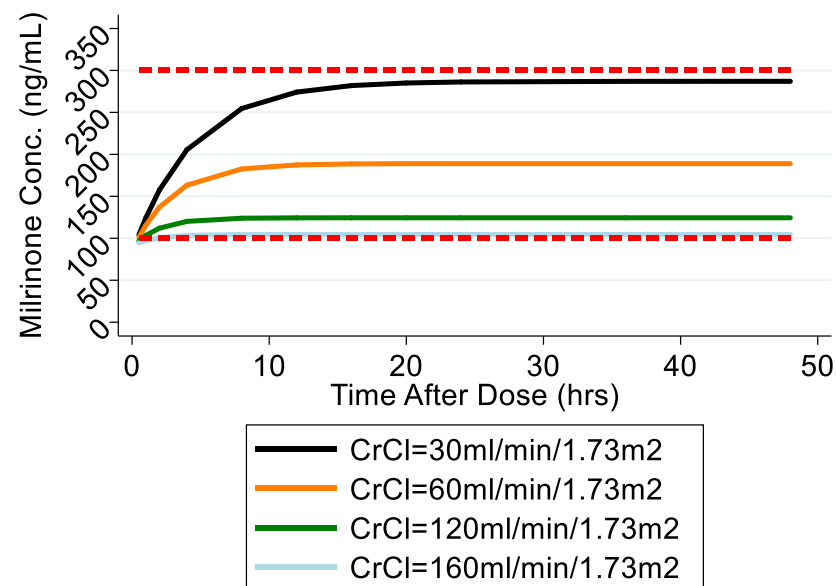50 mcg/kg load followed by 0.5 mcg/kg/min infusion
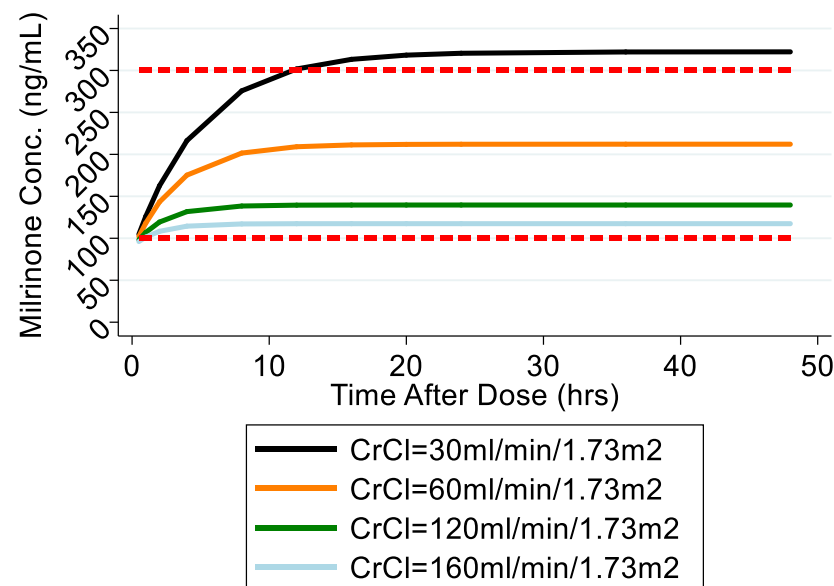
Milrinone dose simulation in 30kg child

25 mcg/kg load followed by 0.25 mcg/kg/min infusion
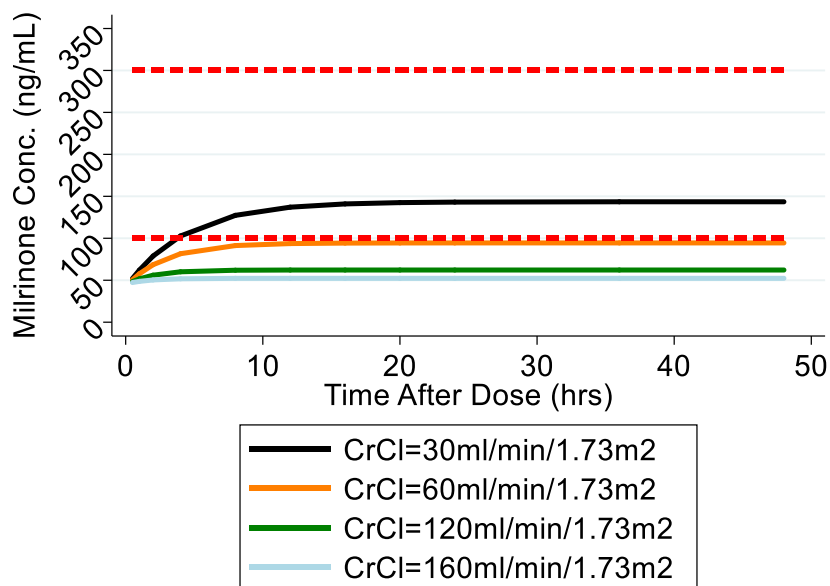
50 mcg/kg load followed by 0.5 mcg/kg/min infusion

Limitations

- Opportunistic design, sparse sampling

- Large inter-individual variability

- Safe exposure limits unknown

- No pharmacodynamic analysis

Conclusions

- Milrinone clearance increases with improvement in creatinine clearance

- ECMO was not a determinant of clearance, possibly because of sample size or changes in renal function

- 50 mcg/kg load & 0.5 mcg/kg/min infusion dosing is appropriate in the setting of normal creatinine clearance in neonates and children

- When creatinine clearance is severely impaired, 25 mcg/kg load & 0.25 mcg/kg/min infusion results in therapeutic exposures after ~5 hours of infusion

Acknowledgement

- We thank the principal investigators, research teams, and patients in their support of the POP01 study.

Site PIs	City	State
Mueller, William & Yogev, Ram	Chicago	IL
Mourani, Peter	Aurora	CO
Watt, Kevin	Durham	NC
Sullivan, Janice	Louisville	KY
Atz, Andrew	Charleston	SC
Speicher, David	Cleveland	OH
Al-Uzri, Amira	Portland	OR
Adu-Darko, Michelle	Charlottesville	VA

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Additional slides

Population PK of Milrinone in Children

Paradisis 2007	Bailey 2004	Bailey 1999	Ramamoorthy 1998
29 infants <29 w GA; 0.52-1.29kg	235 children 0-<6years	20 children 3-22 months, 3.2-12 kg	19 children 0-<=13yrs, 3.5-40kg
1-comp model	1-comp model	3-comp model	2-comp model
0.25-0.75mcg/kg/min	25/75 mcg/kg load then 0.25/0.75mcg/kg/min	50mcg/kg load then 0.5 mcg/kg/min	50mcg/kg load then 0.25-0.75 mcg/kg/min
Cl=0.64ml/kg/min = 2.7 L/hr/70kg	CL=2.42ml/kg/min*[1+0.0396*age] = 10 L/hr/70kg for 0yrs = 12 L/hr/70kg for 5 yrs	CL=2.5ml/kg/min*[1+0.058*age] CL2=14.5(1.7)*weight CL3=5(2.5)*weight	CL=5.67 ml/kg/min =23.8 L/hr/70kg
V=576ml/kg [21%] = 40 L/70kg	V=482 ml/kg = 33.7 L/70kg	Vss=871 ml/kg = 61 L/70kg	Vss=830ml/kg =58.1 L/70kg
Allometrically scaled weight on CL and V	Weight & age linear on CL Weight linear on V	Weight linear for all Weight &age linear on CL	Weight linear for all

Age distribution by ECMO
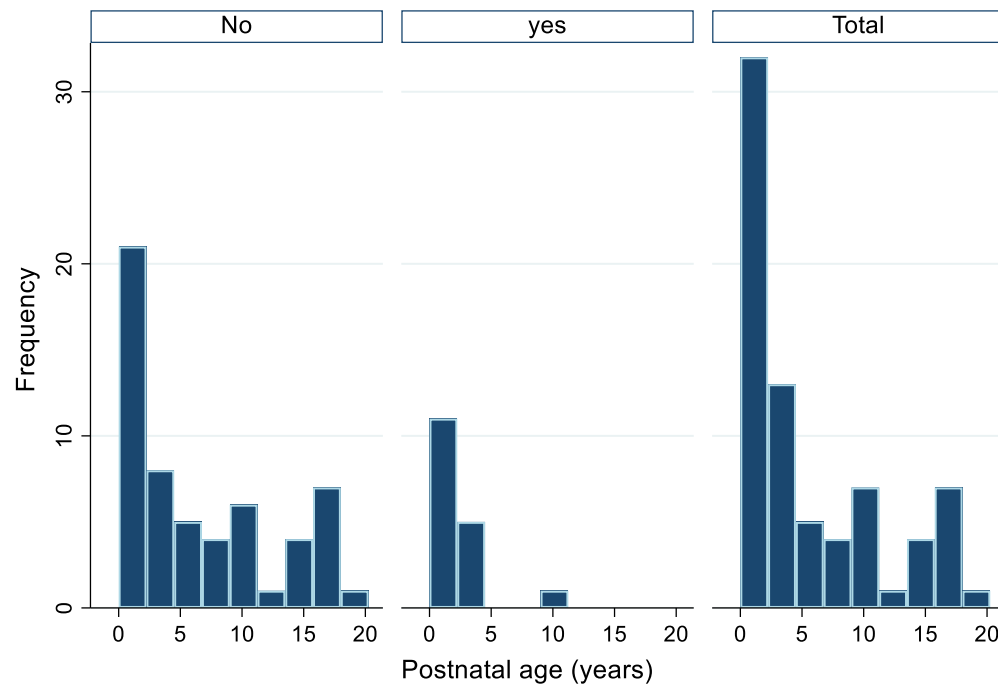
Graphs by ECMO

Observed concentrations vs. time after last dose

All
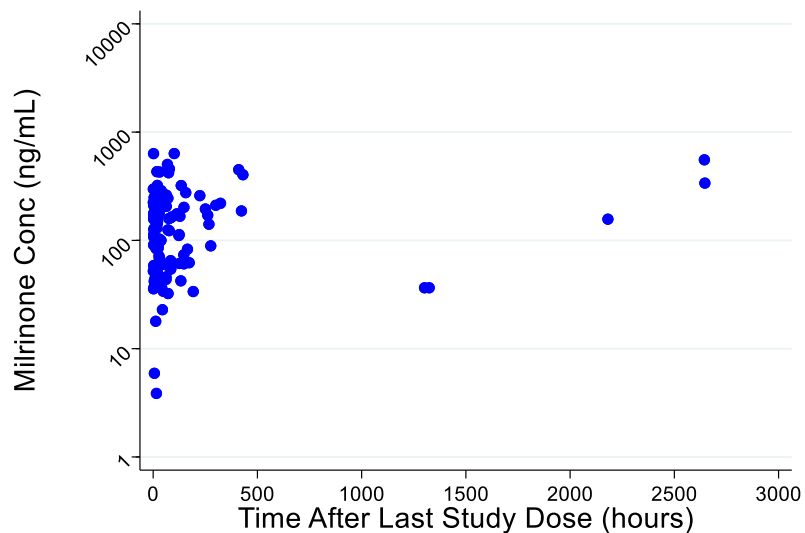
First 500 hours
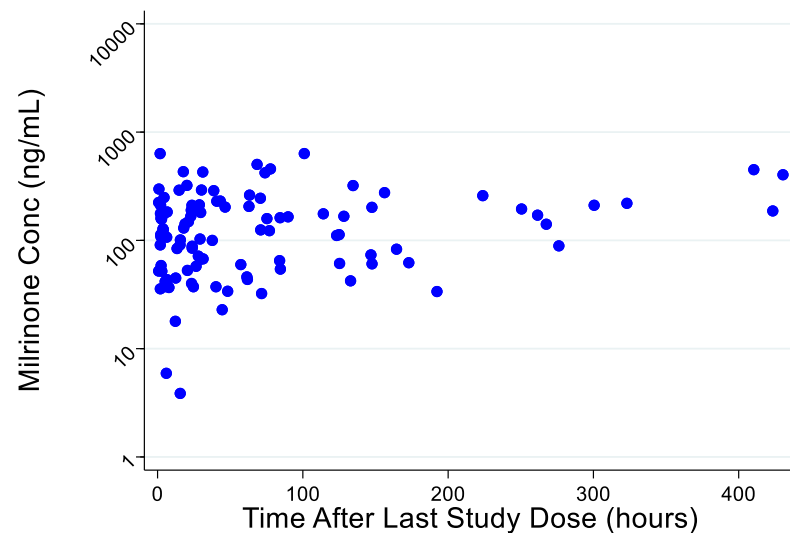
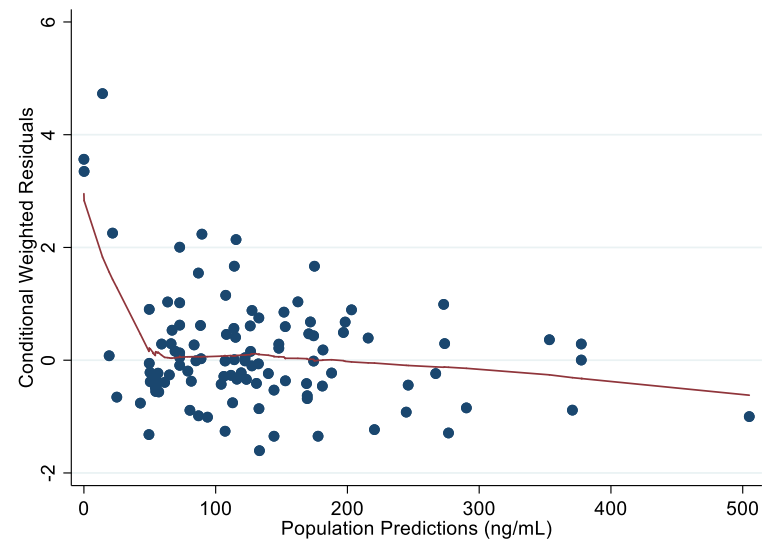# Observed concentrations vs. time after end of last dose
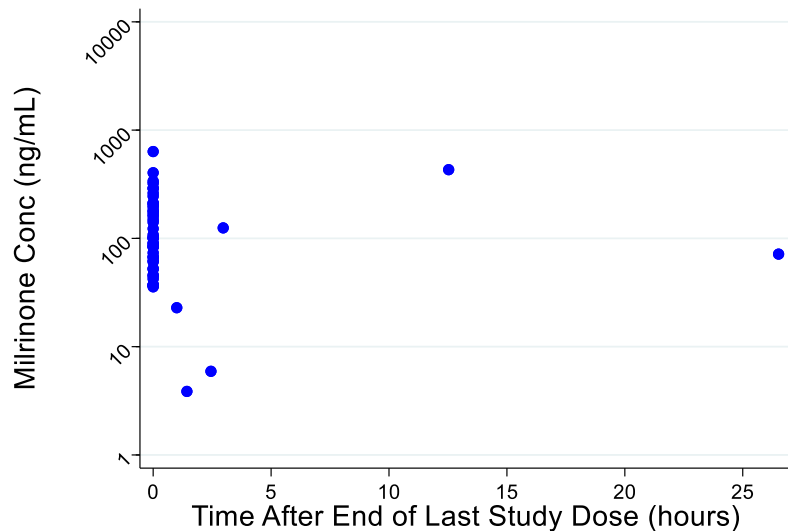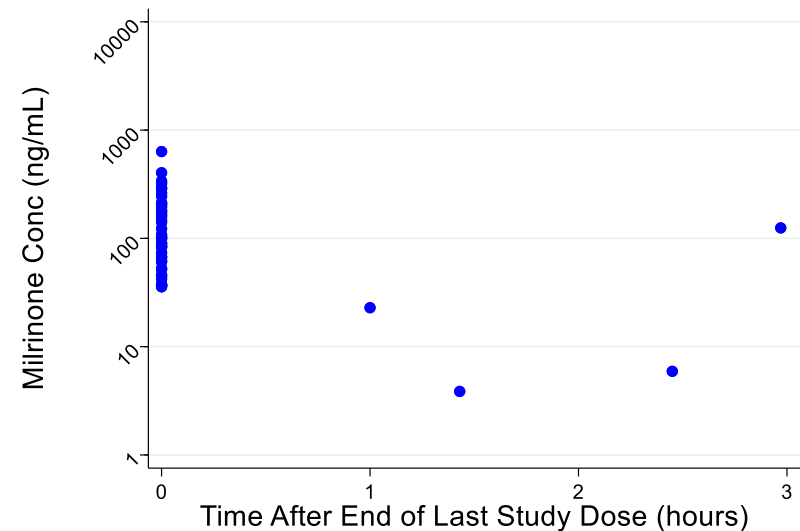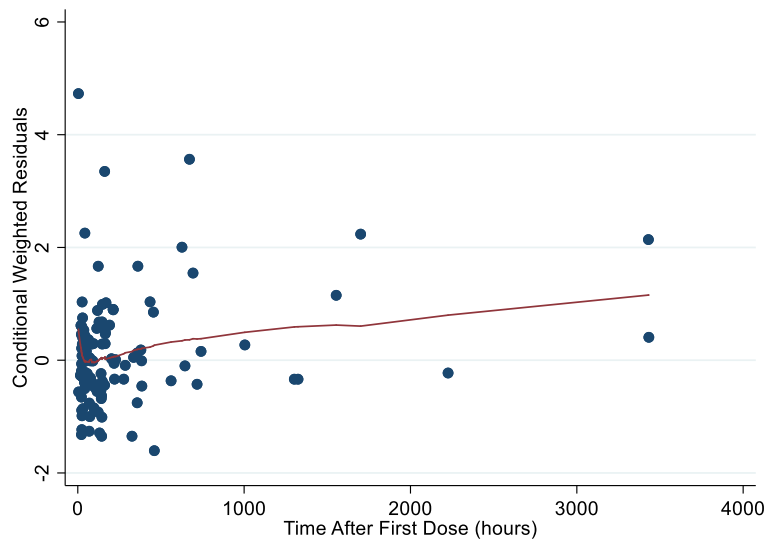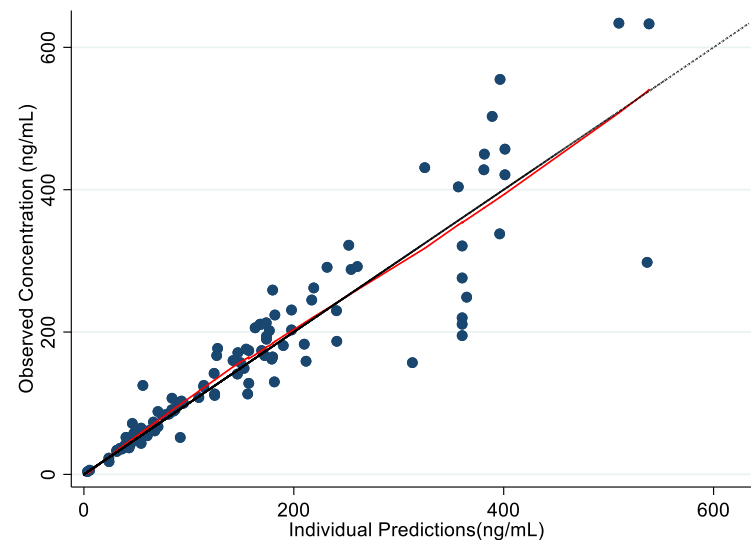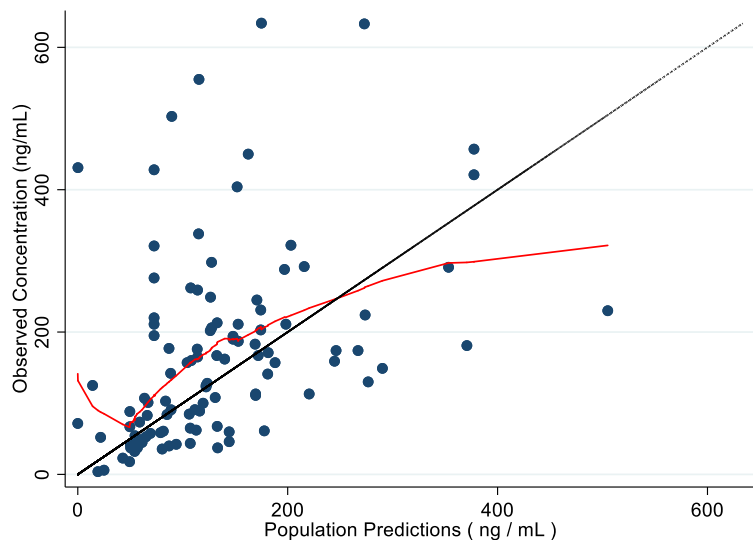
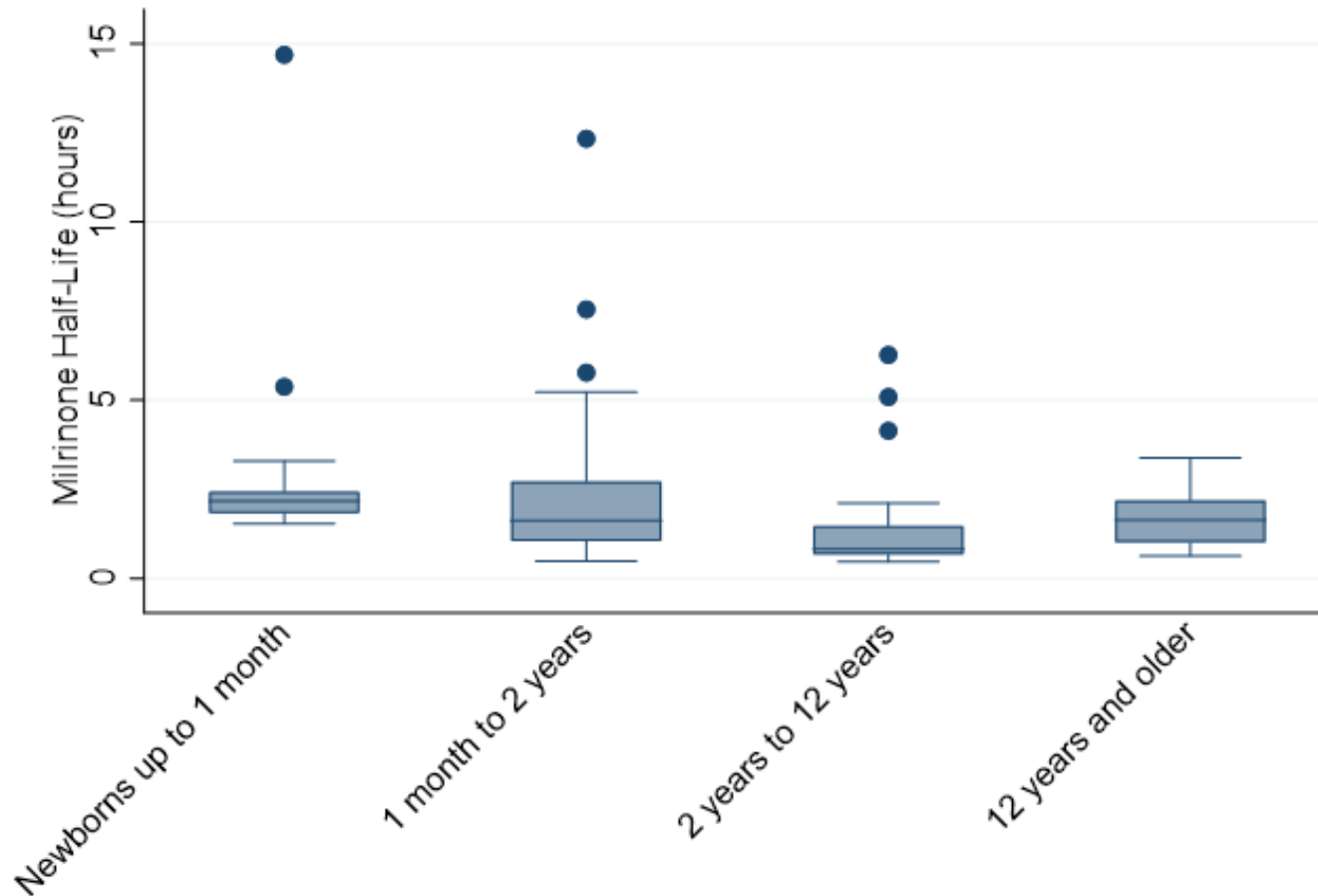# Population PK model equations

- TVCL=THETA(1)*((WT/70)**THETA(4))*(NEWCRCL/110)**THETA(3)
- CL=TVCL*EXP(ETA(1))

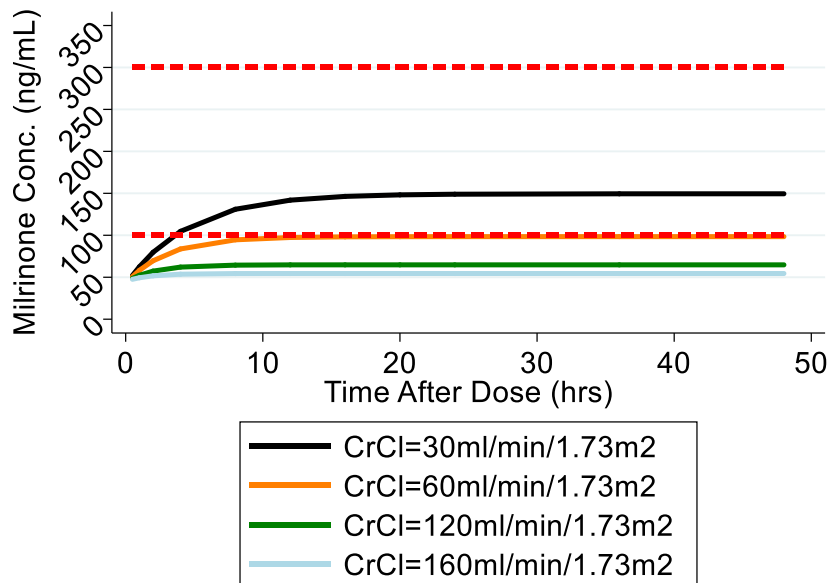- TVV=THETA(2)*(WT/70)
- V=TVV*EXP(ETA(2))
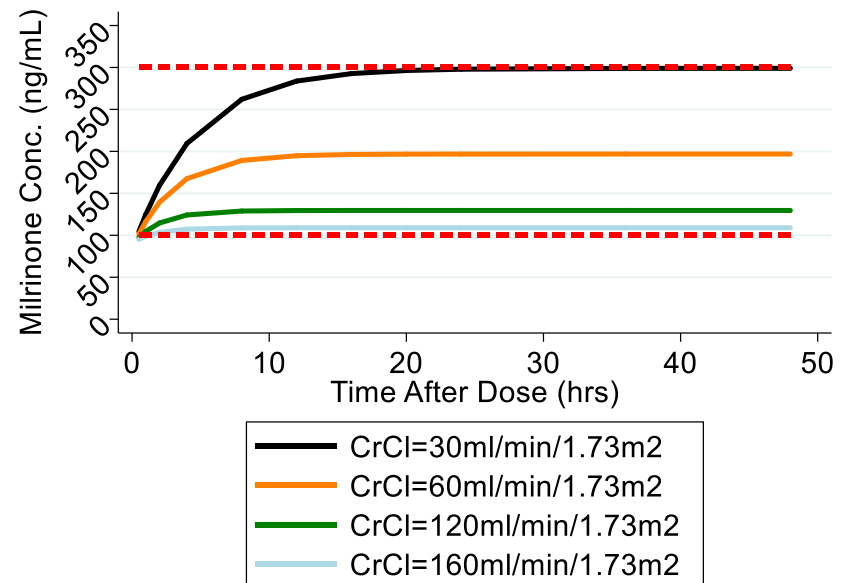
Diagnostic plots

Milrinone half-life by age group

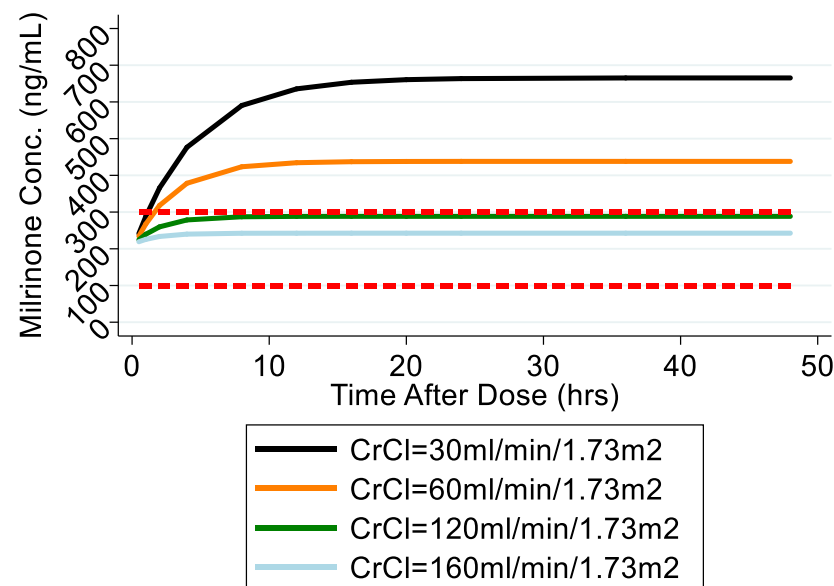# Milrinone dose simulation in 13 kg child

Milrinone dose simulation in 70 kg child

25 mcg/kg load followed by 0.25 mcg/kg/min infusion
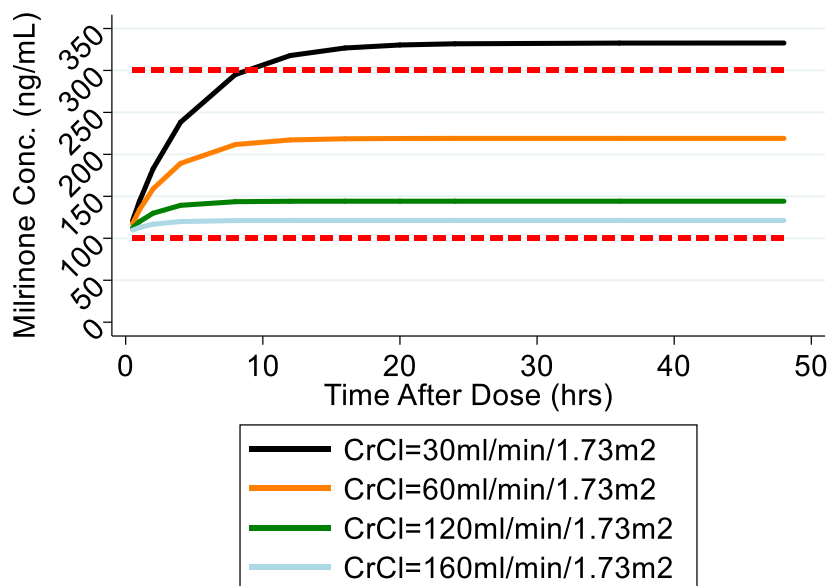
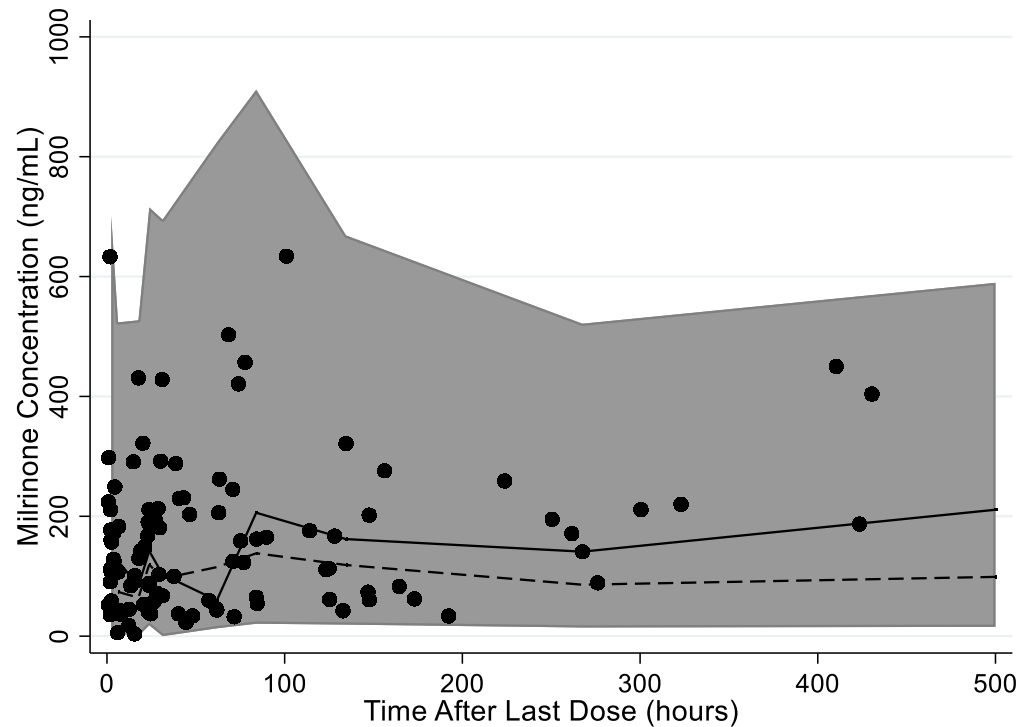50 mcg/kg load followed by 0.5 mcg/kg/min infusion

Modified Schwartz Equation

- crcl=(htcm*0.45)/scr if pnapkwk>=1 & pnapkwk<=52 & gaw>=37 & gaw!=.

- crcl=(htcm*0.33)/scr if pnapkwk<=52 & gaw<37 & gaw!=.

- crcl=(htcm*0.55)/scr if pnapkyr>=1 & pnapkyr<=13 & crcl==.

- crcl=(htcm*0.55)/scr if pnapkyr>13 & pnapkyr<=18 & sex==2 & crcl==.

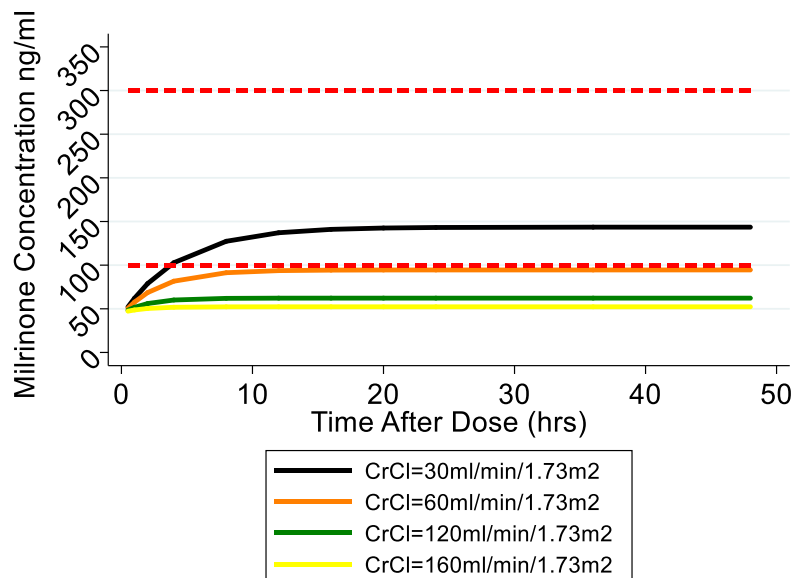- crcl=(htcm*0.7)/scr if pnapkyr>13 & pnapkyr<=18 & sex==1 & crcl==.

Visual Predictive Check

7% of observations outside the 90% prediction interval

Milrinone dose simulation in 30kg child

25 mcg/kg load followed by 0.25 mcg/kg/min infusion

50 mcg/kg load followed by 0.5 mcg/kg/min infusion