

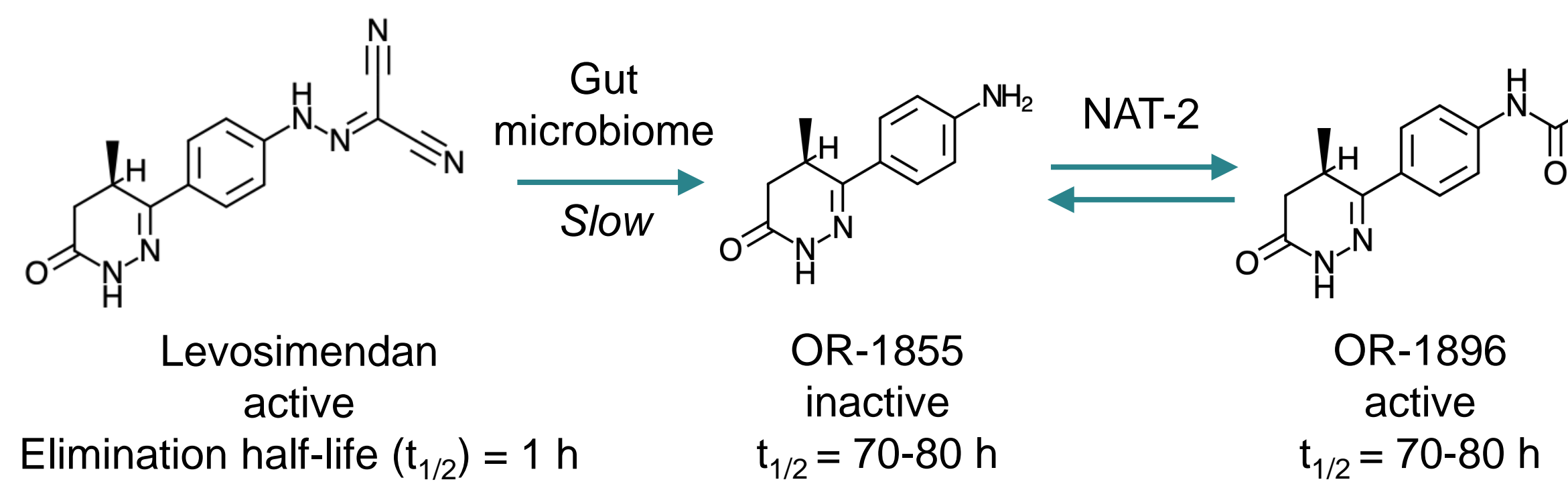
# Population pharmacokinetics of levosimendan and its metabolites OR-1855 and OR-1896 in critically ill adults and children on ECMO

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## Background

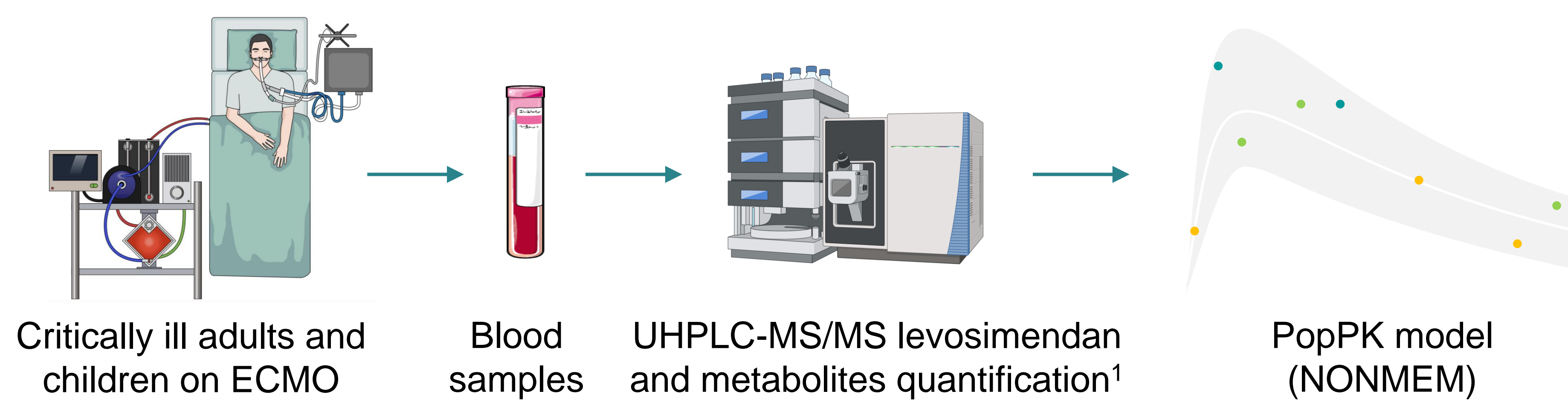
- Levosimendan is an inotrope and vasodilator agent used in critical care, particularly to facilitate weaning from extracorporeal membrane oxygenation (ECMO).
- Critical illness and ECMO may affect levosimendan and its clinically relevant metabolites' pharmacokinetics (PK).
- There is limited data on levosimendan PK in critically ill patients on ECMO.



## Objective

Characterise levosimendan and metabolites PK in critically ill adults and children on ECMO, using a population approach.

## Methods



- Classical stepwise approach for parent-metabolites modelling.
- Evaluation of different transit dispositions for slow apparition of metabolites.
- Covariates tested: body weight, sex, age, height, population difference (child vs adult), GFR, continuous renal replacement therapy, albumin and bilirubin levels, ECMO flow rate, time since ECMO initiation and number of comedications.
- Model-based simulations for various dosing scenarios, for adults and children separately.

## Results

### Population

- 15 adults, 6 children, 155 samples.
- Maintenance dose of 0.1-0.2 µg/kg/min in adults and 0.1 µg/kg/min in children.
- Infusion length: 24 h in adults and 48 h in children.

### Structural model

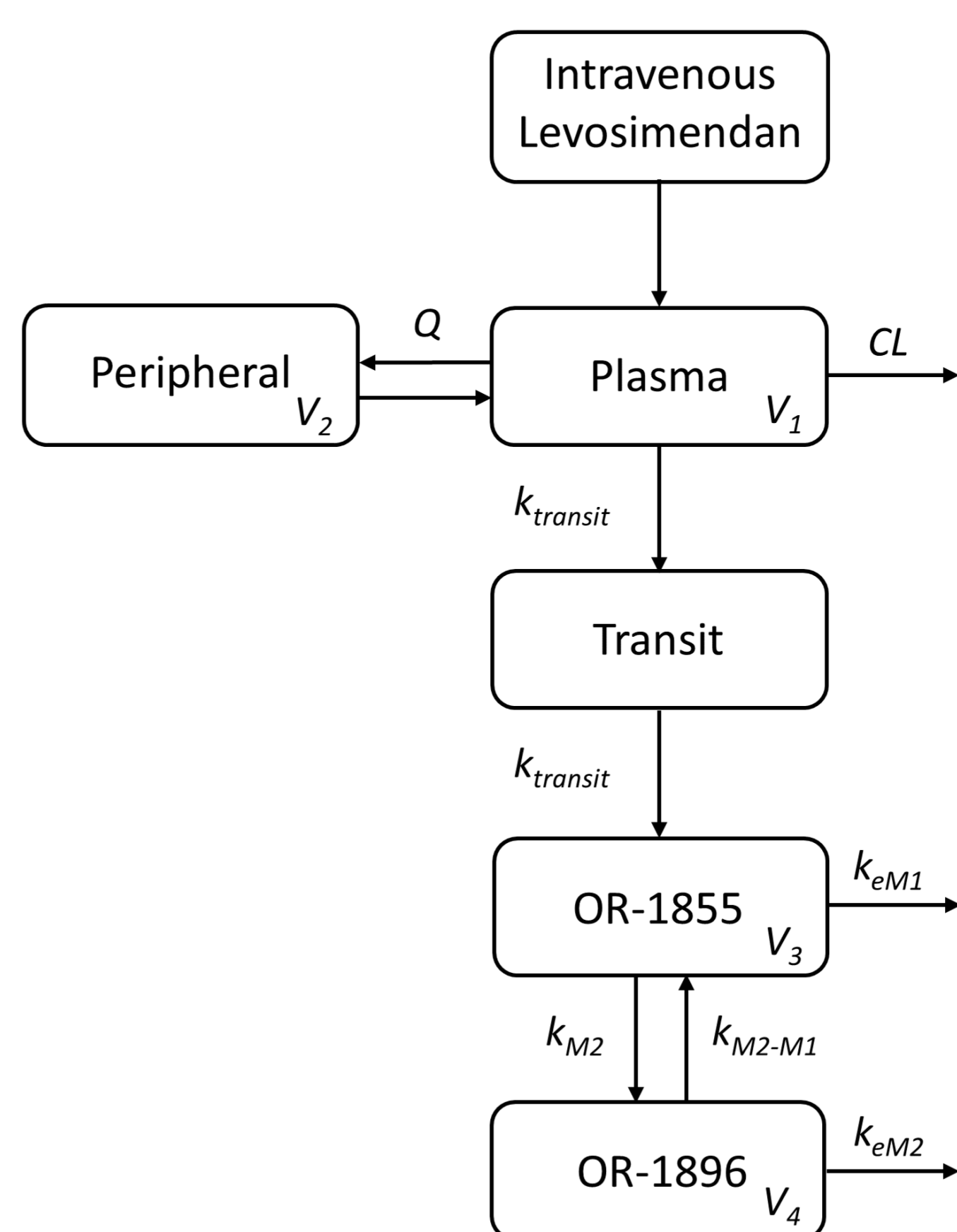


Figure 1: Structural model for levosimendan and metabolites OR-1855 and OR-1896.  $k_{eM1}$  = OR-1855 elimination rate constant;  $k_{eM2}$  = OR-1896 elimination rate constant;  $k_{M2}$  = OR-1896 synthesis rate constant;  $k_{M2-M1}$  = rate constant for the backward transformation of OR-1896 into OR-1855;  $k_{transit}$  = transit compartment rate constant.

### Final popPK model and bootstrap results

Parameters	Final model Estimate (RSE, %) <sup>a</sup>	Bootstrap (n=2000) Median [95% CI]
<b>Fixed effects</b>		
CL (L/h)	13.9 (21%)	14.0 [11.8-16.7]
$\theta_{BW}$	0.75 FIX	0.75 FIX
$V_1$ (L)	15.9 (26%)	16.0 [12.3-20.4]
$\theta_{BW}$	0.57 (32%)	0.58 [0.40-0.77]
Q (L/h)	0.50 (36%)	0.50 [0.30-0.78]
$V_2$ (L)	5.75 (44%)	6.00 [3.55-11.12]
$k_{transit}$ (h <sup>-1</sup> )	0.013 (21%)	0.013 [0.011-0.015]
$k_{eM1}$ (h <sup>-1</sup> )	0.01 FIX	0.01 FIX
$\theta_{BW}$	-0.61 (22%)	-0.63 [-0.92 to -0.21]
$k_{M2}$ (h <sup>-1</sup> )	0.072 (44%)	0.072 [0.047-0.107]
$\theta_{child}$	-0.73 (30%)	-0.74 [-0.88 to -0.40]
$k_{eM2}$ (h <sup>-1</sup> )	0.01 FIX	0.01 FIX
$k_{M2-M1}$ (h <sup>-1</sup> )	0.012 FIX	0.012 FIX
<b>Between-subject variability</b>		
$\omega_{CL}$ (CV% <sup>b</sup> )	32.4 (31%)	31.6 [18.4-44.4]
$\omega_{V1}$ (CV% <sup>b</sup> )	51.5 (48%)	47.6 [26.1-69.3]
$\omega_{V2}$ (CV% <sup>b</sup> )	99.1 (46%)	95.0 [55.4-231.9]
$\omega_{k_{transit}}$ (CV% <sup>b</sup> )	37 (71%)	35.2 [24.5-46.3]
$\omega_{k_{M2}}$ (CV% <sup>b</sup> )	90.6 (88%)	84.2 [57.0-141.6]
<b>Residual variability</b>		
$\sigma_{prop-levosimendan}$ (%)	30.9 (16%)	30.5 [20.7-39.2]
$\sigma_{prop-M1}$ (%)	36.7 (32%)	35.9 [24.5-45.9]
$\sigma_{prop-M2}$ (%)	30.3 (42%)	30.0 [19.3-39.9]

$$CL_i = CL * \left(\frac{BW_i}{70}\right)^{0.75}$$

$$V_{1i} = V_1 * \left(\frac{BW_i}{70}\right)^{\theta_{BW}}$$

Increased levosimendan CL and V in children

$$k_{eM1i} = k_{eM1} * \left(\frac{BW_i}{70}\right)^{\theta_{BW}}$$

$$k_{M2i} = k_{M2} * (1 + \theta_{child}) \rightarrow \text{OR-1855} \rightarrow \text{OR-1896}$$

transformation 3.7 fold slower in children

### Model-based simulations

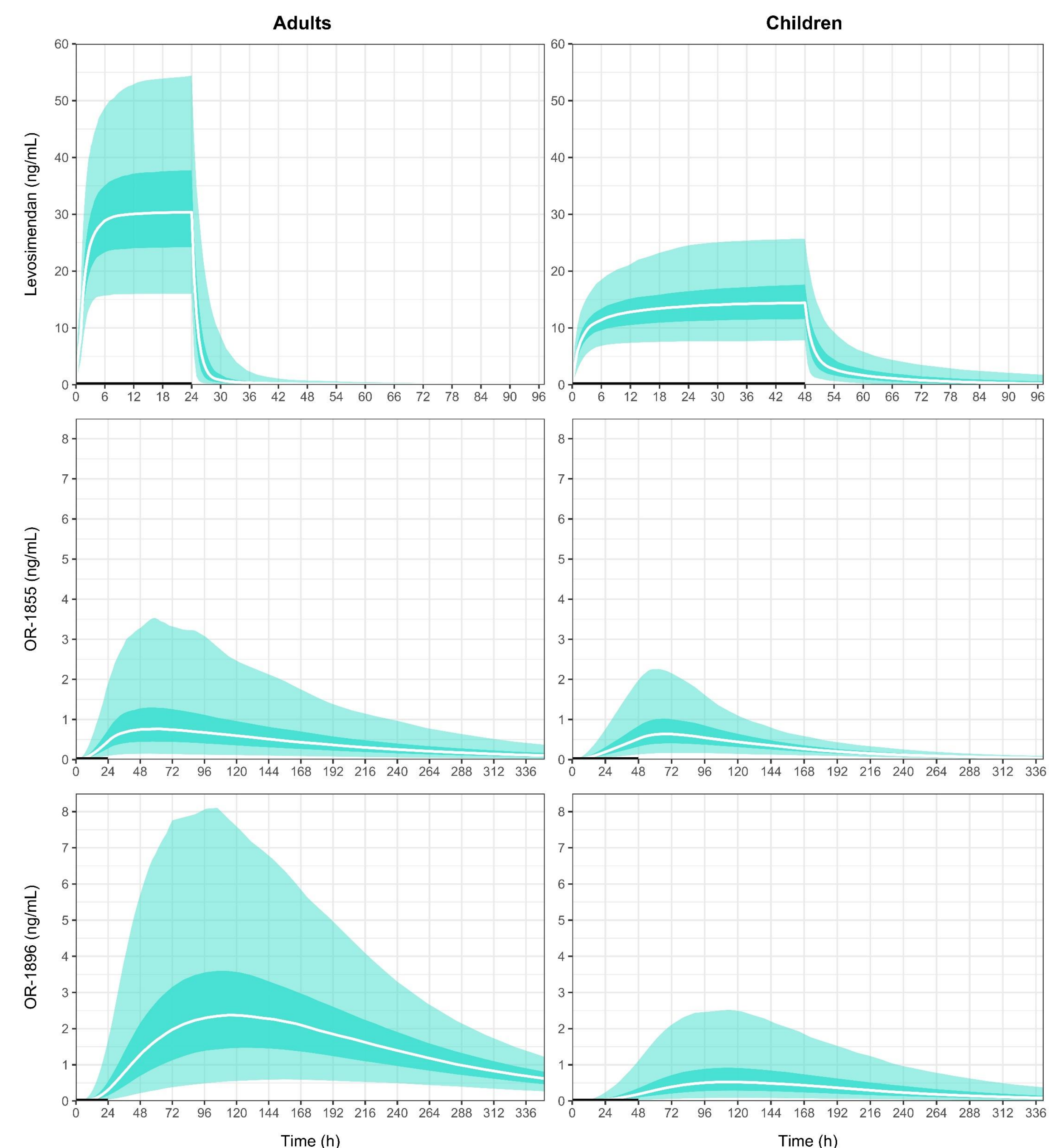


Figure 2: Simulated levosimendan, OR-1855 and OR-1896 concentration-time profiles. Left panels: simulations for a 70 kg adult receiving a standard dosage of 0.05 µg/kg/min for 1 h, followed by 0.1 µg/kg/min during 23 h. Right panels: simulations for a 4 kg child receiving 0.1 µg/kg/min for 48 h. White solid lines represent the median (50% percentile), whereas dark and bright surfaces show the 50% and 95% prediction intervals, respectively. Thick axis segments indicate infusions duration.

## Discussion

### Adults

- Levosimendan concentrations similar to non-critically ill adults<sup>2,3,4</sup>.
- Slightly lower metabolites concentrations compared to non-critically ill adults, likely due to altered microbiota and consequent impaired levosimendan metabolism during critical illness<sup>5</sup>.

### Children

- Low levosimendan concentrations compared to adults, likely due to increased CL by ECMO.
- Low metabolites concentrations, likely due to impaired levosimendan metabolism attributable to immature/altered microbiota<sup>6</sup> and immature NAT-2 enzyme activity<sup>7</sup>, potentially leading to decreased or absent long-term sustained effects.

## Conclusion

Due to impaired levosimendan metabolism in children, effects may only be observed during levosimendan infusion. Levosimendan dosing optimisation deserves to be evaluated in children on ECMO.



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