

Efficacy and toxicity of intravenous salbutamol in children with acute severe asthma: a prospective clinical PKPD study

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Background & Objectives

- Salbutamol is a short-acting selective beta-2 adrenoceptor agonist for treating asthma in adults and children.
- Intravenous salbutamol (IVS) is routinely used as second line treatment for childhood acute severe asthma as per the British Thoracic Society (BTS) [1].
- IVS doses in children are extrapolated from adults based on body weight ($1\text{--}5\text{ mcg/kg/min}$); no maximum dose in children has been recommended while children may receive doses far greater than the maximum adult dose (20 mcg/min).
 - $1\text{--}5\text{ mcg/kg/min} * 20\text{ kg} \geq 20\text{ mcg/min}$
- The current study aimed to develop new rational dosing guidelines for IVS in children through exploring relationships between IVS blood concentrations and efficacy and toxicity measurements in children with acute severe asthma.

Methods

- A prospective study was conducted in Emergency Departments (EDs) and Paediatric Intensive Care Units (PICUs) across London, UK (EudraCT No. 2014-002996-27).
- Plasma concentrations were available from children receiving IVS with intermittent i.v. bolus and nebulised doses.
 - Baseline concentration was estimated due to long and uncertain pre-treatment history of salbutamol.
- Asthma severity was measured by the three-item composite score Paediatric Asthma Severity Score (PASS) [2].
 - PASS: 0-9 (re-categorised into [0,3], [3,6], [6,9])
 - Wheezing: 0-3 (max 2 in the current study)
 - Prolonged expiration: 0-3 (max 2 in the current study)
 - Work of breathing: 0-3 (max 2 in the current study)
- PASS and the individual items were assessed by ordered logistic regression considering time-varying plasma concentrations (Fig 1).
 - Linear or Emax concentration-efficacy relationship

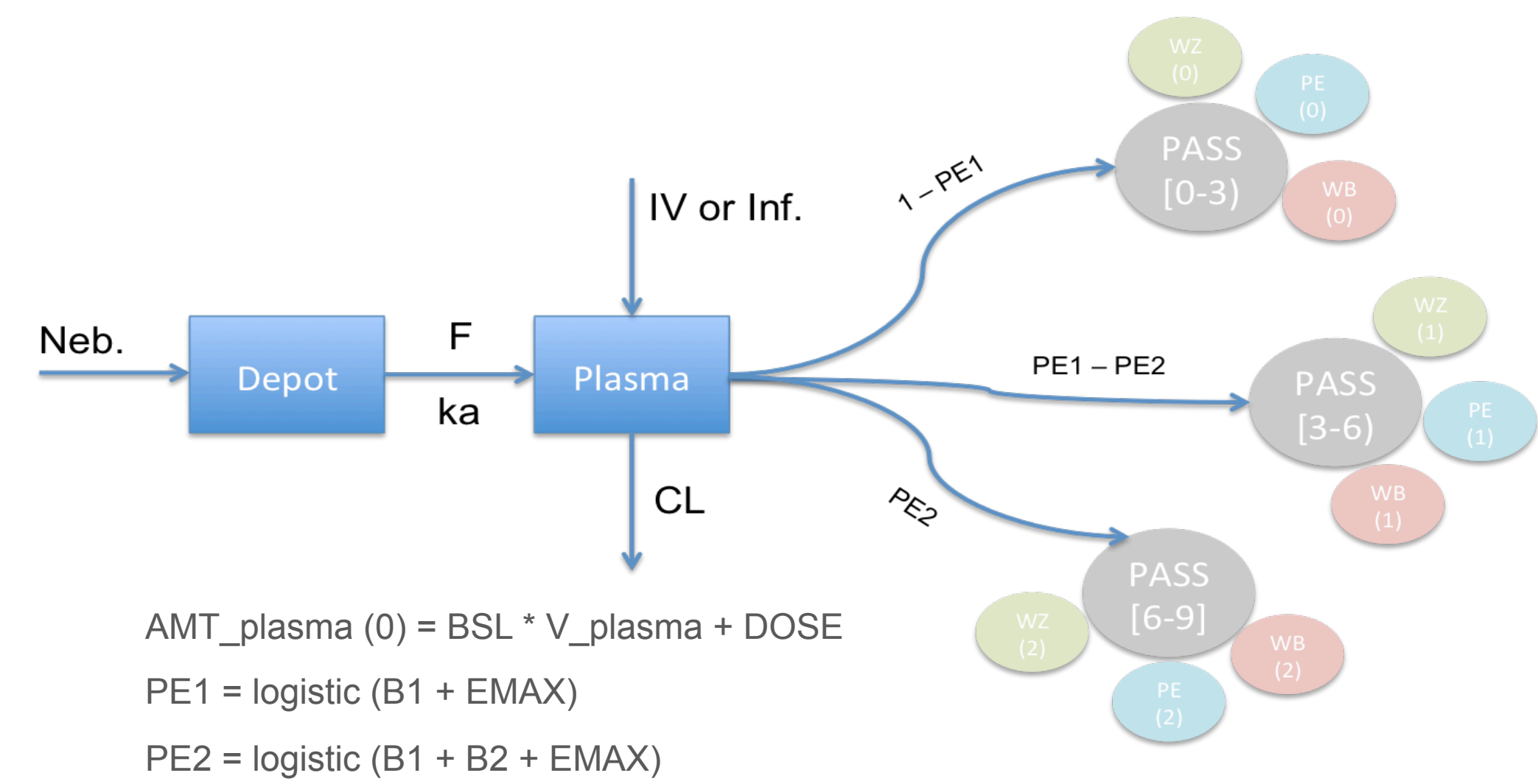


Figure 1. Diagram for PASS and individual items scores after IVS

- Toxicity-associated physiological measurements were collected from blood gas, blood glucose and cardiovascular tests.
 - Blood gas: lactate, pH, base excess
 - Cardiovascular: heart rate, systolic and diastolic blood pressure
- A hypothetical effect compartment was added to examine whether delayed onset in individual toxicity effects occurred after IVS (Fig 2).
 - Sigmoid Emax concentration-toxicity relationship

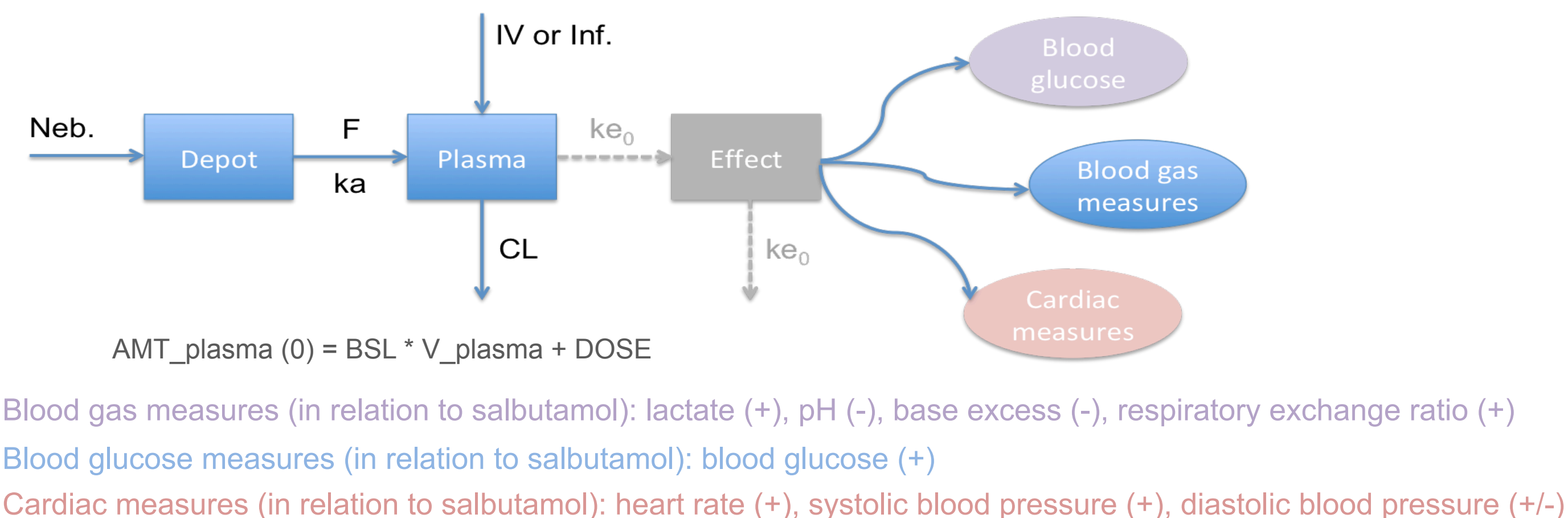


Figure 2. Diagram for blood gas, blood glucose and cardiovascular tests after IVS

Results

- We prospectively recruited 47 patients aged between 1 and 15, with 165 plasma samples, 102 PASS measurements, and 178-245 toxicity measurements.
- A one-compartment PK model well described the time course of salbutamol plasma concentrations after nebulised and intravenous doses.
 - Results were comparable with an adult study [3] (see Table 1).

Table 1. PK comparison with a published adult study

Parameter (unit)	Estimated from an adult study [3]	Scaling from adults to children (WT=13.2 kg)	Scaled values in children	Estimated from the current study
CL (L/hr)	28.8	(WT/70)**0.75	8.2	7.0
V (L)	156.0	(WT/70)**1	29.4	66.2

- Body weight, added allometrically, was found as a significant covariate.
- Age was not found as a significant covariate through maturation function.

- For PASS and the individual items, Emax concentration-efficacy relationship significantly reduced objective function, in comparison to the net or linear relationship (parameters listed in Table 2).

Table 2. Parameter values for PASS and individual items with Emax relationship

Efficacy measure	B1	B2	E _{max}	EC ₅₀ (ng/mL)
PASS	-7.3	-3.5	7.8	0.5
Wheezing	-9.0	-3.1	9.9	0.2
Prolonged expiration	-8.8	-3.2	8.9	0.2
Work of breathing	-4.2	-3.4	6.7	0.2

- Toxic effects increased immediately with the increase of plasma concentrations, the opposite for pH and base excess measures.

Table 3. Parameter values for blood gas, blood glucose and cardiovascular tests

Toxicity measure	E ₀ (ng/mL)	E _{max}	EC ₅₀ (ng/mL)	N
lactate (mmol/L)	1.2	0.4	63.4	8.8
pH	7.4	-0.3	136	1.4
base excess (mmol/L)	10.2	-25.9	27.9	0.3
respiratory exchange ratio	0.6	0.2	101	20.2
blood glucose (mmol/L)	4.8	12.4	360	0.4
heart rate (beats per min)	125	64.3	51.5	0.3
systolic blood pressure (mmHg)	93.1	31.7	94.3	3.3
diastolic blood pressure (mmHg)	51.2	8.7	85.7	3.8

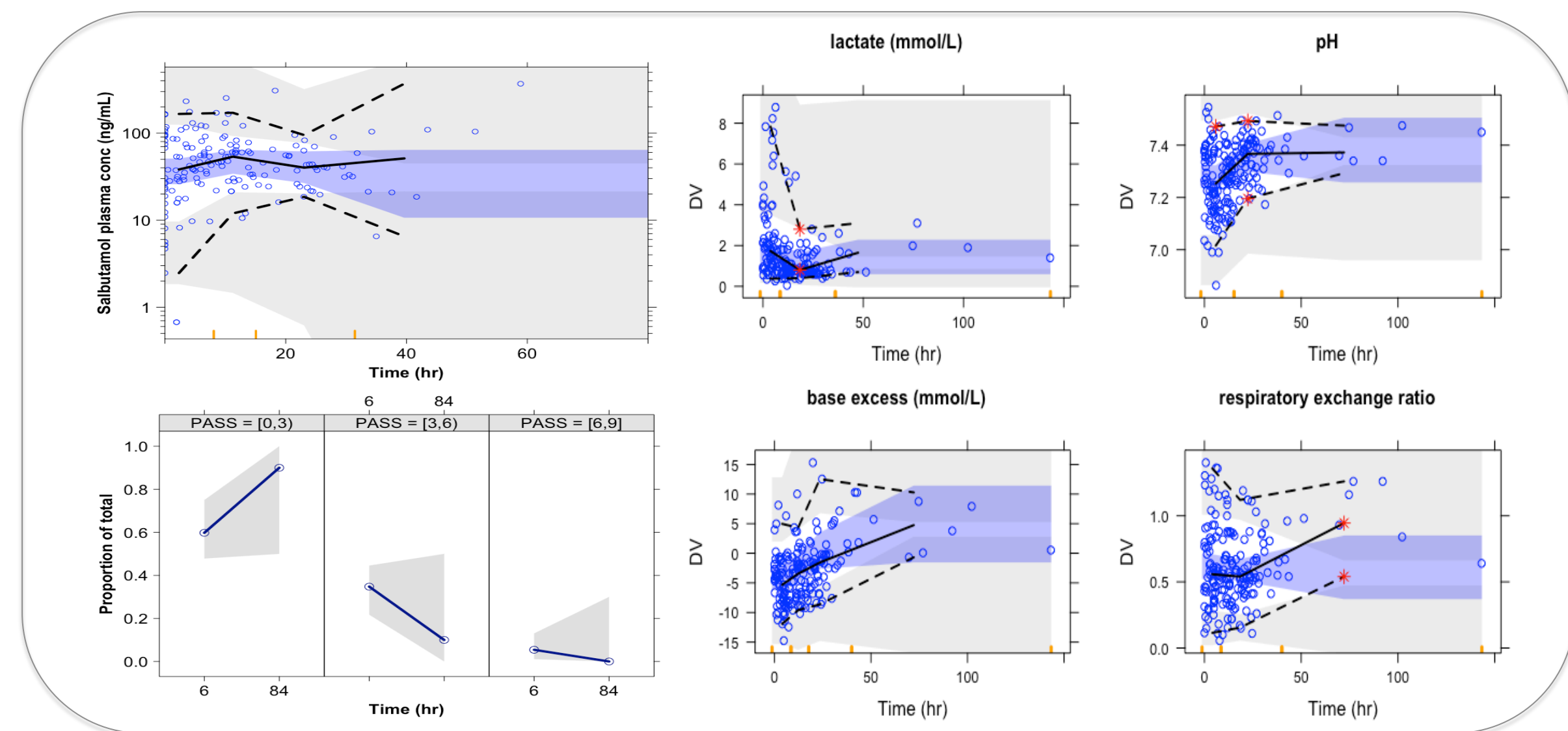


Figure 3. pcVPC results for plasma concentration, PASS and toxicity measures

Conclusions

- The current study explored PKPD relationships for efficacy and toxicity after IVS in children with acute severe asthma.
- Future investigation with genetics data is required to determine the maximum IVS dose in children, with two additional questions to be addressed:
 - Lower infusion rate as starting dose?
 - Higher dose for children with larger body weight?

References

[1] BTS/SIGN Asthma Guideline 2016 [2] Gorelick et al. Acad Emerg Med. 2004;11(1):10-18 [3] Morgan et al. Br J Clin Pharmacol. 1986;22:587-593