UCL
GREAT ORMOND STREET
INSTITUTE OF CHILD HEALTH

Great Ormond Street Hospital for Children
NHS Foundation Trust

Joint Research and Development Office
Division of Research and Innovation

Clinical Study Report

Title: Optimising effectiveness and minimising toxicity of intravenous salbutamol in children with acute asthma

Name of IMP: Salbutamol

Indication: For paediatric PKPD modelling

Description of study:

We undertook to develop a population pharmacokinetic-pharmacodynamics (PKPD) model to explore the relationship between salbutamol dose, blood concentration, effectiveness and side effects in children with acute severe asthma. The results of our study will help develop new rational, evidence-based dosage guidelines for intravenous salbutamol that can be evaluated in future randomised clinical trials.

Sponsor: Great Ormond Street Hospital Children's Charity

Sponsor's Protocol Number: 13CC34

EudraCT Number: 2014-002996-27

REC Ref Number: 14/LO/2103

Phase: 2

Study initiation date: September 2014

Date of early study termination: May 2017

Chief Investigator: Padmanabhan Ramnarayan / Sandra Walsh

Sponsor:

This is to confirm that the study was conducted in compliance with Good Clinical Practice. Archiving responsibility of essential documents located in the TMF has been undertaken by GOSH and the appropriate arrangements are in place.

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Abbreviations

CI	Chief Investigator
GM	genetically modified
GOSH	Great Ormond Street Hospital
GVHD	graft versus host disease
MHRA	Medicines and Healthcare products Regulatory Agency
TMA	Trial Medical Advisor
IVS	IV Salbutamol
ED	Emergency Department
CATS	Children Acute Transport Service

1. Synopsis

Name of Sponsor: Great Ormond Street Hospital Children's Charity
Name of Finished Product:
Name of Active Ingredient: Salbutamol

Title of Study: Optimising effectiveness and minimising toxicity of intravenous salbutamol in children with acute asthma	
Chief Investigator: Padmanabhan Ramnarayan	
Study Centre Great Ormond Street Hospital St Mary's Hospital The Royal London Hospital	
Publication (reference): Presentations (accepted) 1. 7th annual conference European Academy of Paediatric Societies 2018 2. 27th annual Population Approach Group Europe 2018	
Studied period (years): 2.5 **Date of first enrolment:** September 2014 **Date of last completed:** March 2017	**Phase of development:** Phase I/II II **Date of report:** 19/06/2018

2. Ethics

2.1 Independent ethics committee

Brent Ethics Committee

2.2 Ethical conduct of the study

The study was monitored by Great Ormond Street R&D Department according to the Monitoring Plan. Annual progress report and Development Safety Update Report were submitted to ethics committee and MHRA.

2.3 Patient information and consent

Participants were identified by the treating clinical teams, and recruited by site research nurses or the clinical teams. All patients were treated according to local policy for the management of acute severe asthma. All treatments were recorded but no modifications were made for the purposes of the study. Once enrolled, patients continued in the study until 8 hours after stopping IVS, or until hospital discharge.

We followed established procedures for obtaining deferred consent (also called research without prior consent) in emergency situations, since IVS was considered an urgent treatment that could not be delayed while obtaining written informed consent from parents/guardians. Written consent was usually obtained 24-48 hours after recruitment to the study by site research nurses for continuation in the study and for ongoing data collection. Age-specific patient information leaflets were provided to each participant. If required, participants could be spoken to by the research team via the GOSH telephone translator service.

3. Investigators and administrative structure

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4. Introduction

Asthma is the most common long-term condition affecting children and young people in the UK. On average there are three asthma sufferers in every classroom, with a child being admitted to hospital every 20 minutes with an acute asthma attack. (1) Deaths from asthma in the UK are amongst the highest in Europe, with the rate almost 50% higher that the EU average. There has been a 20% rise in UK asthma deaths in the past 5 years.(2) A national review in 2014 found that 90% of children's asthma deaths are considered preventable. The report also showed that half of those who died from asthma had previously been admitted to hospital for their condition, and one third had been to accident and emergency departments because of attacks in the previous year.(3)

The main aim of treatment in acute severe asthma is to reduce mucosal swelling and relieve bronchospasm to allow adequate gas exchange, and β_2-adrenergic receptor agonists such as salbutamol are the mainstay of acute treatment. Current management of childhood acute severe asthma is based on national guidelines from the British Thoracic Society (BTS). BTS guidelines recommend that intravenous salbutamol (IVS) should be started as second line treatment in children who fail to respond to nebulised β_2-agonists and steroids.(4) Whilst in theory IVS can be highly effective in reversing bronchospasm, the overall evidence base for this recommendation is weak and predominantly comes from a single Australian study from 1997.(5) The use of IVS has however been associated with serious side effects such as severe metabolic acidosis, lactic acidosis, hyperglycaemia, ketosis, and diastolic hypotension with myocardial injury and cardiac arrhythmias. There is considerable concern that these metabolic and physiologic derangements are not trivial, and that they pose significant clinical risk. (6-9)

There is also a significant evidence gap regarding the optimal dose of IVS in children. BTS guidelines recommend a bolus dose of 15 microgram/kg of IVS over 10 minutes, followed by an intravenous infusion of 1-5 microgram/kg/min.(4) Importantly while the recommended maximum adult dose is 20 microgram/minute, there is no such recommendation for children (a 2 year old child of 10 kg body weight on 3 microgram/kg/min of IVS would receive far more than the maximum adult dose). Indeed, the British National Formulary (BNF) for children acknowledges that "*BNF Publications is aware that the different dosing regimens may lead to the IVS dose for a child greatly exceeding the adult dose, however at present there is no evidence to change either of these dosage recommendations*". Data from pharmacokinetic/pharmacodynamic (PKPD) models on which to base paediatric IVS dosing are lacking, and extrapolation from adult PK studies does not take into account the effect of prior clinical treatment with

inhaled/nebulised salbutamol or co-treatment with other bronchodilator therapies, common during childhood asthma treatment.

We aimed to conduct a prospective cohort study in the emergency setting to explore the relationship between salbutamol dose, blood concentration, effectiveness and side effects in children with acute severe asthma, through developing a population pharmacokinetic-pharmacodynamics (PKPD) model. We anticipated that the results of our study would help develop new rational, evidence-based dosage guidelines for intravenous salbutamol administration in children that can be evaluated in future randomised clinical trials (RCT).

5. Study objectives

The key objectives were to:

1. Recruit 100 patients with acute severe asthma receiving IVS in two distinct cohorts (children managed in the emergency department and those requiring emergency retrieval to PICU)
2. Obtain blood samples for serial salbutamol concentration levels in these patients
3. Accurately record the dose of IVS being infused in these patients
4. Accurately record serial timing and measures of effectiveness (e.g. asthma severity score); and toxicity (e.g. lactic acidosis)
5. Collect detailed demographic information (including age, sex, and weight) and clinical information (including need for ventilation and duration, and mortality)
6. Assess genotypic variation in ß2 adrenergic receptor genes
7. Develop a population pharmacokinetic model to describe the time-course of salbutamol concentrations following intravenous administration
8. Develop population pharmacodynamics models to describe the time-course of measures of effectiveness and toxicity
9. Determine if there is a PKPD relationship of salbutamol for both effectiveness and toxicity. Establish the strength of this relationship, accounting for demographic factors and other clinical covariates such as concomitant drug therapy and genotypic variation with multivariate analysis.
10. Use the model to produce optimum dosage guidelines to balance effectiveness and toxicity. These guidelines could form the basis of a future RCT.

6. Methodology

Study design

We conducted a prospective cohort study of children admitted to hospital with acute severe asthma, who received IVS in the course of their clinical management.

Patients were recruited in two distinct cohorts between September 2014 and May 2017:

a) ED cohort: In the Emergency Departments at two large children's hospitals in London (St Mary's Hospital and the Royal London Hospital)
b) CATS cohort: Critically ill children retrieved by the Children's Acute Transport Service (CATS) to three tertiary PICUs (Great Ormond Street, St Mary's and the Royal London Hospitals)

Participants

Patients were eligible for inclusion if they were aged 1-15 years (inclusive); admitted to hospital for acute severe asthma, as defined by the BTS guidelines; and about to receive or receiving IVS. Participants were identified by the treating clinical teams, and recruited by site research nurses or the clinical teams.

All patients were treated according to local policy for the management of acute severe asthma, including the route of administration, dosage regimen and treatment period for IVS. All treatments were recorded but no modifications were made for the purposes of the study. Once enrolled, patients continued in the study until 8 hours after stopping IVS, or until hospital discharge.

Samples

Salbutamol levels: Serial blood samples (in lithium heparin bottles) to measure salbutamol levels were taken as and when clinically appropriate, aiming to coincide either with an increase or decrease in the IVS infusion rate, or during a period of steady state administration of IVS. In the ED cohort, salbutamol levels were taken at t_0 (prior to starting IVS, following doses of nebulised salbutamol) and t_{end} (immediately prior to stopping the IVS infusion). Other samples were taken opportunistically with routine sampling. We aimed for a minimum of 3 samples per patient but this was reviewed and revised to 2 samples (provided 5 clinical effectiveness measurements were available) after the second interim analysis. In the CATS cohort, salbutamol levels were taken at t_{CATS} (at first contact with the CATS team at the referring hospital), by which time the child had been started on IVS already. Further samples were taken via indwelling vascular

catheters: once prior to a dose change; once 30 minutes after dose change; once at t_{end}, and one in the eight hour period after stopping the IVS infusion.

Genotype data: One blood sample (EDTA) was taken for single nucleoside polymorphism (SNP) analysis involving the three most common β-2 adrenoceptor genes (ADRB2): Arg16Gly, Gln27Glu and Thr164Ile.

Clinical data

Detailed clinical information was collected in an electronic case report form (Research Electronic Data CAPture, USA) including age, sex, ethnicity, renal function tests; asthma treatments and timing including nebulisers, steroids, magnesium sulphate, aminophylline and IVS; and course of hospital stay including need for PICU admission, length of PICU and acute hospital stay, and need for and duration of mechanical ventilation.

Effectiveness measurements were recorded in patients who were spontaneously breathing by means of the Paediatric Asthma Severity Score (PASS), a validated scoring system incorporating wheezing, prolonged expiration, and work of breathing. This scoring system is non-invasive and has a significant correlation with peak expiratory flow rate (PEFR) and pulse oximetry (10) Serial measurements were recorded by the research nurse hourly or after IVS dosage adjustments.

Toxicity-associated physiological measurements recorded included serum lactate, pH, base excess and blood glucose values as per previous clinical studies.(7) Toxicity-associated cardiovascular instability was measured in the form of heart rate and blood pressure (systolic and diastolic); we also recorded any cardiac arrhythmias.

Sample size and Population PKPD modelling methods are outlined in ‘Statistical Methods’ below.

7. Number of patients (planned and analysed)

Number of patients planned is outlined in Figure 1.

Between September 2014 and May 2017, 576 patients were screened. See Figure 2. Of the 91 eligible patients, 8 refused or were unable to consent, one was previously recruited and 22 were missed. Of the 60 patients subsequently recruited, 2 were found to be underage and removed, IVS was not started in 3 and 1 had insufficient number of samples. The remaining 54 patients were included in the population analysis including dosage analysis. For PKPD modelling, 7 patients had some PK data missing and were excluded. Descriptive data of the study participants is outlined in Table 1. Of note, forty patients had a known history of asthma or viral induced wheeze.

8. Diagnosis and main criteria for inclusion

Patients were included in the above criteria if aged 1-15 years (inclusive); admitted for acute severe asthma as defined by the BTS guidelines; and about to receive or receiving IVS.

9. Exclusion criteria

Patients being admitted for a primary reason other than asthma management were excluded from the study. Specific reasons for exclusion are outlined above and in Figure 2

10. Treatment dose

Children were treated according to local policy. A summary of salbutamol treatment received and baseline concentration levels are outlined in Table 2.

11. Duration of treatment

As anticipated from the current dosage schedule, salbutamol infusion doses ranged from 0-2 µg/kg/min in the ED cohort, and 0-4 µg/kg/min in the CATS cohort. Median duration of IVS treatment was 5 hours in the ED cohort (range 0.5 – 19.1), and 3.5 hours (range 0.2-196.2) in the CATS cohort. Table 2.

12. Criteria for evaluation

From the 54 patients included in the analysis, we obtained 171 salbutamol levels; 111 PASS measurements (ED cohort only); toxicity measurements included lactate (230), pH (244), base excess (243), and blood glucose (225). Twenty patients had samples taken for genotyping.

13. Statistical methods

Sample size

In order to characterise model parameter-covariate relationships, it has been proposed that at least 50 subjects are required in a population PKPD study.(11) We aimed to recruit 100 patients (70 ED and 30 CATS) to ensure the best chance of estimating the model parameter variability in the population of interest. Analysis of prior audit data suggested that we could enrol the target sample size within a 12 month period.

Population PKPD modelling

Sequential population pharmacokinetic/pharmacodynamic (PKPD) modelling was performed with NONMEM® (version 7.3) where a PK model was firstly developed and individual PK parameters were combined with a PD model to describe the time course of PD observations.(12)

One- and two-compartment PK models were tested to describe the time course of salbutamol plasma concentration for individual patients, with baseline plasma

concentration estimated due to uncertain and lengthy dosing history of nebulised salbutamol prior to enrolment. Allometric size scaling with body weight on clearance and volume of distribution was added *a priori*, and a sigmoidal maturation function describing the change of clearance over age was tested.(13)

PASS scores were treated as categorical data and modelled with ordered logistic regression where the bronchodilation effect was linked with the probability of achieving PASS scores. Both linear and Emax concentration-effect relationships were tested with predicted time-varying plasma concentrations from the PK model. Similar modelling approach was also used for individual PASS items: wheezing, prolonged expiration and work of breathing. A schematic of the PKPD models is given in Figure 3 (top panel).

For PASS scores, covariates were examined whether any patient characteristics may influence the estimation of bronchodilation effect for individual patients. Covariates of interest included comedications (steroids, magnesium, aminophylline), mechanical ventiation and Arg16Gly polymorphism (rs1042713) in β-2 adrenoceptor. During model development likelihood ratio test (LRT) or Akaike information criterion (AIC) were used to quantitatively compare the goodness of fit between models, respectively for nested and non-nested models.(14)

The following continuous markers of toxicity were also modelled: lactate, pH, base excess, blood glucose, heart rate, systolic and diastolic blood pressure. Toxicity effects were driven from an effect compartment with first-order equilibration with the plasma compartment, in order to examine whether delayed onset occurred for each toxicity measure after IVS. A sigmoidal Emax model was used to link effect compartment concentration with toxicity effects. A schematic of the PKPD models is given in Figure 3 (bottom panel).

PKPD models for plasma concentrations, PASS scores and toxicity measurements were evaluated by prediction-corrected visual predictive checks (pcVPCs) that were generated using Perl-speaks-NONMEM (PsN) (version 4.8.1). For each pcVPC, 1000 simulations from the PKPD model were conducted and normalised by variable doses (15) It was visually assessed whether the median, 2.5th and 97.5th percentiles of observed data lay within 95% confidence interval of individual percentiles of simulated data.

Dose regimen simulation

To determine the maximum dose of IVS in children, simulations based on the PKPD results are being conducted in 1,000 patients to propose an infusion dose with maximum and sustained bronchodilation effect and with minimum risk of toxicity, in

particular of hyperglycemia, significant deficit of base excess, excessive lactic acidosis and significant change of diastolic blood pressure.

14. Efficacy evaluation

Population PK modelling

A one-compartment PK model well described the time course of salbutamol plasma concentrations after nebulised and intravenous salbutamol doses. Body weight was found as a statistically significant covariate on both clearance and volume of distribution. The covariate effect of age was not found significant. The estimates of clearance and volume of distribution were comparable to that from an adult study after allometric scaling, as listed in Table 3.(16)

Population PD modelling

For PASS and the individual items, Emax concentration-efficacy relationship gave better model fit for all in comparison to null concentration-efficacy relationship. The addition of linear concentration-efficacy relationship only improved the goodness of fit for work of breathing. Parameter values from the Emax drug effect models are outlined in Table 3 for PASS and the individual items. EC50 values were estimated to be between 0.2 ng/mL and 0.5 ng/mL. No covariates were found statistically significant, while less than 3-fold difference in lowering PASS score was estimated for patients with mechanical ventilation and co-medications, and 5.3-fold difference between patients with heterozygous and with homozygous rs1042713 in β-2 adrenoceptor.

Toxic effects increased immediately with the increase of plasma concentrations, the opposite for pH and base excess measures; these findings were consistent with physiological observations. Parameter values for each toxicity measurement are outlined in Table 5. Heart rate and base excess were found to be the most sensitive to a change in IVS, with EC50 values of 6.23 ng/mL and 27.9ng/mL respectively.

Model evaluation

Preliminary diagnostic and pcVPC plots in Figure 4 were reasonable for plasma concentrations, PASS scores and toxicity measurements, suggesting that the developed PKPD models were adequate in describing observed PKPD data in the current study.

Dose regimen simulation

Modelling is still ongoing. Preliminary modelling has been simulated in 1000 patients looking at doses from 0.5-5mcg/kg/min over 6 hours in a 13.2kg patient (as our cohort median) after an initial bolus dose of 15mcg/kg/min. This demonstrated no additional advantage in effectiveness is obtained using dosages above 1mcg/kg/min. We are subsequently simulating alternative dosage regimens over a range of infusion durations in different weight categories.

15. Safety evaluation

As the safety profile of salbutamol is very well known and documented in the Salbutamol (Ventolin) SmPC, we did not record all non-serious AEs outside of those recorded as signs of toxicity as per study protocol. The toxicity values are outlined in Table 5.

16. Discussion and overall conclusions

Key results and interpretation

The study has successfully described a population PK model of salbutamol in children. As body weight was found as a statistically significant covariant on both clearance and volume of distribution, dosage regimens based on weight rather than, for example, age is correct. It was also found that estimates of clearance and volume of distribution were comparable to those reported in adult studies.

Population PD modelling was also successfully performed. 111 effectiveness measurements were obtained within the ED cohort, and an Emax concentration-efficacy relationship gave the best model fit. The EC50 values for PASS and the individual variables were estimated to be between 0.2 ng/mL and 0.5 ng/mL, with Emax from 6.67 to 7.77. No covariants were found to be statistically significant, although a 5.3-fold difference between patients with heterozygous and with homozygous rs1042713 in β-2 adrenoceptor is demonstrated. Examining the baseline salbutamol concentration levels, we can see that many patients are saturated from an effectiveness perspective early in the course of their IVS treatment using current dosage regimens.

942 individual toxicity measurements were obtained for PD modelling. In keeping with the associations previously reported, we validated that toxic effects increased immediately with the increase of plasma concentrations.

Limitations

Recruitment numbers were less than anticipated from our audit data. This was in part due to delays in all some sites launching, as well as a clinical practice shift in some hospitals towards aminophylline as first intravenous agent. Obtaining three blood samples in the ED cohort patients was also having a negative impact on recruitment, so we modified the study protocol after the first interim analysis to include those with only two samples provided there were at least five effectiveness measures. As it has been proposed that at least 50 subjects are required in a population PKPD study, we decided to end the study once we reached this number as the study period had

already been extended. However effectiveness measurements were only available in the self-ventilating ED cohort.

Generalisability

Diagnostic and pcVPC plots show that they were reasonable for plasma concentrations, PASS scores and toxicity measurements, suggesting that the developed PKPD models were adequate in describing observed PKPD data in the current study. To determine the maximum dose of IVS in children, simulations based on the PKPD results are being conducted in 1,000 patients. Preliminary simulation have demonstrated no additional benefit in effectiveness in dosages above 1mcg/min/min. Further modelling is ongoing for a range of weight categories and infusion durations to propose an infusion dose with maximum and sustained bronchodilation effect and with minimum risk of toxicity.

17. Appendices

Figure 1 Flow diagram of planned study recruitment

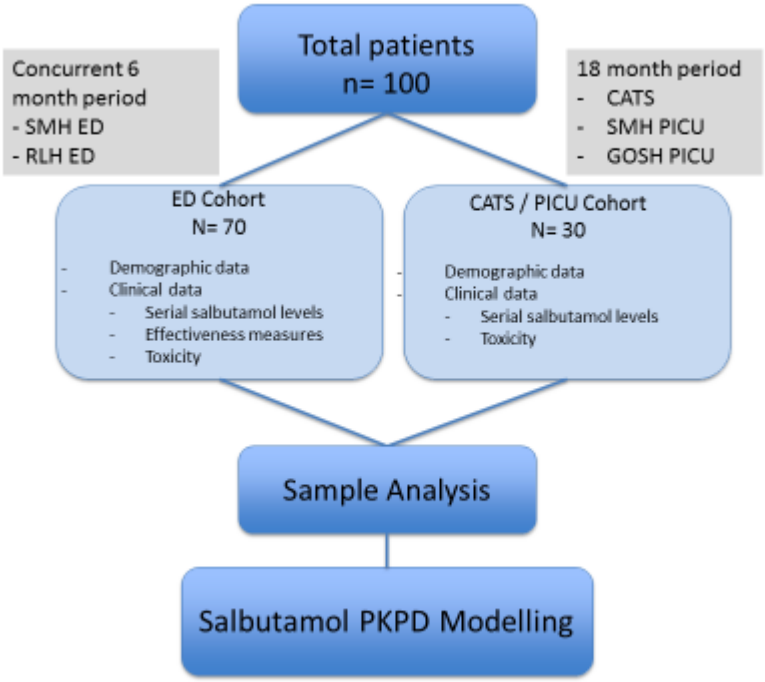


Figure 2 Patient recruitment

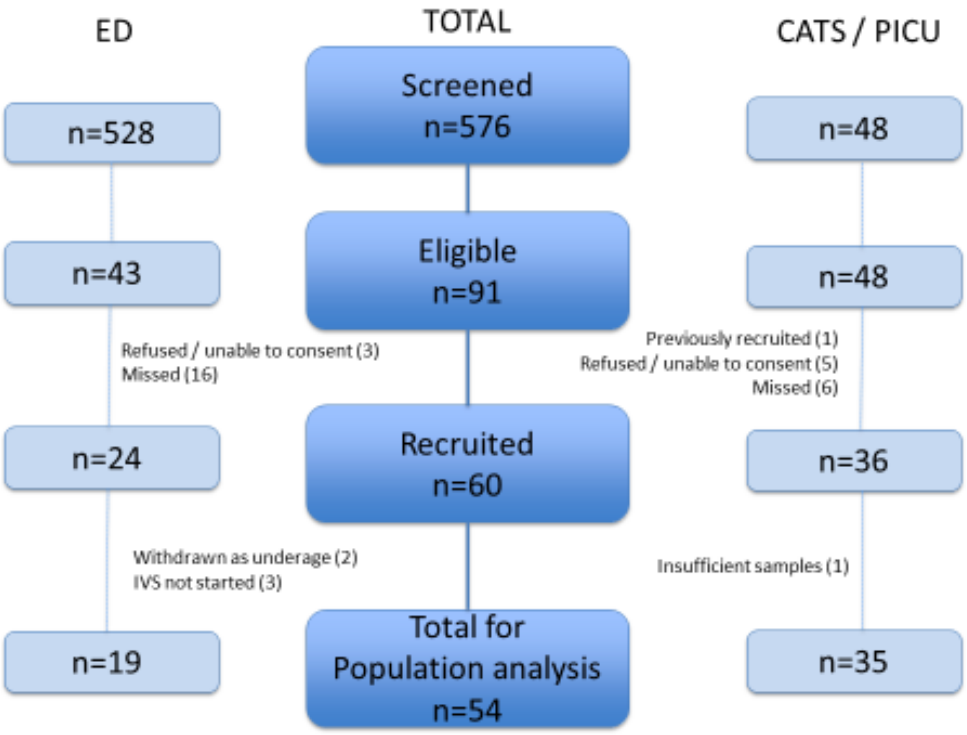


Table 1 Descriptive data of study participants

Variable	CATS (median [range])	ED (median [range])
No. of patients	35	19
Age (year)	2.7 [0-15.2]	3.5 [1.1-15.1]
Weight (kg)	13 [8-46]	14.4 [8.5-57.3]
Height (cm)	91 [72-190]	NA
Female (%)	25.7	57.9
White/ Asian/Black/Chinese/ Mixed (%)	51.4/25.7/17.1/5.7/2.9	21.1/36.8/15.8/21.1/5.3
Co-morbid conditions Known asthma Previous viral induced wheeze Allergies nuts / eggs / wheat / soya Eczema / Hayfever Trisomy 21 Tracheo/broncho/laryngomalacia Reflux Other	 n=11 n=15 n=1 n=1 n=1 n=2 n=3 n=10	 n= 5 n=9 n=1 n=4 n=1 n=0 n=2

Table 2 Summary of salbutamol treatment and baseline concentration measurements

Variable	CATS (median [range])	ED (median [range])
Baseline concentration (ng/mL)	74.5 [1.8-163]	12.3 [2.5-105]
Salbutamol bolus dose (µg)	195 [40-270]	237.5 [47.5-810]
Salbutamol infusion dose (µg/kg/min)	0.5 [0-4]	0.6 [0-2]
Salbutamol infusion duration (hr)	3.5 [0.2-196.2]	5 [0.5-19.1]
Salbutamol nebulised dose (mg)	2.5 [2.5-5]	2.5 [2.5-2.5]
Steroids/Magnesium/Aminophylline (%)	80/45.7/60	73.7/31.6/42.1
Mechanical ventilation (%)	97.1	15.8

Figure 3. Schematic of PKPD models for salbutamol plasma concentration, PASS and individual toxicity measurement

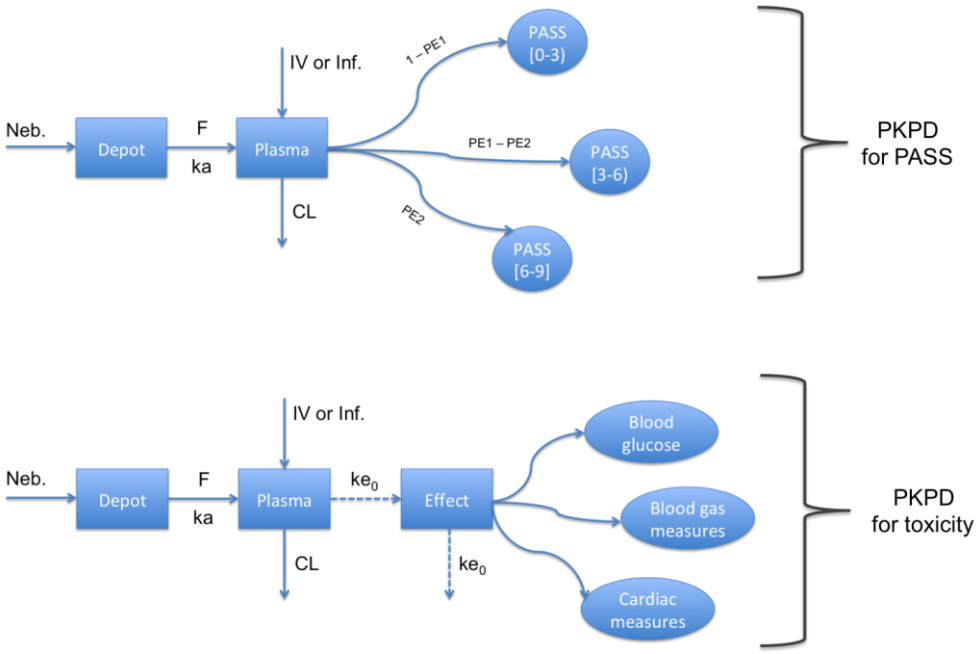


Table 3. Comparison of PK parameter values with a published adult study

Parameter (unit)	Estimated from an adult study	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

Table 4. Parameter values for PASS and individual items with Emax concentration-effect relationship

Effectiveness measure	Emax	EC50 (ng/mL)
PASS	7.77	0.5
Wheezing	9.89	0.2
Prolonged expiration	8.91	0.2
Work of breathing	6.67	0.2

Table 5. Parameter values for blood gas, blood glucose and cardiovascular tests

Toxicity variable	Mean [range]	E0	Emax	EC50 (ng/mL)	N
lactate (mmol/L)	1.6 [0.3-8.4]	1.18	0.349	63.4	8.76
pH	7.3 [6.9-7.5]	7.38	*-0.32*	136	1.39
base excess (mmol/L)	-3.4 [-14.9-15.4]	10.2	*-25.9*	27.9	0.31
respiratory exchange ratio	0.6 [0.1-1.5]	0.568	0.176	101	20.2
blood glucose (mmol/L)	9.1 [4.0-19.6]	4.8	12.4	361	0.354
heart rate	157 [100-214]	127	30	6.23	4.33
systolic blood pressure	104 [64-162]	94.9	27.7	97.3	3.71
diastolic blood pressure	55.5 [16-109]	32.9	42.1	43.7	0.01

Figure 4 Diagnostic plots

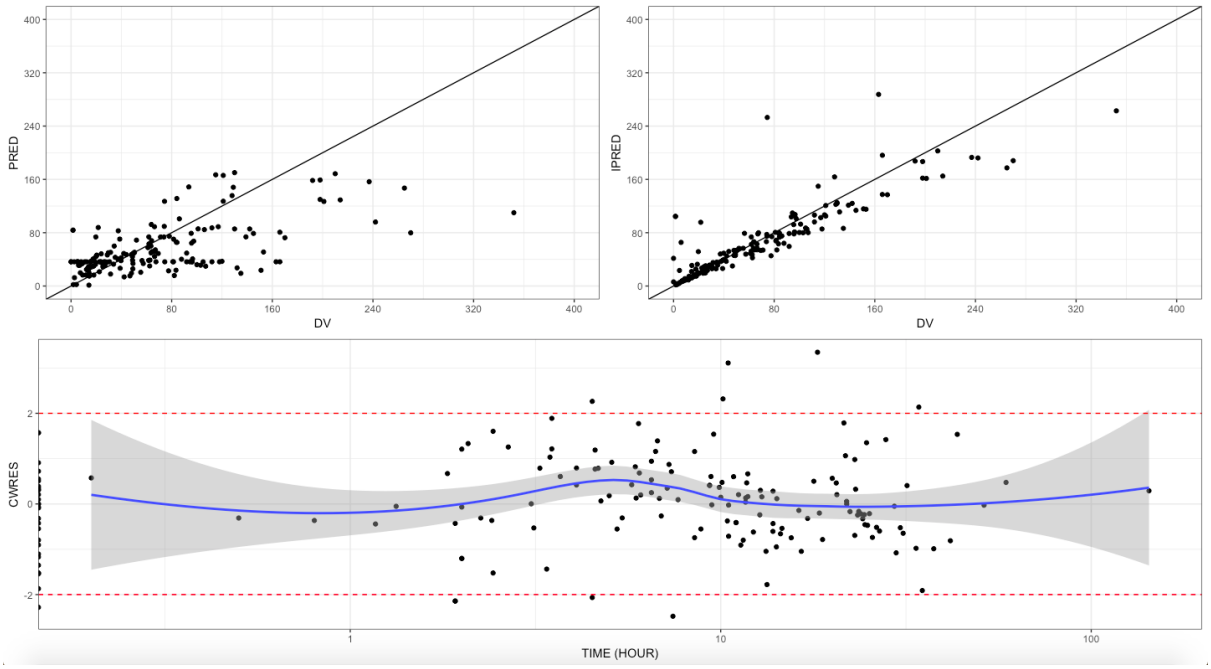
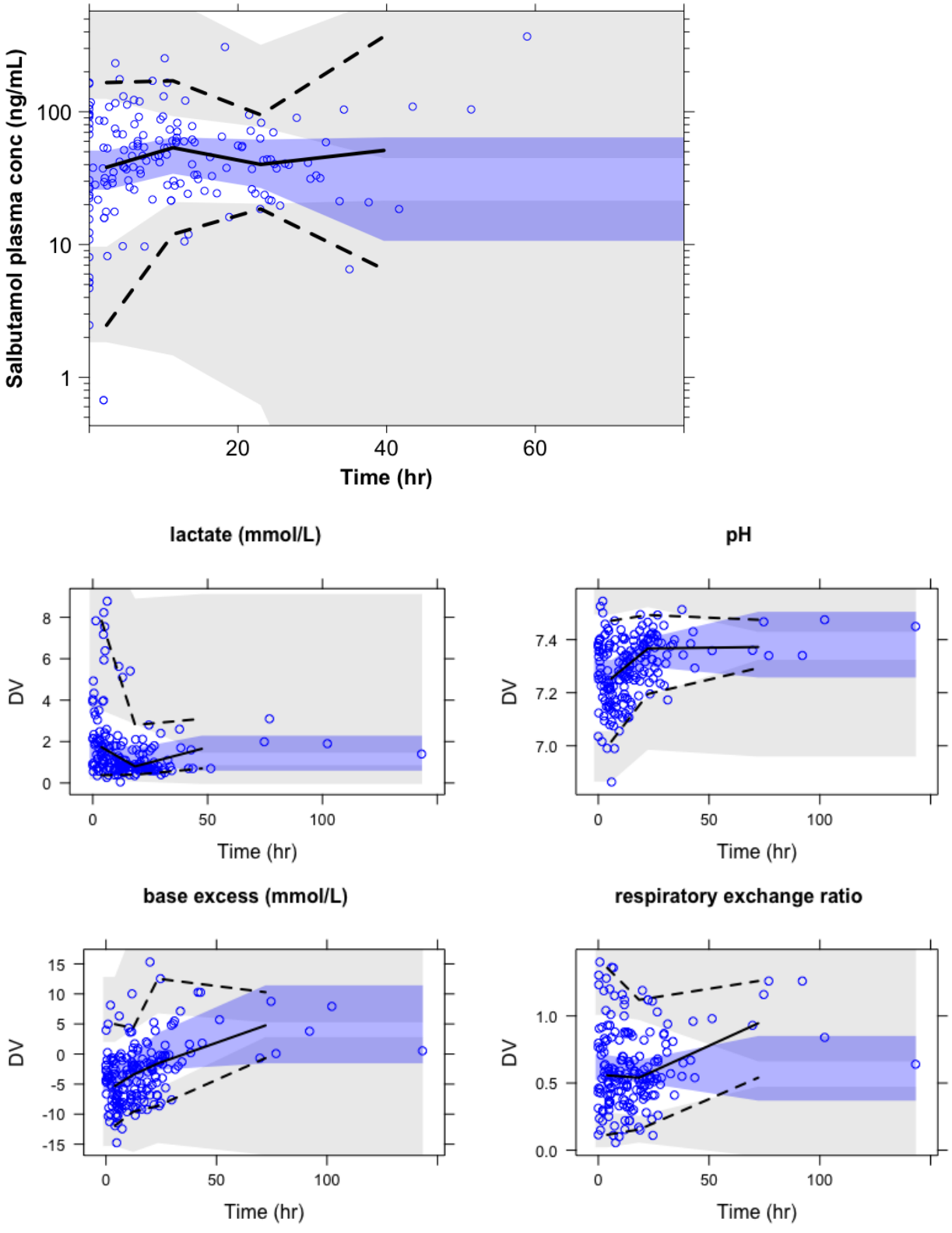
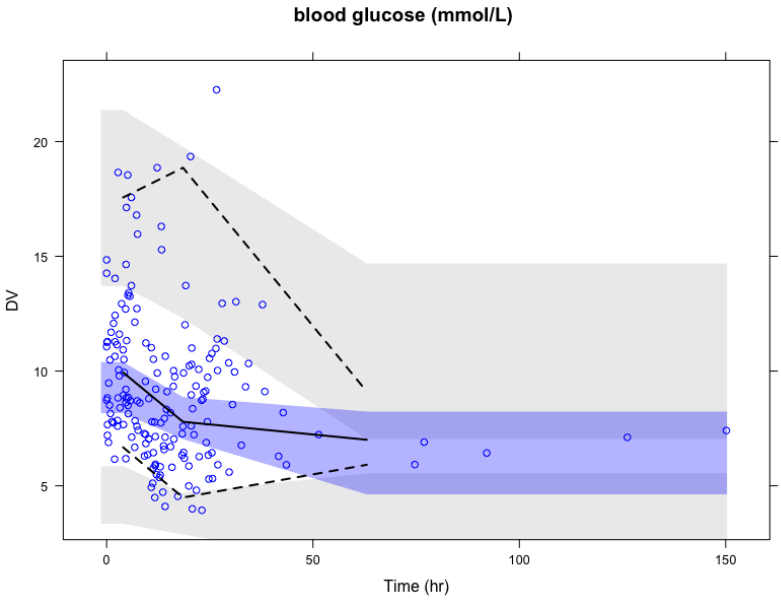
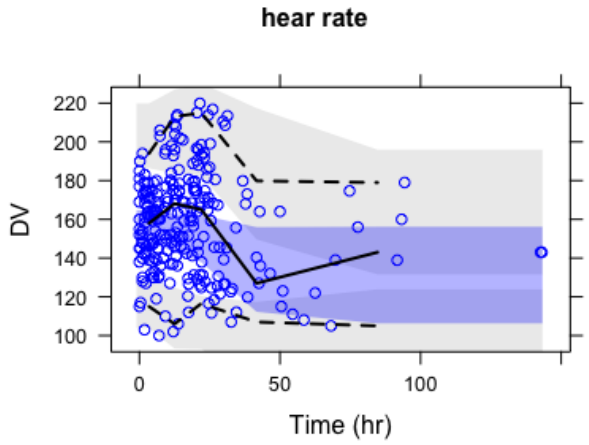
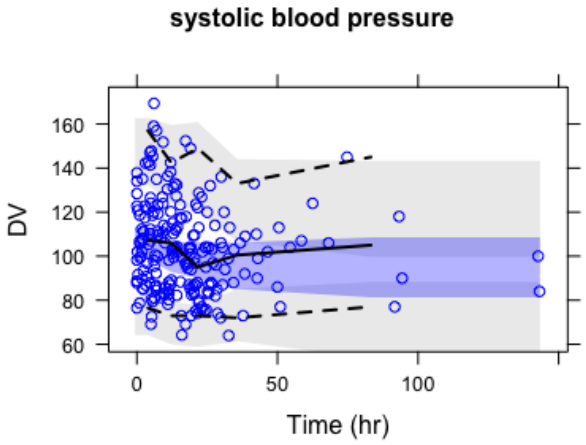


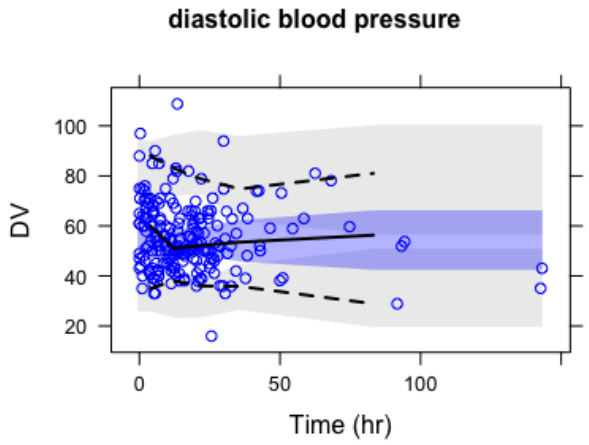
Figure 5 pcVPC graphs for plasma concentration and toxicity measurements




blood glucose (mmol/L)
DV
Time (hr)


hear rate
DV
Time (hr)


systolic blood pressure
DV
Time (hr)


diastolic blood pressure
DV
Time (hr)

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