Optimising intravenous salbutamol in children: A phase 2 study

Sandra Walsh[1], Shan Pan[2], Yucheng Sheng[2], Frank Kloprogge[3], Joseph F Standing[2] , Brian J Anderson[4], Padmanabhan Ramnarayan[2,5] on behalf of the OSTRICH Study Group

1. Paediatric and Neonatal Intensive Care Unit, Great Ormond Street Hospital NHS Foundation Trust, London, WC1N 3JH
2. Infection, Immunity and Inflammation Section, UCL Great Ormond Street Institute of Child Health, London WC1N 1EH
3. Institute for Global Health, University College London, London WC1N 1EH
4. Department of Anaesthesiology, University of Auckland, New Zealand
5. Children's Acute Transport Service, Great Ormond Street Hospital NHS Foundation Trust, London, WC1N 3JH

Corresponding author: Sandra Walsh

Email swalshieis@hotmail.com

OSTRICH Study Group

Prof Mark Peters, Dr David Inwald, Dr Ami Parikh, Dr Ian Maconochie, Prof Mario Cortina-Borja.

Ethical approval:

Ethical approval was provided by the Brent Research Ethics Committee (ref: 14/LO/2103). R&D approval was obtained at all research sites. 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 the MHRA.

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Abstract

Objective

β2-agonist such as salbutamol are the mainstay of asthma management. Pharmacokinetic-pharmacodynamics (PKPD) models to guide paediatric dosing are lacking. We explored the relationship between salbutamol dose, plasma concentration, effectiveness and adverse effects in children, through developing a population PKPD model.

Design

A prospective cohort study of children admitted to hospital with acute asthma, who received intravenous salbutamol.

Setting

Children were recruited in two cohorts: The emergency departments of two London hospitals; or those retrieved by the Children's Acute Transport Service to three London PICUs.

Patients

Patients were eligible if 1-15 years; admitted for acute asthma; and about to receive or receiving intravenous salbutamol.

Interventions

Treatment was according to local policy. Serial salbutamol plasma levels were taken. Effectiveness measurements were recorded using the Paediatric Asthma Severity Score (PASS). Toxicity measurements included lactate, pH, glucose, heart rate, blood pressure and arrhythmias. PKPD modelling was performed with nonlinear mixed effect models.

Main outcomes

Sixty children were recruited with 221 salbutamol concentration measurements from 54 children. Median [range] age 2.9 [1.1-15.2] years; weight 13.6 [8-57.3]kgs. Ninety-five PASS measurements and 2078 toxicity measurements were obtained.

Results

A two-compartment PK model adequately described the time-course of salbutamol-plasma concentrations. An Emax concentration-efficacy relationship described PASS and toxicity measures. PKPD simulations showed an infusion of 0.5 µg/kg/min (maximum 20 µg/min) for 4 hours after bolus achieves >90% maximal bronchodilation for 12 hours..

Conclusion

A paediatric PKPD model for salbutamol is described. A salbutamol infusion of 0.5µg/kg/min achieves effective bronchodilation. Higher rates are associated with greater tachycardia and hyperglycaemia.

What is already known on this topic:

- There is limited evidence for the use of intravenous β2-agonists in children with asthma. Pharmacokinetic-pharmacodynamic models to guide paediatric salbutamol dose are lacking.
- Current paediatric salbutamol dosage regimes are extrapolated from adult PK studies, and result in children receiving far more intravenous salbutamol (1-5 µg/kg/min) than the maximum adult dose (20 µg/min).
- There is growing evidence that the use of salbutamol is associated with adverse effects such as lactic acidosis, hyperglycaemia, ketosis, and cardiac arrhythmias.

Added value of this study

- A two-compartment disposition model described intravenous salbutamol pharmacokinetics. An Emax concentration-efficacy relationship described effectiveness and toxicity measures.
- Blood glucose and heart rate are useful toxicity measurements, with the salbutamol concentration required for maximal therapeutic effect surpassed before toxicity is reached.
- Using the PKPD model, an infusion of 0.5 µg/kg/min for 4 hours after bolus achieved >90% of maximum bronchodilation for 12 hours. A ceiling effect at 20 µg/min is reported.

How this study might affect research, practice or policy

- Current dosage schedules for intravenous salbutamol in children results in salbutamol concentration levels above those required for therapeutic bronchodilation, at the expense of adverse effects.
- Until now, the evidence on which to change current practice has been lacking.
- This study provides the necessary PKPD model on which to base future dosing schedules of intravenous salbutamol in children, thereby maximising effectiveness while minimising toxicity.

Introduction

A child is admitted to hospital every 20 minutes with acute asthma.(1) β2-adrenergic receptor agonists such as salbutamol form the mainstay of treatment. National guidelines from the British Thoracic Society recommend that intravenous salbutamol should be considered as second line treatment in children who fail to respond to nebulised β2-agonists and steroids. They recommend an IV salbutamol bolus 15 µg/kg body weight over 10 minutes, followed by a maintenance infusion of 1-5 µg/kg/min. (2) The evidence-base for this comes predominantly from one small study from 1997.(3) Current paediatric salbutamol dosage regimes are extrapolated from adult pharmacokinetic studies, and result in children receiving far more intravenous salbutamol (1-5 µg/kg/min) than the maximum adult dose (20 µg/min) . Huge variations in clinical practise are reported.(4)

Data from pharmacokinetic/pharmacodynamic (PKPD) models on which to base paediatric salbutamol dose are lacking.(5) There is growing evidence that salbutamol use is associated with adverse effects such as lactic acidosis, hyperglycaemia, ketosis, and diastolic hypotension with myocardial injury and cardiac arrhythmias.(6-9).

We conducted a prospective cohort study to explore the relationship between salbutamol dose, plasma concentration, effectiveness and adverse effects in children, through developing a population PKPD model. We anticipated this model could change dosing recommendations.

Methods

Design

We conducted a prospective cohort study of children admitted to hospital with acute severe asthma, who received intravenous salbutamol during their clinical management. All children were treated according to local policy.

Serial salbutamol concentration levels, effectiveness scores and toxicity measurements were taken as described (See 'Measurements'). PKPD modelling was performed using NONMEM®.

Setting

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

a) The emergency departments at two hospitals in London: St Mary's and the Royal London Hospitals (ED cohort).
b) Critically ill children retrieved by the Children's Acute Transport Service (CATS) to three tertiary paediatric intensive care units: Great Ormond Street, St Mary's and the Royal London Hospitals (CATS cohort).

Participants

Patients were eligible if aged 1-15 years (inclusive), admitted to hospital for acute asthma (defined by the BTS guidelines), and about to receive or receiving intravenous salbutamol. Participants were identified by the clinical teams, and recruited by research nurses. Patients continued in the study until 8 hours after stopping salbutamol, or hospital discharge.

We followed established procedures for obtaining deferred consent in emergency situations.(10-12)

Data sources / measurements

Study data were collected using REDCap database hosted at University College London.(13) Data collected included age, sex, ethnicity, renal function tests; asthma treatments and timing including nebulisers, steroids, magnesium sulphate, aminophylline and intravenous salbutamol; and hospital course including length of stay, PICU admission and use of mechanical ventilation.

Salbutamol concentrations: Serial blood samples to measure salbutamol concentrations were taken. In the ED cohort, samples were taken at t_0 (prior to starting intravenous salbutamol) and t_{end} (prior to stopping the salbutamol infusion). Other samples were taken with routine clinical sampling. We aimed for a minimum of 3 samples per patient. In the CATS cohort, salbutamol concentrations were taken at t_{CATS} (at first contact with the retrieval team, when the child was usually already on intravenous salbutamol). Further samples were taken via indwelling vascular catheters: prior to a dose change; 30 minutes after a dose change; once at t_{end}, and one in the eight hours after stopping intravenous salbutamol. Samples were analysed by ABS Laboratories, using a Liquid chromatography-mass spectrometry method, validated according to EMA and FDA regulatory authority criteria.(14, 15) This assay is validated to a lower limit of 0.1 ng/ml salbutamol.

Genotype data: One blood sample was taken for single nucleoside polymorphism analysis involving the three most common β-2 adrenoceptor genes (ADRB2): Arg16Gly, Gln27Glu and Thr164Ile, to see if they influenced the PKPD model.

Effectiveness measurements were recorded in spontaneously breathing patients by the Paediatric Asthma Severity Score (PASS, 0-15), a validated scoring system incorporating wheezing, prolonged expiration, and work of breathing. This non-invasive scoring system correlates with peak expiratory flow rate and pulse oximetry.(16) Serial measurements were recorded by the research nurse. We did not attempt to measure effectiveness in ventilated patients.

Toxicity-associated physiological measurements recorded included serum lactate, pH, base excess and blood glucose values.(7) Toxicity-associated cardiovascular measurement were heart rate, blood pressure, and cardiac arrhythmias.

Sample size

To characterise model parameter-covariate relationships, it is proposed that at least 50 subjects are required in a population PKPD study.(17) We aimed to recruit 100 patients.

Ethical approval by the Brent Research Ethics Committee (ref: 14/LO/2103).

Statistical methods

Population PKPD modelling

Sequential population 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.(18)

One- and two-compartment PK models were tested to describe intravenous salbutamol disposition. Nebulised salbutamol received was included under the assumption that most drug was deposited in the lung over 5 minutes with estimated inhaled bioavalability [0.9] and absorption rate fixed at $16.7h^{-1}$. An estimated baseline plasma concentration was also tested. 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.(19)

PASS scores were treated as continuous data and modelled with a regression model where salbutamol plasma concentrations were linked with PASS scores.(20) Both linear, E_{MAX} and sigmoidal E_{MAX} concentration-effect relationships were tested. Raw data showed a flat concentration-response relationship indicating current clinical salbutamol concentrations achieve the maximum possible bronchodilation effect. As parameters could not be estimated due to O-gradients, EC_{50} and HILL were therefore fixed to literature values from a dose-ranging study (suppl. Fig 10).(21) Since these values were for R-salbutamol whereas our assay measured total salbutamol, the salbutamol concentrations were converted to total by adding the R-salbutamol to the predicted S-salbutamol concentrations from a recent study. (22)

We examined whether any patient characteristics influenced the estimation of bronchodilation effect (PASS). Covariates analysed were aminophylline, corticosteroids, ipratropium, monteleukast, antibiotics, serum creatinine, and MgSO4. β-2 adrenoceptor genotyping was visually inspected. The likelihood ratio test or Akaike information criterion were used respectively for nested and non-nested models to compare the goodness of fit.(23)

The following markers of toxicity were modelled: lactate, pH, base excess, blood glucose, heart rate, and diastolic blood pressure. Heart rate and diastolic blood pressures were standardised with age appropriate Z-scores.(24, 25) Toxicity effects were estimated from circulating salbutamol with first-order equilibration with the plasma compartment. A sigmoidal E_{MAX} model was used to link salbutamol concentration with toxicity effects. Concomitant therapy with corticosteroids was investigated as a covariate on blood glucose PKPD model parameters E_0, E_{MAX}, and EC_{50}.

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 (version 4.8.1). For each pcVPC, 1,000 simulations from the PKPD model were performed.(26) Whether the median, 2.5th and 97.5th percentiles of observed data lay within 95% confidence interval of simulated data was visually assessed.

Dose regimen simulation

Using our PKPD model, initial simulations were conducted in 2,000 patients to determine the optimal dose of intravenous salbutamol in children. The simulated patient population had body weights ranging from 5 to 54 kg and were given a bolus dose of 15 μg/kg followed by

an infusion of 0.25, 0.5, 1 and 5 μg/kg/min. The target was to propose an infusion dose which achieved >90% of the maximum bronchodilation effect in the majority of patients, with minimum clinical toxicity; in particular of hyperglycaemia (blood glucose > 10mmol/L), and tachycardia (heart rate > 2 Standard Deviations above baseline). We analysed infusion durations up to 24 hours but ultimately focused on a 4 hours infusion as it may obviate the need for out-of-hospital transfer. A 0.5μg/kg/min infusion was further investigated with and without a maximum dosage of 20μg/min using Monte Carlo simulations.

Results

Participants

576 patients were screened. There were 89 eligible patients; 8 refused or were unable to consent, one was previously recruited and 22 were missed. There were 54 of 60 children included in the final analysis. (Figure 1)

Descriptive data

The median [range] age was 2.9 [1.1-15.2] years with 20 (37%) female. There were 40 (74%) children with a known history of asthma or viral induced wheeze. There were 50 children (93%) given salbutamol inhalers / nebulization prior to enrolment. In the CATS cohort, 16 children (47%) had received an IV salbutamol bolus and 11 children (32%) had commenced on salbutamol infusions prior to enrolment. The median [range] duration of these infusions was 5 [0.5-22.7] hours. At enrolment, the median [range] salbutamol concentrations were 86.65 [1.36-166] and 8.04 [2.47-24] ng/ml in the CATS and ED cohorts, respectively. (Table 1)

Following enrolment, 30 children (55%) received further salbutamol nebulisers / inhalers. There were 8 (24%) and 19 (95%) children who received an intravenous bolus in the CATS and ED cohorts respectively. Salbutamol infusions were run at a median [range] rate of 1.0 [0.1- 4] μg/kg/min in the CATS cohort and 1.0 [0.5-2] μg/kg/min in the ED cohort. Salbutamol infusion duration median [range] was 3.33 [0.183-196.2] hours and 5.5 [0.5-48.8] hours in the CATS and ED cohorts respectively after enrolment. Concomitant drugs used during the study period are outlined in Table 2.

Outcome data

We obtained 221 individual salbutamol plasma concentrations from 54 patients. There were 95 PASS measurements, 280 lactate measurements, 295 pH measurements, 294 base excess measurements; 255 blood glucose measures; 290 respiratory exchange ratio measurements; 306 diastolic blood pressure measurements; 358 heart rate measurements (supplementary figure 1-8) and 20 genotype samples. Mechanical ventilation was required in 34 children (97%) of the CATS cohort and 3 children (15.8%) in the ED cohort for a median duration of 91.6 hours and 99.1 hours respectively. Median [range] length of hospital stay was 6 [3-34] days and 2 [1-9] days in the CATS and ED cohorts respectively. (Table 2)

Main results

Population PK modelling

A two-compartment PK model adequately described the time course of salbutamol plasma concentrations. PK parameters were standardised to a 70 kg person using allometry. Our scaled estimated clearance was 16.3L/h. Age had no impact on clearance. Other parameters

included intercompartment clearance (8.58 l/h), central volume (109 l) and peripheral volume (69.4 l). Table 3

Population PD modelling

We found current salbutamol maintenance dosing results in salbutamol plasma concentrations that are above the 90% maximum drug effect (E_{MAX}). Parameter values from the E_{MAX} drug effect models are outlined in Table 3 for PASS. The concentration that achieved a half maximum response (EC_{50}) and slope (HILL) parameters could not be reliably estimated and were subsequently fixed to literature-based FEV_1 estimates at 0.15 ng/ml and 3.2, respectively (Suppl figure 9).

None of the covariates tested: aminophylline, corticosteroids, ipratropium, monteleukast, antibiotics, serum creatinine, and MgSO4, were significant ($p>0.01$) on PASS-score. As genotype samples were only obtained in 20 patients, no discernible trends were identified.

Blood glucose and heart rate increased with increased salbutamol plasma concentrations. Parameter estimates for these toxicity measurements are outlined in Table 3. For both these variables, the concentration-response curve demonstrates that maximum bronchodilation effect is achieved faster than the toxicity effects of hyperglycaemia and tachycardia. Concomitant therapy with corticosteroids or ventilation were not significant covariates on PKPD model parameters. Salbutamol plasma concentration did not correlate with lactate, base excess, respiratory exchange ratio or diastolic blood pressure.

Model evaluation

Visual plots of both PK and PD results (pcVPC) were reasonable for plasma concentrations, PASS scores and toxicity measurements, suggesting that the developed PKPD models were adequate in describing the observed PKPD. (Suppl Fig 10)

Other analyses

Using our PKPD model, we aimed to extrapolate a dose regimen for children. Our target was to achieve 90% of the maximum bronchodilation effect for >12 hours, with minimal toxicity. Using simulations in 2,000 virtual patients after a bolus of 15 μg/kg, infusion rates of 0.25-5 μg/kg/min for four hours were explored (Figure 2). We found that a salbutamol infusion of 0.5 μg/kg/min after bolus with a ceiling rate of 20 μg/min achieved this. (Suppl Fig 11). An ongoing infusion sustained the effect.

Discussion

Key Results

A population PKPD model for intravenous salbutamol in children is reported. A two-compartment disposition model adequately described intravenous salbutamol pharmacokinetics. The clearance and volume of distribution estimates in children are comparable with those scaled from adult volunteers, concurring with a published PK model.(22) Dosing per body weight appears appropriate in children.

Our observed plasma concentrations were substantially higher than levels regarded as toxic in adults, but in keeping with other reports of children receiving intravenous salbutamol

according to current guidelines.(22, 27) Many patients had plasma salbutamol concentrations associated with near maximum possible effect before receiving any intravenous therapy.

PD modelling was performed for all toxicity variables, although correlation with salbutamol EC_{50} estimates were only demonstrated for heart rate Z score and blood glucose. The blood glucose effect was independent of corticosteroids as a covariant. The concentration-response curve demonstrates that the maximum bronchodilation effect is achieved faster than the toxicity effects of hyperglycaemia and tachycardia.

The use of PKPD simulation is well-established in drug development.(28) Using our PKPD model, simulations showed that after a bolus of 15 μg/kg , an infusion of 0.5 μg/kg/min for 4 hours achieved our target of >90% of the maximum bronchodilation effect for 12 hours in the majority of patients. We report a ceiling effect and a maximum infusion rate of 20 μg/min is adequate. Higher infusion rates did achieve bronchodilation above 90%, but at the cost of increased toxicity.

Limitations

We aimed to recruit 100 patients but fewer patients received intravenous salbutamol, and research nurses' hours caused a number of missed eligible patients. Fifty subjects are suggested for a population PKPD study and we stopped recruitment once that number was achieved. The requirement for 3 salbutamol concentration samples was also restrictive, with the protocol adjusted to include those with only 2 samples after the first interim analysis (provided 5 clinical effectiveness measurements were available). The CATS cohort was more data-rich but PASS scores were only obtained in non-ventilated patients. Height

measurements were unavailable in most children (74.1%), preventing the exploration of height / body mass index on PK.

The high salbutamol concentrations at point of enrolment presented a mathematical challenge for EC_{50} modelling. This is a common phenomenon in pharmacology where a 10-fold range around the expected EC_{50} is desirable. The EC_{50} for effectiveness (i.e. PASS), could not be reliably estimated and was fixed to FEV_1 literature-based EC_{50} estimate of 1.15 ng/ml. (29)

Interpretation

A population PKPD model for intravenous salbutamol in children is now described, and provides an evidence-base for future RCTs. Current dose regimens do achieve therapeutic bronchodilation, but at the expense of adverse effects. A lower dose of 0.5 μg/kg/min after bolus would achieve the desired bronchodilation while minimising toxicity; with a ceiling effect at 20 μg/min. Demonstration that a 4 hour infusion sustained >90% maximum bronchodilation for 12 hours may obviate the need for high-dependency transfer. Understanding the salbutamol plasma-concentration effects on blood glucose and heart rate may allow titration of ongoing salbutamol infusions to these variables.

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	All patients (n=54)	**CATS cohort (n=35)**	**ED cohort (n=19)**
Age (years), median [range]	2.9 [1.1-15.2]	2.7 [1.1-15.2]	3.5 [1.1-15.1]
Weight (kg), median [range]	13.6 [8-57.3]	13 [8.34-46]	14.4 [8.5-57.3]
Female, n (%)	20 (37)	9 (25.7)	11 (55)
Ethnicity, n (%)			
White	21 (38.9)	17 (48.6)	4 (21.1)
Asian	15 (27.8)	8 (22.9)	7 (36.8)
Black	8 (14.8)	5 (14.3)	3 (15.8)
Chinese	5 (9.3)	1 (2.9)	4 (21.1)
Mixed	1 (1.9)	0 (0)	1 (5.3)
Missed	4 (7.4)	4 (11.4)	0 (0)
Co-morbid conditions, n (%)			
Known history of asthma	16 (9)	11 (31)	5 (14)
Previous viral induced wheeze	24 (44)	15 (43)	9 (47)
Allergies nuts/eggs/wheat/soya	2 (4)	1 (3)	1 (5)
Eczema / Hayfever	5 (9)	1 (3)	4 (21)
Trisomy 21	2 (4)	1 (3)	1 (5)
Tracheo/broncho/laryngomalacia	2 (4)	2 (6)	··
Gastro-oesophageal Reflux	3(6)	3 (9)	··
Other	12 (22)	10 (29)	2 (10)
Medications prior to enrolment, n (%)			
Inhaled salbutamol	9 (17)	2 (6)	7 (35)
Nebulised salbutamol	41 (76)	27 (79)	14 (70)
Intravenous salbutamol bolus	16 (30)	16 (47)	··
Intravenous salbutamol infusion	11 20)	11 (32)	··
IVS dose µg/kg/min, median [range]	1	1 [1-5]	··
IVS duration hrs, median [range]	5 [0.5-22.7]	5 [0.5-22.7]	··
Concomitant medications, n (%)			
Nebulised ipratropium	35 (65)	26 (74)	9 (47)
Corticosteroids	34 (63)	27 (77)	7 (37)
Intravenous magnesium	34 (63)	27 (77)	7 (37)

Intravenous aminophylline	20 37)	19 (54)	1 (5)
Ketamine	8 (15)	8 (23)	··
Plasma salbutamol level at enrolment (ng/ml), median [range]	22.4 [1.36-166]	86.65 [1.36-166]	8.04 [2.47-24]

Table 1: Descriptive data of study participants at enrolment

	CATS (median [range])	ED (median [range])
Treatment during study period		
Salbutamol bolus dose (μg/kg)	13.1 [4.95-15]	13.9 [3.97-17.9]
Salbutamol infusion dose (μg/kg/min)	1 [0.1-4]	1 [0.5-2]
Salbutamol infusion duration (hr)	3.33 [0.183-196.2]	5.5 [0.5-48.8]
Salbutamol nebulised dose (mg)	2.5 [2.5-5]	2.5 [2.5-2.5]
Other medications		
Steroids n (%)	28 (80)	13 (68)
IV magnesium sulphate, n (%)	18 (51)	5 (26)
Aminophylline infusion, n (%)	22 (63)	8 (53)
Ipatropium bromide n (%)	20 (57)	12 (63)
Montelukast n (%)	8 (23)	2 (13)
Ketamine infusion, n (%)	13 (37)	0 (0)
Outcome		
Mechanical ventilation, n (%)	34 (97)	3 (20)
Hours mechanical ventilation	91.6 [10.9-294]	99.1 [96-147.2]
Length of stay in hospital, days	6 [3,34]	2 [1,9]

Table 2: Treatment and outcomes of study patients

	Fixed effects	Random effects	Residual variability
Pharmacokinetic parameters			
Bioavailability [0-1]	0.0925	··	··
ka (h^{-1})	16.7	··	··
CL (l/h)	16.3	0.522	··
Vc (l)	109	1.79	··
Q (l/h)	8.58	··	··
Vp (l)	69.4	6.45	··
BASE (ng/ml)	1.04	··	··
Proportional Error	··	··	0.0629
Additive Error (ng/ml)	··	··	0.220
Effectiveness parameters			
E_0 (fraction of PASS-score [0-9])	0.381	0.257	
E_{MAX} (fraction of PASS-score [0-9])	0.25	··	··
EC_{50} (ng/ml)	1.15 (*fixed*)	··	··
HILL	3.2 (*fixed*)		
Additive on logit-scale			0.461
Glucose parameters			
E_0 (mmol/l)	5.03	··	··
E_{MAX}	3.86	0.258	··
EC_{50} (ng/ml)	1.08	1.11	··
Proportional Error	··	··	0.0747
Tachycardia parameters			
E_0 (z-score)	3.08	0.809	··
E_{MAX}	4.16	··	··
EC_{50} (ng/ml)	385	0.732	··
Additive Error (bpm)	··	··	1.41

Table 3: Parameter estimates from pharmacokinetic and pharmacokinetic-pharmacodynamic effectiveness and toxicity models. ka: absorption rate constant CL: clearance, V_C: apparent volume of distribution central compartment, V_P: apparent volume of distribution peripheral compartment, Q: inter-compartmental clearance, PASS: Paediatric Asthma Severity Score . PK parameters standardised to a 70 kg person using allometry. E_0 measurement in the absence of salbutamol; E_{max}: Maximum drug effect; EC_{50} Drug concentration producing 50% of the maximum effect; HILL: shape parameter in the Emax model (higher values indicate a steeper dose response curve)