Population Pharmacodynamic Model of Bronchodilator Response to Salbutamol in Wheezy Preschool Children

Thu Thuy Nguyen (1), Francis Amsallem (2), André Denjean (3), Grazia Fenu (4), Paul Seddon (5), France Mentré (1), Corinne Alberti (6,7), Enrico Lombardi (6), Nicole Beydon (8,9)

(1) IAME, UMR 1137, INSERM, Université Paris Diderot, Sorbonne Paris Cité, Paris, France ; (2) Unité de Pneumologie pédiatrique. CHRU de Montpellier, Montpellier, France ; (3) AP-HP, Service de Physiologie-Explorations Fonctionnelles Respiratoires, Hôpital Robert Debré, Paris, France ; (4) Paediatric Pulmonary Unit, "Meyer" Paediatric University-Hospital, Florence, Italy ; (5) Respiratory Care, Royal Alexandra Children's Hospital, Brighton, United Kingdom ; (6) AP-HP, Hôpital d'Enfants Robert Debré, Unité d'Epidémiologie Clinique, Paris, France ; (7) INSERM CIE5, Université Paris Diderot, Sorbonne Paris Cité, Paris, France ; (8) AP-HP, Unité Fonctionnelle de Physiologie-Explorations Fonctionnelles Respiratoires, Hôpital d'Enfants Armand-Trousseau, Paris, France; (9) INSERM U938 Centre de Recherche Saint Antoine, Paris, France

Introduction

Background

- Short-acting beta2-agonists such as Salbutamol are used to relieve acute symptoms of asthma in clinical settings and to measure airway reactivity during routine lung function testing.
- Preschool wheezing is a heterogeneous condition characterised by inconsistent effect of asthma medications [1]: it is not known whether the dose-response to high dose of salbutamol specific of asthma in adults exists in young children.

Objectives

- We studied for the first time the population dose-response relationship of salbutamol in preschool wheezers using the interrupter resistance (Rint), which is an appropriate measurement technique in children [2].
- A simulation study was performed to determine the relevant Salbutamol dose to administer for this age group.

Methods

Study design

- Children (3 to 6 years) with wheezing episodes in the previous year were enrolled in a multicenter study.
- Each child received successive doses of Salbutamol in 4 groups:
  (0, 100, 400) µg **(0, 200, 400)** µg
  (0, 100, 600) µg **(0, 200, 800)** µg
- Rint was measured after each dose
- Design evaluation was performed using PFIM3.2 [3].

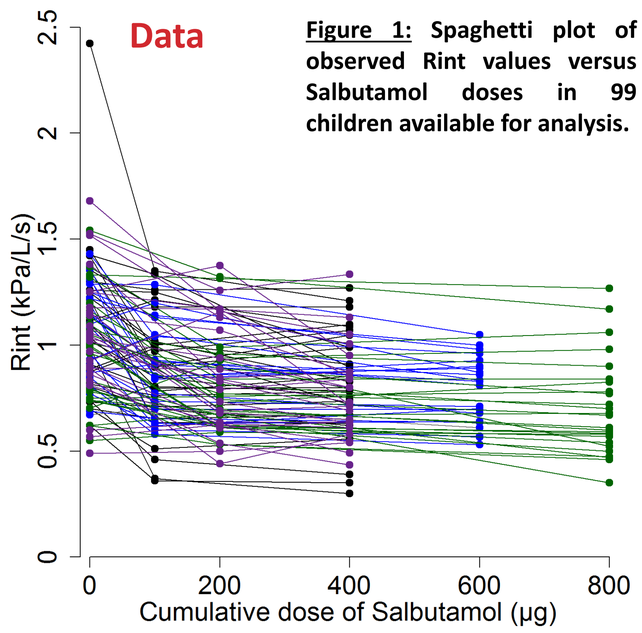


Figure 1: **Spaghetti plot of observed Rint values versus Salbutamol doses in 99 children available for analysis.**

Evaluation criterion

- Rint values were expressed in % of the predicted $Rint_{pred}$ for a given height, defined from reference equations for expiratory interrupter resistance [4]:

$$Rint_{pred\ (male)} = -0.1337+7631.3\ height^{-2}$$
$$Rint_{pred\ (female)} = -0.1725+7281.0\ height^{-2}$$

- At each dose, the variation of Rint (in % of $Rint_{pred}$) from baseline $Rint_{base}$ was calculated as $\Delta = (Rint-Rint_{base})*100/Rint_{pred}$
- Different levels of Rint reversibility were defined based on different levels of Rint decrease (in % of $Rint_{pred}$): significant reversibility if $\Delta \geq 35\%$

Population analysis

- Data were analysed by nonlinear mixed effect models with SAEM algorithm [5] in MONOLIX v4.3, using a sigmoid I_{max} model: $Rint = S_0\left(1 - I_{max}\frac{D^{\gamma}}{D_{50}{}^{\gamma}+D^{\gamma}}\right)$
- A covariate analysis was performed, using forward selection based on likelihood ratio test (LRT), to study the effect of the following factors: age, height, weight, sex, asthma symptom control, treatments with inhaled corticosteroids, leukotriene antagonists or long acting bronchodilator during last month, allergy, passive smoke during pregnancy, current exposure to tobacco smoke and history of hospitalization for acute wheezing.

Simulation and prediction

- Using the final model, individual Rint values (expressed in % of the predicted Rint for a given height [4]) were simulated for 5000 children at doses from 0 to 800 µg.
- We predicted at each dose the proportion of children with different levels of Rint reversibility ($\Delta \geq 25\%$, 30%, 35% and 40%).

Conclusions

- Interrupter resistance could measure a dose-response curve to Salbutamol in wheezy preschool children, which was similar to that of older patients.
- These young children require a high dose of Salbutamol to correctly assess airway bronchodilator response (at least 400 µg).
- Poor symptom control was associated with reduced bronchodilation.

References

[1] Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, de Blic J, de Jongste JC, Eber E, Everard ML, Frey U, Gappa M, Garcia-Marcos L, Grigg J, Lenney W, Le Souëf P, McKenzie S, Merkus PJ, Midulla F, Paton JY, Piacentini G, Pohunek P, Rossi GA, Seddon P, Silverman M, Sly PD, Stick S, Valiulis A, van Aalderen WM, Wildhaber JH, Wennergren G, Wilson N, Zivkovic Z, Bush A. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008;32:1096-1110.

[2] Beydon N, M'buila C, Bados A, Peiffer C, Bernard A, Zaccaria I, Denjean A. Interrupter resistance short-term repeatability and bronchodilator response in preschool children. *Respir Med* 2007;101:2482-2487.

[3] Bazzoli C, Retout S, Mentré F. Design evaluation and optimisation in multiple response nonlinear mixed effect models: PFIM 3.0. *Comput Methods Programs Biomed* 2010;98:55-65. www.pfim.biostat.fr

[4] Merkus PJ, Stocks J, Beydon N, Lombardi E, Jones M, McKenzie SA, Kivastik J, Arets BG, Stanojevic S. Reference ranges for interrupter resistance technique: the Asthma UK Initiative. *Eur Respir J* 2010;36:157-163.

[5] Kuhn E, Lavielle M. Maximum likelihood estimation in nonlinear mixed effects models. *Comput Stat Data Anal* 2005:49;1020-1038.

Results

- Data from 99 children were available for analysis.
- The sigmoid Imax model adequately fitted the data with satisfactory goodness-of-fit plots.

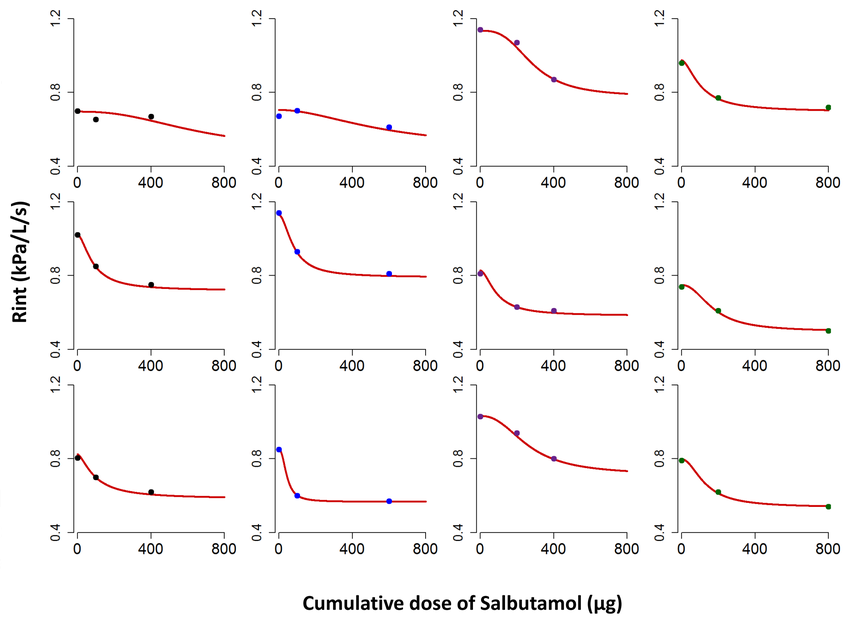


Figure 2: **Observations (dots) and individual fits with the basic model (red lines) in some patients**

- Following the covariate analysis, following effects were found:
  - Asthma symptom control (LRT, P = 0.03) and Weight (P = 0.01) on I_{max}
  - Height ($P < 10^{-5}$) on S_0
  => Uncontrolled symptoms and low weight decreased I_{max} whereas height negatively influenced S_0

Table 1: **Population estimated values and relative standard errors (RSE) of for the basic model (without covariate) and the final model (with covariates).**

Parameter	Basic model (N=99)		Final model (N=92)	
	Estimate	RSE (%)	Estimate	RSE (%)
Fixed effects				
μ_I_{max}	0.31	5	0.23	11
$\beta_{weight\_I_{max}}$	-	-	0.70	39
$\beta_{asthma\_I_{max}}$	-	-	0.30	39
μ_D_{50} (µg)	84.0	24	51.0	30
μ_γ	1.96	27	1.81	28
μ_S_0 (kPa/L/s)	1.01	3	1.00	2
$\beta_{height\_S_0}$	-	-	-1.64	20
Inter-patient variability				
ω_I_{max} (%)	0.28	16	0.25	10
ω_D_{50} (%)	1.87	10	2.52	18
ω_γ (%)	1.09	31	0.87	46
ω_S_0 (%)	0.26	8	0.21	8
Residual variability				
σ_{prop}	0.08	13	0.08	12

- Impact of asthma symptom control on the bronchodilator response

Table 2: **Fixed effect of I_{max} and expected Rint decrease from baseline (Δ, in % of median predicted Rint) at several doses, according to symptom control for a patient with median weight and height**

Uncontrolled symptoms	μ_I_{max} = 0.23	Δ_{D50} = 14.8% Δ_{D90} = 20.7% $\Delta_{D\infty}$ = 29.6%
Totally/partly controlled symptoms	μ_I_{max} = 0.31	Δ_{D50} = 20.0% Δ_{D90} = 27.9% $\Delta_{D\infty}$ = 39.9%

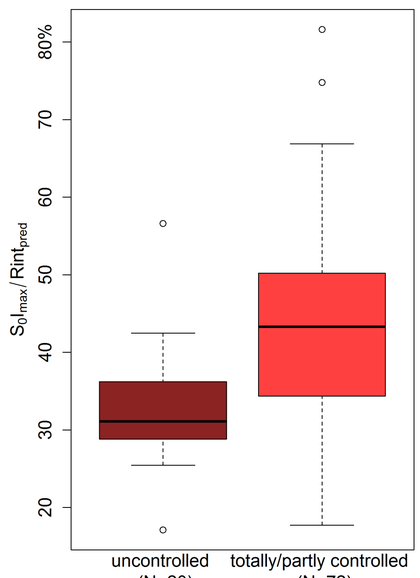
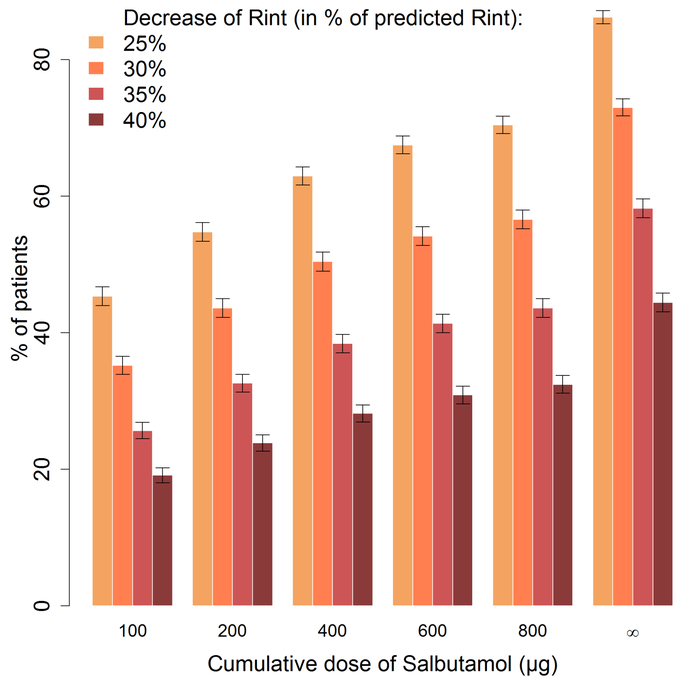


Figure 3: **Distribution of individual maximal decreases of Rint from baseline (at an infinite dose), according to symptom control.**

- Predicted proportion of children at each dose for different levels of Rint reversibility



According to simulation, 88.1% of children with significant reversibility at 800 µg would already show significant reversibility at 400 µg.

Figure 4: **Proportion of children (for 5000 patients simulated using the final model) with a decrease in Rint ≥25%, 30%, 35% and 40% of predicted Rint, respectively, at several doses of Salbutamol, as well as the 95% confidence intervals of these proportions.**