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, 600) µg
  - (0, 300, 800) µg
  - (0, 400, 1000) µg
- Rint was measured after each dose.
- Design evaluation was performed using PIM3.2 [3].

Evaluation criterion

- Rint values were expressed in % of the predicted Rintpred, for a given height, defined from reference equations for expiratory interrupter resistance [4]:
  \( \text{Rint}_{\text{pred}} \text{(male)} = 0.1337 + 763.13 \times \text{height}^{-2} \)
  \( \text{Rint}_{\text{pred}} \text{(female)} = 0.1725 + 7281.0 \times \text{height}^{-2} \)
- At each dose, the variation of Rint (in % of Rintpred) from baseline Rintbase was calculated as Δ = (Rint - Rintpred)\times 100/Rintpred
- Different levels of Rint reversibility were defined based on different levels of Rint decrease (in % of Rintpred): significant reversibility if Δ ≥ 35%

Population analysis

- Data were analysed by nonlinear mixed effect models with SAEM algorithm [5] in MONOLIX v4.3, using a sigmoid Rint pred model: \( \text{Rint} = S_{0} + \frac{S_{\text{max}} - S_{0}}{\left(1 + \frac{D}{\gamma D_{50}}\right)^{\alpha}} \)
- A covariance 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 having different levels of Rint reversibility (Δ ≥ 35%, 30%, 25%, 30% 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 bronchodilatation.

Results

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

Following the covariate analysis, following effects were found:
- Asthma symptom control (LRT, \( P = 0.03 \)) and Height (\( P = 0.01 \)) on Imax
- Uncontrolled symptoms and low weight decreased Imax whereas height negatively influenced S0

Impact of asthma symptom control on the bronchodilator response

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

- Table 2: Fixed effect of Imax and expected Rint decrease from baseline (6, in % of median predicted Rint) at several doses, according to symptom control for a patient with median weight and height

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

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

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

References