Effect of long-acting β-agonist on bronchodilator response in children with asthma

To the Editor:

Spirometry is the most common pulmonary function test (PFT) used to follow asthma patients. It is recommended to withhold short-acting β2-agonists (SABA) a few hours before pulmonary function testing and to withhold long-acting β2-agonists (LABA) for diagnosis purpose but not for the assessment of response to a current treatment [1]. In children with asthma, the addition of LABA to inhaled corticosteroids (ICS) has no clear clinical benefit, but it has proved to improve baseline forced expiratory volume in 1 s (FEV_1) [2]. The maximal increase in FEV_1 after a single dose of formoterol was measured 3 h after administration, but the remaining effect after 12 h would depend on the inhaled dose [3]. Finally, 25 or 50 µg of salmeterol inhaled at 22:00 h resulted in higher baseline pulmonary function and decrease in exercise-induced bronchoconstriction 10 and 12 h later [4]. In routine practice, children are tested with various delays since the last LABA inhalation, but LABA is usually inhaled on the morning of the test (<12 h before), in the evening the previous day (12–24 h) or on the morning the previous day or before (>24 h). It is thought that children with the most recent inhalation should have the best pulmonary function and the lowest reversibility, but the latter has not been studied.

To study the effect of the delay since the last dose of LABA on the bronchodilator response (BDR), we prospectively and consecutively included, from May 2015 to April 2016, children 6–18 years of age, referred for PFT from the outpatient clinic of our tertiary paediatric hospital with typical asthma treated with an association of ICS and LABA.

Exclusion criteria were 1) SABA inhaled <8 h before PFT; 2) other chronic diseases potentially affecting PFT results; 3) moderate (⩾2 days of rescue bronchodilator) or severe (⩾3 days of oral corticosteroids) asthma exacerbation [5] within the last 7 or 15 days, respectively, or current acute asthma symptoms; and 4) patient unable to perform spirometry. Parents and patients over 8 years of age gave informed consent for the study, which was approved by the Institutional Review Board of the French learned society for respiratory medicine – Société de Pneumologie de Langue Française (CEPRO 2015-017).

Anthropometric and clinical characteristics of asthma disease were recorded, including environmental tobacco smoke exposure (ETS), history of hospitalisation for an asthma flare-up, asthma exacerbations within the last 3 months and asthma symptom control according to the Global Initiative for Asthma (www.ginasthma.org). The child's ability to use his/her inhaler (including a demonstration using an empty disposal and questions on how he/she knew when it was empty) was determined using a standardised questionnaire. The child then performed baseline and post-bronchodilator (salbutamol 400 µg metered-dose inhaler in a spacer) spirometry (BodyBox, Medisoft, Sorinnes, Belgium) according to international guidelines [6].

The lower limit of normal (LLN) for spirometry indices was set at −1.64 z-score [7] and FEV_1 BDR was positive when ⩾12% predicted, without absolute change criterion as children younger than 10 years were included [8]. Quantitative variables were compared using the Wilcoxon–Mann–Whitney test. The relationships between the delay since the last inhalation of LABA and baseline obstruction or FEV_1 BDR were studied using the Cochran–Armitage test for trend. Univariate analyses between FEV_1 BDR and clinical characteristics, the type of inhaler, the last dose of LABA (full dose (*i.e.* 12 µg for formoterol,

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If long-acting beta-2-agonists are not withheld before pulmonary function tests in children with asthma, their effect on baseline function will be evaluated, but significant FEV_1 reversibility could still occur https://bit.ly/2zGn8PG

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50 µg for salmeterol) or half dose), baseline FEV_1 and FEV_1 to forced vital capacity (FVC) ratio were performed. Significant covariates at a 20% threshold were retained for the final multivariate model. The p-value confirmed a statistical relationship when <0.05 (two-sided). All statistical analysis was performed with SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA).

We enrolled 267 patients and secondarily excluded seven children with an unclear delay since the last inhalation of LABA. The 260 children (median (interquartile range) age 12.2 (9.6–14.9) years, 163 males) included fell into three groups of analysis according to the last LABA inhalation (<12 h, n=126; 12–24 h, n=88 and >24 h, n=46). Children were mostly Caucasian (67.7%) and African–Caribbean (19.2%). Frequencies of ETS (25.1%), history of hospitalisation (39.8%), moderate or severe asthma exacerbations in the previous 3 months (37.8%) and the use of antileukotriene medication (39.5%) were similar across groups. During the previous month, asthma was well, partly or not controlled in 84.9, 12.0 and 3.1% of cases, respectively. One-third of the children were prescribed a Turbuhaler device (n=85), half had a Diskus (n=131) and a sixth a metered-dose inhaler (n=44). The children demonstrated the correct use of their devices in 85.4% of cases. The last dose of LABA taken before PFT was equally full dose (52.1%) or half dose (47.9%).

The baseline and post-bronchodilator PFT results across the three groups are shown in table 1. The logistic regression including FEV_1 BDR as the dependent variable showed significant independent relationships with full dose of LABA inhaled (OR 0.24, 95% CI 0.08–0.77; p=0.016), baseline FEV_1>LLN (OR 0.14, 95% CI 0.04–0.53; p=0.003) and FEV_1/FVC>LLN (OR 0.24, 95% CI 0.08–0.75; p=0.014). In contrast, there was no relationship between the delay since the last dose of LABA and positive BDR (12–24 h OR 0.54, 95% CI 0.13–2.16; p=0.381; >24 h OR 1.38, 95% CI 0.41–4.64; p=0.605). It is to be noted that there was no interaction between baseline FEV_1 and FEV_1/FVC (p=0.114) and that the molecule inhaled did not influence the results.

The children with an inhalation technique judged as correct were younger than those with an incorrect technique (median 11.8 (interquartile range 9.3–14.3) *versus* 13.2 (11.8–15.4) years; p=0.010), but showed similar results than the whole population for all the findings.

In our study, exacerbation, a known factor for future risk in asthma [9], was not associated with a different frequency of positive BDR, contrasting with longitudinal studies showing that a low BDR during childhood is related to poor pulmonary function from childhood into adulthood [10, 11]. We did not observe any relationship between FEV_1 BDR and asthma symptom control, but there were very few children with uncontrolled asthma in our study population.

The delay since the last LABA inhalation was declared, which could be a limitation, but we took great care about the schedule reported by the child and his/her parents and unreliable cases were excluded. The difference in pulmonary function in the three groups is in agreement with our assessment of the delay (table 1).

Our results suggest that it was mainly the persistence of bronchoconstriction that influenced the occurrence of a positive BDR independent of the delay since the last LABA inhalation. The lack of BDR under treatment might also reveal ongoing airway remodelling [12]. In contrast, the persistence of a positive BDR under treatment suggests that there are still therapeutic possibilities to improve pulmonary function, especially in children taking an insufficient dose of LABA.

TABLE 1 Baseline and post-bronchodilator spirometry, and bronchodilator response in three groups of children according to the delay since last long-acting β2-agonist dose

	<12 h (n=126)	12–24 h (n=88)	>24 h (n=46)	p-value
Baseline FVC (z-score)	0.14 (−0.47 to 0.82)	0.03 (−0.69 to 0.79)	0.07 (−0.49 to 0.66)	
Baseline FEV_1 (z-score)	−0.24 (−0.89 to 0.46)	−0.37 (−0.92 to 0.58)	−0.55 (−1.38 to 0.10)	0.079
Baseline FEV_1/FVC (z-score)	−0.67 (−1.53 to 0.05)	−0.84 (−1.28 to 0.32)	−1.05(−1.94 to −0.34)	0.047
Baseline obstruction	26 (21)	15 (17)	16 (35)	0.055
Post-BD FVC (z-score)	0.15 (−0.48 to 0.83)	−0.09 (−0.62 to 0.79)	0.19 (−0.44 to 0.67)	
Post-BD FEV_1 (z-score)	0.12 (−0.61 to 0.73)	0.08 (−0.57 to 0.91)	−0.14 (−0.53 to 0.55)	0.445
Post-BD FEV_1/FVC (z-score)	−0.27 (−0.84 to 0.72)	0.11 (−0.82 to 0.65)	−0.13(−1.01 to 0.31)	0.317
FEV_1 BDR ⩾12% pred	10 (8)	4 (5)	7 (15)	0.098

Data are presented as median (interquartile range) or n (%). FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; post-BD: post-short-acting bronchodilator inhalation; BDR: bronchodilator response.

In conclusion, baseline bronchial obstruction in children with asthma without current exacerbation is related to a significant FEV_1 reversibility. The delay since the last LABA inhalation should not interfere in the interpretation of BDR, but the dose of LABA has to be considered. However, LABA improve baseline pulmonary function and should, therefore, not be withheld before PFT if its effect on baseline function is to be evaluated.

Further studies looking at changes in clinical and PFT (including BDR) outcomes before and after the initiation of LABA treatment could give insight in persistent reversibility under treatment.

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