

CORRESPONDENCE

Methacholine is more sensitive than mannitol for evaluation of bronchial hyper-responsiveness in youth athletes with exercise-induced bronchoconstriction

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To the Editor,

In a recent paper (1), we reported that methacholine testing was more sensitive than mannitol challenge for assessing bronchial hyper-responsiveness (BHR) in children presenting with asthma symptoms. In adult athletes, Anderson et al. (2) found that mannitol and methacholine tests had similar sensitivity and specificity when used to diagnose exercise-induced bronchoconstriction (EIB). However, Sue-Chu et al. (3) reported that in adult winter-sport athletes, methacholine was much more sensitive than adenosine or mannitol in demonstrating BHR. In spite of contradictory results regarding its sensitivity, mannitol challenge is the recommended test for the diagnosis of exercise-induced asthma (4). The aim of this study was to examine the diagnostic properties of methacholine and mannitol challenge for assessment of BHR in a pediatric athlete population presenting with asthma symptoms during exercise.

Twenty-three children under the age of 18 yr were enrolled in the study, all of whom had current (over previous 4 wk) asthma-related symptoms during exercise (chest tightness, cough, wheezing). The subjects were involved in a variety of organized sports that they played on a regular basis, namely football, tennis, aerobics, ballet, judo, swimming, volleyball, and field hockey.

At the clinic, all participants underwent skin prick testing with common aeroallergens, fraction of exhaled nitric oxide (FeNO) (NIOX MINO®; Aerocrine, Solna, Sweden), and spirometry. Bronchial provocation testing with methacholine was performed with inhaled mannitol at the beginning of the study and on a subsequent day (1). Tests were carried out between 9:00 AM and noon. The Fundación Jiménez Díaz Review Board approved the study protocol, and all subjects and their parents gave written informed consent to participate in all tests performed.

Dry-powder mannitol (Aridol; Pharmaxis, Sydney, Australia) was administered according to manufacturer recommendations. FEV1 recorded after inhalation of a 0-mg placebo capsule constituted baseline lung function. The challenge was discontinued when FEV1 decreased by 15% or more with respect to baseline values or once the maximum cumulative dose of 635 mg had been administered. On a different day (minimum 2 days, maximum 4 days), a methacholine test was performed using the tidal volume technique as previously described (1). Asthma drugs were withheld for the generally recommended interval (use of short- and long-acting inhaled beta-2 adrenergic agents was discontinued for at least 8 h before and 48 h before the challenge, respectively), leukotriene modifiers were not taken for 7 days prior to testing, and patients abstained from using inhaled steroids for at least 2 wk before the procedures.

Patients had a mean age of 12.9 ± 2.9 yr (range 7–17), and 14 were boys. Table 1 displays participant characteristics and test results. All but two of the patients showed at least one positive skin prick test. Response to methacholine ($PC_{20} < 8$ mg/ml) was positive in 18 patients (78%), with geometric mean (GM) PC_{20} of 2.20 (95% CI, 0.6–1.5) mg/ml; only 10 patients (43%) had positive results to mannitol ($PD_{15} < 635$ mg/ml), with a GM PD_{15} of 216.7 mg (95% CI, 90.5–360.4). No significant correlation was found between the results of the two tests. In five patients, both tests produced negative results, and in 10 both tests were positive. Eight patients had positive methacholine and negative mannitol tests, while none of the patients exhibited positive mannitol and negative methacholine tests. The sensitivity of methacholine was 79.2%, and the sensitivity of mannitol was 47.5%. Mean FeNO value was 32.9 ± 21.2 ppb. In 11 patients, FeNO was > 30 ppb (eight with both tests positive, one with both tests negative, and two with positive methacholine and negative mannitol tests). A higher and significant kappa agreement ($\kappa = 0.563$; $p = 0.003$) was found between positive response to mannitol and high FeNO (> 30 ppb) levels in comparison with positive response to methacholine ($\kappa = 0.236$; $p = 0.08$); this association was confirmed by tetrachoric correlation between high FeNO and positive mannitol, $r = 0.78$ vs. $r = 0.51$ for methacholine.

The presence of atopy and predicted FEV1% were not associated with positive results for any of the tests.

As we previously described in a population of children with asthma symptoms (1), methacholine testing demonstrated greater sensitivity than mannitol testing in demonstrating BHR in a population of youth athletes with symptoms suggestive of EIB. Our aim was not to compare laboratory exercise tests with these tests, because exercise tests have a lower sensitivity than methacholine or mannitol for demonstrating BHR (5, 6). We also found that a positive mannitol test was associated with higher FeNO as previously described through indirect bronchial challenge tests (7–9). Of note, 15 patients had methacholine $PC_{20} < 4$ mg/ml (the sport agencies' criterion for BHR), thus sanctioning treatment with antiasthma drugs. Five of them (30%) had negative mannitol test; therefore, in spite of the presence of asthma symptoms, these 5 (30%) patients could not receive antiasthma medication if only mannitol test was used for diagnosis. The results from our patients resonate with those of one of the phenotypes described in a study on Finnish Olympic athletes (10). This phenotype includes patients with early-onset childhood asthma, positive methacholine test, atopy, and signs of eosinophilic airway inflammation as reflected by increased FeNO. The other phenotype includes

Table 1 Characteristics and results of the participants

Age(yr)	Sex	Methacholine test	Mannitol test	PC ₂₀ methacholine (mg/ml)	PD ₁₅ mannitol (mg)	Atopy	FEV ₁ (l)	%Predicted FEV ₁	FeNO (ppb)	Previous treatment
13	F	Positive	Positive	1	273.9	No	1.75	108	10	No
15	M	Positive	Positive	0.41	418.8	Yes	0.97	95	32.7	No
15	M	Negative	Negative	>8	>635	Yes	1.10	90	28	No
14	M	Positive	Negative	7.8	>635	Yes	1.00	100	17	No
17	F	Positive	Positive	0.81	142.9	Yes	0.75	107	39	No
17	M	Negative	Negative	>8	>635	Yes	0.97	97	19	No
12	M	Positive	Negative	0.125	>635	Yes	0.99	91	42.5	No
11	M	Positive	Positive	1.19	150	Yes	1.20	97	91.8	No
11	M	Positive	Positive	0.48	315.8	Yes	1.15	99	30.3	No
11	M	Negative	Negative	>8	>635	Yes	1.10	102	55	No
17	F	Positive	Negative	4.5	>635	Yes	0.97	106	22.3	No
16	F	Negative	Negative	>8	>635	Yes	0.88	100	16.5	ICS
16	M	Positive	Positive	0.5	410	Yes	0.95	95	63.3	No
12	M	Positive	Negative	2.58	>635	Yes	1.12	97	16	ICS
13	M	Positive	Negative	0.36	>635	Yes	1.25	99	22	No
8	M	Positive	Positive	0.125	11.8	Yes	1.01	94	45.3	No
10	F	Positive	Positive	3.02	375	Yes	0.87	92	17	No
11	M	Positive	Positive	0.26	15	Yes	0.77	90	46.3	No
12	M	Negative	Negative	>8	>635	Yes	0.90	94	16.4	No
17	F	Positive	Negative	14.48	>635	No	1.10	98	8.9	No
13	M	Positive	Positive	0.86	54.17	Yes	1.20	93	54.2	No
9	F	Positive	Negative	0.77	>635	Yes	1.81	100	31	No
9	F	Positive	Negative	0.29	>635	Yes	0.97	96	6.3	No

ICS, inhaled corticosteroids.

late-onset symptoms; bronchial responsiveness to eucapnic hyperventilation test, although not necessarily to inhaled methacholine; and a variable association with atopic markers and FeNO. They suggest that methacholine responsiveness is mainly associated with childhood asthma. However, while all of the children but two were atopic, only two had current asthma and need for inhaled steroids. Of note, in the latter patients, mannitol test was negative but methacholine was positive. Our results suggest that the role of mannitol challenge must be reappraised in the context of diagnosing BHR in children with asthma symptoms or with symptoms sugges-

tive of EIB, because methacholine testing is clearly more sensitive and therefore should be the first option for diagnostic testing in this population.

Victoria Andregnette-Roscigno, Mar Fernández-Nieto,
 Lourdes Arochena, Manuela García Del Potro, Erika
 Aguado & Joaquín Sastre

Department of Allergy, Fundación Jiménez Díaz and CIBER
 de Enfermedades Respiratorias (CIBERES) Madrid, Spain.

Email: jsastre@fjd.es

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ERRATUM

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Our paper entitled “Limited agreement between current and long-term asthma control in children: the PACMAN cohort study” has been published in *Pediatric Allergy and Immunology* (2011; 22: 776–83). During further analysis of our dataset, we have noticed an error in one of the syntaxes we have used for the definition of long-term asthma control described in our paper. This mistake resulted in an overestimation of children in the uncontrolled group.

Incorrect distribution	Correct distribution
During the previous season (3 months):	During the previous season (3 months):
22.6% well controlled	22.6% well controlled
30.6% partially controlled and	44.6% partially controlled and
46.8% not well controlled	32.6% not well controlled
During the previous year (12 months):	During the previous year (12 months):
25.4% well controlled	25.4% well controlled
33.7% partially controlled and	60.9% partially controlled and
40.9% not well controlled	13.7% not well controlled

This shift from uncontrolled to partially controlled asthma does, however, not change our conclusions.

We apologize for any inconvenience caused.

Ellen S. Koster, Jan A. Raaijmakers, Susanne J. Vijverberg, Leo Koenderman, Dirkje S. Postma, Gerard H. Koppelman, C. Kors van der Ent, Anke-Hilse Maitland-van der Zee.