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Changes in sensitivity to methacholine after inhalation with distilled water: the role of the bronchoconstrictive response

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Changes in sensitivity to methacholine after inhalation with distilled water: the role of the bronchoconstrictive response. S. Kivity, R. Poterman, Y. Schwarz, R. Soferman, M. Topilsky. ©ERS Journals Ltd 1995.

ABSTRACT: The inhalation of distilled water can induce bronchoconstriction and a transient increase in sensitivity to methacholine in asthmatics. The purpose of this study was to determine the role of the induced bronchoconstriction in the increased sensitivity to methacholine which follows the challenge with distilled water.

Eighteen asthmatic children (age 9–17 yrs) were challenged by inhalation of distilled water. Bronchial responsiveness, the provocative concentration of methacholine producing a 20% decrease in forced expiratory volume in one second (PC20), was determined before inhalation of distilled water, and 1.5 and 24 h thereafter.

Following inhalation of distilled water, eight patients (Group I) had a greater than 15% decrease in FEV_1 (mean 23%); whereas, in the remaining 10 (Group II) the decrease was less than 7% (mean 1%). PC20 to methacholine, geometric mean and 95% confidence interval (CI), decreased transiently only at 1.5 h following inhalation of distilled water. The decrease was from 0.78 mg·ml^{-1} (95% CI 0.11–5.54 mg·ml^{-1}) at baseline to 0.25 mg·ml^{-1} (95% CI 0.03–2.14 mg·ml^{-1}) after challenge in Group I; and from 2.67 mg·ml^{-1} (95% CI 0.35–20.34 mg·ml^{-1}) at baseline to 0.72 mg·ml^{-1} (95% CI 0.18–14.87 mg·ml^{-1})after challenge in Group II.

The transient increase in sensitivity to methacholine observed following inhalation of distilled water occurred independently of the bronchoconstrictive response. This finding may have important clinical implications when hypo-osmolar solutions are used for delivery of drugs.

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It has been well-documented that the inhalation of distilled water can provoke bronchoconstriction in a large proportion of patients with bronchial asthma [1–4]. A transient increase in sensitivity to methacholine occurs following provocation with distilled water [5]. The increase in sensitivity to methacholine is thought to be due either to the inflammatory response [6], or to the increased permeability of the airway mucosa that is associated with water challenge [7].

It is not known whether an increase in sensitivity to methacholine occurs following a challenge with water that is not associated with bronchoconstriction.

For this reason, we studied the response to methacholine after water challenge in two groups of asthmatic children who differed in their response to water. Our results demonstrate that, in asthmatic children as in adults, there is an increase in sensitivity to methacholine after challenge with water. This increase occurred in asthmatic children independently of any bronchoconstriction provoked by the water challenge.

Patients and methods

Patients

Eighteen children of both sexes, aged 9–17 yrs, with mild bronchial asthma (as defined by the American Thoracic Society [8]) were included in the study. Each patient signed an informed consent form, according to the requirements of the local Ethics Committee. None of the patients had been taking daily preventative medicine (including bronchodilators or anti-inflammatory drugs) during the previous 3 months, and all were tested during a stable period of their disease, when they used salbutamol only as needed. All children were atopic, as measured by the skin-prick test response to eight common environmental allergens. The group was divided into two subgroups, based on their airway response to inhaled water: Group I included eight patients who had ≥15% decrease in forced expiratory volume in one second

Table 1. – Airway response in patients with bronchoconstriction (>15% decrease in FEV_1) (Group I) and without bronchoconstriction (Group II) to inhalation of water

Pat. No.	Baseline				Water challenge		Post-water challenge					
							1.5 h			24 h		
	FEV_1		PC_{20}	PD_{20}	FEV_1†	ΔFEV_1	FEV_1	PC_{20}	PD_{20}	FEV_1	PC_{20}	PD_{20}
	l	% pred	mg·ml^{-1}	µg	*l*	%	*l*	mg·ml^{-1}	µg	*l*	mg·ml^{-1}	µg
GROUP I												
1	3.0	79	2.2	125	2.9	-29	2.8	0.6	45	2.9	2.9	185
2	1.8	92	0.9	80	1.7	-32	1.6	0.1	7	1.7	1.2	90
3	1.6	74	0.2	17	1.7	-21	1.7	0.07	3	1.8	0.1	7
4	3.0	86	3.2	190	3.0	-17	3.1	0.9	75	3.1	3.5	200
5	2.8	74	0.5	28	2.9	-23	2.9	0.2	17	3.0	0.4	25
6	4.0	89	0.3	21	3.9	-25	3.9	0.1	7	4.0	0.1	7
7	1.6	72	1.5	110	1.7	-20	1.8	1.1	90	1.6	1.4	105
8	1.7	77	0.5	28	1.6	-19	1.6	0.2	17	1.7	0.4	25
Mean	2.46	84	0.78	52	2.4	-23	2.42	0.25	18	2.47	0.69	43
±SD	0.89	8			0.86	5.0	0.86			0.89		
95% CI			0.11–5.54	27–100				0.03–2.14	8–42		0.04–4.03	16–110
GROUP II												
1	1.9	81	5.4	290	1.8	0.0	1.9	2.1	120	1.9	5.7	370
2	1.8	89	3.2	190	1.8	-3.5	1.7	2.9	193	1.8	8.0	590
3	2.2	103	6.8	410	2.3	-5.0	2.4	3.1	197	2.3	6.2	390
4	2.4	91	8.9	610	2.3	3.0	2.3	1.9	110	2.4	7.2	580
5	4.0	93	1.0	81	4.1	5.0	4.0	0.3	210	3.9	0.9	80
6	2.9	77	3.5	210	3.0	-4.5	2.9	3.7	210	3.0	3.6	220
7	3.0	79	4.5	280	3.0	-6.5	3.1	0.7	60	3.0	3.7	220
8	1.8	85	0.3	21	1.9	-2.0	1.8	0.2	17	1.9	0.4	25
9	2.1	76	1.5	100	2.2	0.0	2.1	0.07	3	2.2	1.0	80
10	1.7	74	2.5	190	1.8	4.0	1.7	0.1	7	1.7	2.0	120
Mean	2.42	83	2.67	176	2.42	-1.0	2.39	0.73	46	2.41	2.78	184
±SD	0.72	9			0.74	4.0	0.74			0.7		
95% CI			0.35–20.34	98–317				0.18–14.87	18–119		1.02–7.57	98–346

Pat.: patient; FEV_1: forced expiratory volume in one second; % pred: percentage of predicted; PC_{20}: provocative concentration producing a 20% decrease in FEV_1; PD_{20}: provocative dose producing a 20% decrease in FEV_1; 95% CI: 95% confidence interval; ΔFEV_1: difference in FEV_1. †: measured 30/60s after 10 min inhalation period.

(FEV_1) following inhalation of water (table 1). Group II included 10 patients who had <7% decrease in FEV_1 following inhalation of water (table 1). The mean age of the patients of both groups was 13 yrs. There were 5 males and 3 females in Group I, and 4 males and 6 females in Group II. Patients with an intermediate response (7–14% decrease of FEV_1 following inhaled water) were excluded from the study.

Methods

Methacholine challenge. The method of CHAI *et al*. [9] was used to deliver the aerosol, using a Morgan dosimeter (model 145, UK). Each patient inhaled the following increasing concentrations of methacholine: 0.07, 0.15, 0.3, 0.6, 1.5, 3.0, 6.0, 10.0 and 25.0 mg·ml^{-1}. Each concentration was inhaled five times during inspiration from functional residual capacity (FRC) to total lung capacity (TLC), as described previously [9]. The provocation challenge was terminated when a decrease of FEV_1 ≥20% was achieved. The concentration provoking a 20% decrease of FEV_1 (PC_{20}) was calculated from the dose response curve relating the percentage fall in FEV_1 to log methacholine concentration. The cumulative dose of methacholine provoking a 20% decrease in FEV_1 was also calculated (PD_{20}).

Pulmonary function test. Spirometry (Fukuda spiroanalyzer ST-300, Japan) was used to carry out pulmonary function tests (PFTs) at baseline and following challenge with distilled water or methacholine. Forced expiratory manoeuvres were repeated until two readings of FEV_1 within 100 ml of one another were obtained. The larger FEV_1 value was retained for analysis.

Inhalation challenge with distilled water. A Devilbiss ultrasonic nebulizer (Pulmosonic, model 2511, output 0.5 ml·min^{-1}) was used for water inhalation. This low-output nebulizer was chosen in order to prevent coughing in highly sensitive asthmatics. Each patient inhaled water for 10 min using the tidal breathing method. FEV_1 was measured at baseline and 30 and 60 s following the inhalation of water. The lower value of FEV_1 was retained for analysis.

Experimental protocol. Each patient participated in three consecutive study days. Inhaled β_2-agonists were withheld 24 h prior to the study. The patients were instructed not to participate in any strenuous physical activity for 24 h before entering the study.

On the first study day, the sensitivity to methacholine was measured (PC20 and PD20). On the second study day, the airway response to distilled water was measured. Ninety minutes following this challenge, a second methacholine challenge was performed and the PC20 measured. On the third study day, a third methacholine challenge was carried out. The study was conducted at the same time on each day. Two weeks later, six patients underwent two challenges, 24 h apart, for repeatability evaluation of methacholine inhalation challenge in our laboratory.

Statistical analysis

The baseline FEV_1, log transformed PC20 and doubling dose of log transformed cumulative PD20 were analysed. The results were expressed as geometric means and 95% confidence interval (CI). In the control group, comparison was made by paired t-test. Analysis of variance for repeated measures was used to compare the effect of water on bronchial responsiveness to methacholine. Unpaired t-test was used for comparing the date of the two groups. Results were considered at a p-value of less than 0.05.

Results

In Group I, the mean baseline FEV_1 was 84%±8% (SD) predicted, and in Group II it was 83%±9% (SD). There was no significant difference between the baseline FEV_1 of the two groups. The baseline PC20 was 0.78 mg·ml^{-1} (95% CI 0.11–5.54 mg·ml^{-1}) for Group I, and 2.67 mg·ml^{-1} (95% CI 0.35–20.34 mg·ml^{-1}) for Group II ($p<0.05$).

Following water inhalation, the mean decrease in FEV_1 from baseline in Group I was 23±5%, significantly greater than the mean change of 1%±4% ($p<0.0001$) seen in Group II. Both at 1.5 and at 24 h following water inhalation FEV_1 had returned to baseline. However, at 1.5 h after water inhalation, there was a significant decrease in PC20 ($p<0.005$) in both groups (table 1).

Table 2. – Repeatability of methacholine inhalation challenge

Pat. No.	Baseline			24 h later		
	FEV_1 *l*	PC20 mg·ml^{-1}	PD20 µg	FEV_1 *l*	PC20 mg·ml^{-1}	PD20 µg
1	1.9	3.2	198	1.8	3.6	220
2	4.2	0.7	63	4.1	0.9	80
3	2.0	7.0	470	2.3	8.5	530
4	1.6	0.5	32	1.6	0.2	12
5	2.9	0.7	63	2.7	0.5	32
6	2.2	1.7	120	2.2	2.0	160

For abbreviations see legend to table 1.

When the analysis was carried out by using doubling doses of PD20, the change at 1.5 h following water inhalation was even more significant ($p<0.0001$). There was no significant difference between the geometric means of the PC20 values of study days 1 and 3 in either groups.

Six of the patients served as controls for evaluating repeatability of methacholine challenge (the data for each patient appear in table 2). No significant difference was seen between baseline FEV_1, log transformed PC20, or doubling dose PD20 of the two days, indicating that this methodology has a good repeatability.

Discussion

We evaluated whether the bronchoconstrictive response to inhaled distilled water affected the degree of sensitivity to methacholine challenge in a group of asthmatic patients. In spite of the fact that the two study groups differed in their airway response to inhaled water, there was no difference in the pattern of change in sensitivity to methacholine. Both groups, one with a significant decrease in FEV_1 to inhaled water and one without, showed a significant increase in sensitivity to methacholine. This change was only transient, and the PC20 to methacholine returned to baseline values within 24 h. This change in sensitivity was seen when relatively small amounts of water were inhaled (5 ml), even less than the recommended dose for routine inhalation challenge with water [10].

The fact that inhaled water induced a transient increase in airway sensitivity regardless of the degree of bronchoconstriction supports the idea that inhalation of water had two different effects on the airways: one which is bronchoconstrictive and may be *via* mediator release [6]; and the second occurring directly on the mucosa by increasing permeability, thereby affecting the threshold for methacholine-induced bronchoconstriction [7]. One cannot exclude a third possibility, *i.e.* that water causes the release of small amounts of mediators which are insufficient to cause bronchoconstriction in the group of subjects with mild bronchial hyperresponsiveness, but enough to cause a minor change in methacholine responsiveness, as shown for a subconstrictor dose of prostaglandin D_2 (PGD_2) [11]. The findings of the study by BLACK *et al*. [12], demonstrating that sodium cromoglycate abolishes the increased sensitivity to methacholine following inhalation of water, support the mediator release theory. Methacholine and histamine, which are believed to act directly on smooth muscle, are not known to be associated with mediator release [13, 14], and unsurprisingly did not increase sensitivity *per se*. The PC20 and the doubling dose PD20 methacholine in the six patients who had repeated challenge did not change significantly indicating a good repeatability of our technique of methacholine inhalation challenge.

Our findings are in agreement with those of WEINER *et al*. [15] and SOFERMAN *et al*. [16], who elaborated upon the osmolarity of inhaled solutions and showed improved protection from inhalation of isotonic sodium cromoglycate

compared to a hypo-osmotic solution. We recommend that more attention is paid to the osmolarity of inhaled drugs, because hypo-osmolar solutions can aggravate bronchial sensitivity.

The clinical significance of this study is that, even in patients in whom bronchoconstriction does not develop following the inhalation of hypo-osmolar solutions, there might be worsening of the bronchial sensitivity, thereby aggravating the patient's condition.

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