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Diagnostic and Therapeutic Methods

Inhaled Mannitol Identifies Methacholine-Responsive Children With Active Asthma

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Summary. Inhaled mannitol has been developed for bronchial challenge testing in adults. This study determined if mannitol could identify children with active asthma and responsive to methacholine, and whether mannitol challenge was faster to complete than methacholine challenge. Twenty-five children (aged 6–13 years) responsive to methacholine and 10 nonasthmatic children unresponsive to methacholine were studied. The methacholine challenge (Cockcroft protocol) was followed by a mannitol challenge on separate days.

Twenty-one asthmatic children were positive to mannitol. Three taking inhaled corticosteroids with borderline methacholine responsiveness did not respond to mannitol, and one could not complete the mannitol challenge due to cough. The geometric mean (GM) and 95% confidence interval (CI) for PD_{15} for mannitol was 39 mg (19, 78), and PC_{20} for methacholine was 0.6 mg/mL (0.35–1.02) ($r_p = 0.75$, $p < 0.001$, $n = 21$). Responses to mannitol were repeatable: GM PD_{15} for the first challenge was 29 mg (CI: 17,50), and for the second challenge, 33 mg (CI: 20, 55) ($P = 0.44$, $n = 9$). Mannitol was faster to administer than methacholine (median (range)) 14 min (5–32) vs. 29 min (19–49), respectively ($P < 0.001$). Time to recover to baseline FEV_1 spontaneously and after bronchodilator administration was similar for both challenges. There were no significant falls in arterial oxygen saturations. During mannitol challenge, the mean (SD) fall in FEV_1 in nonasthmatic children was 3.1% (2.9).

We conclude that mannitol identifies children with airway hyperresponsiveness and is faster to perform than the methacholine challenge. **Pediatr Pulmonol. 2000;29:291–298.**

Key words: asthma; child; airway hyperresponsiveness; bronchial challenge; methacholine; mannitol.

INTRODUCTION

Bronchial provocation tests (BPTs) are used to confirm the diagnosis and to assess severity of asthma in both adults and children. Recent Canadian consensus guidelines continue to recommend their use in the diagnosis and assessment of asthma.[1] The most commonly used BPTs utilize the pharmacological agents methacholine and histamine given by inhalation.[2] There are many techniques used to administer methacholine challenge.[3,4] However, the technique used in our institution and in most other centers in North America is the Cockroft technique.[3] This technique is also the standard method recommended by the Canadian Thoracic Society. Pharmacologic challenges are less sensitive in pediatrics and can fail to identify children with exercise-induced asthma.[5,6] In addition, they are not specific for identifying asthma, as healthy children can also be responsive to them.[7] The reason for this may be explained by the mechanism of action of the drugs used. Pharmacological agents cause airway narrowing by directly stimulating receptors on

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bronchial smooth muscle causing its contraction. Thus, in a healthy child a response to a pharmacological agent may be dependent on the inherent sensitivity of the airway smooth muscle to that agent rather than the presence of airway inflammation, the hallmark of asthma. These limitations have decreased the clinical utility of current pharmacologic challenges.

A new BPT using a simple dry powder inhaler to administer increasing doses of mannitol has been developed.[8] Inhaled mannitol, an osmotic stimulus, has been demonstrated to be effective in identifying active asthma in adults with responses that are repeatable over a month. Mannitol is also effective in identifying individuals responsive to dry air hyperpnea induced by exercise or voluntary hyperventilation.[9] Both hyperpnea and mannitol are thought to cause airway narrowing in asthmatics indirectly by increasing the osmolarity of the airway surface liquid.[9] This leads to the release of inflammatory mediators that cause the contraction of airway smooth muscle.[10] Thus, the airway response to osmotic stimuli is thought to be dependent upon the presence as well as the severity of airway inflammation. Bronchoprovocation using exercise was initially developed for use in children; however, the time and difficulties associated with children performing exercise challenges led to the development of faster and more cost effective laboratory-based challenges such as hyperpnea with dry air and hypertonic saline. It is not known whether a mannitol challenge, using the same protocol previously used in adults, is a faster, repeatable, safe, and effective alternative to methacholine challenge in children.

The purpose of this study was to determine whether a mannitol provocation test could identify children with active asthma and responsive to methacholine; we also wanted to assess the response of nonasthmatic healthy children to mannitol. This investigation was also designed to detect whether the mannitol challenge gave repeatable results and was faster to perform than the methacholine challenge using the Cockroft protocol.

Abbreviations

ANOVA	Analysis of variance
BPT	Bronchial provocation tests
CI	Confidence interval
FEV_1	Forced expiratory volume in 1 sec
GM	Geometric mean
PC_{20}	Provocative concentration to produce a 20% fall in FEV_1
PD_{15}	Provocative dose to produce a 15% fall in FEV_1
PD_{20}	Provocative dose to produce a 20% fall in FEV_1
r_p	Pearson's correlation coefficient
r_s	Spearman's correlation coefficient
SaO_2	Arterial oxygen saturation
SD	Standard deviation

METHODS

Subjects

Asthmatic and nonasthmatic healthy children aged between 6 and 13 years were recruited using a variety of methods, including advertisements displayed in the hospital, notices to local schools, chart review, and referral from pediatricians in the greater Toronto area. The parents of children were interviewed by telephone. All children were required to be cooperative, to be nonsmokers, and to have had no chest infection for at least 6 weeks prior to the initial study day.

Asthmatic children were required to have a clinical diagnosis of asthma at the time of the study and be taking prescribed medication for their asthma. Parents were asked to make certain that the children refrained from taking short-acting bronchodilators for 6 hr, long-acting bronchodilators for 8 hr, nedocromil sodium or sodium cromoglycate for 24 hr, and antihistamines for 72 hr prior to the study day. No inhaled corticosteroids were to be taken on the day prior to testing, and children were asked to maintain their daily dose of inhaled corticosteroids throughout the study. No strenuous exercise was permitted on the study day.

Nonasthmatic healthy children with a negative response to methacholine served as controls. They had to be nonatopic, with no current, past or family history of asthma, and no history of any lung disease. The study was approved by the Institutional Review Board of the Hospital for Sick Children (no. 98/034), and the parents signed consent for participation on their child's behalf prior to commencement of the study.

Study Design

All children were asked to attend the Pulmonary Function Laboratory on either two or three occasions. All children performed the methacholine challenge at the initial visit and the mannitol challenge on subsequent visits. Asthmatic children were asked to perform either one ($n = 16$) or two ($n = 9$) mannitol challenges to establish repeatability, whereas the healthy nonasthmatic children performed only one mannitol challenge. The rates of recovery to baseline FEV_1 after the challenges were measured in the asthmatic children, and recovery occurred either spontaneously ($n = 9$) or by using a bronchodilator ($n = 11$). For the asthmatic children, challenges were performed at approximately the same time of the day separated by a minimum of 2 days. The time to administer mannitol and methacholine challenges was compared using a stopwatch. Timing commenced on administration of the first dose (isotonic saline or placebo capsule) and stopped when the desired airway response was obtained.

Skin Prick Testing

All subjects had skin prick tests with common aeroallergens, including Alternaria, Hormodendrum, Aspergillus mix, house dust mites, cat, dog, horse, feathers, wool, tree mix, grass mix, ragweed, and cockroach (Omega Laboratories, Montreal, Quebec, Canada). Atopy was defined as a greater than 3 mm wheal response to skin tests in addition to a history of symptoms to the aeroallergen eliciting the positive response. Positive symptoms indicating an allergic response as reported by the patients included sneezing; itchy, watery eyes; or runny nose when exposed to the aeroallergen.

Lung Function Measurements

Spirometry was performed on SensorMedics V'_{max} series spirometers (SensorMedics Corp., Yorba Linda, CA). Spirometers were calibrated with a 3 L syringe on the morning of each study day. The index to measure change in airway caliber was forced expiratory volume in one second (FEV_1). Before each challenge, triplicate FEV_1 values were obtained, and this was repeated 10 min later to confirm stability. The best FEV_1 obtained at the beginning and end of the 10-min period could not vary by more than 10%. The best FEV_1 of the second set of three spirometric measurements performed 10 min after the initial set of three tests was used as the baseline value and had to be at least 70% of the predicted FEV_1.[11] Subjects were required to have a less than a twenty percent variation from baseline FEV_1 on subsequent study days.

Methacholine Challenge

The protocol used to administer the methacholine has been previously described.[3] In brief, a nose clip was applied and children inhaled for 2 min periods isotonic saline; then doubling concentrations of methacholine chloride were generated by a Wright nebulizer. The aerosol generated was inhaled through a two-way nonrebreathing valve (Hans Rudolph 1410, Hans Rudolph Inc., Kansas City, MO) up to a concentration of 16 mg/mL. At least two FEV_1 measurements beginning 30 sec after each dose were performed. The test was terminated when a 20% fall in FEV_1 had occurred. The FEV_1 value measured after the isotonic saline was taken as the prechallenge FEV_1 and was used to calculate the percentage decrease in FEV_1 in response to the methacholine challenge.

On completion of the challenge, subjects received either 200 mcg of salbutamol actuated into an Aerochamber® (Trudell Medical, London, Ontario, Canada) or were allowed to recover spontaneously. Spirometry was then measured after 5 min and 10 min, and then at 10-min intervals for 1 hr following completion of the challenge.

Mannitol Challenge

The preparation of the dry powder mannitol has been described in detail previously.[6] In brief, mannitol powder (Mannitol BP, Rhône-Poulenc Rorer Chemicals Pty. Ltd., Brookvale, New South Wales, Australia) was prepared by spray-drying (Buchii 190 Mini Spray Dryer, Flawil, Switzerland) to produce a powder containing 50 mg/mL. The particle size of the mannitol powder was measured with a multistage liquid impinger (Astra Pharmaceuticals, Lund, Sweden) and assayed by vapor pressure osmometry. The mannitol powder used had 66% of particles under 7 μm in diameter, measured at an inspiratory flow of 60 L/min. The mannitol was then gamma-irradiated (Steritech, Wetherill Park, Australia), and a bioburden analysis was performed to confirm sterility (Stanford Consulting Laboratories, Rydelmere, Australia). Gelatine capsules (Gallipot, St. Paul, MN) were hand filled with 5, 10, 20 (± 0.2), and 40 (± 0.5) mg of mannitol powder using an analytical balance (Mettler AE200, Greifensee, Switzerland). The filled capsules were stored in dry conditions using an airtight container that contained silica gel. A Halermatic™ (Rhône-Poulenc Rorer, Baulkham Hills, Australia) dry powder inhaler was used for the delivery of the mannitol.

On arrival at the laboratory, each subject had baseline FEV_1 measured. Nose clips were applied and the children were instructed to take a deep forced inhalation through the Halermatic™ and then hold their breath for 5 sec. Children then performed the challenge with doses consisting of 0 mg (empty capsule acting as placebo), 5, 10, 20, 40, 80, 160, 160, and 160 mg of mannitol via the Halermatic™ inhaler. The 80 mg and 160 mg doses were given in multiple doses of 40 mg capsules. At least two repeatable FEV_1 maneuvers were performed 60 sec after each dose, and the highest FEV_1 was used in the calculation. The FEV_1 value measured after the 0 mg capsule was taken as the prechallenge FEV_1 and was used to calculate the percentage decrease in FEV_1 in response to the mannitol challenge. If the child had a greater than 10% fall in FEV_1 in response to a single dose, the same dose was repeated. The challenge was complete when a 20% fall in FEV_1 was documented or a cumulative dose of 635 mg of mannitol had been administered. On completion of the challenge, subjects received either 200 mcg of salbutamol actuated into an Aerochamber® (Trudell Medical, London, Ontario, Canada) or were allowed to recover spontaneously. Spirometry was measured after 5 min and 10 min, and then at 10-min intervals for 1 hr after the administered dose or following the end of the challenge. The provoking dose of mannitol to cause a 15% (PD_{15}) and 20% (PD_{20}) fall in FEV_1 was calculated by linear interpolation using the relationship between percent fall in FEV_1 and the cumulative dose required to provoke this.

Oxygen Saturation

Oxygen saturation (SaO_2) was measured by finger pulse oximetry before and during the challenges to monitor possible changes due to airway narrowing (N-200 Pulse Oximeter, Nellcor, Inc., Hayward, CA).

Statistical Analysis

The geometric means (GM) ± 95% confidence interval (CI) were calculated using the $\log_{10}$ values for PD_{15}, PD_{20}, and PC_{20} which were normally distributed. Pearsons correlation (r_p) and significance values were used to investigate the relationship between $\log_{10}$ PD_{15}, $\log_{10}$ PD_{20}, and $\log_{10}$ PC_{20}. Spearman's rank correlation (r_s) was also used to test the relationship between the severity of the airway response to both challenges in the same subjects.

The repeatability of two mannitol challenges was expressed in terms of doubling doses according to the equation of Peat et al.,[12] and is illustrated according to Bland and Altman.[13] The difference between the two challenges was compared using a Student's paired t-test. Repeatability was also analyzed using the intraclass correlation coefficient.[14]

Values for FEV_1 are expressed as mean ± SD of the percentage of predicted normal FEV_1. The baseline values for FEV_1 and the prechallenge FEV_1 following placebo (0 mg capsule or 0.9% saline) were expressed as a percentage of predicted values and were compared using Student's paired t-test.[15] The FEV_1 values as a percentage of predicted FEV_1 were used to compare recovery to baseline FEV_1, using analysis of variance (ANOVA) with repeated measures.

RESULTS

Asthmatic Children

Children with active asthma and a positive methacholine challenge were identified using inhaled mannitol. Twenty-one children had a positive response to both challenges, and three children who took inhaled corticosteroids daily had borderline methacholine responsiveness (≥4 mg/mL) and did not respond to mannitol (Table 1). One child was unable to complete the mannitol challenge due to significant cough during inhalation of the powder. Children who responded to mannitol were identified after the administration of a median of 4 capsules (range, 1 to 18) or the inhalation of a median cumulative dose of 75 mg (range, 5 to 635 mg). The mannitol challenge identified asthmatic children in less than half the time of the methacholine challenge. The median time to complete a mannitol provocation was 14 min (range, 5 to 32 min) compared to 29 min (range 19 to 49 min) for a methacholine challenge ($P < 0.001$, $n = 24$).

In the 21 children who showed a positive response in both tests, the GM PD_{15} for a mannitol challenge was 38.5 mg (CI: 19.1 to 77.8 mg), and this compared with a PC_{20} to methacholine of 0.6 mg/mL (CI: 0.35 to 1.02 mg/mL). Twenty children recorded a 20% fall in FEV_1 to mannitol, and their GM PD_{20} was 54 mg (CI: 28 to 104.7 mg). For the total group of 25 asthmatic children, the GM PC_{20} to methacholine was 0.84 mg/mL (CI: 0.47 to 1.48 mg/mL). There was no significant difference between the baseline spirometry expressed as a % of predicted FEV_1 for the mannitol 82.6 ± 11.5% (mean ± SD) and methacholine 83.3 ± 11.2 challenge days ($P = 0.7$).

There was a significant relationship between the responses to mannitol and methacholine challenge. For children responding to both challenges, the PD_{15} to mannitol compared well with the PC_{20} for methacholine ($r_p = 0.75$, $P < 0.001$, $r_s = 0.71$, $P < 0.001$, $n = 21$) (Fig. 1). The good relationship was maintained when PD_{20} (mannitol) was compared with PC_{20} (methacholine) ($r_p = 0.75$, $P < 0.001$, $r_s = 0.73$, $P < 0.001$, $n = 20$).

There was good repeatability of the PD_{15} results to mannitol, and this was independent of dose (Fig. 2). The mannitol challenge was performed twice in nine children, and there was no significant difference between the PD_{15} for the first challenge [GM 28.6 mg (CI: 16.5 to 49.6 mg)] compared with the second challenge [32.8 mg (CI: 19.6 to 54.9 mg), $P = 0.44$]. There was also no significant difference between the mannitol PD_{20} for the first challenge [41.6 mg (CI: 25.9 to 66.9 mg)] compared with the second challenge [44.5 mg (CI: 26.5 to 74.8 mg) $P = 0.69$]. The repeatability of the PD_{15} and PD_{20} response was calculated to be within ±0.75 and ±0.72 doubling doses, respectively. However, the intraclass correlation coefficient for PD_{15} and PD_{20} were low at 0.52 and 0.69, respectively. There was no difference in baseline FEV_1 values expressed as % predicted for the first challenge [84.2 ± 14.2 % (mean ± SD)] compared to the second challenge [87.1 ± 14.9% ($P = 0.07$)]. The time interval between repeated mannitol challenges was a median of 6 days (range, 2 to 11 days).

There was no significant mean decrease in oxygen saturation during the challenges. During the mannitol challenges, the saturation fell by 1.5% (range, 0–4%) and this was not significantly different from the reduction in saturation seen during the methacholine challenges of 2.0% (range, 0 to 5%) ($P = 0.3$).

The rate of recovery to baseline FEV_1 in asthmatic children was similar in mannitol and methacholine challenges, both spontaneously (Fig. 3) and following the administration of a bronchodilator (Fig. 4). The 20 children who had a greater than 20% fall in FEV_1 to both challenge tests were used for the comparison. There was no significant difference in the final % fall in FEV_1 after mannitol [26.6 ± 6.5% (mean ± SD; range, 20.5 to 42.5%)] compared to methacholine [25.7 ± 7.0 % (range,

TABLE 1—Anthropometric Data: FEV_1% Predicted, Daily Medication, Dose of Steroids, and Doses of Mannitol and Methacholine Required to Induce a 15% or 20% Reduction in FEV_1 (PD_{15}, PD_{20})[1]

Subject no.	Asthmatic/ control	Age (years)	Gender	Height (cm)	Weight (kg)	Atopic	FEV_1% predicted before mannitol challenge	Medication	Steroid (μg/day)	Methacholine PC_{20} (mg/mL)	Dry mannitol PD_{15} 1st (mg)	Dry mannitol PD_{15} 2nd (mg)
1	Asthmatic	11	f	166	62	Yes	75.6	S, BUD	400	0.26	28	21
2	Asthmatic	12	m	161	60	Yes	73.9	S, BEC	500	0.82	50	25
3	Asthmatic	6	m	134	31	Yes	84.2	S		5.15	181	
4	Asthmatic	7	m	124	24	No	103.4	S		0.40	74	117
5	Asthmatic	9	f	143	32	Yes	78.8	S, SCG		0.97	31	31
6	Asthmatic	10	m	138	48	Yes	109.1	TS, BUD, SLM	800	0.23	13	33
7	Asthmatic	12	m	151	87	Yes	84.2	S, BEC, IB	2,000	1.00	115	
8	Asthmatic	8	f	138	54	Yes	98.9	S, BEC	500	0.97	226	
9	Asthmatic	8	m	133	27	No	95.0	S, Hydroxyine HCI		1.36	281	
10	Asthmatic	11	m	148	40	Yes	77.4	S, BEC	200	0.22	31	
11	Asthmatic	9	m	138	34	Yes	77.8	S, BEC	200	0.24	92	
12	Asthmatic	13	f	162	62	Yes	85.4	S, BEC	1,000	0.23	34	
13	Asthmatic	8	f	122	21	Yes	86.3	S		0.08	2	
14	Asthmatic	6	m	110	18	Yes	78.4	S		0.07	1	
15	Asthmatic	12	f	162	88	Yes	70.9	S, BEC, SLM	1,000	4.51	112	
16	Asthmatic	11	m	143	51	Yes	91.7	S, BEC	500	0.31	11	21
17	Asthmatic	12	m	157	47	Yes	68.3	S, BEC, SLM	1,000	3.27	70	65
18	Asthmatic	11	f	139	29	Yes	74.3	S, SLM		0.97	13	12
19	Asthmatic	7	m	124	26	Yes	82.8	S, BEC	300	0.50	29	41
20	Asthmatic	11	m	152	66	Yes	73.3	TS, BUD	400	1.17	315	
21	Asthmatic	11	m	153	65	Yes	65.4	TS, BUD	200	0.90	73	
22	Asthmatic	7	f	129	27	Yes	95.4	S, BEC, SCG	200	1.47	Cough	
23	Asthmatic	8	f	118	24	No	116.5	S, BEC	1,000	5.83	Negative	
24	Asthmatic	10	m	143.5	44		83.9	S, FLU	500	14.40	Negative	
25	Asthmatic	10	m	143	37		101.4	TS, BUD	800	5.19	Negative	
26	Control	11	f	150	35.9	No	95.7	None		Negative	Negative	
27	Control	8	m	132	28.2	No	95.5	None		Negative	Negative	
28	Control	12	f	149	36	No	93.5	None		Negative	Negative	
29	Control	8	f	145	34.7	No	112.7	None		Negative	Negative	
30	Control	6	m	123	23.1	No	86.5	None		Negative	Negative	
31	Control	13	m	167	50.7	No	99.7	None		Negative	Negative	
32	Control	11	m	152	36.7	No	80.6	None		Negative	Negative	
33	Control	11	m	150	44.2	No	87.6	None		Negative	Negative	
34	Control	11	f	156	50.4	No	92.1	None		Negative	Negative	
35	Control	9	f	147	34.8	No	95.0	None		Negative	Negative	

[1]S, salbutamol; TS, terbutaline sulfate; BEC, beclomethasone propionate; BUD, budesonide; SCG, sodium cromoglycate; SLM, salmeterol; FLU, fluticasone dipropionate; IB, ipratropium bromide.

20.0 to 43.8%; $P = 0.7$, n = 20)]. There was no significant difference in the % reduction in FEV_1 from baseline after the 60-min recovery periods following the two challenges when either bronchodilator was given ($P = 0.3$, n = 11) or when subjects recovered spontaneously ($P = 0.7$, n = 9). Of the 11 children who were given bronchodilator following both challenges, nine recovered to within 5% of baseline FEV_1 in 10 min after mannitol, compared to 10 after methacholine. Of the nine children who recovered spontaneously following either challenge, recovery to within 5% of baseline FEV_1 within 60 min was achieved in six children after mannitol compared to four after methacholine.

No child had a significant fall in FEV_1 (>15% or 20%) after administration of the placebo dose (empty capsule or 0.9% saline) during the mannitol or methacholine challenges. There was, however, a significant difference between the falls after the placebo dose in both challenges, with the % difference in FEV_1 after the empty capsule being 1.4 ± 2.0% (mean ± SD) (range, 0 to 8.0%), and following the 0.9% saline, 2.5 ± 3.0 % (range, 0 to 11.9%) (significance of difference, $P = 0.04$; n = 25).

Seventeen of the recruited children were not entered into the study due to failure to meet the entry criteria. Reasons for exclusion included: negative methacholine challenge (n = 4), abnormal spirometry (n = 2), exacerbations of asthma (n = 1), recent chest infection (n = 1), uncooperative behavior (n = 3), asthma not current as confirmed by staff respiratory physician (n = 1), not returning to clinic for follow-up challenge (n = 2), vio-

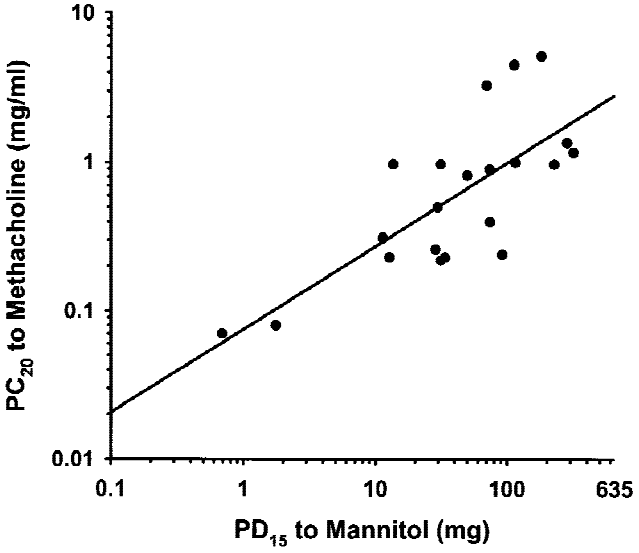

Fig. 1. Values for the provoking cumulative dose of mannitol in mg required to induce a 15% fall in FEV_1 (PD_{15}) in relation to the provoking concentration of methacholine required to induce a 20% fall in FEV_1 (PC_{20}) (r_p = 0.75, P < 0.001, n = 21).

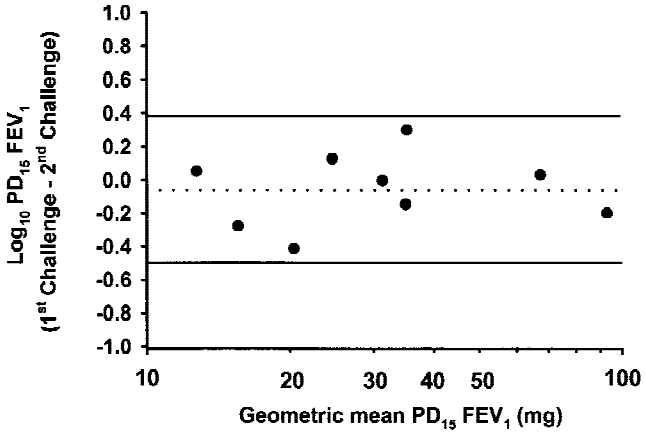

Fig. 2. Bland and Altman plot relating the geometric mean for the PD_{15} for the first and second challenges with mannitol to the difference between the log_{10} PD_{15} values for the nine subjects who returned for a repeat challenge. The dashed line illustrates the point of no difference between the first and second challenge. The repeatability was independent of dose (r_p = 0.09, P = NS). The difference in $log_{10}PD_{15}$ was between −0.5 and +0.4 for all subjects.

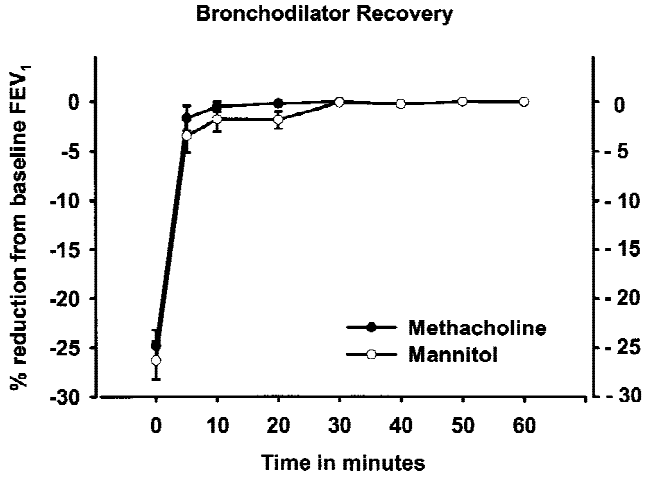

Fig. 3. Mean ± SEM for FEV_1, expressed as percent reduction from baseline values in nine subjects who spontaneously recovered after the challenge with mannitol and the challenge with methacholine. There was no significant difference in the recovery between the two challenge tests (P = 0.7).

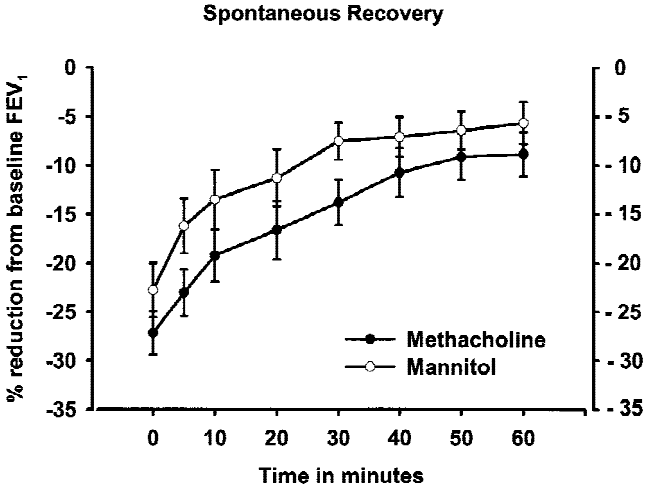

Fig. 4. Mean ± SEM for FEV_1 expressed as percent reduction from baseline value in 11 subjects who were given 200 mcg of salbutamol aerosol through a spacer immediately after the challenge with mannitol and the challenge with methacholine. There was no significant difference in the recovery between the two challenge tests (P = 0.3).

lation of protocol (n = 2), or not abstaining from required medication (n = 1).

Nonasthmatic Children

Nonasthmatic, healthy children with a negative response to methacholine did not respond to mannitol (Table 1). The final % fall in FEV_1 to mannitol was 3.4 ± 2.9% (mean ± SD; range 0 to 7.9%) after the maximum cumulative dose of 635 mg. This compared to a final % fall in FEV_1 after methacholine of 6.8 ± 4.7 % (mean ± SD; range, 0 to 14.1%). All children had normal spirometry, and the baseline FEV_1 was not significantly different on the day of the mannitol challenge 93.9 ± 8.6% (mean ± SD) compared to the day of the methacholine challenge 95.3 ± 5.9% (P = 0.4, n = 10).

Twelve healthy children recruited were not entered into the study due to failure to meet the entry criteria. The 12 children who were excluded were either atopic, having a positive skin test and associated symptoms to an identified responsive allergen (n = 4), or had a positive response to the methacholine challenge (n = 8). Al-

though, these 8 children met the criteria for nonasthmatic healthy subjects on all other grounds and were nonatopic, they had PC_{20} responses ranging from 0.3–15.4 mg/mL.

DISCUSSION

This study demonstrated that mannitol can identify children with currently active asthma and those who are responsive to methacholine. The results also showed that nonasthmatic healthy children who are not responsive to methacholine are unresponsive to mannitol.

The relationship between response to mannitol and methacholine was strong, the mannitol response was repeatable, and the results were analogous to those in adults.[8] Three children with borderline methacholine responsiveness were on inhaled steroids and had a negative response to mannitol. This was not an unexpected finding and is in agreement with previous studies in which steroids have been shown to reduce and even abolish airway responsiveness to mannitol[16] and to hypertonic saline.[17,18] The response to mannitol was repeatable in all but one of the children who returned for a second mannitol challenge and had responses to mannitol of less than 100 mg. For this reason we can only report repeatability in children with moderate airway responsiveness.

A limitation of the mannitol challenge itself was cough that appeared to be specific to the powder preparation and mode of delivery that was used. Cough prolonged the length of time of the challenge in mildly responsive children and in one instance, prevented completion of the challenge. While for some children cough made testing difficult, it did not appear to affect the airway response to mannitol. The mannitol challenge must be performed quickly because it is theorized that it is the rate of change in airway surface liquid osmolarity that is the determinant of airway response.[19] Thus, prolonging the time between inhalation of mannitol and spirometry could potentially lead to a decrease in the effectiveness of the osmotic stimulus and give falsely negative results. Therefore, in order to reduce cough brought about by impaction of powder on the oropharynx, some minor modifications to the particle size and method of delivery are needed. These modifications would lead to an administration system that is similar to the currently available systems for the delivery of asthma medication as a fine powder.

The mannitol challenge was faster to perform than methacholine. To have a direct comparison to the methacholine challenge, the endpoint in time for the mannitol challenge was chosen at a fall in FEV_1 of 20%. The mannitol challenge would have taken even less time to perform had a 15% rather than 20% fall in FEV_1 been accepted as the endpoint.

This study was not designed to establish the specificity of the mannitol challenge. We found that nonasthmatic healthy children who did not respond to methacholine did not respond to mannitol. However, we also found a large proportion (30%) of healthy children with no asthma history who had a positive methacholine challenge. These findings highlight the fact that positive responses to methacholine often occur in normal healthy children.[6,7,20,21] A positive response to mannitol was not elicited in these patients, as it was not part of the study protocol. However, further studies are needed to determine the airway response to mannitol in healthy children with positive responses to pharmacological stimuli to determine the specificity of mannitol for identifying asthma.

In conclusion, this study demonstrates that children with currently active asthma can be identified with a mannitol challenge in less time than is required for a methacholine challenge. Nonasthmatic healthy children who were negative to a methacholine challenge did not respond to mannitol. The practical advantages of simplicity of equipment, and time and mode of delivery, make mannitol an attractive agent for bronchial provocation testing and especially useful for testing children. Further studies are required to investigate the sensitivity and specificity of mannitol to identify currently active asthma in a random pediatric population.

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