

Mannitol Dry Powder Challenge in Comparison With Exercise Testing in Children

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Summary. Rationale: Mannitol dry powder (MDP) challenge is an indirect bronchial provocation test, which is well studied in adults but not established for children. Objective: We compared feasibility, validity, and clinical significance of MDP challenge with exercise testing in children in a clinical setting. Methods: Children aged 6–16 years, referred to two respiratory outpatient clinics for possible asthma diagnosis, underwent standardized exercise testing followed within a week by an MDP challenge (Aridol™, Pharmaxis, Australia). Agreement between the two challenge tests using Cohen's kappa and receiving operating characteristic (ROC) curves was compared. Results: One hundred eleven children performed both challenge tests. Twelve children were excluded due to exhaustion or insufficient cooperation (11 at the exercise test, 1 at the MDP challenge), leaving 99 children (mean $\pm$ SD age 11.5 ± 2.7 years) for analysis. MDP tests were well accepted, with minor side effects and a shorter duration than exercise tests. The MDP challenge was positive in 29 children (29%), the exercise test in 21 (21%). Both tests were concordant in 83 children (84%), with moderate agreement ($\kappa = 0.58$, 95% CI 0.39–0.76). Positive and negative predictive values of the MDP challenge for exercise-induced bronchoconstriction were 68% and 89%. The overall ability of MDP challenge to separate children with or without positive exercise tests was good (area under the ROC curve 0.83). Conclusions: MDP challenge test is feasible in children and is a suitable alternative for bronchial challenge testing in childhood. **Pediatr Pulmonol.** © 2011 Wiley-Liss, Inc.

Key words: mannitol dry powder; exercise test; bronchial provocation test; pediatrics.

Funding source: Swiss National Science Foundation, Number: 3200B0-122341, AstraZeneca (Switzerland), the Lung Association St. Gallen, the Schmidheiny Foundation (Heerbrugg, St. Gallen).

INTRODUCTION

In clinical practice, the relation between exercise and airway narrowing in children with asthma has been used as a diagnostic tool for years, especially when the diagnosis of asthma is unclear.¹ Exercise provokes significant bronchoconstriction in 70–80% of children with clinically recognized asthma.² Hyperventilation resulting in increased airway osmolarity of the airway surface liquid is believed to be the underlying mechanism.³ Testing for exercise-induced bronchoconstriction (EIB) is not very sensitive in children, but highly specific for asthma compared to direct airway challenges.^{4–6} In adults, exercise testing has an established role in the diagnosis of asthma.^{7,8} In children, its utility is limited by a relatively low sensitivity and the dependence on steady cooperation. In addition, methodological differences give rise to discrepant results, particularly for field studies on pediatric asthma and bronchial hyperresponsiveness (BHR).^{9,10}

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Received 10 November 2010; Revised 17 January 2011; Accepted 21 January 2011.

DOI 10.1002/ppul.21453
Published online in Wiley Online Library
(wileyonlinelibrary.com).

In an attempt to make BHR testing more practical, the mannitol dry powder (MDP) challenge has been developed and evaluated in various settings. This test shares the characteristics of indirect BHR tests, that is, a higher specificity and a lower sensitivity for asthma than direct bronchial provocation tests (BPTs), but is easier to perform than exercise testing.^{11–14} In children, MDP challenge seems to be efficacious, safe, and reproducible in well-defined study settings, but published field experience is limited.^{13,15–18} Also, while the accuracy of the MDP challenge for a clinical diagnosis of asthma is good when comparing subjects with known asthma and healthy controls,¹² its validity appears limited in more heterogeneous populations with lower pre-test probabilities, such as subjects with very mild or doubtful asthma.¹⁵ Therefore, before the MDP challenge may be recommended as an alternative to exercise testing, its performance and usefulness in daily practice need further corroboration.

In this study, we aimed to evaluate the MDP challenge as a potential surrogate marker for EIB assessed by exercise testing in a cohort of children referred to respiratory outpatient clinics for possible asthma diagnosis.

MATERIALS AND METHODS

Study Design and Subjects

We studied 111 children (Caucasian Europeans), aged 6–16 years, referred for the first time to our pediatric respiratory outpatient clinics (St. Gallen; $n = 84$ and Basel; $n = 27$) for evaluation of a possible asthma diagnosis with a history of wheezing, dyspnea, or cough. Children with chronic respiratory diseases (e.g., cystic fibrosis, primary ciliary dyskinesia), or a respiratory tract infection within 4 weeks were excluded. Children withheld short acting β_2 -agonists for 8 hr, inhaled corticosteroids (ICS), leukotriene antagonists, and long acting β_2 -agonists for 24 hr, and antihistamines and sodium cromoglycate for ≥ 72 hr. The local ethics committee and the Swiss agency for the authorization and surveillance of therapeutic products (Swissmedic) approved the study and all parents and children gave informed consent.

The study comprised two visits. At the first visit, all children underwent clinical evaluation, skin prick testing unless printed results of recent tests were available, spirometry, and body plethysmography. All children performed the exercise challenge on the same day or a few days later and came back for MDP testing within a week of the exercise test, a period during which repeatability of MDP tests is excellent.¹⁶ Between visits, the family completed a modified ISAAC-questionnaire.¹⁹ Treatment was not changed before the last visit.

Exercise Testing

The children performed the exercise challenge using a treadmill (T-2100, GE Healthcare, Freiburg, Germany) or a bicycle ergometer (ER Ergoselect 200, Ergoline GmbH, Bitz, Germany) for 8 min, inspiring room air according to published ATS and ERS guidelines.^{7,20} At one site, children chose between treadmill and bicycle, at the other only a treadmill was available. We performed exercise testing under controlled conditions (maintaining inspired air temperature at 20–25°C and humidity of <10 mg water/L)²¹ and measured heart rate and oxygen saturation by pulse oximeter with a forehead sensor (Nellcor N595 OxiMax, Tyco Healthcare, Neustadt/Donau, Germany). After baseline spirometry we started exercise testing at 60% target workload (defined as $\text{Watt} = \text{measured FEV}_1 \times 53.76 - 11.07$), rapidly increasing workload aiming at 75% of the target in the second minute, 90% in the third minute, and 100% in the fourth minute, sustaining the latter for ≥ 4 min. We increased workloads more rapidly if the heart rate was not expected to reach at least 85% of the predicted maximum (220-age in years).⁷ Spirometry was performed 1, 3, 5, 7, 10, and 15 min after exercise, in duplicate,³ using a Jaeger masterscope (Erich Jaeger GmbH, Würzburg, Germany, with JLAB software version 4.52.0). If lung function had not returned to baseline after 15 min or in case of dyspnea, children received a short-acting β_2 -agonist (salbutamol pMDI 100 μg 2–4 puffs via spacer). Exclusion criteria for exercise testing were significant airflow obstruction ($\text{FEV}_1 \leq 65\%$) at baseline and unwillingness to cooperate. A fall of $\text{FEV}_1 \geq 15\%$ was considered as positive.⁷ Reference for prediction of lung function measurements were based on Zapletal et al.²²

Mannitol Dry Powder Challenge

The MDP challenge (AridolTM, Pharmaxis, French Forests, New South Wales, Australia) was conducted as described previously.^{13,16} Briefly, subjects inhaled the contents of an MDP capsule through the delivery device (OsmohalerTM). We increased doses step-wise until reaching a 15% fall in FEV_1 by cumulative doses, or a 10% fall in FEV_1 between two doses. An MDP challenge was considered to be negative if no significant fall had occurred after a cumulative dose of 635 mg. Dosing steps were: 0 (empty capsule acting as a placebo for baseline measurement), 5, 10, 20, 40, 80, 160, 160, and 160 mg. We administered multiples of 40 mg capsules to achieve doses of 80 mg and more. After each dose, children performed a 5-sec breath-hold, followed 1 min later by spirometry in duplicate, and the higher FEV_1 was recorded. We reported results categorically and as percent decrease of FEV_1 from baseline, and used the cumulative provocative dose inducing a 15%

fall of FEV₁ (PD₁₅) to define severe (PD₁₅ ≤35 mg MDP), moderate (PD₁₅ >35 to ≤155 mg), and mild response (PD₁₅ >155 to ≤635 mg).²³ At the end, children received a short-acting beta₂-agonist (salbutamol 2–4 puffs via spacer) to reverse bronchoconstriction.

Clinical Assessment

The responsible pediatric respiratory physicians made a clinical diagnosis (asthma, or alternative diagnoses) for every child after the first visit, taking into consideration medical history, clinical examination, and all conventional test results (including bronchodilator response) before exercise test and MDP challenge were performed.

Skin Prick Tests

We performed skin prick tests using birch, grass, mugwort, alternaria, cat, house dust mites (*D. pteronyssinus*), and positive and negative controls, considering a wheal of >3 mm as positive. These allergens cover 95% of inhaled allergies in Switzerland.²⁴

Statistical Analysis

To assess agreement corrected for chance, we calculated Cohen's kappa (κ), which compares the observed agreement between two tests with the agreement expected by chance.²⁵ We interpreted κ coefficients of ≤0.4 as poor, values of 0.41–0.60 as moderate, 0.61–0.80 as good, and ≥0.8 as excellent.²⁶ We also calculated sensitivity, specificity, and positive and negative predictive values of the MDP challenge to predict a 15% fall of FEV₁ in the exercise test. We constructed a receiving operating characteristic (ROC) curve plotting PD₁₅ against the exercise test (positive (>15% fall in FEV₁) or negative), with the area under the ROC curve representing the overall accuracy of MDP as a marker of BHR to exercise test. To examine which factors might influence agreement, we stratified analyses by type of exercise test (treadmill/bicycle) and age group (6–11 years/12 years and more), and tested the equality of subgroup agreement measurements using the methods of Donner et al.^{27,28} We analyzed the data with STATA, version 10.0 (Stata Corporation, Austin, Texas).

RESULTS

All 111 children participating in the study performed both tests. In total, 12 subjects were excluded: 7 because of exhaustion after the challenge so that no reliable spirometry could be performed (1 after MDP, 6 after exercise challenge); in 2, the test was stopped because of an inspiratory stridor during exercise (vocal cord dysfunction, VCD); 2 did not cooperate with exercise testing; and 1 had technical problems with the spirometer, leaving 99 children (median age 12 years,

range 6–17) for analysis (Table 1). Eighty-one children (82%) were atopic, and 60 (60%) were clinically diagnosed with asthma before BPTs were performed. Few children had an airway obstruction at baseline. Only 11/99 (11%) had an FEV₁ of <80% (69–79%) predicted at baseline. Fifty-eight (59%, median age 10 years, range 6–15) children performed a treadmill test and 41 (41%, median age 14 years, range 9–17) a bicycle exercise test. All 99 children reached the expected heart rate of at least 85% of the predicted maximum during the exercise test with a mean (SD) heart rate during the last 4 min of 187 (9) beats per minute.

The mean (SD) duration of the MDP challenge (n = 99, including reversibility test) was 34 (6) minutes (30 (7) minutes for a positive, and 35 (5) minutes for a negative result, $P < 0.001$). For an exercise test the mean duration was 49 (6) minutes, significantly higher than for the MDP challenge (34 min, $P < 0.001$). This includes the time necessary for changing clothes, installation of pulse oximetry and instruction of the exercise test. The MDP challenge provoked in 41 children (40%) a cough which was mild and lasted only a few seconds. It occurred usually after inhaling one of the higher dosage capsules (20 or 40 mg). No other side effects occurred, and no MDP challenge had to be stopped.

The MDP challenge was positive in 29 (29%) children, with PD₁₅ ranging from 8 to 634 mg (median 172 mg, Table 2). Twenty-one children had a positive exercise test with a fall of FEV₁ between 15% and 75%. The relative fall in FEV₁ after the exercise test was correlated with PD₁₅ in the MDP challenge test, although not strongly ($\rho = -0.374$, $P < 0.001$).

In total, 83 (84%) children were concordant. Agreement between MDP and exercise challenge was moderate with a Cohen's kappa of 0.58 (95% CI 0.39–0.76, Table 3). The sensitivity and specificity of the MDP challenge to detect a positive exercise test were 81% and 85%, respectively. The overall accuracy of MDP as a marker of EIB was good (area under the ROC curve 0.83, Fig. 1). Agreement between the challenge tests did not depend on the age of the children ($P = 0.99$) but agreement was better with treadmill than with bicycle challenge ($P = 0.11$, Table 3).

Sixteen (15%) children had discrepant results for MDP and exercise challenges (Table 2). All 12 children with a positive MDP challenge and a normal exercise test, and 3 of the 4 children with a normal MDP challenge but positive exercise tests, received a diagnosis of asthma. Of the 11 children on ICS, 7 children were negative for both tests, 3 were only negative in the exercise test, and 1 was positive in both tests.

After completing both BPTs, the physicians finally diagnosed asthma in 62/99 children (63%). Other diagnoses were: isolated cough (12 (12%)), dysfunctional

TABLE 1—Characteristics of Study Participants (n = 99)

Characteristics	Values
Anthropometric data	
Male gender, no (%)	63 (64%)
Age, yr ¹	12 (9–14; 6–17)
Height, cm ¹	147 (132–164; 115–182)
Weight, kg ¹	38 (29–55; 20–84)
Clinical features ²	
Reported wheeze, no (%)	73 (74%)
More than 4 attacks of wheeze, no (%)	36 (49%)
Use of inhaled corticosteroids, no (%)	11 (15%)
Exercise-induced wheeze, no (%)	60 (82%)
Positive skin prick test, no (%)	81 (82%)
Spirometry (at baseline) ¹	
FEV ₁ , % predicted	97 (88–104; 69–123)
FVC, % predicted	99 (90–108; 65–128)
FEV ₁ , % FVC	83 (75–88; 61–99)
MEF ₅₀ , % predicted	75 (61–91; 29–126)
MEF ₂₅ , % predicted	65 (51–84; 23–137)
Clinical diagnosis of asthma, no (%) ³	60 (60%)

yr, year; FEV₁, forced expiratory volume in 1 sec; FVC, forced volume capacity; MEF_{50/25}, maximum expiratory flow at 50(25)% of expired vital capacity.

¹Results are reported as median (interquartile range; range).

²In the past 12 months.

³Made after the first visit, based on medical history, clinical examination, and all conventional test results before exercise test and MDP challenge were performed.

breathing disorders such as VCD (11 (11%)) or miscellaneous (14 (14%)). Taking this final physician's diagnosis as "gold standard," we reassessed the validity of exercise and MDP challenge tests. None of the tests performed really well. Sensitivity and specificity for the final doctor's diagnosis of asthma were 32% and 97% for the exercise test (using a strict cut-off of 15% fall in FEV₁) and 44% and 95%, respectively, for the MDP challenge.

DISCUSSION

This study, to our knowledge the first comparing MDP challenge to exercise testing in children in a clinical setting, suggests that the MDP provocation test is a suitable alternative for exercise challenge. It is well accepted, takes little time, is less observer-dependent, and at least as valid when compared to exercise-testing to establish a clinical diagnosis of asthma.

In our study, MDP challenge could be performed by nearly all children, was well accepted by families and took about two-thirds of the time needed for an exercise challenge. In contrast to the frequent problems with insufficient cooperation and exhaustion occurring during exercise tests only one child was unable to finish the MDP challenge. Apart from a mild short lasting cough after higher doses, no side effects occurred. This is similar to other studies using MDP in children.^{13,15–17}

In this heterogeneous group of children assessed for possible asthma diagnosis, agreement between MDP challenge and exercise testing was moderate ($\kappa = 0.58$). Agreement was slightly better with treadmill than with bicycle tests ($P = 0.11$).

Comparisons between MDP and other BPTs in children are limited. Subbarao et al.¹⁷ using a direct provocation test found that the MDP challenge identified 21 of 25 (84%) methacholine-responsive school children

TABLE 2—Children With Positive and Negative Exercise Test and Mannitol Dry Powder (MDP) Test, Respectively (n = 99)

MDP challenge	Positive exercise test (n = 21)	Negative exercise test (n = 78)	Total
Severe (≤ 35 mg)	3 (14.3%)	2 (2.6%)	5 (5.1%)
Moderate (35 to ≤ 155 mg)	6 (28.6%)	4 (5.1%)	10 (10.1%)
Mild (> 155 to ≤ 635 mg)	8 (38.1%)	6 (7.7%)	14 (14.1%)
Normal (> 635 mg)	4 (19.0%)	66 (84.6%)	70 (70.7%)
Total	21 (100%)	78 (100%)	99 (100%)

TABLE 3—Agreement Between Mannitol Dry Powder (MDP) Challenge Test and Exercise Test (n = 99), Stratified by Age Group, and Type of Exercise Test

	Ex+ MDP+	Ex− MDP+	Ex+ MDP−	Ex− MDP−	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	P _O	P _{pos}	P _{neg}	κ	95% CI	P-value
All children	17	12	4	66	81	85	59	94	83.8	68.0	89.2	0.58	0.39–0.76	
By age group														
6–11 years (n = 53)	8	5	3	37	73	88	62	93	84.9	66.7	90.2	0.57	0.31–0.83	
12 years and more (n = 46)	9	7	1	29	90	81	56	97	82.6	69.2	87.9	0.58	0.33–0.83	0.99
By type of exercise test														
Treadmill exercise test (n = 58)	12	4	3	39	80	91	75	93	87.9	77.4	91.8	0.69	0.48–0.90	
Bicycle exercise test (n = 41)	5	8	1	27	83	77	39	97	78.0	52.6	85.7	0.41	0.11–0.70	0.11

PPV, positive predictive value; NPV, negative predicted value; Ex+MDP+, positive exercise and MDP tests; Ex−MDP+, normal exercise and positive MDP tests; Ex+MDP−, positive exercise and normal MDP tests; Ex−MDP−, normal exercise and MDP tests; P_O, proportion of observed total agreement; P_{pos}, proportion of observed positive agreement; P_{neg}, proportion of observed negative agreement; κ, kappa; 95% CI, 95% confidence interval of kappa. Level of agreement indicated by kappa: ≤0.4 poor, 0.41–0.60 moderate, 0.61–0.80 good, >0.8 excellent.

The *P*-value indicates difference between groups.

with asthma. Brannan et al. compared MDP challenge with hypertonic (4.5%) saline (HS) in 592 subjects, including 109 children. The sensitivity for MDP to identify a positive HS test in children (<12 years) was 86% and the specificity was 68%.¹³ Only two studies are, to some extent, comparable with ours: Anderson et al.¹⁵ investigated the validity of MDP challenge to predict EIB and a clinical diagnosis of asthma in a large, mixed-aged population of 509 subjects including 68 children younger than 16 years. Total agreement between MDP and exercise tests for children <18 years using a 10% fall in FEV₁ was 62% and the sensitivity

and specificity of MDP to identify an EIB was 60% and 59%, respectively. However, Anderson et al.¹⁵ performed two exercise tests, defining a positive response as a ≥10% fall in any of the two tests, in a population of mostly adolescents and young adults. Recently, Kersten et al.¹⁸ compared MDP challenge with exercise tests inhaling cold air in 25 children with allergic asthma. Positive and negative predictive value of the MDP challenge for EIB was 69% and 91%, respectively, similar to our results (68% and 89%). It is not surprising that MDP challenges do not identify all exercise positive tests, because repeatability of exercise tests is poor.^{9,15,29}

In the absence of a gold standard for the diagnosis of asthma in children we could not compare the validity of the two challenge tests against “true” asthma. As a surrogate measure, we used the final doctor’s diagnosis, which was made by considering all aspects given by history, clinical examination, conventional test results (lung function, allergy tests), and both BPTs. Although the MDP challenge performed slightly better than the exercise test, the sensitivity of both indirect challenge tests for a doctor’s diagnosis of asthma was relatively poor. In the subgroup of younger patients (6–18 years) studied by Anderson et al.,¹⁵ sensitivity and specificity for mannitol to identify a clinical diagnosis of asthma were 63% and 81%, respectively.

The main strength of our study is the clinical design which reflects the common work place situation and the patient mix in a pediatric outpatient clinic. All children were first-time referrals to the pediatric respiratory clinic for evaluation of possible asthma diagnosis. Only 15% had used inhaled corticosteroids prior to the visit. Therefore, the study population was unselected representing the commonly mild asthmatic population representative of our daily work. This contrasts clinical

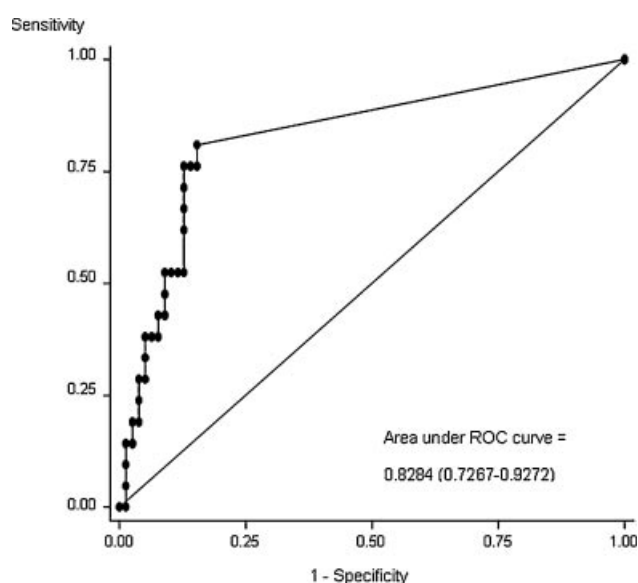


Fig 1. Receiver operating characteristics (ROC) for bronchial hyperresponsiveness (BHR) to MDP challenge as a predictor of BHR to exercise test (n = 99). Positive exercise test results reported as a 15% fall in FEV₁. BHR, bronchial hyperresponsiveness; MDP, mannitol dry powder.

trials,¹³ which often selectively include well-defined moderately severe asthmatics and healthy controls, leaving out patients with unclear degrees of airway reactivity typical for clinical practice. Our study was carefully conducted, with short intervals (≤ 7 days) between the two challenge tests, a period within repeatability of MDP challenge is good.¹⁶ Workload and intensity of exercise throughout the challenge were continuously assessed, and humidity and temperature of the inspired air were always within the limits required for exercise testing. A potential limitation of the study was that the order of the two tests was not randomized, for example, the exercise test came always first. However, we strongly believe that this had no influence on the results since there was an appropriate interval of at least 24 hr between the tests and no change in respiratory health or medication from one test to the other.

In conclusion, we found that MDP is a convenient challenge test for children in a clinical context, is easy to administer and well tolerated. Compared to exercise testing, MDP challenge takes less time, is independent of humidity and temperature and needs less equipment. Agreement between MDP and exercise tests, particularly treadmill tests, was fair and the validity to identify a doctor's diagnosis of asthma was similar for both tests. Except when exercise-induced symptoms are the focus of interest in clinical practice (e.g., to differentiate exercise-induced asthma from other exercise-induced respiratory problems like dysfunctional breathing disorders, etc.), MDP challenge seems a suitable alternative for the traditional exercise test in children, especially when compliance for or performance of exercise-testing is limited by the age or the gusto of the child.

ACKNOWLEDGMENTS

We thank all lab technicians of the pulmonology department in the children's hospitals in Basel and St. Gallen for their assistance in our study. Marie-Pierre Strippoli was supported by the Swiss National Science Foundation (grant 3200B0-122341). The study was funded by AstraZeneca (Switzerland), the Lung Association St. Gallen, and the Schmidheiny Foundation (Heerbrugg, St. Gallen). Mannitol dry powder challenge tests were provided by Pharmaxis (New South Wales, Australia).

There are no competing interests.

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