Sample size estimation in studies monitoring exercise-induced bronchoconstriction in asthmatic children

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Abstract

Background – The repeatability of the response to standardised treadmill exercise testing using dry air and monitoring of heart rate in asthmatic children suffering from exercise-induced bronchoconstriction (EIB) has not been well established.

Methods – Twenty seven asthmatic children with known EIB performed standardised exercise testing twice within a period of three weeks. The tests were performed on a treadmill while breathing dry air. During both tests heart rate had to reach 90% of the predicted maximum. Response to exercise was expressed as % fall in forced expiratory volume in one second (FEV₁) from baseline and as area under the curve (AUC) of the time-response curve.

Results – The intra-class correlation coefficients for % fall and AUC (log-transformed) were 0.57 and 0.67, respectively. From these data, power curves were constructed that allowed estimations to be made of sample sizes required for studies of EIB in children. These indicated that, if a drug is expected to reduce EIB by 50%, as few as 12 patients would be sufficient to demonstrate this effect (90% power) using a parallel design study.

Conclusions – Standardised exercise testing for EIB using dry air and monitoring of heart rate is adequately repeatable for use in research and clinical practice in children with asthma.

(Thorax 1997;52:739–741)

Keywords: exercise-induced asthma, reproducibility, childhood asthma.

At present exercise-induced bronchoconstriction (EIB) is regarded as an expression of airway hyperresponsiveness to non-sensitising bronchoconstrictor stimuli, which is a common characteristic of current symptomatic asthma. One of the goals of asthma treatment is to enable the patients to participate in activities and exercise without limitations. Exercise testing for determining the severity of EIB can therefore be a helpful tool in the diagnosis and management of asthma, and in research studies investigating drug therapy, provided the method of exercise testing is standardised and reproducible. It is recommended that inspired dry air should be used and that the work intensity of the subject should be adjusted to achieve 40–50% of predicted maximal voluntary ventilation or, alternatively, a heart rate ≥90% of maximum predicted during the last minute of the test. Although data are available on the reproducibility of the response to standardised exercise testing, data for dry air exercise testing in children are lacking. We have therefore investigated the repeatability of EIB induced by standardised treadmill exercise testing while breathing dry air in asthmatic children with documented EIB, and used the data to estimate the sample size necessary for studies of EIB.

Methods

Patients

Twenty seven asthmatic children (12 boys) aged 6–14 years with a current history of EIB were recruited from the clinic of the Juliana Children’s Hospital, The Hague, and ‘t Lange Land Hospital in Zoetermeer. Pre-exercise forced expiratory volume in one second (FEV₁) was above 70% of predicted for all children, while post-exercise testing showed a fall of ≥15% in FEV₁, compared with baseline in all subjects. Four children used continuous inhaled corticosteroids, but these were withheld in the week before and during the study period. All children used short acting inhaled bronchodilators on demand only, which were withheld for eight hours before exercise testing.

Study Design

After the screening exercise the children attended at approximately the same time of day on two separate days (interval range 6–24 days). At both visits a standardised treadmill exercise challenge was performed. The two tests were considered to be acceptable for analysis if the child had reached the target heart rate in both tests, regardless of the speed of the treadmill used, and if the duration of the two tests did not differ by more than 30 seconds.

Exercise Challenge

Before exercise the baseline FEV₁ was measured in triplicate and the highest value was used for analysis. Exercise testing was performed by running on a treadmill (LE 2000, Jaeger, Germany or Tunturi J880, Finland), while breathing dry air (relative humidity <10%) during running. Dry air was obtained by pressurised medical air collected in a Douglas bag (contents 150 litres) and inhaled by the child through a face mask (Hans-Rudolph) with an inspiratory and expiratory port. The heart rate was monitored by a radiographic device (Polar...
Sport Tester). The incline of the treadmill was set at 5–10%, depending on the physical condition of the child. During the first minute of the test, the children walked at a slow speed to familiarise themselves again with the procedure. Subsequently, the speed of the treadmill was increased during the first three minutes of the test to induce a heart rate of ≥90% of the predicted maximum (approximately 210 – age) by the third minute of the test. Thereafter, the children ran for another three minutes unless dyspnoea made further running impossible. FEV1 was measured in duplicate at 1, 3, 5, 7.5, 10, 15, 20 and 30 minutes after running, with the highest FEV1 at each time point being retained for analysis.

ANALYSIS OF DATA

The severity of EIB was expressed as the maximal percentage decrease in FEV1 after exercise compared with the baseline FEV1 (% fall) and as the area under the time-response curve (AUC) between 0 and 30 minutes after exercise. The values on the test days of heart rate (AUC) between 0 and 30 minutes after exercise. The values on the test days of heart rate (AUC) were proportional to their mean, both parameters were log-transformed, thereby achieving normality of the change over time in the outcome variable. Assuming absence of period or carryover effects, the approximate number of subjects required in a crossover design study was subsequently calculated using the formula:

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N (\text{number of subjects}) = \frac{[\text{Sdd} \times (Z_a - Z_p)]/D]^2}{\text{2}}
\]

where Sdd is the standard deviation of the change in outcome variable, Z_a is the standard normal deviate corresponding to a right-hand tail area of α, Z_p is the standard normal deviate corresponding to a left-hand tail area of β, and D is the expected mean change in EIB produced by treatment – that is, 40%, 50%, etc.

For a parallel group design study, comparing the change over time of the outcome variable for the two groups, the number of subjects was calculated according to the formula:

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N (\text{number of subjects}) = 2 \times \frac{[\text{Sdd} \times (Z_a - Z_p)]/D]^2}{\text{2}} \text{ in each group.}
\]

(Caveat: With estimated sample sizes of ≤30, Z values should be replaced by Student’s t values for the same α and β, but based on n – 1 degrees of freedom (with n = estimated sample size).)

Results

All children completed the study according to the protocol. Between children, the duration of the exercise tests varied from 3.5 to 6 minutes. Mean (SD) heart rate during the last minute of the test did not differ significantly between the test days (188 (9)/min and 189 (8)/min, respectively, p = 0.44). The mean (SD) % fall for the first test was 32.1 (10.3)% and for the repeat test 31.7 (10.3)% Mean AUC was 582 (307)%min for test 1, and 596 (297)%min for test 2. Severity of EIB did not differ significantly between the two tests (% fall, p = 0.87; AUC: p = 0.80). Because the differences in % fall and AUC between the two tests were proportional to their mean, both parameters were log-transformed, thereby achieving normality of the differences (fig 1). The intra-class correlation coefficients (based on these log-transformed data) were 0.57 for % fall and 0.67 for AUC. Curves for estimation of sample sizes at given power levels to discriminate statistically significant reductions in EIB of 40% and 50%, respectively, are presented in table 1, the required number of subjects being dependent on

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\text{Figure 1 Repeated measures of log-transformed % fall in FEV1 (A) and area under the curve (AUC) (B), the difference in repeated measures plotted against their means and shown with line of no difference (dotted lines) and 95% agreement limits (dashed lines).}
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\text{56 5.5 6.5 7 7.5}
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\[
\text{Average % fall (log transformed)}
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\[
\text{Average AUC (log transformed)}
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Sample size estimation in studies in asthma

The choice of design (crossover or parallel) and outcome variable (% fall or AUC). For example, if a drug-induced reduction of 50% is considered to be clinically effective, only five (% fall) or six (AUC) patients are needed to achieve statistical significance (α = 0.05, two-sided, β = 0.90, one-sided) using a crossover design, while a parallel group design requires a total of 12 (% fall) to 20 (AUC) patients.

Discussion

This study has shown that the response to standardised dry air exercise testing is adequate enough to allow drug evaluation for EIB in limited numbers of children, with the required study sample sizes being influenced by the choice of design (crossover or parallel) and the outcome variable (% fall or AUC). Thus, standardised dry air exercise testing can be an important tool in the management of childhood asthma. Whether repeatability can be improved by measuring ventilation instead of heart rate during testing remains to be investigated.

The authors wish to thank T P Haine-Rooos and M van der Heul-van Smalde for technical assistance, and the Medical Department of GlaxoWellcome for financial support.

2 The British Thoracic Society, the British Paediatric Association, the Research Unit of the Royal College of Physicians of London, the King’s Fund Centre, the National Asthma Campaign, the Royal College of General Practitioners, et al. Guidelines on the management of asthma. Thorax 1993; 48:51–24.