Relationship between exhaled nitric oxide levels and compliance with inhaled corticosteroids in asthmatic children

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Summary Levels of exhaled nitric oxide (eNO) are elevated in subjects with asthma and fall in response to oral or inhaled steroids. This study explored the possibility the measurement of eNO levels could be used to identify subjects who were not adhering to their treatment regimen.

Twenty children with asthma attending the respiratory clinic were recruited. Each attended on four occasions 1 month apart when eNO levels were measured. A data logger attached to a pressurised metered dose inhaler was used to objectively monitor use of inhaled corticosteroids (ICSs). The correlation between day and dose compliance with eNO was assessed.

The data demonstrated a weak but non-significant correlation between eNO and both day ($r = 0.055$, $P = 0.67$) and dose ($r = 0.153$, $P = 0.23$). A recorded value of eNO less than 12 was associated with day compliance rates of 3–97%. Of the 19 recorded eNO values greater than 12 ppb almost 80% were from subjects with a day compliance of less than 50% during the preceding month. Of the four values greater than 12 ppb and day compliance $> 60\%$ one subject had a poor inhaler technique, one had a mild viral exacerbation and one appeared to be associated with increase pollen exposure.

The measurement of eNO may prove to be a useful tool in helping to manage children with asthma but further work is required to define its precise role. Elevated eNO levels in asthmatic children taking ICSs are likely to reflect poor compliance but confounding factors such as disease activity and inhaler technique need to be carefully considered.

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Introduction

The introduction of inhaled corticosteroids (ICS) in the early 1970s transformed the management of asthmatic patients. It has been shown that the use of ICSs reduces day and night-time symptoms, reduces exercise induced fall in lung function, reduces the frequency and severity of exacerbations and has probably had some impact on mortality. A systematic review comparing ICS treatment against placebo in children with asthma suggested that corticosteroids produce a 50% reduction in asthma symptoms and 68% reduction in the need for rescue therapy with oral corticosteroids following acute exacerbations compared to control groups. However, in order to obtain these benefits ICSs must be taken regularly and many studies have shown that compliance with a treatment regimen amongst asthmatic patients in routine practice is frequently poor. Poor regimen compliance (poor adherence) has been shown to result in increased morbidity and has probably had some impact on mortality. The introduction of inhaled corticosteroids (ICS) in the early 1970s transformed the management of asthma.

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Reliably identifying non-compliance may prove to be very valuable in attempting to understand the factors contributing to on-going symptoms in asthmatic patients under medical review. Unfortunately, there is currently no reliable means to assessing compliance in routine practice. The few objective studies assessing health-care professionals assessment of compliance amongst asthmatic subjects indicated that this is generally no more accurate than tossing a coin. Indeed, in one large study physicians were found to greatly over estimate compliance and physician assessment was found to be less reliable than either canister weighing or patient completed questionnaires, both of which significantly over-estimated compliance. Personal characteristics provide few immediate clues in that compliance with a given asthma treatment regime does not appear to be influenced by age, socio-economic status, knowledge of the disease or disease severity. However, psychological factors, and depression in particular, are thought to have some correlation with poor regime compliance. Anxiety is associated with over-reliance on β agonist use and is not associated with improved adherence to in ICS use. Personal reporting of compliance is notoriously unreliable.

Over the past few years there have been many papers indicating that exhaled nitric oxide (eNO) levels are elevated in untreated asthmatics and during acute exacerbations and that these fall in response to treatment with oral or inhaled steroids. On the basis of these observations it has been proposed that measurement of eNO levels may be a useful and reliable non-invasive means of diagnosing and monitoring airways inflammation in patients with asthma. However, others have questioned its value in monitoring disease activity in treated patients. One study did find a correlation between fall in eNO and compliance, as measured by counting unused doses in a Turbohaler, when budesonide was commenced in children with mild-to-moderate asthma irrespective of atopic status. However, the authors did not report any correlation between absolute eNO levels and compliance.

Despite the lack of any study using objective measures of compliance to determine the relationship between compliance and eNO levels it has been frequently suggested that measurements of eNO would be of considerable value in monitoring compliance with treatment regimens. The purpose of this study was to obtain objective data relating to regime compliance amongst asthmatic children and correlate this with eNO levels. In this 'real-life' study all children with a diagnosis of asthma based on a clear response to therapy were eligible for inclusion and no attempt was made to select on the basis of atopic status or disease severity.

Method

Twenty children aged between 7–14 years of age with a diagnosis of asthma based on a clear response to therapy attending asthma clinics at the Sheffield Children’s Hospital were recruited over a 12-month period. Local Ethics Committee approval was obtained for the study. Patients were on a stable dose of ICSs for at least 3 months prior to entry into the study. All were reporting experiencing symptoms at least three times per week but they had not experienced an exacerbation with the previous 6 weeks. All subjects entering the study were using pressurised metered dose inhalers and holding chambers as their delivery system for ICS as we did not wish to change delivery systems at entry to the study and the data loggers were pMDI specific. In this 'real-life' study patients with asthma were included irrespective of their atopic status. The study was approved by the South Sheffield Ethics committee and all subjects and their parents provided written consent.

Patients attended on four occasions at 1-monthly intervals. At each visit, eNO measurements were obtained together with lung function measure-
ments and clinical assessment based on reported symptoms. At visit 1 patients were issued with a standard pressurised metered dose inhaler containing their normal ICS. Attached to the inhaler was a datalogger (Medtrac Technologies, Lakewood, USA), which recorded time and date of all actuations. Patients were fully informed regarding the purpose of these monitoring devices.

eNO recordings were made at each visit using a Logan Sinclair chemiluminescence analyser (Logan Research, Rochester, UK). eNO levels were recorded following the ERS task force recommendations using an expiratory flow of 50 ml/s and measurements taken from the plateau portion of the curve.

The correlation between eNO and both day and dose compliance was assessed. Day compliance reflects the number of days the advised number of doses were taken while dose compliance reflects the number of doses taken as a proportion of the nominal prescribed doses during that period. A patient prescribed a twice-daily regimen who only administered a single dose each day would have a day compliance of zero but a dose compliance of 50%.

The Spearman correlation coefficient was used to assess the relationship between the variables as the data in all the variables of interest was not normally distributed.

Results

Of the children included in the study 13 had clear evidence of personal atopy with raised IgE, positive skin prick tests, or on-going atopic dermatitis and/or ‘hay fever’. Of the remainder four had a very strong family history with at least one first-degree relative and three appeared not to be atopic. FEV1 ranged from 73% to 120% at entry to the study.

The relationships between day and dose compliance and measured eNO are shown in Figs. 1a and 1b. Each point represents data from an individual visit with three data points per patient. There was a negative non-significant correlation between day compliance and eNO (r = –0.055, P = 0.67). An apparently stronger negative correlation between dose compliance and eNO was observed but again this was not statistically significant (r = –0.153, P = 0.24).

A number of patterns emerged from examining individual patient data as shown in Fig. 1a. Seven subjects appeared to have satisfactory levels of compliance (day compliance >60%) and eNO levels below 10. Of these six had a personal evidence of personal atopy with hayfever and or eczema in addition to asthma and the seventh had a strong family history of atopy.

Of the three subjects in whom there was no clear evidence either personal atopy or close family history of atopy, two subjects had elevated eNO levels on at least one occasion. Three subjects had eNO levels <10 ppb at each visit but had evidence of poor compliance throughout. Two of these had clear personal evidence of atopy (one elevated IgE and one with eczema and hayfever) while a fourth had very variable rates of compliance which was not reflected in the eNO levels which remained low throughout.

Nine subjects had persistently or intermittently raised eNO. Of these, three subjects had poor regime compliance throughout (day adherence <40%) with elevated eNO. One subject appeared to have good day compliance (>75% at each visit) but despite this had an eNO level of 19 ppb at one visit. In four subjects, day compliance fell following the first period and this was accompanied by a marked increase in eNO.

eNO levels of >12 ppb where recorded on 19 occasions. Of these 15 were associated with day compliance during the previous month of less than 50%. However, four (>20%) of these values were associated with a day compliance of >60%.
suggesting that factors other than compliance may influence eNO measurements during clinic visits. Alternative explanations were apparent in three. One appeared to be attributable to poor inhaler technique and in one subject the elevated eNO appeared to be attributable to a mild viral exacerbation of asthma. For a third subject the elevated eNO was associated with increase hay fever symptoms and presumably reflected increased lower airways inflammation in response to the allergen or contamination from the upper airway.

Discussion

The data obtained in this study undertaken in unselected children with a clinical diagnosis of asthma suggests that the measurement of elevated levels of eNO may be helpful in identifying patients with poor regime compliance but caution must be exercised when interpreting results. When considering the group as a whole there was weak but non-significant negative correlation between eNO and day compliance. The only other significant negative correlation between eNO and exercise when interpreting results. When considering factors such as poor inhaler technique, mild viral-induced exacerbations and hay fever may result in elevated eNO levels independent of the patient’s compliance.

Our data indicates that poor regimen compliance is the most likely explanation for elevated eNO levels in asthmatic patients attending the clinic but other causes need to be considered. In our study more than 20% of elevated levels were attributable to causes other than poor regimen compliance. As noted above, regime compliance amongst those with eNO levels in the ‘normal’ range was highly variable and therefore a ‘normal’ value does not indicate ‘good’ adherence. The ‘day compliance’ during the preceding month in those whose eNO was less than 10 ppb ranged from 3–97%.

A number of factors may have contributed to the lack of a significant correlation. It is possible that improved correlation may have been achieved if more subjects had been included but this would still not alter the findings that in some subjects, eNO are elevated despite good compliance and in others low levels are recorded despite poor compliance. Recognition of the reasons for these ‘outliers’ is important when using eNO measurements in the clinic.

The inclusion of three children without clear evidence of atopy may have contributed since there is evidence that eNO levels are more closely related to atopic asthma. However, this seems unlikely in that elevated eNO levels were recorded in two of the three ‘non-atopic’ children, that is those who did not have a clear personal history of atopy or strong family history of atopy in first-degree relatives while two of the three with persistently poor compliance and low eNO were atopic. We deliberately did not undertake skin prick tests or measure total IgE and RASTS in those who had not already had such investigations. We wished to undertake a ‘real life’ to explore the possible application of eNO in a standard clinic. In the UK, the majority of subjects with asthma would be managed in primary care and the majority would not have had skin prick tests or RASTS performed.

In part the poor correlation observed in our study can be attributed to those low levels of eNO in subjects with poor compliance. This is unlikely to be due to the inclusion of non-atopic subjects as two of the three subjects had unequivocal evidence of being atopic individuals. A more likely explanation is that these subjects had relatively mild disease despite reporting significant symptoms. Alternatively they may represent subjects in whom adherence improved during the few days prior to assessment since eNO levels are reported to respond rapidly to the administration of systemic or inhaled steroids but the data did not support this suggestion.

High levels of eNO despite adequate compliance will also tend to reduce the correlation between compliance and eNO and contribute to the lack of significant correlation. When considering patients with an eNO level above 12 ppb the majority had a day compliance level below 50% suggesting that elevated levels do reflect poor compliance. However, in more than 20% of subjects the elevated levels of eNO were derived from subjects who would appear to be an acceptable day compliance of greater than 60%. Regimen compliance is only one of a number of factors that may influence a therapeutic response to ICSs. Even if a patient adheres with a treatment regimen they may still have on-going inflammation in the lower airway with elevated eNO levels if their inhaler technique is poor and drug is not being delivered to the lungs. Similarly the underlying inflammation may be increased in the short term due to exacerbations
induced by inter-current respiratory viral infections or allergen challenges. In two subjects studied during the summer, hay fever appeared to be a possible confounding factor contributing to elevated eNO levels. Indeed the highest levels were recorded in an individual in whom upper rather than lower airways symptoms were most troublesome at the time. However, the technique used to measure eNO should minimise contamination from the upper airway and normal levels of eNO were observed in other subjects with symptomatic hay fever. It has been proposed that elevated eNO may also be attributed to being on 'inadequate dose'\textsuperscript{34} but this did not appear to be a factor in any of the children in our study. If patients with a good inhaler technique were compliant but on an inadequate dose we would have expected to see persistently elevated eNO levels despite good compliance but this pattern was not observed in any of the subjects.

Our findings that there is a relatively poor correlation between eNO and therapy are not unique. A previous study assessing the response to prednisolone in 23 atopic subjects with severe asthma found that eNO levels were in the 'normal range' both before and after prednisolone despite on-going symptoms in more than a quarter of subjects.\textsuperscript{34} Similarly eNO remained elevated in 20% of subjects despite apparently complying with prednisolone therapy monitored by measuring serum levels. These results combined with our findings suggest that the relationship between eNO, treatment and symptoms is more complex than is often portrayed and further work is required to clarify the role of eNO measurements in the clinic.

In summary this study, using an objective assessment of compliance, indicates that there is negative but non-significant correlation between compliance and eNO in unselected asthmatic patients. The detection of elevated levels of eNO may be clinically valuable and appears to be associated with poor regimen compliance in the majority of subjects but confounding factors such as poor inhalation technique, hay fever or inter-current exacerbation must be taken into account when interpreting such findings. Further work is required to clarify the role of eNO measurement in clinical practice.

Acknowledgements

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References


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Further reading
