Primary Care Respiratory Journal (2007); **16**(6): 349-356
Copyright GPIAG - Reproduction prohibited

Primary Care
RESPIRATORY JOURNAL
www.thepcrj.org

ORIGINAL RESEARCH

The use of exhaled nitric oxide monitoring in primary care asthma clinics: a pilot study

Kevin Gruffydd-Jones[a,b], Sabbi Ward[c], Carol Stonham[d], Tatiana V Macfarlane[e], *Mike Thomas[f,g]

[a] Honorary Research Fellow, Department of General Practice and Primary Care, University of Aberdeen, Aberdeen, Scotland, UK
[b] General Practitioner, Box Surgery, Wiltshire, UK
[c] Research Nurse, Box Surgery, Wiltshire
[d] Nurse Practitioner, Minchinhampton Surgery, Gloucestershire, UK
[e] Medical Statistician, Department of General Practice and Primary Care, University of Aberdeen
[f] Asthma UK Senior Research Fellow, Department of General Practice and Primary Care, University of Aberdeen
[g] General Practitioner, Minchinhampton Surgery, Gloucestershire, UK

Received 13th February 2007; accepted 8th August 2007

Abstract

Aim: Although asthma is defined as a chronic inflammatory disease, inflammation is rarely assessed. The fraction of exhaled nitric oxide (FeNO) is a biomarker of airways inflammation. We assessed the feasibility of FeNO monitoring in general practice.

Methods: Prospective observational study of volunteers attending primary care asthma clinics. Consenting subjects were seen at their own surgery for 2-weekly reviews over 12 weeks, with assessment of FeNO, lung function, symptoms and health status.

Results: 22 adults and 15 children provided informed consent. Two subjects were unable to perform the FeNO expiratory manoeuvre. In the remaining subjects, measurements conforming to highest ERS/ATS recommendations were made on 211 of 236 occasions, and on 21 further occasions acceptable readings were made. Acceptability was high to subjects and staff. Correlations between FeNO readings and other parameters were weak and non-significant except for statistically significant correlation between longitudinal FeNO changes and changes in lung function ($r = -0.33$, $p<0.001$) and health status ($r = -0.22$, $p=0.022$).

Conclusions: Exhaled nitric oxide monitoring is technically feasible and acceptable to staff and patients within the context of a primary care asthma clinic.

© 2007 General Practice Airways Group. All rights reserved.
K Gruffydd-Jones, *et al. Prim Care Resp J* 2007; **16**(6): 349-356.
doi:10.3132/pcrj.2007.00076

Keywords asthma, monitoring, exhaled nitric oxide, primary care

Copyright General Practice Airways Group
Reproduction Prohibited

Introduction

Asthma is a common illness, with over 5 million patients with asthma in the UK,[1] an age-specific prevalence rate ranging from approximately 20% in children to 10% in the over-65 years age group, and an increasing prevalence over the last 30 years.[2] In spite of effective medication, outcomes of asthma care are sub-optimal and avoidable morbidity is common.[3,4] Asthma results in high costs to the individual and to the community, with poor asthma control accounting for up to 75% of all asthma costs.[5,6]

Asthma is defined as a 'chronic inflammatory disorder of the airways',[7] yet inflammation is not routinely measured in practice. Decisions on the use and dose-adjustment of anti-inflammatory medications are made on the basis of non-specific symptoms and measures of airflow obstruction.[8,9] Inhaled corticosteroid drugs (ICS) are the principal class of treatment for persistent asthma,[10] and they have an excellent safety profile in moderate doses. However, there is concern that high doses can result in steroid-related adverse outcomes,[11-13] particularly in paediatric age groups.[14,15] There is evidence that high-dose ICS treatment may be common in adults[16] and children[17] in the UK. The correlation between

* **Corresponding author:** Cotswold Cottage, Oakridge, Stroud, Gloucs, GL6 7NZ, UK. Tel: +44 (0)1285 760671 E-mail: mikethomas@doctors.org.uk

Copyright GPIAG - Reproduction prohibited

asthma symptoms and lung function is poor,[18] and psychosocial factors,[19] anxiety[20] and functional breathing disorders[21] may complicate asthma and result in respiratory symptoms that may require treatment other than increased doses of anti-inflammatory medication. Using the current symptom-based approach to determine doses of anti-inflammatory ICS medication consequently may lead to both under- and over-treatment.

It is possible, therefore, that direct assessment of airway inflammation may lead to better diagnosis and more accurate dose-titration of anti-inflammatory medication. Recent technological advances have allowed non-invasive assessments of airway inflammation to become possible. Some technologies – such as induced sputum for differential cell counting – are labour-intensive and impractical in primary care settings, but others – such as exhaled nitric oxide monitoring – are relatively quick and simple to perform and equipment is becoming more affordable. Portable nitric oxide monitors are now available for use in community settings, and only require a steady exhalation from the patient into the mouthpiece of the monitor to allow measurement. Currently, such technologies are being increasingly used in secondary and tertiary care settings, but there has been little work evaluating their feasibility in primary care. The cost of a portable hand-held monitor is approximately 3000 euros (a similar cost to a good quality spirometer) with additional consumable costs of approximately 8 euros/test.

Exhaled nitric oxide (eNO) is produced in increased amounts in inflamed lungs, and the fraction of exhaled nitric oxide (FeNO) may be measured in exhaled air; it is suppressed by inhaled corticosteroids, and has been proposed as an inflammatory biomarker in asthma.[22] FeNO has been shown to correlate with eosinophilic airway inflammation,[23,24] and to be raised in most cases of corticosteroid-naïve, and in 40-60% of ICS-treated, patients with asthma.[25] Measurement of exhaled nitric oxide is non-invasive and is carried out by steady rate single breath exhalation through a mouthpiece into an NO analyser. The technique is simple to use and provides repeatable and reproducible results in adults and in children as young as 4 years old.[26] Although FeNO and eosinophilic inflammation do not relate closely to markers of asthma control (i.e. symptoms and disordered airway function), they do relate to asthma exacerbations,[27,28] implying that assessment of inflammation provides information about asthma not available through other means. A dose-titration adult study reported that adjustments of ICS dose informed by FeNO estimation allowed a reduction in ICS dose without loss of control,[29] and a paediatric study reported improved bronchial hyperresponsiveness without any difference in the overall ICS load received.[30] In a paediatric dose-reduction study, a normal FeNO reading was able to predict successful ICS dose reduction, and raised readings predicted loss of control even in children who were clinically stable.[28] A raised FeNO value is a marker for corticosteroid-responsive airways disease,[31] and has better sensitivity and specificity than commonly used diagnostic strategies for asthma.[32] There is, therefore, considerable interest in the possibilities of using this technology in routine asthma care, and interest in the possibility that such monitoring may allow appropriate ICS doses to be prescribed and might allow identification of patients with ICS-unresponsive disease in whom ICS treatment can be discontinued.

All current studies are hospital-based, requiring subjects to attend hospital clinics for detailed assessment. Most asthma care now occurs in the community, and over 80% of people with asthma do not attend hospital.[32,33] The use of FeNO in everyday clinical practice will require the demonstration of practicality, acceptability, clinical effectiveness and cost-effectiveness of this technology in primary care settings. The availability of portable and relatively inexpensive FeNO monitors[34] means that if effectiveness is demonstrated the technology can potentially be widely applied.

The primary aim of this study was to investigate the feasibility of measuring exhaled nitric oxide in children (6 years old and over) and in adults, during asthma review in general practice. We also aimed to measure the variability of FeNO readings over time and to collect comparative data on the relationship between FeNO and measures of asthma control such as symptoms, exacerbation, medication use and asthma-related health status.

Copyright General Practice Airways Group Reproduction Prohibited

Methods

Study design

This was a prospective observational study. Consenting subjects were seen at their local general practice by their usual asthma nurse at 2-weekly intervals over 12 weeks (a total of seven visits for each subject). Daily diary cards were completed by subjects and/or parents, with data recorded on symptoms and morning pre-bronchodilator peak expiratory flow rate (PEF) (Wright's mini peak flow meter). At each visit the following assessments were made:

- Exhaled nitric oxide (FeNO): Measurements were performed on the Niox chemiluminescence eNO analyser (Aerocrine Ltd, Sweden) at an expiratory flow of 50ml/sec as per guideline recommendations.[35] It was aimed to obtain three NO values that agreed within 10% of each other (as per ERS guidelines), and repeated exhalations were performed up to a maximum of 10 or when the subject tired.
- Spirometry: (Vitalograph), performed as per ERS guidelines.
- Health status: in adults – the Asthma Mini Quality of Life

http://www.thepcrj.org

Copyright GPIAG - Reproduction prohibited

Questionnaire (AQLQ);[36] and in children – the Paediatric Caregivers Quality-of-life Questionnaire (PQLQ).[37]

- Short-term symptomatic asthma control – the Asthma Control Questionnaire[38] (ACQ) in adults only (this instrument has not been validated in children.)

At the final visit, or on withdrawal from the study, (other than those withdrawing unexpectedly for personal reasons) subjects were asked to rate the ease of use of eNO monitoring and acceptability of FeNO monitoring on a 7-point scale ranging from 'completely acceptable' (+3) via 'acceptable' (+2), 'just acceptable' (+1), 'neither acceptable nor unacceptable' (0), to 'just unacceptable' (-1) etc. The practice asthma nurses performing the readings were also asked to rate for each individual patient the ease of measuring FeNO over the course of the study on the same 7-point scale from +3 ('very easy') to -3 ('very hard').

Normal care was allowed to continue through the 3-month study period, with medication changes supervised by the usual attending clinicians. Ethical approval was provided by the Bath Local Research Ethical Committee.

Subjects

Consenting adults (17 years and older) and children (6 to 16 years) attending the nurse-led asthma clinics in two general practices in the South-West of England were invited in person to participate in the study. Inclusion criteria were all of the following: willingness to attend for the study monitoring visits; documented evidence of asthma (by characteristic symptomatology, variable or reversible airways obstruction and response to treatment); current use of inhaled beta2 agonists (usage $\geq$ 1 canister in previous 6 months); and provision of informed consent. Exclusion criteria were: current smoking (since eNO is suppressed by smoking and so may be an unreliable signal in smokers); maintenance treatment with inhaled corticosteroids at a dose exceeding 2000mcg/day of beclomethasone or equivalent (e.g. 1000mcg/day fluticasone); or maintenance treatment with oral corticosteroids. In the analyses of ICS dosage, beclometasone and budesonide are assumed as equipotent with double potency for fluticasone.

Statistical analyses

Data were entered in an Excel spreadsheet and analyzed using SPSS version 15 (SPSS Inc., 2006). Analysis was performed separately for adults and children. Non-parametric data are presented as medians and interquartile ranges (IQR). Wilcoxon signed ranks test and the Mann-Whitney test were used as appropriate. Significance level was set to 0.05. Kappa statistics were used to assess agreement between participants and operators.

Correlation coefficient within subjects was used to assess whether longitudinal changes in individual FeNO measurements at different visits were associated with changes in other parameters of asthma control.[39]

In order to investigate the cross-sectional relationship between FeNO and other asthma control parameters between subjects, weighted correlation between subject means was used[40] for all variables other than mean daily bronchodilator use in the past two weeks, for which Spearmans rank correlation coefficient was calculated.

Results

Subjects

Thirty-seven subjects provided informed consent and entered the study (22 adults and 15 children). The demographic detail of consenting subjects is shown in Table 1. One subject (adult male) withdrew consent prior to visit 1 for personal reasons, one subject (adult male) withdrew at visit 1 as he was unable to perform the expiratory manoeuvre needed for the FeNO readings, and one subject (adult female) withdrew at visit 2 as she was unable to perform the expiratory manoeuvre needed for the FeNO readings. One further subject (adult female) withdrew at visit 2 for personal reasons, and two (adult male, adult female) missed one or more visits for personal reasons.

Normal care was allowed to proceed through the study,

Table 1. Baseline demographic and clinical data on study participants.

	Adults (n=22)	Children (n=15)
Age, median (IQR) yrs	56.5 (37.75-60.5)	9 (8-12)
Male sex (%)	8 (36%)	11 (73%)
Former smokers (%)	8 (36%)	0 (0%)
Beclometasone equivalent ICS dose (mcg/day), median (range)	400 (400-800)	200 (0-300)
FEV_1 % predicted, median (IQR)	86.5 (57.25-101.75)	82 (76-94)
PEF l/min, median (IQR)	435 (400-457)	310 (280-410)
AQLQ/PQLQ score (median, IQR)	5.6 (4.1-6.7)	6.1 (5.0-6.7)
ACQ score (median, IQR)	1.1 (0.4-2.3)	
Patient-reported daily bronchodilator use doses/day (median, IQR)	0 (0-1.0)	0 (0-2.0)
Exhaled nitric oxide, ppb, (median IQR)	31.2 (11.5-61.9)*	55.3 (11.6-102.1)**

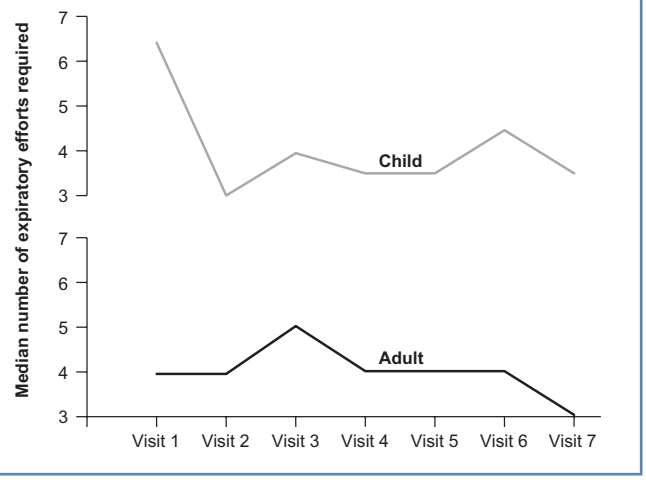
*n=19 **n=14

Copyright General Practice Airways Group Reproduction Prohibited

http://www.thepcrj.org

Copyright GPIAG - Reproduction prohibited

Figure 1. Median number of expiratory attempts needed to produce FeNO readings conforming to ATS/ERS recommendations in adults and children at each visit.



and in total 24 changes in treatment were made in 15 subjects (9 adults, 6 children), all of which were changes in ICS dose (14 increases in dosage including three commencements of ICS treatment, and 10 reductions in ICS dosage including one cessation of ICS treatment). There was a non-significant decrease in daily ICS dose at the end of the study from that at the first visit (median, IQR, dose as beclomethasone equivalent mcg/day: 400, 200-700 vs. 400, 200-650, p=0.110).

Success of FeNO measurements

Two subjects (5.4%) were unable to perform the necessary exhaled manoeuvre to allow an FeNO reading to be made, and so withdrew from the study.

In the remaining subjects, measurements were attempted on 236 study visit occasions; successful measurements conforming to highest ERS/ATS recommend standards (average value of three technically acceptable readings) were made on 211 occasions (90.1%), and on a further 21 occasions it was only possible to achieve two successful readings, which are also acceptable by international standards; it was not possible to measure FeNO acceptably on four visits (1.7% of occasions) in the case of two subjects.

The number of expiratory efforts required to produce three acceptable readings or until the subject tired (maximum of 10 efforts) reduced from a median of 5.0 (IQR 4.0-7.0) attempts at the first visit to 3.0 (IQR 3.0-4.5) at the final visit (p<0.001). A 'learning effect' was observed in adults and children over time, with a reduction in the number of expiratory attempts needed to produce valid readings (Figure 1). The number of expiratory efforts required was lower in adults than in children at visit 1: median (IQR) 4.0 (3.5-7.0) vs. 6.5 (5.0-8.0), p=0.040, but not at visit 7 [3.0 (3.0-6.0) vs. 3.5 (3.0-4.0), p=0.570].

Table 2. Patient- and operator-reported ease and acceptability of FeNO testing.

Characteristic	Child (n=14)	Adult (n=20)
Subject-reported ease:		
Number (%) of easy or very easy	10 (71.4)	14 (70.0)
Operator-reported ease:		
Number (%) of easy or very easy	11 (78.6)	15 (75.0)
Subject-reported acceptability:		
Number (%) of acceptable or completely acceptable	13 (92.9)	19 (95.0)

Acceptability and ease of testing for patients and staff (Table 2)

The median (IQR) score for patient-reported acceptability of FeNO monitoring was 3.0 (2.0 to 3.0) in both children and adults; all patients bar two (6%, one adult and one child) found the testing 'acceptable' or 'completely acceptable' and none found it unacceptable. The median (IQR) score for patient-reported ease of use was 2.00 (0.75-3.0); five subjects (15%) found the readings 'quite hard' and two more (6%) found it 'hard' or 'very hard', both of whom withdrew from the study at an early stage as they were unable to master the technique.

The median (IQR) rating score by practice asthma nurses was 2.0 (1.7-2.0) for children and 2.0 (1.3-3.0) for adults, with testing rated as easy or very easy in 79% of children and 75% adults. There was fair agreement between operator and child in assessment of easiness (kappa=0.43, p=0.099) and between operator and adult (kappa=0.48, p=0.091). The proportion of children finding FeNO measurement 'acceptable' or' very acceptable' (93%) and 'easy' or 'very easy'(71%) was similar to that of adults (95% and 70% respectively; p=0.09 and 0.616 respectively).

FeNO readings

Considerable variation was found in FeNO levels in adults and in children both between subjects and within individuals over repeated visits (Figures 2 and 3). FeNO levels (all values as parts per billion, ppb) at each visit and the change in eNO level from the previous visit are shown in Table 3. There was no statistically significant difference in the coefficient of variation (CV) between children and adults (median (IQR) 35.0 (29.6-48.4) and 32.4 (20.9-51.7) respectively, p=0.515).

Overall there was a significant reduction in FeNO between the first and the last study visit in children (median, [IQR] change in FeNO =14.5 [-41.5 to -0.2] ppb, p=0.014) but not significantly in adults (-9.1 [-28.7 to 2.7] ppb, p=0.136). FeNO was non-significantly lower at baseline in adults than children

Copyright General Practice Airways Group Reproduction prohibited

http://www.thepcrj.org

Copyright GPIAG - Reproduction prohibited

Figure 2. Exhaled nitric oxide levels (parts per billion) in individual adult subjects at successive study visits.

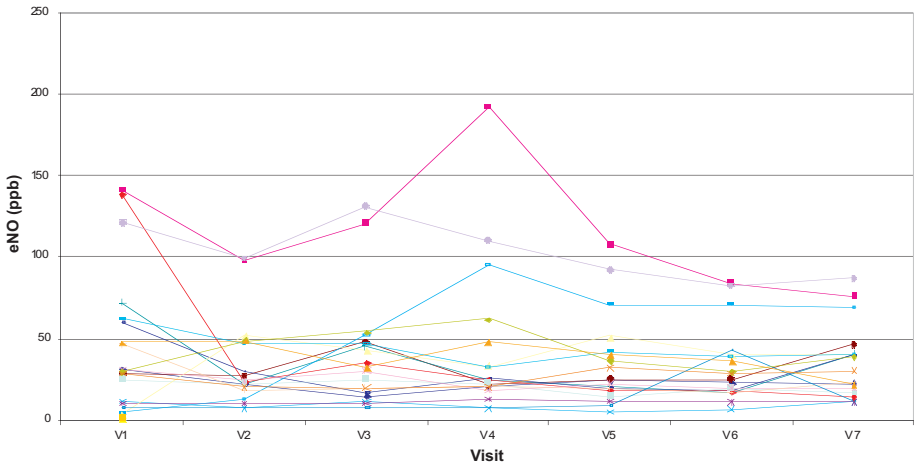
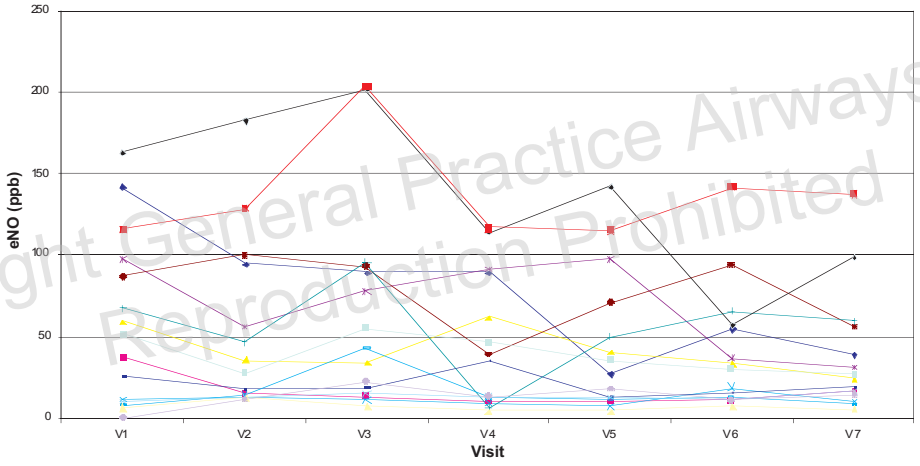


Figure 3. Exhaled nitric oxide levels (parts per billion) in individual paediatric subjects at successive study visits.



Copyright General Practice Airways Group Reproduction Prohibited

Table 3. Exhaled nitric oxide (FeNO) levels (parts per billion, ppb) and change in FeNO levels from previous visit (ppb) in adults and children at each study visit.

Measure	Visit						
	1	2	3	4	5	6	7
FeNO adults Median (IQR)	31.2 (11.5, 61.9)	23.6 (18.9, 48.1)	32.1 (16.3, 32.1)	23.2 (20.3, 36.9)	23.6 (17.5, 44.4)	26.4 (17.5, 40.8)	30.7 (15.7, 43.2)
FeNO children Median (IQR)	55.3 (11.6, 102.1)	28.0 (13.9, 94.3)	43.0 (14.9, 92.6)	34.8 (10.0, 89.3)	27.5 (11.0, 70.5)	30.4 (12.0, 57.4)	24.8 (14.7, 55.7)
Change in FeNO from Visit 1 (adults) Median (IQR)	-	-7.2 (-27.1, 0.1)	2.9 (-0.3, 21.6)	0.2 (-10.6, 8.4)	-1.3 (-7.3, 4.1)	-2.0 (-5.6, -0.2)	0.5 (-2.8, 5.2)
Change in FeNO from Visit 1 (children) Median (IQR)	-	-3.1 (-3.4, 8.2)	1.6 (-3.1, 26.6)	-3.8 (-53.9, 0.0)	-0.8 (-10.6, 6.0)	1.8 (-6.5, 16.4)	-4.1 (-8.9, 4.1)

http://www.thepcrj.org

Copyright GPIAG - Reproduction prohibited

Table 4. Between-subjects correlation coefficient of exhaled nitric oxide (FeNO) and parameters of asthma control.

Parameter correlated with exhaled nitric oxide (FeNO)	Between subjects correlation coefficient (p-value) Children	Adults
Mean daily bronchodilator use in the past 2 weeks*	-0.33 (0.226)	-0.014 (0.954)
Mean morning PEF in previous 2 weeks	0.59 (0.020)	-0.19 (0.433)
% predicted forced expiratory volume in the 1st second (FEV_1)	-0.10 (0.712)	-0.13 (0.594)
Asthma Quality of Life Questionnaire, AQLQ (adults) / Pediatric Caregivers Quality-of-life Questionnaire, PALQ (children)	-0.08 (0.771)	-0.22 (0.365)
Asthma Control Questionnaire score (ACQ)		0.15 (0.540)

* Spearmans rank correlation was used

Table 5. Within-subject correlation coefficient in exhaled nitric oxide (FeNO) and in other parameters of asthma control.

Parameter correlated with exhaled nitric oxide (FeNO)	Within subjects correlation coefficient (p-value) Children	Adults
Mean daily bronchodilator use in the past 2 weeks*	-0.02 (0.899)	0.17 (0.101)
Mean morning PEF in previous 2 weeks	0.07 (0.536)	0.06 (0.551)
% predicted forced expiratory volume in the 1st second (FEV_1)	0.001 (0.997)	-0.33 (<0.001)
Asthma Quality of Life Questionnaire, AQLQ (adults) / Pediatric Caregivers Quality-of-life Questionnaire, PALQ (children)	-0.02 (0.868)	-0.22 (0.022)
Asthma Control Questionnaire score (ACQ)	0.01 (0.965)	0.13 (0.184)

* Spearmans rank correlation was used

Copyright General Practice Airways Group Reproduction Prohibited

(median, [IQR] eNO: 31.2 [11.5-61.9] vs. 55.3 [11.6-102.1] ppb, p=0.377), but not at the final visit (30.7 [15.7, 43.2] vs. 24.8 [14.7, 55.7] ppb, p=0.602).

Correlations between FeNO and asthma control parameters

The cross-sectional correlation coefficients in adult and paediatric subjects between FeNO readings and other parameters of asthma control at study visits are shown in Table 4. The observed correlations were weak and not generally statistically significant.

Within-subject longitudinal relationships between FeNO and other parameters of asthma control are shown in Table 5. Again, observed correlations were generally weak and not statistically significant. However, significant correlations were observed in adults between changes in lung function and changes in FeNO (a rise in FeNO was moderately correlated with a fall in % predicted FEV_1, r= -0.33, p<0.001), and between changes in FeNO and changes in Asthma Quality of Life Questionnaire scores (a rise in FeNO was weakly correlated with worsening asthma related health status, r= -0.22, p=0.022).

Discussion

Exhaled nitric oxide is now widely used as a research tool in asthma, and the positioning of this technology in clinical practice is beginning to come under the spotlight.[41] However, the acceptability and clinical utility of eNO monitoring in primary care clinical settings – where most asthma is treated – needs to be established if it is to become a standard clinical tool in asthma assessment in the community. In this pilot study we assessed the acceptability and ease of use of eNO monitoring in the setting of nurse-led general practice asthma clinics. Although both practices hosting the study have previous asthma research experience, neither had any experience of eNO monitoring prior to the study, and the clinic nurses performing the study had only brief and basic training in the use of the equipment. Subjects attending standard primary care asthma clinics were asked to participate in the study. The process of care and the practice demographic profiles of the study practices are typical of modern UK community-based asthma care.

It was found that only two subjects out of the 37 who

http://www.thepcrj.org

Copyright GPIAG - Reproduction prohibited

consented to participate in the study were unable to perform the controlled respiratory manoeuvre required for eNO analysis, but that in the remaining subjects acceptability of use and ease of use were rated highly. The ease of measurements and the number of expiratory measurements needed to produce accurate results improved with time in adults and in children. Similarly, the asthma nurses performing the measurements rated ease of use as being high for most subjects, adults and children alike. It appears that there will be a minority of patients in primary care who will not be able to perform the measurements, but that it will be an acceptable technique to most patients and will also be acceptable to practitioners running primary care asthma clinics.

The stability of eNO measurements in individual patients, and the relationship between changes in eNO readings and changes in other parameters of asthma control, were assessed in this pilot study. Previous hospital-based studies have reported weak cross-sectional and longitudinal correlations between eNO readings and other parameters of asthma control such as lung function, symptomatic control, and asthma-related health status. In this study, correlations of a similar magnitude were observed and generally failed to reach statistical significance given the relatively low numbers of adults and children participating in the study. In adults and children we found in cross-sectional analysis weak and inconclusive relationships between FeNO readings and both physiological and patient-centred outcome measures, and in longitudinal analysis fairly weak though non-significant relationships between FeNO score and other parameters. There were, however, statistically significant relationships found between rising FeNO and worse lung function, and between rising FeNO and worse asthma-related health status.

The weakness of the observed relationships may reflect the multi-dimensional nature of asthma; it is recognised that no single outcome measure encompasses the entirety of asthma,[42] and that inflammatory parameters may give information on asthma control not provided by other measures – particularly in relation to exacerbations and optimisation of ICS dose.[27,29] The size and limited time course of this study did not enable us to investigate the relationship between eNO readings, exacerbations and ICS dose; no exacerbations occurred during the study and dose-titration decisions were made on clinical grounds. There is a need therefore for adequately-powered controlled effectiveness trials comparing FeNO-guided management with standard 'guideline-driven' management which can investigate whether the clinical efficacy observed in hospital-based studies can be translated into primary care practice and whether or not FeNO-guided management can prove to be clinically effective and cost-effective in community settings. In addition, health economic evaluations are required to assess the costs and benefits of monitoring in different patient groups and different clinical settings. However, the demonstration from this study that FeNO monitoring is technically and logistically feasible for many patients attending primary care asthma clinics means that such studies will be practicable in a primary care setting.

The strength of this study is that it was performed in a routine primary care setting by clinicians who had little additional training in inflammatory monitoring. Both practices had established asthma clinics and had GPs and nurses with an interest in asthma management, but this situation is not unusual in the UK. Further studies are required to investigate whether non-asthma interested practices have similar success in monitoring – but we feel that with minimal training this should be a feasible technology in most primary care settings if clinical effectiveness and cost-effectiveness are confirmed.

A weakness of this study is that it was a small pilot study and was not structured or powered to confirm clinical effectiveness. As we wished to perform regular monitoring on subjects, we were limited to volunteers who were willing to comply with the study protocol which involved frequent practice visits. Further studies will need to evaluate the technology on less motivated patients and on less frequent monitoring visits.

In summary, this community-based pilot study investigated the use of FeNO monitoring in primary care asthma clinics. It was found that most patients aged 6 and over were able to use the FeNO monitoring equipment and found it acceptable and relatively easy to use, with ease of use improving with repeated use. Weak, but statistically significant, correlations, or non-significant correlations, were observed between FeNO readings and lung function, and symptomatic or health status assessments of asthma control. Exhaled nitric oxide monitoring is feasible in community settings. Further studies are needed to investigate the clinical effectiveness and cost-effectiveness of such technology in terms of the diagnosis and management of asthma.

Copyright General Practice Airways Group Reproduction Prohibited

Funding

The study was funded by a grant from the Royal College of General Practitioners Scientific Foundation Board.

Ethics approval

Ethical approval for the study was granted by Bath and Gloucestershire Local Ethical Research Committees.

Acknowledgements

The authors wish to thank the patients and staff of Box and Minchinhampton Surgeries for their patience, help and co-operation. We would like to thank Dr Sergei Kharitinov for invaluable advice in devising the study, Professor David Price and Professor Amanda Lee for advice on the manuscript, and Aerocrine Ltd for loaning the Niox equipment free of charge for the duration of the study and for technical assistance.

http://www.thepcrj.org

Copyright GPIAG - Reproduction prohibited

Conflict of interest declaration

The authors have declared that there are no conflicts of interest.

References

1. Smith NM. The 'Needs of People with Asthma' survey and initial presentation of the data. *Asthma J* 2000;**5**:133-6.
2. British Thoracic Society. The Burden of Lung Disease. British Thoracic Society. 2002.
3. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000;**16**:802-07.
4. Rabe KF, Adachi M, Lai CKW, *et al*. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004;**114**:40-7.
5. Barnes PJ, Jonsson B, Klim JB. The costs of asthma. *Eur Respir J* 1996;**9**:636-42.
6. Stevens CA, Turner D, Kuehni CE, Couriel JM, Silverman M. The economic impact of preschool asthma and wheeze. *Eur Respir J* 2003;**21**:1000-06.
7. International consensus report on the diagnosis and treatment of asthma. *Eur Respir J* 1992;**5**:601-41.
8. British Thoracic Society, Scottish Intercollegiate Guideline Network. British Guidelines on the Management of Asthma. *Thorax* 2003;**58**:1-94.
9. Global Initiative for Asthma (GINA). Asthma management and prevention. NIH Publication No. 96-3659A. 1995. Bethesda, Maryland, NHLBI.
10. Barnes PJ. Current issues for establishing inhaled corticosteroids as the antiinflammatory agents of choice in asthma. *J Allergy Clin Immunol* 1998; **101**:S427-33.
11. Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids: new developments. *Am J Respir Crit Care Med* 1998;**157**:S1-S53.
12. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. *Arch Intern Med* 1999;**159**:941-4.
13. Pedersen S, O'Byrne P. A comparison of the efficacy and safety of inhaled corticosteroids in asthma. *Allergy* 1997;**52**(suppl 39):1-34.
14. Drake AJ, Howells RJ, Shield JPH, *et al*. Lesson of the week: Symptomatic adrenal insufficiency presenting with hypoglycaemia in children with asthma receiving high dose inhaled fluticasone propionate * Commentary: Exogenous glucocorticoids influence adrenal function, but assessment can be difficult. *BMJ* 2002;**324**:1081-3.
15. Todd GRD, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child* 2002;**87**:457-61.
16. Thomas M, Leather D, Price D. High-dose inhaled corticosteroids and add-on therapy use in adults in the UK in 2003: an observational study. *Prim Care Resp J* 2006;**15**:166-72. doi:10.1016/j.pcrj.2006.02.009
17. Thomas M, Turner S, Leather D, Price D. High dose inhaled corticosteroid use in childhood asthma: an observational study. *Br J Gen Pract* 2006;**56**:788-90.
18. Teeter JG, Bleecker ER. Relationship between airway obstruction and respiratory symptoms in adult asthmatics. *Chest* 1998;**113**:277.
19. Rimington LD, Davies DH, Lowe D, Pearson MG. Relationship between anxiety, depression, and morbidity in adult asthma patients. *Thorax* 2001;**56**:266-71.
20. Thomas M, Grifiths C. Asthma and panic: scope for intervention? *Am J Respir Crit Care Med* 2005;**171**:1197-8.
21. Thomas M, McKinley RK, Freeman E, Foy C. Prevalence of dysfunctional breathing in patients treated for asthma in primary care: cross sectional survey. *BMJ* 2001;**322**:1098-100.
22. Taylor D, Pijnenburg MW, Smith AD, De Jongste JC. Exhaled nitric oxide measurements: clinical application and interpretation. *Thorax* 2006;**61**:817-27.
23. Berry MA, Shaw DE, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. *Clin Exp Allergy* 2005;**35**:1175-9.
24. Berlyne GS, Parameswaran K, Kamada D, Efthimiadis A, Hargreave FE. A comparison of exhaled nitric oxide and induced sputum as markers of airway inflammation. *J Allergy Clin Immunol* 2000;**106**:638-44.
25. Magnussen H, Hargreave FE. Non-invasive monitoring of airway inflammation. *Eur J Respir Dis* 2000;**16**:1-2.
26. Kharitonov S, Gonio F, Kelley C, Meah S, Barnes PJ. Reproducibility of exhaled nitric oxide measurements in healthy asthmatic adults and children. *Eur Respir J* 2003;**21**:1-6.
27. Green RH, Brightling CE, McKenna S, *et al*. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2003;**360**:1715-21.
28. Zacharasiewicz A, Wilson N, Lex C, *et al*. Clinical Use of Noninvasive Measurements of Airway Inflammation in Steroid Reduction in Children. *Am J Respir Crit Care Med* 2005;**171**:1077-82.
29. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of Exhaled Nitric Oxide Measurements to Guide Treatment in Chronic Asthma. *N Engl J Med* 2005;**352**:2163-73.
30. Pijnenburg MW, Bakker EM, Hop WC, De Jongste JC. Titrating Steroids on Exhaled Nitric Oxide in Children with Asthma: A Randomized Controlled Trial. *Am J Respir Crit Care Med* 2005;**172**:831-6.
31. Smith AD, Cowan JO, Brassett KP, *et al*. Exhaled nitric oxide: A predictor of steroid response. *Am J Respir Crit Care Med* 2005;**171**:453-9.
32. Smith AD, Cowan JO, Filsell S, *et al*. Diagnosing Asthma- Comparisons between Exhaled Nitric Oxide Measurements and Conventional Tests. *Am J Respir Crit Care Med* 2004;**169**:473-8.
33. Price D, Wolfe S. Delivery of asthma care: patients' use of and views on healthcare services, as determined from a national interview survey. *Asthma J* 2000;**5**:141-4.
34. Silkoff PE, Carlson M, Bourke T, Katial R, Ogren E, Szefler SJ. The Aerocrine exhaled nitric oxide monitoring system NIOX is cleared by the US Food and Drug Administration for monitoring therapy in asthma. *J Allergy Clin Immunol* 2004;**114**:1241-56.
35. American Thoracic Society. Recommendations for standardized procedures for the on-line and off-line measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide in adults and children-1999. *Am J Respir Crit Care Med* 1999;**160**:2117.
36. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of life Questionnaire. *Eur Respir J* 1999;**14**:32-8.
37. Connolly MA, Johnson JA. Measuring quality of life in paediatric patients. *Pharmacoeconomics* 1999;**16**:605-25.
38. Juniper EF, O'Byrne P, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;**14**:902-07.
39. Bland JM, Altman DG. Calculating correlation coefficients with repeated observations: Part 1 - correlation within subjects. *BMJ* 1995;**310**:446.
40. Bland JM, Altman DG. Calculating correlation coefficients with repeated observations: Part 2 - correlation between subjects. *BMJ* 1995;**663**:1995.
41. Taylor DR, Pijnenburg MW, Smith AD, Jongste JC. Exhaled nitric oxide measurements: clinical application and interpretation. *Thorax* 2006;**61**:917-827.
42. Barnes N. Outcome measures in asthma. *Thorax* 2000;**55**(suppl 1):S70-S74.

Copyright General Practice Airways Group
Reproduction prohibited

Available online at **http://www.thepcrj.org**

http://www.thepcrj.org