Exhaled nitric oxide and inhaled corticosteroid dose reduction in asthma: a cohort study

Corresponding author: Dr Dominick Shaw

E-mail; dominic.shaw@nottingham.ac.uk

Tel; 01158231709

Emma Wilson PhD[1], Tricia McKeever PhD[2], Beverley Hargadon BN[3], Glenn Hearson[1], John Anderson MRCP[1], David Hodgson MRCP[1], Helen Bailey BSc[1], Garry Meakin BSc[1], Mike Thomas PhD[4], Ian D Pavord FRCP[5], Tim Harrison FRCP[1], Dominick Shaw FRCP[1].

1. Nottingham Respiratory Research Unit, the University of Nottingham.
2. Department of Epidemiology and Public Health, the University of Nottingham
3. Institute for Lung Health, Glenfield Hospital, Leicester.
4. Department of Primary Care, University of Southampton.
5. University of Oxford.

Nitric oxide and inhaled steroid dose reduction

Change in FeNO, 7 days following a 50% drop in ICS dose, does not identify people who are at risk of losing asthma control within the next 3 months.

To the Editor

Inhaled corticosteroids (ICS) are the mainstay of treatment in asthma and act to reduce airway inflammation, however guidelines recommend titrating ICS dose based on the assessment of symptoms (1) which are not closely associated with airway inflammation (2). Once symptoms and exacerbations are controlled for at least 3 months, ICS reduction is recommended (3). However step-down is often not implemented, leaving people over-treated. There are few studies investigating the most appropriate way to reduce ICS dose. Clinical trials suggest that the majority of patients currently treated with ICS plus long acting beta agonists can have their therapy successfully stepped down, but there is no clear evidence on how best to achieve this (4).

We assessed whether exhaled nitric oxide (FeNO) measurements could predict a loss of symptom control or exacerbation following a reduction in ICS dose in a cohort study of people with well controlled asthma recruited from primary care.

Methods

All participants had an asthma diagnosis recorded in their records, were aged between 18 and 75 years, and had received at least one ICS prescription in the last year. The study was restricted to non-smokers with a less than 10 pack year history. Poorly compliant participants, participants with an asthma exacerbation requiring oral steroids in the previous 12 weeks, or with an Juniper Asthma Control Questionnaire- 5 (ACQ$^®$) (5) score greater than 1.5 at visit 1 (indicating poor control) were excluded. Ethics approval and written informed consent was obtained.

Participants were seen at the same time of day on four occasions; day 0, 14, 21 and 110. At each visit ACQ, FeNO (Aerocrine Flex flow) and spirometry were performed. Symptoms were assessed using the (ACQ) (6). Airway inflammation was measured using FeNO at flows of 10, 30, 50, 100, 200 ml/sec; participants were blinded to their FeNO measurements. Differential cell counts were performed on induced sputum. Spirometry was performed. Airway hyperresponsiveness was assessed using methacholine challenge to determine the concentration of methacholine required to provoke a 20% fall in the FEV_1 (PC_{20}). Blood tests for differential eosinophil count and IgE were performed. (Figure 1- on line supplement)

Participants were re-assessed at visit 2; if their ACQ score remained <1.5, and had not increased by more than 0.5, their ICS dose was reduced by 50%. Inhaler types were kept the same. Participants were asked to take the half dose of ICS for seven days and then return for visit 3. When participants returned for visit 3 their ACQ-5 score was re-measured.

A loss of control was defined as an increase in ACQ score of greater than 0.5 (the minimal important difference in asthma control (7)). An exacerbation was defined as increasing asthma symptoms requiring a course of antibiotics or oral steroids (8). All participants who contacted the emergency team were assessed by a physician (blinded to data) within 24 hours and their ACQ recorded; decisions on how to treat were based on BTS guidelines.

Using data from previous studies we estimated that a sample of 154 subjects would provide 80% power to show that a low FeNO, or lack of change in FeNO following ICS reduction could successfully predict stable control (8, 9). Assuming a 10% drop out rate we aimed to recruit 200 subjects.

We analysed the data in two ways: firstly we assessed whether a low baseline FeNO predicted successful ICS dose reduction; secondly we evaluated whether an increase in FeNO following dose reduction predicted deterioration. We also evaluated whether other clinical measures predicted successful dose reduction at three months. Measures included: Baseline spirometry, methacholine PC_{20}, blood IgE, blood eosinophil count, ACQ score, differential sputum eosinophil and neutrophil count.

Results

191 participants had their FeNO level measured at visit 2, and seven days after a 50% reduction in ICS dose (visit 3) (Table 1). 128 (67%) participants completed the three month study period (post ICS reduction) with no loss of control or exacerbation, and 63/191 (33%) experienced either a loss of control (32=17%) or exacerbation (31=16%). (Figure 2 online supplement). The median (IQR) baseline ACQ was 0.6 (0.2-1.0) for the stable group and 0.8 (0.2-1.0) for the deterioration group (p=0.53). The mean ICS dose reduction across the study was 363± 267mcg beclomethasone dipropionate.

Baseline FeNO

There were no significant differences in baseline FeNO (visit 2) between those successfully reducing ICS dose and those suffering from a loss of control or exacerbation at any of the five

FeNO flows. At a flow of 50ml/sec, the mean baseline FeNO was 18.9ppb (95% CI 16.8-21.5) in the stable group and 19.7ppb (95% CI 16.4-23.6ppb) in the deterioration group (p=0.76).

Change in FeNO

There was no significant difference in the change in FeNO in the week following ICS reduction (visit 2 to visit 3) between the stable and deterioration groups at the 50ml/sec (Table 2). The mean absolute change between visit 2 and 3 was 1.58 ± 11.9ppb for the stable group and 1.03 ± 14.88ppb for the deterioration group (p=0.80). There were no statistically significant differences in any of the baseline clinical measurements between groups.

Conclusion

Although guidelines recommend a 50% reduction in ICS dose after three months of good symptom control, there is evidence of over treatment with ICS (10), and a reluctance to reduce treatment (11). Consequently using inflammometry to guide treatment decisions may be beneficial. We addressed previous criticisms by evaluating both individual baseline FeNO and change from baseline. We found that neither baseline FeNO measurements nor change at 7 days following ICS dose reduction could predict which participants would remain stable or lose control over the next 3 months.

In our study participants were not blinded to their treatment allocation and a period of 7 days was used post step down before repeating the FeNO measurements. This design was chosen to reflect real life practice and for maximum future practical benefit. A 50% reduction was chosen as being consistent with guideline recommendations and was felt to be ethically justified.

Our study was well powered to identify any change in FeNO values; the relationship between sputum eosinophilia and FeNO levels is strongest between 100-800mcg of ICS (BDP) equivalent (12); previous studies have shown that ICS dose reductions less than the mean reduction in our study result in an increase in FeNO levels (13); dose-dependent onset and cessation of action of ICS on FeNO levels have been demonstrated, with levels rising after one day of treatment reduction (14); and the largest change in FeNO values is found at 400mcg BDP equivalent (15), the mean value prescribed in our population.

The lack of change in FeNO following dose reduction may be due to one of several factors: i) FeNO measurements do not correlate well enough with airway inflammation in mild to

moderate asthma; ii) ICS dose reduction was not large enough; iii) the episodes of symptomatic loss of control were not due to increased airway inflammation.

In addition to the failure to predict ICS reduction using FeNO we found that none of the baseline clinical indices (including induced sputum, methacholine responsiveness and spirometry) had predictive value for future stability following ICS step down. This has important implications for ICS dose reduction and suggests better methods of identification of those at risk of a loss of control following ICS dose reduction are needed.

VARIABLE	RESULT
Age*	$54\cdot15 \pm 13\cdot50$
Gender	
Male	83 (43·5%)
Female	108 (56·5%)
When Diagnosed	
0-5 Years	16 (8·4%)
>5 Years	175 (91·6%)
BTS Treatment Step	
2	57 (29·84%)
3	111 (58·12%)
4	23 (12·04%)
Smoking Pack Years†	0 (0-4)
Height (cm)*	169·24 ±9·89
Mass (kg)*	81·14 ± 17·31
BMI (kg/m^2)*	28·27 ±5·36
BDP Equivalent Daily Dose (mcg/day)†	400 (200-1000)
FEV_1(L)*	$2\cdot68 \pm 0\cdot85$
FEV_1 % predicted (%)*	89·85 ±19·15
FVC (L)*	$3\cdot65 \pm 1\cdot00$
FVC % predicted (%)*	99·81 ±16·87
Airway hyperresponsiveness (PC_{20})#	8·02 (95%CI 6·31-10·17)
Blood IgE (kIU/L)†	91·5 (28·50 - 253·50)
Blood Eosinophils (x10^9/L)†	0·20 (0·12-0·32)
Sputum Eosinophils (%)†	0·80 (0·25-4·75)
Sputum Neutrophils (%)†	64·75 (42·25-84·00)
ACQ Questionnaire 1-5†	0·60 (0·20-1·00)

Table 1

Baseline demographics presented for study population (n=191).

Data are presented as: * Mean and standard deviation, † Median and Interquartile range, #

Geometric Mean and 95% confidence intervals·

BMI = Body Mass Index
ACQ = Juniper Asthma Control Questionnaire·
BDP Equivalent = Beclometasone Dipropionate Equivalent
(QVAR = 2:1BDP, Flixotide = 2:1 BDP, Budesonide = 1:1BDP)

Table 2

Change in FeNO between stable group and deterioration group

Change in FeNO between visit 2 and visit 3 50ml/sec flow	Stable Group: n=124[†]	Deterioration Group: n=49*	Significance level: (T-test)
Absolute Change in FeNO (ppb)	1·58 ± 11·9	1·03 ± 14·88	p=0·80
Percentage Change in FeNO (%)	17·60 ± 69·97	11·01 ± 41·05	p=0·54
Fold Change in FeNO	1·18 ± 0·70	1·11 ± 0·41	p=0·54

Data is presented as Mean and Standard Deviation

* 8 participants did not return after exacerbation/loss of control; 6 patients were unable to perform FeNO due to equipment breakdown·

[†] 4 participants were unable to produce FeNO readings due to equipment breakdown

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