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Investigating the Safety of Capsaicin Cough Challenge in Severe Asthma

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To the Editor:

Asthma is a clinical syndrome which manifests symptoms of variable wheezes, cough and breathlessness. Our current understanding of the mechanisms underlying asthma include airway inflammation, remodelling and hyper-responsiveness but evidence is emerging suggesting cough reflex hypersensitivity may be an independent factor [1].

Cough is one of the most common symptoms in asthma and is associated with increased severity and poor prognosis [2, 3], yet tools commonly used to evaluate asthma in clinical studies including the Asthma Control Questionnaire (ACQ) do not fully capture cough-related morbidity [4]. Cough is the archetypal airway neuronal reflex, but how this reflex may be modulated in asthma remains poorly understood. In mild/moderate asthma, Satia *et.al* [5] recently demonstrated heightened capsaicin-evoked cough responses. Inhaled capsaicin is a transient receptor potential vanilloid 1 channel agonist which activates vagal afferent fibres that play an important role in mediating cough [6]. However, transient bronchoconstriction after its use has been reported in patients with asthma [7]. Inhaled capsaicin has been safely used in patients with mild/moderate asthma [5], but not yet in severe disease, likely due to concerns about patients developing bronchoconstriction [7].

A recent study has suggested that a significant proportion of patients with severe asthma demonstrate high levels of cough-related morbidity [4], however little is known about cough reflex responses in severe asthma. We have therefore performed the first study to explore the safety and feasibility of performing capsaicin-cough challenges in patients with severe asthma.

Methods

This two-visit observational study was approved by the local research ethics committee (16/NM/0210). Participants were recruited from tertiary severe asthma clinics. At visit 1,

written consent and measurements of baseline asthma characteristics were completed; history and examination, questionnaires [ACQ, Leicester Cough Questionnaire (LCQ)] and spirometry were performed. A 24-hr cough monitor (VitaloJAK, Vitalograph, Buckinghamshire, UK) was attached. At visit 2, a full-dose capsaicin cough challenge was performed via a nebulizer pot through a dosimeter (KoKo Dosimeter; Ferraris, Hertford, UK) [8]. Spirometry was performed, and symptoms of breathlessness assessed with modified Borg Scale (mBorg) and dyspnea Visual Analogue Score (dVAS) immediately before and after capsaicin challenge. Adverse events (AEs) were recorded during and following the challenge, and by telephone calls at 48hr, on day 3 and day 7.

All summary data are presented as median (range).

Results

Participants

Four of the 10 participants were male, age 57 (27, 70) years, FEV₁ 72 (54, 85) % predicted, ACQ and LCQ scores 1.5 (0.14, 3.71) and 19.4(11.1, 20.6) respectively. All participants were on British Thoracic Society steps 4/5. Three had bronchial thermoplasty (BT). Objective cough frequency was highly variable [45 (8, 442) coughs/24h]. Table 1 summarizes the findings in individual participants.

Safety and tolerability

No participant had a significant drop in FEV₁ post-challenge ($\geq 20\%$) [change in FEV₁ -0.82 (-12.88 to 7.97) %]. Despite this, half of participants took rescue medication (inhaled salbutamol via spacer) to alleviate sensations of breathlessness, chest tightness and wheeziness; for those who reported the sensation of wheeziness, none had audible wheeze on auscultation. The change in dVAS and mBorg were +11 (-8 to +32) mm and +1 (0 to 2), respectively. Three participants reported AEs within 7 days. None of these were thought to be directly related to capsaicin challenge. Participant 6 reported breathlessness at night 72-hours post-challenge that was no different than baseline. Participant 7 reported increased cough that subsided without treatment. This coincided with cold weather which normally

triggers her cough. Participant 8 reported a sore throat on the night of the challenge and chest tightness at day 3. Symptoms subsided after taking 5 days of prednisolone.

Participant's family had a common cold at the time of study.

Cough Responses to Capsaicin

The capsaicin concentration reached was 46.95 (15.6, 1000) $\mu\text{mol/L}$ with 74 (24, 155) coughs during the challenge before opting to stop. The Emax (the maximum number of coughs evoked at any dose during challenge [8]) was 23 (9, 39) coughs and ED50 (the dose eliciting at least half of Emax [8]) 11.7 (1.0, 62.5) $\mu\text{mol/L}$. Females appeared to cough at lower concentrations [ED50 females 7.8 (0.97, 62.5) *versus* male: 23.5 (3.9, 125) $\mu\text{mol/L}$] and have greater cough responses compared with males [Emax female 36 (9, 39) *versus* male 19 (12, 24) coughs], figure 1. The cough responses in patients who have had BT do not appear to differ from the remainder of the participants, table 1.

Relationship between lung function, subjective dyspnea and rescue medication

The increases in dVAS in participants who required rescue medication tended to be higher than in participants not requiring rescue medication [15 (4, 32) *versus* 8 (-8, 15) mm], although the mBorg suggested little difference [1 (0.5, 1) *versus* 1 (0, 2) respectively]. The change in FEV1 was very similar in those requiring rescue medications [-0.8 (-12.9, 8.0) %] to those who did not [-0.8 (-7.1, -1.7) %]. Interestingly, the cumulative cough counts in participants who required rescue medication was 110 (24, 147) compared with 43 (36, 155) in those who did not.

Discussion

Our initial experience of capsaicin challenge in a small number of well-characterised severe asthma patients suggests that this method of assessing cough responses may be feasible and safe. There are several interesting observations arising from this dataset that warrant further investigation. The first is that this small group of severe asthma patients seem to cough markedly more during capsaicin-evoked cough challenges than our previous data

collected from mild/moderate asthma patients – almost twice as much [5], intimating that airway neuronal dysfunction might play a significant role in severe asthma. Secondly, it is particularly interesting that despite little change in measurable lung function, 50% of patients felt the need for rescue medication describing symptoms of chest tightness, breathlessness and wheeze. It may be that capsaicin activation of airway afferent nerves or indeed coughing provokes these sensations in the absence of significant bronchoconstriction in severe asthma, which if confirmed in larger studies has potential clinical importance. Whilst it might be assumed that patients took bronchodilators to relieve coughing following the challenge, this was only the case in one participant. Of note, three participants had undergone BT prior to cough challenge; a therapy thought to significantly reduce airway innervation [9]. However, capsaicin cough responses in these individuals did not appear particularly different from the remainder of the group. Clearly, much larger scale studies are required to further investigate these early findings, but these initial reassuring data should facilitate further study of the cough reflex in severe asthma.

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TABLES

Table 1: Individual participant characteristics.

ID No	1	2	3	4	5	6*	7*	8*	9	10
Age, yrs	53	57	70	60	27	62	57	67	35	39
Sex	Male	Male	Male	Female	Female	Female	Female	Male	Female	Female
Baseline FEV1 %pred	72	72	79	60	85	77	54	69	84	59
ACQ	3.4	1.3	0.4	0.7	1.1	2.7	3.7	2.6	0.1	1.7
LCQ	14.8	19.4	19.4	20.6	18.9	11.1	13.9	19.6	20.5	20.4
Asthma treatments:										
Daily ICS dose, mcg of BDP equivalent	1600	1000	2000	800	1000	2000	2000	1000	1000	1600
LABA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
LAMA	No	No	No	No	No	No	No	No	No	Yes
LTRA	No	No	No	No	No	Yes	Yes	No	Yes	No
Theophylline	No	No	No	No	No	No	Yes	No	Yes	No
Systemic steroids	No	No	Yes	No	No	No	No	No	No	Yes
Omalizumab	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes
BT	No	No	No	No	No	No	No	Yes	Yes	Yes
Other	No	No	No	No	No	No	SCG	No	No	Neb BD
24hr cough (n)**	39	n/a	50	8	155	341	442	n/a	18	29
Max. capsaicin dose tolerated (μmol/L)	1000	31.3	1000	125	31.3	15.6	15.6	31.3	62.6	125

E_{max}	12	16	22	37	39	36	14	24	9	35
ED₅₀ (μmol/L)	125	15.6	31.3	15.6	3.9	1.0	7.8	3.9	7.8	62.5
Cumulative cough during capsaicin challenge (n)	43	39	110	155	121	147	24	74	36	73
Change in dVAS (mm)	-8	8	7	14	15	4	26	15	0	32
Change in mBorg	0	1	0.5	2	1	1	1	1	0	1
Change in FEV1 (%)	-7.1	-0.8	+7.5	-0.8	-0.8	-8.3	+8.0	-2.0	+1.7	-12.9
Need for rescue meds	No	No	Yes	No	Yes	Yes	Yes	No	No	Yes

Participants reported adverse events. Two participants opted out of 24-hr cough monitoring.*

ACQ: asthma control questionnaire; LCQ: Leicester cough questionnaire; ICS: inhaled corticosteroid; LABA: long-acting β2 agonist inhaler; LAMA: long-acting muscarinic receptor antagonist inhaler; LTRA: leukotriene receptor antagonist; BDP: beclometasone dipropionate; BT: bronchial thermoplasty; SCG: sodium cromoglycate; Neb BD: nebulised bronchodilators;

FIGURES

Figure 1 Dose response curves of the raw data of inhaled capsaicin challenge in severe asthma patients compared to mild to moderate asthma patients from previous study, stratified by gender [5].

