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Safety of research bronchoscopy, biopsy and bronchoalveolar lavage in asthma

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Safety of research bronchoscopy, biopsy and bronchoalveolar lavage in asthma. W.J. Elston, A.J. Whittaker, L.N. Khan, P. Flood-Page, C. Ramsay, P.K. Jeffery, N.C. Barnes. ©ERS Journals Ltd 2004.

ABSTRACT: Bronchoscopy with endobronchial biopsy (EBB) and/or bronchoalveolar lavage (BAL) has become an important research tool in asthma. A recent report has suggested audit and reporting of the safety of these procedures.

A total of 159 asthmatic patients (84 males, 75 females), aged 18–52 (median 27) yrs, forced expiratory volume in one second 53–120 (median 88) % predicted, underwent 273 bronchoscopies in six clinical research studies. On 228 occasions, EBB and BAL were performed and, on 45 occasions, EBB was performed alone. On 48 occasions, bronchoscopy was performed 24 h post-allergen challenge.

Adverse events occurred on 34 out of 273 occasions, none of which were following allergen challenge. Post-EBB and BAL, four patients developed pleuritic chest pain, shortness of breath and fever. A further two patients experienced pleuritic chest pain alone post-EBB/BAL. Bronchospasm or worsening of asthma symptoms occurred on 14 occasions, 13 post-EBB/BAL and on one occasion post-EBB alone. Fever/flu-like symptoms were reported on nine occasions following EBB and BAL. One subject had haemoptysis post-EBB/BAL, but required no intervention.

In conclusion, bronchoscopy, endobronchial biopsy and bronchoalveolar lavage can be performed safely in asthmatic patients. Most of the complications were seen where bronchoalveolar lavage and endobronchial biopsy were both performed, suggesting that bronchoalveolar lavage accounts for most of the adverse events.
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Fibreoptic bronchoscopy with endobronchial biopsy (EBB) or bronchoalveolar lavage (BAL) has become an important tool in asthma research over the last two decades. These techniques have led to significant advances in the understanding of the pathogenesis of asthma and, in particular, the role of inflammatory cells and mediators [1–4]. In addition, intervention studies with new and existing treatments have provided useful insight into the mechanisms of action and efficacy of these treatments [5–7]. Following initial concerns over the safety of these techniques in asthmatic patients [8, 9], consensus guidelines were published by the National Heart, Lung and Blood Institute [10, 11]. More recently, three papers have reported bronchoscopy to be safe and well-tolerated in a relatively small number of asthmatic patients [12–14]. Despite this, concerns still remain and a recent report has suggested audit and continued reporting of the safety of these procedures. The current authors report their experience of adverse events related to fibreoptic bronchoscopy performed in asthmatic subjects taking part in six clinical research studies.

Methods

Study subjects

A total of 159 patients with asthma (84 males, 75 females), forced expiratory volume in one second (FEV_1) 53–120 (median 88) % predicted, aged 18–52 (median 27) yrs were recruited for six studies and underwent a total of 273 bronchoscopies. On 228 occasions, subjects underwent EBB and BAL, 48 of which were performed 24 h post-allergen challenge. On 45 occasions, subjects had EBB alone. Subjects were recruited from chest clinics at the London Chest and Royal Brompton Hospitals (London, UK), advertisements in local press and from primary care. Ethics committee approval for each study was obtained from the research ethics committees of the relevant hospitals and each subject gave written informed consent. Eligible subjects were males or females, aged 18–52, with a clear clinical history of asthma, reversible airflow obstruction spontaneously or following β_2-agonists, histamine provocative concentration causing a 20% fall in FEV_1 (PC_{20}) <8 mg or a history of mild asthma precipitated by an aeroallergen (entry criteria depending on the individual study).

PC_{20} was measured for three of the studies; for one study, the data was not recorded, but entry criteria included a PC_{20} <4 mg. For the other two studies, PC_{20} ranged from 0.06–6.0 (median 1.0). In the multicentre studies, only subjects who underwent bronchoscopy at the London Chest Hospital or the Royal Brompton Hospital are included in this report.

Study 1 was a multicentre, double-blind, randomised, placebo-controlled, parallel group study using an anti-interleukin-5 monoclonal antibody. This study required subjects to undergo two bronchoscopies, with EBB and BAL 8 weeks apart [15].

Study 2 was a multicentre, randomised, double-blind, placebo-controlled parallel group study investigating the effects of zafirlukast and beclomethasone dipropionate on allergen-induced airway inflammation. Subjects underwent bronchoscopy with EBB and BAL on two occasions 8 days apart and, on the second occasion, the bronchoscopy was performed 24 h post-allergen challenge [16].

Study 3 was a randomised, placebo-controlled study to examine whether cyclosporin A inhibited allergen-induced airway inflammation. Subjects underwent two bronchoscopies with EBB and BAL 3 days apart; the second was performed 24 h post-allergen challenge [17].

Study 4 was a multicentre, randomised, placebo-controlled comparison of the effects of oral pranlukast on bronchial mucosal immunopathology. Subjects underwent two bronchoscopies with EBB and BAL 12 weeks apart.

Study 5 was a single-centre study to compare the inflammatory profile in asthmatic smokers and nonsmokers. Subjects had one bronchoscopy with EBB alone.

Study 6 was a randomised, double-blind, placebo-controlled study investigating the effects of montelukast on eosinophils in bronchial biopsy specimens. Subjects underwent two bronchoscopies with EBB and BAL 6 weeks apart.

Bronchoscopy

Fibreoptic bronchoscopy was performed on an outpatient basis at the London Chest Hospital and Royal Brompton Hospital in accordance with established guidelines [11]. Following an overnight fast, patients were admitted to the day-case unit and baseline observations were performed. All bronchoscopies were performed in the morning. Patients were premedicated with 2.5–5 mg nebulised salbutamol. Immediately before bronchoscopy, midazolam was administered *i.v. via* a cannula, which remained *in situ* until the patient was fully recovered. Subjects in studies 4 and 6 also received 600 μg atropine as a pre-med. During the procedure, subjects had continuous monitoring of pulse oximetry (Nellcor Symphony N-300; Nellcor Puritan Bennett, Pleasanton, CA, USA) and received oxygen *via* nasal cannulae as required to maintain oxygen saturations >93%. The nose and oropharynx were anaesthetised with lignocaine spray, the vocal cords with 4% lignocaine delivered *via* the bronchoscope and the tracheobrochial tree with 2% lignocaine delivered *via* the bronchoscope. The bronchoscope, either a Pentax FB 19 TX (Pentax, Tokyo, Japan) or an Olympus mode OSE (Olympus Corp., Lake Success, NY, USA) was inserted nasally where possible and the oral route was used as a second choice. After inspection of the bronchial tree when BAL was performed, 60–180 mL (depending on the study) of prewarmed 0.9% saline were instilled into the right middle lobe and then gently aspirated. Bronchial biopsies were then obtained from the subsegmental carinae of the right or left lower lobes or right middle lobe. Following bronchoscopy, subjects were observed with regular monitoring of oximetry and vital signs. Patients were discharged after an observation period of $\geqslant$2 h, once safe swallowing had returned and observations were satisfactory. All were given an emergency contact number and follow-up was performed within a week of the procedure on most occasions. Adverse events were documented either at the time of bronchoscopy or at follow-up.

Results

Adverse events occurred on 34 out of 273 occasions; none of these were following allergen challenge (table 1). There were no differences in adverse events between subjects receiving placebo and active drug. Where subjects had two bronchoscopies, there were no differences in the frequency of adverse events during the first or second bronchoscopy. On one occasion, a subject who experienced pleuritic chest pain following the first bronchoscopy withdrew from the study and, thus, declined to have a further bronchoscopy.

Table 1. – Adverse events

Adverse event	EBB/BAL	EBB alone	Total
Occasions n	228	45	
Bronchospasm during procedure	2	0	2
Bronchospasm pre-discharge	6	0	6
Worsening asthma post-discharge	5	1	6
Fever/influenza-like illness	9	0	9
Pleuritic chest pain	2	0	2
Pleuritic chest pain/SOB/fever	4	0	4
Lethargy/malaise	1	1	2
Nonspecific chest pain	2	0	2
Bleeding	1	0	1
Total	32	2	34

Data are presented as n. EBB: endobronchial biopsy; BAL: bronchoalveolar lavage; SOB: shortness of breath.

Four patients developed pleuritic chest pain, fever and shortness of breath within 12–24 h of EBB and BAL. Two of these had changes on chest radiograph consistent with pneumonitis and required hospital admission. They were treated with *i.v.* antibiotics, to cover possible infection, and nebulised bronchodilators and were discharged after 2 days. Oral antibiotics were continued to complete a 1-week course. One patient experienced pleuritic chest pain and breathlessness 24 h post-procedure when, as a result of technical problems with suction equipment during BAL, only ~10% of the BAL fluid was recovered. These symptoms were associated with a fall in FEV_1 from 88% to 70% pred. Symptoms and spirometry resolved within 6 days without any treatment. One patient experienced chest pain and shortness of breath with no radiological changes and no treatment was required. Two further patients experienced pleuritic chest pain alone, without fever or dyspnoea.

Bronchoconstiction episodes or worsening of asthma symptoms occurred on 14 occasions, 13 post-EBB/BAL and once post-EBB alone. On two occasions, the patient experienced problems during the procedure, and the procedure was terminated to allow treatment with nebulised bronchodilators and *i.v.* steroids. On six occasions, the symptoms occurred prior to discharge and required treatment with nebulised bronchodilators, and six subjects experienced an increase in symptoms within 24–48 h post-discharge and required the additional use of inhaled salbutamol for 3–25 days.

Fever or flu-like symptoms were reported on nine occasions following EBB and BAL. On each occasion, the symptoms that started 12–24 h after the procedure were short-lived and settled spontaneously with no treatment in 2–5 days. Nonspecific chest discomfort occurred on two occasions post-EBB/BAL. A minor haemoptysis occurred on one occasion post-EBB/BAL; the subject was admitted for observation overnight and no treatment was required. Two patients reported general lethargy/malaise for 1 week post-bronchoscopy, one after EBB alone and one post-EBB/BAL.

Discussion

In this paper, the current authors have demonstrated that research bronchoscopy, including BAL and EBB, has an

acceptable safety profile in asthmatics of mild-to-moderate severity. To our knowledge, this is the largest series reporting the safety of research bronchoscopies in asthmatic subjects. A low incidence of adverse events has been found and it has been shown that the procedure is well-tolerated by the majority of subjects. Most of the adverse events experienced by the studied patients were minor, requiring no specific treatment and with no prolonged morbidity.

On two occasions following bronchoscopy with biopsy and BAL, subjects required hospital admission. On each occasion, they complained of pleuritic chest pain and fever, and developed chest radiograph infiltrates consistent with a diagnosis of pneumonitis. Treatment was instituted with *i.v.* antibiotics to cover possible infection and both subjects were fit to be discharged after 2 days. There were no long-term sequelae in either case.

On a further nine occasions, patients reported fever or flu-like symptoms. These events are not specific to asthmatic patients; fever following bronchoscopy is well-recognised, with previous studies estimating an incidence of 1.2–16% [18, 19] for all bronchoscopic procedures and an incidence of 2.5–50% amongst patients undergoing BAL [20, 21]. In the current patients, only those undergoing BAL experienced fever or pneumonitis, and subjects who only had biopsy performed reported only nonspecific side-effects, such as mild deterioration in asthma symptoms and general lethargy. This would suggest that BAL accounts for the majority of adverse events and, although a direct comparison cannot be made as a result of the relatively small numbers of subjects undergoing biopsy alone, this is in keeping with the findings of HUMBERT *et al.* [14] who observed a trend towards a smaller reduction in peak expiratory flow when only biopsies were taken.

No adverse events were reported in the 48 patients who had bronchoscopy post-allergen challenge, suggesting that bronchoscopy can be safely performed following allergen challenge. This is consistent with previous studies. GIANORIO *et al.* [22] showed that BAL performed either 4 or 24 h post-allergen challenge neither deteriorated lung function nor increased airway responsiveness in a group of atopic patients with a history of rhinitis and/or bronchial asthma.

Bronchoscopy with endobronchial biopsy and/or bronchoalveolar lavage has become an important research tool. It can be performed safely and is well-tolerated by asthmatic subjects. Continued surveillance and reporting of the use of these techniques is recommended.

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