BRONCHIECTASIS

Comparison of exhaled and nasal nitric oxide and exhaled carbon monoxide levels in bronchiectatic patients with and without primary ciliary dyskinesia

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Background: Primary ciliary dyskinesia (PCD) is associated with chronic airway inflammation resulting in bronchiectasis.

Methods: The levels of exhaled nitric oxide (eNO), carbon monoxide (eCO) and nasal NO (nNO) from bronchiectatic patients with PCD (n=14) were compared with those from patients with non-PCD bronchiectasis without PCD (n=31) and with cystic fibrosis (CF) (n=20) and from normal subjects (n=37) to assess the clinical usefulness of these measurements in discriminating between PCD and other causes of bronchiectasis.

Results: Exhaled NO levels were lower in patients with PCD than in patients with non-PCD non-CF bronchiectasis or healthy subjects (median (range) 2.1 (1.3–3.5) ppb vs 8.7 (4.5–26.0) ppb, p<0.001; 6.7 (2.6–11.9) ppb, p<0.001, respectively) but not lower than bronchiectatic patients with CF (3.0 (1.5–7.5) ppb, p>0.05). Nasal levels of nNO were significantly lower in PCD patients than in any other subjects (PCD: 54.5 (5.0–269) ppb, non-PCD bronchiectasis without CF: 680 (310–1000) ppb, non-PCD bronchiectasis with CF: 343 (30–997) ppb; control: 663 (322–1343) ppb). In contrast, eCO levels were higher in all patient groups than in control subjects (PCD: 4.5 (3.0–24.0) ppm, p<0.01, other bronchiectasis without CF: 5.0 (3.0–15.0) ppm, p<0.001; CF: 5.3 (2.0–23.0) ppm, p<0.001 v 3.0 (0.5–5.0) ppm). Low values in both eNO and nNO readings (<2.4 ppb and <187 ppb, respectively) identified PCD patients from other bronchiectatic patients with a specificity of 98% and a positive predictive value of 92%.

Conclusion: The simultaneous measurement of eNO and nNO is a useful screening tool for PCD.

With PCD and the level of eCO may reflect the chronic inflammatory process in these subjects.

We have therefore measured eNO, eCO, and nNO levels simultaneously in bronchiectatic patients with PCD and compared these values with those obtained from age matched healthy subjects, and patients with non-PCD bronchiectasis, with and without cystic fibrosis (CF). We included bronchiectatic patients with CF because CF may present with symptoms of chronic inflammation of the upper and/or lower airways, similar to PCD. Furthermore, eNO and nNO levels are lower than normal not only in PCD, but also in CF.

METHODS

Subject characteristics

Four groups of subjects participated in the study (tables 1 and 2). Patients with bronchiectasis (PCD and non-PCD without CF) were recruited from the Host Defence Unit at the Royal Brompton Hospital and control subjects were recruited from staff members and examined at the Asthma Laboratory at the Royal Brompton Hospital, London. Bronchiectatic patients with CF were recruited from those attending an outpatient clinic for a scheduled visit at the National Korányi Institute for Pulmonology, Budapest and examined at the Department of Pathophysiology at the same institute. Patients had no evidence of exacerbations for at least 4 weeks before the study. PCD was proved clinically and confirmed functionally (saccharin test >60 min and abnormal ciliary beat frequency/dyskinetic beat pattern) and morphologically at the PCD clinic of the Royal Brompton Hospital. Patients with PCD had ciliary defects (dynein arm abnormalities, n=6; microtubular transposition, n=1, documented by electron microscopy of ciliary nasal epithelium obtained either by nasal brushing or biopsy).
Exhaled and nasal NO and exhaled CO levels in bronchiectasis with and without PCD

**Table 1** Mean (SD) subject characteristics

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex (M/F)</th>
<th>FEV1 (% predicted)</th>
<th>FVC (% predicted)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis</td>
<td>PCD (n=14)</td>
<td>Non-PCD Without CF (n=31)</td>
<td>With CF (n=20)</td>
<td></td>
</tr>
<tr>
<td>32 [2.8]</td>
<td>20/17</td>
<td>94 [0.8]</td>
<td>79 [0.4]</td>
<td>None</td>
</tr>
<tr>
<td>35 [4.6]*</td>
<td>8/6</td>
<td>51 [5.1]†</td>
<td>72 [4.2]†</td>
<td>0.62 [0.04]†</td>
</tr>
<tr>
<td>45 [5.1]*</td>
<td>16/15</td>
<td>58 [6.1]†</td>
<td>77 [3.1]†</td>
<td>0.65 [0.02]†</td>
</tr>
<tr>
<td>25.7 [2.4]</td>
<td>12/8</td>
<td>53 [5.9]†</td>
<td>74 [3.3]†</td>
<td>0.62 [0.04]†</td>
</tr>
</tbody>
</table>

PCD= primary ciliary dyskinesia; CF= cystic fibrosis; FEV1= forced expiratory volume in 1 second; FVC= forced vital capacity; IS= inhaled steroids; OS= oral steroids.

*p<0.05 v CF group; †p<0.05 v healthy control group.

**Table 2** Clinical characteristics of patients with bronchiectasis

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>PCD</th>
<th>Non-PCD Without CF</th>
<th>With CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic sputum production</td>
<td>12 [86]</td>
<td>23 [74]</td>
<td>14 [70]</td>
</tr>
<tr>
<td>Rhinosinusitis</td>
<td>13 [93]</td>
<td>3 [10]</td>
<td>11 [56]</td>
</tr>
<tr>
<td>Situs inversus</td>
<td>6 [43]</td>
<td>0 [0]</td>
<td>0 [0]</td>
</tr>
<tr>
<td>Infertility/subfertility</td>
<td>11 [79]</td>
<td>0 [0]</td>
<td>1 [5]</td>
</tr>
</tbody>
</table>

Data are given as number (%) of patients.

or primary ciliary disorientation (n=7, verified using a computerised improvision image analysis system). Bronchiectasis was diagnosed clinically and confirmed by high resolution computed tomographic (CT) scanning of the thorax in all patients. CF was confirmed by genetic analysis and a positive sweat test (chloride values >60 mM). Patients with atopy, asthma, or reversible (>12%) airway obstruction were excluded from the study. Normal control subjects had no history of chronic disease, were not receiving any regular medication, and had been free of respiratory infections for at least 6 weeks before the study. None of the subjects reported being current cigarette smokers or being exposed to smoke for more than 0.5 hours/day; this was confirmed by testing their urinary cotinine level with NicCheck I (DynaGen Inc, Cambridge, MA, USA).

**Statistical analysis**

Age, FEV1, and FVC values are given as mean (SE). Mediator values are expressed as median (range). Differences between groups were analysed non-parametrically using the Kruskal-Wallis test (p values of <0.0001 were considered significant). Pairwise comparisons using the Dunn’s multiple comparison test were then carried out. Spearman’s rank correlation was used to determine the relationship between variables. Mean ± 2SD values were calculated for nNO to obtain a cut off value for determining the specificity and sensitivity of the measurements. A p value of <0.05 was considered significant.

**RESULTS**

**Exhaled NO**

The concentration of eNO in patients with PCD and CF was significantly lower than that in healthy subjects (median (range) 2.1 (1.3–3.5) ppb; p<0.001 and 3.0 (1.5–7.5) ppb;
Patients with non-CF bronchiectasis (680 (310–1000) ppb) were not significantly different from those in normal subjects. Patients with non-PCD, non-CF bronchiectasis had significantly lower nNO levels than normal controls (343 (30–997) ppb; \( p<0.05 \)), compared with normal controls. Bronchiectatic patients with CF also had significantly higher NO values than those of the normal control group (\( p<0.001 \)).

**Exhaled CO**

Levels of eCO were significantly higher than normal in all patient groups (bronchiectasis with PCD: 4.5 (3–24) ppm, \( p<0.001 \); non-PCD, non-CF bronchiectasis: 5 (3–15) ppm, \( p<0.001 \); CF: 5.3 (2–23) ppm, \( p<0.001 \); controls: 3 (0.5–5) ppm). No differences in eCO values were seen between the different groups of patients (fig 1). There were a few outliers in eCO data (24 ppm in the PCD group, 19 and 23 ppm in the CF group) so the results were also analysed without these values, giving the following results: PCD patients: 4 (3–8) ppm, CF patients: 5 (2–11) ppm; the values in both groups were significantly higher than those of the normal control group (\( p<0.01 \) and \( p<0.001 \), respectively). No significant difference was detected between patients with and without steroid treatment.

**Sensitivity and specificity of the measurement of eNO and nNO**

The sensitivity of eNO measurement in selecting PCD patients (number of PCD patients with low eNO reading/number of all patients with PCD in the population) was 79% when a cut-off value of 2.4 ppm was chosen. The specificity of eNO measurement (number of non-PCD bronchiectatic patients with negative test/number of all non-PCD bronchiectatic patients) at this cut-off value was 85%. The predictive value of a positive test (PPV; percentage of PCD patients with a positive result) was 69% and the predictive value of a negative test (NPV; percentage of patients with a negative test result from those who did not have PCD) was 94%.

The sensitivity of nNO measurement was 93% and the specificity was 95% when the mean – 2SD of the nNO level in healthy subjects (187 ppb) was used as a cut-off value (only two patients with CF had a value below the cut-off level). The PPV of nNO measurement was 87% and its NPV was 97% in discriminating between PCD and non-PCD bronchiectatic patients.

If a positive result was described as low values in both eNO and nNO readings together in the same patient (eNO <2.4 ppb + nNO <187 ppb), this identified PCD patients with a specificity of 98%, PPV of 92%, and NPV of 93%.

**Correlations between variables**

There was no correlation between lung function and eNO, nNO, or eCO values either when data were pooled or when data from steroid treated and non-treated subgroups were analysed separately or different subject groups were analysed separately (data not shown).

**DISCUSSION**

We have assessed the clinical usefulness of the simultaneous measurement of eNO and nNO in discriminating between PCD and other types of bronchiectasis. The reported specificity and sensitivity of the simultaneous measurements suggest that their combined use can be a valuable non-invasive screening tool for PCD. The measurement of nNO by itself has good diagnostic value. However, if a low nNO value is observed, determination of eNO and the combined evaluation of the two test results improves the diagnostic value by increasing its specificity and PPV. The measurement of eNO, however, cannot be used by itself for this purpose because of its low sensitivity and PPV. This study shows for the first time...
that patients with PCD have lower nNO values than those with any other types of bronchiectasis. It also shows that eNO values are lower in patients with PCD than in those with non-PCD, non-CF bronchiectasis, although there is no difference in eNO values between patients with PCD and CF bronchiectasis.

In addition, we have shown that the eCO concentration is increased in patients with PCD to a similar extent to that in other types of bronchiectasis.

There was a significant difference in the mean age of the patients with CF and the other groups. This difference, however, probably did not influence our results because eNO and eCO values have been found not to be age related in adults. Furthermore, there was no evidence of any relation between age and nNO values. Some of our patients were treated with inhaled and/or oral steroids, but we could not detect any difference in eNO and eCO levels between patients with or without this treatment. Corticosteroids have been shown to reduce eNO levels profoundly in asthmatic patients and to decrease nNO levels in patients with allergic rhinitis. However, in patients with chronic suppurative upper and/or lower airway inflammation the results are somewhat contradictory. No difference was found in the eNO level between steroid treated and non-treated patients with CF, while in patients with bronchiectasis one study showed a difference in the eNO level but another did not. Differences between the results of these studies can be explained by differences in the techniques used for eNO measurement and by the fact that all of these studies (including the present one) were cross-sectional. Prospective follow up studies are required to investigate the possible influence of steroid treatment on eNO values in bronchiectatic patients.

Because nasal symptoms (nasal polyps, sinusitis, persistent serous otitis media) are the main presenting features of PCD, it is important to consider the diagnosis of PCD in these cases. Could the measurement of nNO and eNO help to exclude PCD as an underlying cause of chronic upper airway symptoms? Nasal NO levels are extremely low in PCD. However, low NO levels are also found in patients with chronic rhinosinusitis and may therefore influence the diagnostic value of nNO measurement in discriminating between patients with PCD and those with rhinosinusitis from other causes. Although not specifically investigated in the present study, subjects with non-PCD, non-CF upper airway and sinus diseases had normal NO levels in the lower airways. The use of the combination of eNO and nNO measurements would therefore still have good specificity in identifying PCD.

In contrast to the results on NO levels, we found that eCO levels were raised in all patient groups studied compared with controls, with no difference between different conditions. In chronic airway infections increased HO-1 protein expression may result from the induction of the enzyme by inflammatory mediators such as interleukin-1β, tumour necrosis factor-α, interferon-γ and hydrogen peroxide (H₂O₂) present in the inflamed airways. HO-1 may be induced in various cells in the respiratory tract, including airway macrophages, epithelial cells, and infiltrating inflammatory cells such as neutrophils. In the present study there was no correlation between eCO levels and FEV₁. This is not surprising as the decrease in FEV₁ may be the result of structural changes due to repeated inflammation while increased eCO levels are more closely linked with the ongoing inflammatory process. Increased CO production may have multiple functions in the airways including antioxidant, pro-inflammatory, and anti-inflammatory effects.

The finding that eCO is increased equally in different inflammatory airway diseases including asthma, bronchiectasis, and CF suggests that CO production has a profound link with inflammatory processes regardless of their atopic or non-atopic nature.

In conclusion, this study has shown that combined measurement of eNO and nNO levels discriminates between bronchiectatic patients with PCD and those with bronchiectasis from other causes, which suggests that this measurement can be used as a non-invasive screening tool for PCD. On the other hand, increased levels of eCO found in all patient groups indicate that the activation of CO production is generally involved in these airway conditions.

References


LUNG ALERT

Thrombolysis for submassive pulmonary embolism

This was a randomised placebo controlled trial of alteplase (100 mg over 2 hours) with heparin vs placebo with heparin in 256 patients with submassive pulmonary embolism (PE) defined as echocardiographically detected PE; pulmonary artery hypertension with confirmation of PE by spiral computed tomography (CT); precapillary pulmonary hypertension with confirmation by CT; or new electrocardiographic signs of right ventricular strain followed by CT. Exclusion criteria included age >80 years, haemodynamic instability, and presentation more than 96 hours after onset of symptoms. In the alteplase group there was less escalation of treatment (p=0.004) and a greater chance of 30 day event free survival (p=0.005). There was no difference in mortality or adverse events between the two groups.

This is the largest trial of thrombolysis in PE ever conducted, and it looks at the controversial group of patients with submassive PE showing significant benefit of alteplase. The absence of haemorrhagic complications was surprising.

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Variations in mortality in acute COPD may reflect nihilism as well as resources

I read with great interest the paper by Roberts et al. and the accompanying editorial by Rudolf. The study highlights important variations in the outcomes of patients with a common chronic disease, and once more illustrates that doctor-patient ratios may be an important contributor to this. It is also likely that some of the observed variation may arise as a result of variations in decision making by individual clinicians.

A recent study carried out in the eight hospitals in the Heart of England Critical Care network interviewed 98 clinicians who made end-of-life decisions for patients with chronic obstructive pulmonary disease (COPD). Each had made a median of 10 end of life decisions for COPD patients in the previous 12 months. There was considerable variability in the decision whether or not to admit identical patients to the critical care unit, with those choosing not to admit patients forming very pessimistic predictions of outcome compared with clinicians who would admit. It seems possible that poor outcomes for patients with COPD may not simply reflect a lack of resources, but also therapeutic nihilism that may have grown up over the years in response to the cognitive dissonance that arose when beds in critical care units could not be found for COPD patients in extremis. It seems likely that reversing variations in outcome will require both changes in resources and changes in clinicians’ expectations. In this respect, the GMC guidance on withholding and withdrawing life prolonging treatments may well be helpful, particularly section 20 which recommends that ‘where there is a reasonable degree of uncertainty about the appropriateness of providing a particular treatment, treatment which may be of some benefit to the patient should be started until a further assessment can be made’. The Heart of England Critical Care network study over one third of clinicians would not admit a 75 year old COPD patient with single organ respiratory failure, yet in a recent study of over 3700 admissions of COPD patients of median age 67 years to UK intensive care units, those with single organ respiratory failure had a hospital survival of over 70%.

It is important that chest physicians continue to advocate for COPD patients admitted as emergencies, and take every opportunity to point out to their colleagues in general medicine and intensive care how well patients with COPD can do with both invasive and non-invasive ventilation.

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References

Authors’ reply

We thank Dr Wildman for his letter suggesting a further possible reason for the variation in outcome that we reported for the acute care of COPD patients in different hospital centres. In a further unpublished multiple regression analysis of the RCP/BTS 2001 audit we found that 26% of the variation in the outcome of death at 90 days following admission could be accounted for by factors measured in the study that included patient characteristics such as performance status and resource and organisational issues, as described in our paper. Dr Wildman suggests that individual clinicians might vary in determining admission to the ITU for COPD patients in respiratory failure, and suggests that respiratory physicians need to be advocates for their patients in this arena. Attitudes and beliefs in what might be achieved are important but are difficult to measure in clinical practice. They might account for some of the variation in outcome but, if so, the therapeutic nihilism would have to vary systematically between whole hospitals to be a factor in our study. Admission to the ITU depends on more than the individual attitude of the referring doctor. A lack of availability of beds may raise thresholds, and an institutional nihilism within the ITU may lead to rejection of suitable patients.

Perrin et al. reported a study in which questionnaires regarding initiation of mechanical ventilation in end stage COPD patients were completed by 150 doctors subdivided by speciality (intensivists, respiratory specialists and other physicians). As in the paper by Wildman et al., there was considerable individual variation in decision making but no overall difference between the three types of specialist studied. However, no analysis by hospital or trust was made to identify local patterns. We believe all respiratory physicians will share Dr Wildman’s call that referring physicians should be advocates for their patients, and this has to be matched by a willingness of the ITU staff to accept such patients and the availability of beds within an ITU/HDU facility to accommodate them. Perrin’s paper provides hope of a generic match although individual disagreements may still occur. It is, however, not only admission to the ITU that matters, as in many hospitals non-invasive ventilatory support is provided on general wards by respiratory units without input from intensivists. In the BTS/RCP 2003 national audit of the acute care of COPD patients, 95% of all acute admitting sites have now registered to participate and data collection is nearing completion. Within the clinical data gathering there is a question that attempts to document clinical decision making when a patient eligible for ventilation on blood gas criteria does not receive ventilatory support. In addition to this, data on available resources such as ITU beds, bed occupancy, and numbers of ITU candidates transferred off site will be recorded. We may be in a position to shed further light on the issues of individual versus institutional nihilism or rationing in due course.

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References

Do inhaled corticosteroids slow FEV1 decline in COPD after all?

I question the findings of the meta-analysis by Sunderland et al. and the content of the associated editorial by Burge and Lewis. The meta-analysis has drawn from available long term data from randomised controlled studies (RCTs) of inhaled corticosteroids (ICS) in chronic obstructive airways disease (COPD). The whole purpose of meta-analysis is to synthesise such data systematically to answer a question. This study seems to use the data selectively to demonstrate an effect. Another recent meta-analysis—in my opinion properly conducted—drew on the same studies and reached the opposite conclusion. The fact is that four long term, adequately powered RCTs have examined the effect of ICS, and all of these studies failed to show an effect of ICS on the primary outcome measure of decline in forced expiratory volume in

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Ethics of placebo controlled studies of inhaled steroids for COPD

The meta-analysis by Sutherland et al 1 of the effect of inhaled corticosteroids on the progression of airflow limitation in patients with chronic obstructive pulmonary disease (COPD) found a small improvement in forced expiratory volume in 1 second (FEV1) of 7.7–9.9 ml in FEV1 decline compared with placebo. This is not used in the UK. Fluticasone is the opposite? We need better data to do more long term trials: surely the conclusion is the opposite? We need better data to justify the widespread use of ICS in COPD.

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References
2 Burge PS, Lewis SA. Inhaled corticosteroids, the rate of decline of FEV1 in patients with COPD after all? Thorax 2003;58:911–3.
6 Burge PS, Lewis SA. So inhaled corticosteroids slow the rate of decline of FEV1 in patients with COPD after all? Thorax 2003;58:911–3.

Authorsʼ reply

To make randomised controlled studies ethical, the investigator must believe that neither treatment is known to be superior to the other. If the trial is to be placebo controlled, the investigator must believe that no non-allowed treatment is known to be of benefit. Both Drs Duerden and Hahn want more placebo controlled trials of inhaled corticosteroids (ICS) in COPD before they recommend their use. It is important to point out that ICS were of established benefit in reducing exacerbations of COPD, so any future placebo controlled study would need to be in patients without a history of exacerbations. As exacerbations are associated with disease severity, and as about 80% of patients with an FEV1 < 50% predicted have at least one exacerbation over a 3 year period, any trial would need to be in those with early disease. The Copenhagen City Lung Study found that inhaled budesonide 800 μg/day had no benefit in a population of smokers in whom exacerbation led to a reduced FEV1/FVC ratio, the majority of whom had an FEV1 above 80% predicted. This leaves the group with an FEV1 between 50% and 80% predicted, many of whom have not been identified by their medical practitioners. This was the group included in the EUROSCOP and Lung Health 2 studies, where the results included in the meta-analysis were the most divergent, probably because of the relatively low dose of ICS used in the Lung Health study. In the symptomatic patient with more severe disease, the combination of a long acting β2 agonist and an ICS has been shown to be superior to either alone and is now the treatment of choice. This leaves the symptomatic population in whom a decline in FEV1 is the only practical outcome measure. No randomised study using an intention to treat analysis has shown a reduction in FEV1 decline with ICS therapy in any disease, including ICS in asthma, although several studies have shown an improvement in FEV1 in COPD. * * * Our editorial tried to explain why changes in FEV1, decline with ICS therapy, are not shown in patients with COPD. Patients with progressive disease are likely to be given ICS by their clinicians outside any trial, reducing the power of any study. Any treatment should weigh the potential risks against any benefit Dr Duerden wants a better analysis of the risks of ICS in patients with COPD, particularly related to bone loss, and points out the reduced bone mineral density in the triamcinolone group in the Lung Health 2 study. The reported results are in 359/412 of a convenience sample who had three measurements of bone density. After 3 years the lumbar spine density decreased from 0.976 g/cm2 to 0.958 g/cm2 (P = 0.006), and the femoral neck from 0.762 to 0.747 g/cm2 in the triamcinolone group. EUROSCOP studied bone density measurements in 194 subjects and showed very small changes which were significantly less at the femoral neck in the budesonide group (0.04%/year vs 0.36%/year in the placebo group). Randomised controlled studies are probably not the best method for assessing the extent of long term adverse effects, but the evidence from the randomised studies to date shows that the risks are relatively minor compared with the risks of death from the natural progression of the disease. Introducing ICS at an earlier stage may alter the risk/benefit ratios. The adverse effects on the bones are probably best studied in asthmatics of whom many are already taking long term ICS in equivalent dose.

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Delay in diagnosis of OSAHS

We very much enjoyed the first paper in the review series on sleep and admired Stradling and Davies’s honest appraisal of the current difficulties in defining disease and the lack of a relationship between symptoms and the results of investigations. One of the problems of truly determining the size of the health burden associated with the obstructive sleep apnoea/hypopnoea syndrome (OSAHS) is that much of the burden may occur before the diagnosis is made. Others have shown however that use of hospital resources and use of cardiovascular medication is high in those with undiagnosed obstructive sleep apnoea. We administered a questionnaire to 166 consecutive patients with diagnosed OSAHS on continuous positive airway pressure treatment and asked them to identify how long they could recall having symptoms at the time of diagnosis. In 155 cases (93.4%) someone had previously complained of the patient’s loud snoring and first mention of this had been made a median of 12 years (range 2–52) before diagnosis of OSAHS. In 84.3% of respondents excessive daytime sleepiness had been present for a median of 8 years (range 0.5–62) and 133 patients (80.1%) reported that their bed partner had witnessed apnoea a median of 8 years (range 1–49) before diagnosis. We also found that, of the 119 (71.7%) who were drivers, 26 (21.8%) reported at least one or more automobile crashes in the previous 5 years, with seven respondents having had two and one having had four.

These results suggest a lack of awareness of sleep related breathing disorders among the general population and probably among health professionals. The delay in diagnosis is likely to have significant effects on morbidity, and in recent preliminary work it has been shown that those with OASHS have structural changes to brain morphology compared with healthy controls. In addition to the health and quality of life benefits to the individual to be gained by prompt diagnosis, there are also economic aspects in favour of prompt diagnosis and treatment and early benefits in terms of driving performance.

References


Prophylactic antibiotic treatment of bronchiectasis with azithromycin

Once a treatable cause of bronchiectasis such as hypogammaglobulinaemia has been excluded, management largely involves physiotherapy and treatment of infective exacerbations with appropriate antibiotics. In a proportion of patients this is not adequate to prevent frequent infective exacerbations. Prophylactic antibiotic treatment can be used to try to prolong the exacerbation free period. This may be administered orally, via a nebuliser, or a regular regimen of intravenous antibiotics. Prophylactic treatment may be problematic due to side effects and development of antibiotic resistance. Macrolide antibiotics exhibit immunomodulatory properties. Long term low dose erythromycin has been shown in diffuse panbronchiolitis, a disease with some similarities to idiopathic bronchiectasis, to be effective in controlling chronic suppurative airways disease. Recently published research has shown benefits of long term azithromycin treatment in patients with bronchiectasis. These results led us to consider using azithromycin as prophylaxis in patients with non-cystic fibrosis bronchiectasis with frequent infective exacerbations. Patients attending the outpatients department between February 1999 and April 2002 who fulfilled the following criteria were considered for azithromycin prophylaxis:

- bronchiectasis defined by CT scan;
- any causal condition had been treated if possible;
- general management optimised;
- >4 documented infective exacerbations requiring oral or intravenous antibiotic treatment during the last 12 months;
- Pseudomonas aeruginosa respiratory infection, if present, had not responded to nebulised antibiotic prophylaxis or this had not been tolerated;
- failure to control chronic symptoms.

Exclusions included allergy to macrolides and abnormal liver function tests. The mean study length was 30 months (range 12–60). All patients had been on a long term antibiotic prophylaxis regime with no change in dosage, in two new inhaled corticosteroids with no change in dosage, in two new inhaled corticosteroids with no change in dosage, and one patient was given a short 7 day reducing course of oral prednisolone for a discoid eruption. All patients were on a regular 1 day reducing course of oral corticosteroids. The mean (SD) length of time taking azithromycin, excluding those who stopped because of side effects, was 20 (10.1) months (range 4–38). Twenty six patients are continuing with the prophylaxis at the present time; in the other seven treatment was discontinued because of improvement in their condition.

Changes in bronchiectasis were assessed on a 0 (no growth) to 4 (massive growth) scale. At the time of diagnosis a total of 270 episodes had been documented of side effects: abnormal liver function tests (n = 2), diarrhoea (n = 2), rash (n = 1), and tinnitus (n = 1). All occurred during the first month of treatment. Other side effects experienced were mild and mainly gastro-intestinal. Five patients were on long term oral corticosteroids with no change in dosage, in two new inhaled corticosteroids with no change in dosage, in two new inhaled corticosteroids with no change in dosage, and one patient was given a short 7 day reducing course of oral prednisolone for a discoid eruption. All patients were on a regular 1 day reducing course of oral corticosteroids. The mean (SD) length of time taking azithromycin, excluding those who stopped because of side effects, was 20 (10.1) months (range 4–38). Twenty six patients are continuing with the prophylaxis at the present time; in the other seven treatment was discontinued because of improvement in their condition.

Of the 113 patients who had no growth (n = 18), P aeruginosa (n = 5),

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Early life antibiotics and asthma

Cullinan et al. present interesting data on the association between exposure to antibiotics in early life and the subsequent expression of atopy and asthma. In keeping with other studies, they report a positive association between antibiotic receipt over the first 5 years of life and asthma. The association was, however, largely accounted for by factors such as sex, smoking, and parental history of asthma. It seems likely from the data presented that antibiotic exposure did not play a major causal role in promoting the asthma phenotype over 30 years ago when both the prevalence of asthma and antibiotic prescribing to young children were significantly less than they are now, but the question of whether it may now be significant and potentially modifiable factor remains unanswered.

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References


Recurrent of acute respiratory failure following use of waterproofing sprays

Between January and March 2003 six patients were admitted to hospital in the Lausanne area of Switzerland with acute respiratory failure following use of a waterproofing spray for clothes and leather. Within hours of exposure all patients developed a dry cough and rapidly progressive dyspnoea. The clinical picture included severe hypoxaemia, increased white blood cell count, raised C-reactive protein, and reduced carbon monoxide levels.

S aureus (n = 1), S pneumoniae (n = 1), not done (n = 10). In three patients who had cultured P aeruginosa before starting azithromycin prophylaxis the organism was not recultured at follow up.

In the 33 patients completing at least 4 months treatment there was a statistically significant reduction in infective exacerbations requiring oral antibiotics from a mean of 0.71 per month to 0.13 per month (p < 0.001). There was also a reduction in the requirement for intravenous antibiotics from a mean of 0.08 courses per month to 0.003 courses per month (p < 0.001). Subgroup analysis of patients with P aeruginosa isolated before starting azithromycin prophylaxis showed no difference compared with all patients included (p = 0.22). Twenty five patients had lung function tests before and after at least 4 months of treatment (range 4–20 months). There was an improvement in all lung function parameters but the improvement in carbon monoxide transfer factor (T LCO) was the only one to reach statistical significance (p = 0.01).

Wheeze 2.6 0.8 0.14 0.011
Exercise tolerance 3.8 0.9 0.16 0.002
Sputum consistency 2.5 0.6 0.11 0.006
Cough 2.4 0.7 0.12 0.001
Fatigue 2.1 1.0 0.18 0.001
Symptoms scored on a 5-point scale: 1 = large decrease, 2 = decrease, 3 = no change, 4 = increase, 5 = large increase in symptoms.

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Table 1 Change in symptoms while taking azithromycin prophylaxis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spumon volume</td>
<td>1.6</td>
<td>0.8</td>
<td>0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spumon colour</td>
<td>2.1</td>
<td>0.7</td>
<td>0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spumon consistency</td>
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<td>0.11</td>
<td>0.006</td>
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<td>1.0</td>
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<td>0.001</td>
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<td>0.9</td>
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<td>0.002</td>
</tr>
<tr>
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<td>0.8</td>
<td>0.14</td>
<td>0.011</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>2.3</td>
<td>0.7</td>
<td>0.13</td>
<td>0.002</td>
</tr>
</tbody>
</table>

References


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patients were admitted to hospital in the
consumers. During the same period five
were withdrawn before they reached the
tributed in Germany, the Netherlands, and
had been reported in the previous 7 years.

related to waterproofing sprays were reported
were withdrawn from the market at the
respiratory symptoms in October 2002 and
solvent. Consumers started complaining of
solvent had to be replaced with a heptane
manufacturer of the fluorinated resin chan-

negative.

mycoplasma were performed on two patients
following exposure, the diffuse ground glass
of the sudden occurrence of symptoms
inhalation of the waterproofing spray in view
predicted value) could be seen for more
dual dyspnoea and reduced T LCO (80%
of
sparing the subpleural areas (fig 1). Every
diffuse bilateral ground glass opacities on
opacities after using industrial waterproofing
nebulisers. That air pollution, and specifically particles,
are harmful to health is well accepted,\(^1\)
causes such as lung inflammation
resulting in exacerbations of lung and cardiac conditions \(^1\)
and being associated with an increased risk of mortality.

Effect of PM\textsubscript{10} on H influenzae and S pneumoniae

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In the first experiment the number of viable cells increased progressively and in the expected pattern over time (fig 1A and B), whether in the presence or absence of PM$_{10}$ for both H influenzae and S pneumoniae. In the growth kinetics experiment the only consistent finding was an inhibition of growth at a PM$_{10}$:broth medium dilution of 1:1 compared with the PM$_{10}$ free control.

Growth of H influenzae and S pneumoniae is therefore neither inhibited nor promoted by incubation with PM$_{10}$ at concentrations of diluted particles which are known to be able to exert pro-inflammatory effects in vitro. There was a constant inhibitory effect at a PM$_{10}$ dilution of 1:1, possibly due to the particles themselves or to dilution of the broth by the added saline. These findings suggest that the association of air pollution with hospital admissions for exacerbations of COPD and for pneumonia is probably not mediated through direct promotion of bacterial growth. If particles alone are responsible for these effects, they are likely to be mediated by particles causing lung inflammation, thus encouraging penetration and growth of bacteria in the respiratory tract. Alternatively, gaseous pollutants may be responsible for the epidemiological findings, either directly or in conjunction with particles. This interactive mechanism is supported by the association of ambient nitrogen dioxide levels with admissions for croup, and is analogous to the potentiation of the airway response to inhaled allergen by both nitrogen dioxide and ozone. Finally, it is possible that the particles have an effect on bacterial virulence and toxin production rather than growth. This possibility has not been tested here but warrants further study.

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References
6. Tunnicliffe WS, Burge PS, Ayres JG. Effect of domestic concentrations of nitrogen dioxide on nasal NO and exhaled CO concentrations in normal subjects, patients with primary cell dyskinesia (PCD) with documented bronchiectasis, and patients with non-PCD bronchiectasis with and without CF. The Kruskal-Wallis test showed significant differences between mediator levels (p<0.0001).

CORRECTIONS
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PAPER BY BALDI ET AL (THORAX 2004;59:428–32)

In the paper entitled “Prognostic significance of cyclooxygenase-2 (COX-2) and expression of cell cycle inhibitors p21 and p27 in human pleural malignant mesothelioma” by A Baldi, D Santini, F Vasaturo, et al published in the May 2004 issue of Thorax (2004;59:428-32) there was an error in the sentence beginning on line 14 of the left hand column on page 430. The sentence should have read “The median survival in patients with low p21 or p27 expression was shorter than in those with high p21 or p27 expression.” The publishers apologise for this error.