Risk factors for death from asthma

Guite and colleagues recently attempted to identify risk factors for certain causes of death among patients admitted to hospital with asthma. The data were originally collected for a different purpose, however, and problems of data quality and completeness limit the conclusions that can be drawn from this analysis.

The current study is based on follow up of 2242 (68%) of the original cohort of 3292 patients. An expert panel identified 22 patients who died from asthma, 21 from COPD, and 21 cardiovascular deaths. Because both papers relied on the same expert panel, these discrepancies raise fundamental questions about the interpretation of this paper.

The fact that drugs are prescribed to patients who differ according to baseline risk poses an extraordinary methodological challenge to any epidemiological study. Guite and colleagues concluded that “ipratropium bromide is associated with increased risk of death from asthma even after adjustment for a range of markers of COPD.” Even after including extra deaths not identified by the expert panel as asthma deaths and controlling for a marker of COPD co-morbidity but for no markers of asthma mortality, the 95% confidence interval for the odds ratio for ipratropium bromide and death from asthma is extremely imprecise (1.2 to 11). Reducing the number of cases to the original 22 asthma deaths identified by the expert panel and controlling for validated markers of asthma mortality would only further degrade the precision of this estimate.

Boehringer Ingelheim has marketed ipratropium bromide for 25 years and its impressive safety profile has been firmly established by hundreds of randomised, controlled studies and epidemiological studies evaluating tens of thousands of patients. Limitations of the current data—understandable from the fact that the study was not originally designed to meet this challenge—preclude them from providing a reliable empirical basis for suggesting an adverse effect of ipratropium.

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AUTHORS’ REPLY We understand the concern that representatives of Boehringer Ingelheim have expressed about the interpretation of our paper which finds an association between prescription of ipratropium and death among asthmatic patients. In the paper we were also cautious about the interpretation and stated that “the ratio of information to cases is high and therefore results should be regarded as preliminary and should be tested in a larger study”. There are, however, a number of issues that deserve additional comment. They state that this study was not originally designed to address cause of death among patients admitted to hospital for asthma. The original study plan was always to conduct such a study. Our first report of the cohort described the identification of the cohort and established the accuracy of classification of cause of death. The focus of this paper on establishing the accuracy of recording of cause of death on the death certificates by an expert panel explains why only 22 deaths were discussed. Seven further patients who were certified as having died from asthma were not reviewed by the expert panel as there was insufficient further information on which to base a different opinion than that given on the death certificate (table 1). However, the high specificity of the diagnosis on the death certificates that were studied leads us to believe that assigning these seven deaths to death from asthma, as on the certificate, is reasonable. As we are concerned with deaths from any cause, this is not a critical issue.

Lanes and Wilson assume that the cohort consisted of 2392 people, but this refers to all admissions including re-admissions. The cohort consisted of 2392 individuals, as stated in both papers, and follow up information was available for 2242 (94%). They are concerned that the risk estimates might be confounded by the severity of the disease. Although this is possible, we believe that their argument is misdirected. Most studies of asthma deaths have looked at death due to asthma as defined on the death certificate (table 1). This association is real and, if so, how it might be explained.

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Nebulised taurodilin and B cepacia bronchiectasis

We have already reported a unique case of bronchiectasis with chronic colonisation by UK epidemic (ET12) Burkholderia cepacia in a previously well woman which developed following an acute infection acquired from her two B cepacia colonised children with cystic fibrosis. This has intermediate sensitivity to only co-trimoxazole and ceftazidime and, despite several intravenous courses of these antibiotics, the patient has remained chronically colonised for more than four years. We have therefore looked for other antibiotics which may have action against this multidrug resistant pathogen. Taurodilin acts by disrupting the cell wall, diminishing bacterial adherence, and neutralising toxins. It has good in vitro anti-B cepacia activity (MIC 0.4 mg/ml) but is currently used as an aminoglycoside combined with colistin. We gave nebulised taurodilin to our non-cystic fibrosis patient in a randomised, double blind, placebo controlled, crossover fashion (“n-of-1 trial”) to assess its effect on her chronic respiratory B cepacia colonisation (primary outcome measure), spirometric tests, and inflammatory markers (serum and sputum concentrations of interleukins 6 and 8, C
reactive protein, total white cell count, erythrocyte sedimentation rate) (secondary outcome measures). She was given 4 mL 2% taurodilone twice daily in the active arm and 4 mL 0.9% saline twice daily in the placebo arm, each for four weeks separated by a two-week washout period. Every two weeks sputum counts of B cepacia (colony forming units/ml) were determined by two independent microbiologists blinded to each other’s results; concordance between them was >95%. A bioassay was performed on the sputum by agar diffusion to confirm that taurodilone was not active. There was no change in the placebo arm (fig 1). The only side effects noted during taurodilone treatment were transient mild pharyngitis and cough. There was no difference in geometric parameters or inflammatory markers between the active and control arms. No changes in medication occurred during the trial.

UK epidemic (ET12) B cepacia is innately resistant to many antibiotics and therefore the discovery of a different antimicrobial agent that has activity against this organism is important. Whilst a pilot study of taurodilone in patients with cystic fibrosis suggested that it may reduce colony counts, in a formal double blind placebo controlled crossover trial the results were disappointing. However, in our non-cystic fibrosis patient B cepacia disappeared from the sputum within two weeks of commencement of treatment and remained absent for two weeks after treatment stopped. Dilutional studies showed no taurodilone activity in the sputum samples so recurrence of the organism in sputum after cessation of treatment may reflect recolonisation from her children or spread of residual colonisation in her upper respiratory tract. The apparent difference between the effect of taurodilone in this formulation in our patient and in patients with cystic fibrosis raises interesting questions as to the mechanisms by which B cepacia survives in subjects with cystic fibrosis. These include the presence of a biofilm and intracellular survival of organisms allowed by the defective CFTF protein.

The current formulation of taurodilone uses povidone as a solubilising agent which improves its efficacy in patients with cystic fibrosis.

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Figure 1 Effect of treatment with taurodilone on colonisation with Burkholderia cepacia in a non-cystic fibrosis patient.

Effect of salmeterol on airway eosinophils

Dente et al. used the examination of induced sputum cell counts (as well as sputum eosinophil cationic protein (ECP), blood eosinophils and serum ECP) to examine the inhibitory effects of a single dose of placebo and salmeterol on allergen induced inflammatory (as well as asthmatic) responses. They performed a crossover randomised study in 11 subjects who had two allergen challenges four weeks apart and found that salmeterol inhibited the allergen induced increases in sputum eosinophils but had no effect on the other inflammatory parameters.

The results differ from the negative results reported by us and Dante et al. attribute this to differences in study design. We agree with this explanation but not for the reasons given. Their study design has a major flaw in the use of only one baseline measurement to investigate two distinct interventions four weeks apart. The time of baseline measurements in relation to the randomised crossover design study was not given; we presume that it was at some appropriate point before the first allergen challenge. It will therefore be relevant only for half of the subjects. This design therefore ignores a basic rule of the randomised crossover trial—namely, to provide evidence that the baseline measurements of the outcome of interest before each challenge are similar. The absence of a baseline measurement is even more crucial in their study because there was a wide variation in the baseline proportion of sputum eosinophils and the randomisation of subjects was not performed after stratification for this.

Therefore the claim cannot be made that salmeterol prevents sputum eosinophilia because there were no baseline measurements in at least half of the subjects to prove or disprove this assumption.

The authors suggested that differences between their results and ours may be due to the fact that we performed four allergen challenges and four hypertonic saline inductions for each allergen and say that “this could have resulted in a progressive increase in airway inflammation in each subject during the progression of the study, leading to a more persistent eosinophilic inflammation and consequently to the low repeatability reported by these authors in sputum eosinophil percentages measured before each allergen challenge.” Although a small change in airway inflammation can be induced by repeated hypertonic saline challenges, this statement has three inaccuracies. Firstly, in our study the repeated allergen challenges did not lead to a progressive sputum eosinophilia as can be clearly seen in fig 4 which shows individual values of sputum eosinophil percentages before and after each intervention. Secondly, the authors incorrectly translate the baseline period variations in sputum eosinophils as “low repeatability”. This was not a repeatability study but an intervention study. Repeatability refers to, and reflects, the amount of error both random and systematic inherent in any measurement. Our study shows that the method of sputum examination we used is responsive to longitudinal changes, which occurring by regression to the mean after an intervention. Finally, the study by Holz et al. refers to the effect of repeated inductions on neutrophils and not eosinophils, a point which is irrelevant to the interpretation of the results of our study.


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conditions; this assumption is used to consider unchanged cell counts in spum in two tests with hypertonic saline performed under the same conditions except for allergen challenge or premedication as intervention; (2) it is a good rule to perform only a few challenge tests as it is less likely that the character-istics of the subjects will change if they are examined over a short period of time than when they have to perform many tests over a longer period of time. We have previously reported an influence of the shortness of the time interval between two subsequent aller-gen challenges. Moreover, the number of subjects in our study was adequate to study a difference in spum eosinophils due to an intervention, as calculated by power analysis, but the number was too small to permit stratification for spum eosinophils in the baseline evaluation.

In the second part of their letter Pizzichini et al quote from our paper that differences between their results and ours may be due to the large number of challenges that each patient performed in their study. Our sentence referred directly to the large number of allergen challenges. In fact, if a lot of allergen challenges are performed over a short time there will probably be a worsening of asthma symptoms and late asthmatic response, and consequently an increase in the airway inflammation. If the large number of allergen challenges is performed over a longer period of time with an adequate interval between subsequent allergen challenges, there is a greater probability that different conditions will occur as a result, for example, of respira-tory infections or allergen exposure, and consequently a poorer repeatability is likely.

Finally, we think that the calculation of repeatability evaluating the baseline series of data in the study by Pizzichini et al is correct. In fact, if similar conditions are maintained, having two or more different series of data of the same component is good for performing repeatability tests (as performed in our study).

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NOTICES

ARTP Millenium Meeting

The Association for Respiratory Technology and Physiology (ARTP) Millenium Meeting will be held on 10–12 February 2000 at The Hanover International Hotel & Club, Davent-ry, Northamptonshire NN11 5SG, UK and will include keynote speeches on Smoking Cessation and Pulmonary Vascular Disorders and plenary sessions on Thoracic Surgery, Sleep Breathing Disorders, Exercise and Respiratory Medicine, and Allergy. There will also be poster presentations from successful submitted abstracts. The meeting has been approved for CME accreditation. For further information and registration forms contact the ARTP Secretariat on 0121 622 3644; email: uccbham@compuserve.com

Scadding-Morriston Davies Joint Fellowship in Respiratory Medicine 2000

This fellowship is available to support visits to medical centres in the UK or abroad for the purpose of undertaking studies related to respi-ratory medicine. Applications are invited from medical graduates practising in the UK, including consultants and irrespective of the number of years in that grade. There is no application form but a curriculum vitae should be submitted together with a detailed account of the duration and nature of the work and the centres to be visited, confirming that these have agreed to provide the facilities requested. Please state the sum of money needed for travel and subsistence. A sum of up to £15 000 can be awarded to the successful candidate, or the sum may be divided to support two or more applications. Applications should be sent to Dr I A Campbell, Secretary to the Scadding-Morriston Davies Fellowship, Llandough Hospital, Penarth, Vale of Glamorgan, CF64 2XX by 31 January 2000.

The Dr H M (Bill) Foreman Memorial Fund

The Trustees of the Dr H M (Bill) Foreman Memorial Fund invite applications for grants relating to study in respiratory disease. Limited funds are available for registered medical practitioners to assist in travelling to countries other than their own to study respiratory disease, and also for support for clinical research abroad. Intending applicants should write for further details to Dr Brian H Davies, Llandough Hospital, Penarth, Vale of Glamorgan CF64 2XX, UK.