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LOW DOSE INHALED CORTICOSTEROIDS AND THE PREVENTION OF DEATH FROM ASTHMA

J C Kips, R A Pauwels

Introductory article

Low-dose inhaled corticosteroids and the prevention of death from asthma

S Suissa, P Ernst, S Benayoun, M Baltzan, B Cai

*Background: Although inhaled corticosteroids are effective for the treatment of asthma, it is uncertain whether their use can prevent death from asthma. Methods: We used the Saskatchewan Health data bases to form a population-based cohort of all subjects from 5–44 years of age who were using antiasthma drugs during the period 1975–1991. We followed subjects until the end of 1997, their 55th birthday, death, emigration, or termination of health insurance coverage, whichever came first. We conducted a nested case-control study in which subjects who died of asthma were matched with controls within the cohort according to the length of follow-up at the time of death of the case patient (the index date), the date of study entry, and the severity of asthma. We calculated rate ratios after adjustment for the subject's age and sex; the number of prescriptions of theophylline, nebulized and oral beta-adrenergic agonists, and oral corticosteroids in the year before the index date; the number of canisters of inhaled beta-adrenergic agonists used in the year before the index date; and the number of hospitalizations for asthma in the two years before the index date. Results: The cohort consisted of 30,569 subjects. Of the 562 deaths, 77 were classified as due to asthma. We matched the 66 subjects who died of asthma for whom there were complete data with 2681 controls. Fifty-three percent of the case patients and 46% of the control patients had used inhaled corticosteroids in the previous year, most commonly low-dose beclomethasone. The mean number of canisters was 1.18 for the patients who died and 1.57 for the controls. On the basis of a continuous dose-response analysis, we calculated that the rate of death from asthma decreased by 2% with each additional canister of inhaled corticosteroids used in the previous year (adjusted rate ratio 0.79; 95% confidence interval 0.65 to 0.97). The rate of death from asthma during the first three months after discontinuation of inhaled corticosteroids was higher than the rate among patients who continued to use the drugs. Conclusions: The regular use of low-dose inhaled corticosteroids is associated with a decreased risk of death from asthma. (**N Engl J Med** 2000;343:332–6)*

ASTHMA AS AN INFLAMMATORY DISORDER OF THE AIRWAYS

As insight into the pathogenesis of asthma increases, so does the appreciation of the complexity of the disease. Detailed morphological analysis of asthmatic airways reveals a combination of acute inflammatory changes characterised by vasodilatation, increased vascular permeability and an influx of activated inflammatory cells, together with more chronic structural alterations, so-called "airway remodelling".[1] This process is thought to be largely orchestrated by allergen specific Th2 cells and to involve a wide range of inflammatory cells as well as structural tissue elements. However, the precise functional role of each of the cells and the mediators, cytokines, or growth factors they release within this inflammatory process needs to be examined further. In addition, it is still not clear exactly how the various components of this inflammatory process relate to the clinical and lung function characteristics of the disease.

It follows that the proper evaluation of a treatment strategy in asthma should not be based on a single outcome measure. Instead, several indices of disease activity should be assessed as they might all represent another aspect of the disease process and therefore respond differently to treatment. Ideally, this evaluation should include clinical markers that reflect short term disease control such as symptoms, baseline forced expiratory volume in one second (FEV_1), bronchial responsiveness, exacerbation rate, or disease related quality of life, in addition to a direct assessment of the degree of airway inflammation. This evaluation then needs to be complemented by the long term monitoring in large groups of patients of asthma related

Department of Respiratory Diseases, Ghent University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium
J C Kips
R A Pauwels

Correspondence to: Dr J Kips

johan.kips@rug.ac.be

mortality and health care utilisation elements such as hospital admissions or emergency department visits.[2]

Inhaled glucocorticosteroids in asthma

Most of the above mentioned data are available for inhaled steroids. Numerous studies consistently show in both children and adults that, compared with monotherapy with short acting inhaled β_2 agonists, inhaled steroids are superior at improving symptoms, lung function, bronchial responsiveness, and the quality of life,[3–6] as well as reducing the number of exacerbations.[7–11]

As confirmed by several biopsy studies, these clinical effects are accompanied by an effect on acute inflammation, with a reduction in plasma exudation and cellular influx as well as a more limited dose dependent effect on airway remodelling.[12–18]

Moreover, larger population studies indicate that the use of inhaled steroids protects against severe exacerbations requiring hospitalisation and reduces the likelihood of readmission or death following discharge from hospital.[19–22] Analysis of the Saskatchewan Health Insurance data indicates that treatment with inhaled steroids also diminishes the risk of fatal and near fatal asthma in the community.[23] The study by Suissa *et al* (introductory article) further strengthens this concept by establishing that the use of inhaled steroids is associated with a reduction in asthma related mortality.[24] This is in line with studies from the UK that have reported a reduction in asthma mortality in patients aged 65 years or less in conjunction with increased prescription of inhaled steroids.[25]

The confirmation that treatment with inhaled steroids is associated with reduced asthma related mortality in a large community survey obviously is of interest and further underlines the potential of inhaled steroids in the treatment of asthma. At the same time, this study raises a number of unanswered questions.

Mortality in asthma

Asthma related mortality is a rare event. The incidence over the past 30 years in industrialised countries has varied from <1 to 8 per 100 000 inhabitants per year.[26 27] Mortality in the USA has traditionally been lower than in European countries including the UK.[27] However, whereas in the UK a decrease in mortality has been observed in nearly all age groups from 1983 to 1995[25] despite the increase in the prevalence of asthma,[28] mortality in the USA has risen by 46% from 1980 to 1990.[29] In addition, the USA data indicate that asthma mortality continues to affect non-white subjects, urban areas, and the deprived population disproportionately.[30] It needs to be remembered that, even in these patient groups, the overall asthma related mortality is low compared with other pulmonary diseases such as lung cancer or chronic obstructive pulmonary disease (COPD). Some studies have even questioned the impact of asthma on expected longevity.[31 32] Most studies, however, confirm that asthma is associated with increased mortality, mainly from respiratory diseases[33–36] including status asthmaticus and concomitant COPD.[31 33] Notwithstanding the potential for diagnostic inaccuracy,[37] this presumably reflects in large part the additional risk associated with cigarette smoking.[35 38]

From the description of cases of fatal and non-fatal asthma it appears that asthma deaths can be divided into two groups: a few cases experience a sudden attack without apparent worsening[39] but, in the majority, a more gradual deterioration leading to increasing airflow obstruction over a period of several hours to days has been observed.[40] The risk factors that have been identified relate mainly to this latter group and include environmental as well as patient and physician related factors.[41]

Exposure to high levels of outdoor allergens has been shown to increase the risk of respiratory arrest from asthma.[42] This might also explain the observation in Britain that the incidence of asthma related deaths in young patients shows a seasonal increase in the summer.[25] Although increased hospital admissions have been related to pollution, longer term studies do not support the relationship between mortality rate and the concentration of air pollutants.[43]

Probably more important than environmental factors are patient and physician related elements.[44] The most consistent risk factor for fatal asthma is admission to hospital because of asthma in the previous 12 months, particularly if there was a need for mechanical ventilatory support. Most of these patients are considered to have severe asthma, although "uncontrolled asthma" would seem to be a more appropriate label.[45] Even patients considered to have mild asthma are at risk of fatal attacks if their asthma is poorly controlled.[46 47] Various elements can contribute to the lack of proper asthma control. Patient related factors include poor perception and reporting of symptoms, psychiatric caseness, poor socioeconomic status, low level of education, and suboptimal compliance with treatment.[43 48–51] It is conceivable that the combination of these different elements results in limited access to care and/or poor adherence to proper treatment regimens. In addition, studies conducted in the 1980s, such as the retrospective analysis performed by the British Thoracic Society panel on asthma deaths, have drawn attention to deficiencies in aspects both of primary and hospital based care.[52–54] Problems highlighted included failure to diagnose asthma, undertreatment, and inadequacies in severity assessment or treatment of fatal attacks.[52 55–57] At the same time it was shown that, by increasing the availability of dedicated pre-hospital emergency services and the accessibility to hospital emergency care, asthma related mortality can be effectively reduced.[58 59]

Nearly 20 years have elapsed since these observations and during that period intensive efforts have been made, towards both the public and health care professionals, to increase the awareness of the high prevalence and morbidity associated with asthma. Consensus reports on the diagnosis and treatment of asthma that include patient orientated education have been widely disseminated.[60] It can be postulated that this has resulted over the past two decades in an overall increase in the quality of asthma care, of which the increased prescription of inhaled steroids is only one element. The observation that asthma mortality has decreased despite the increase in prevalence in countries such as the UK would seem to support this hypothesis. However, this does not mean that we should become complacent. Recent surveys in Europe, Australia, Canada, and the USA have shown that asthma management is still not optimal.[61–65] One of the striking observations emerging from the AIRE study is that, whereas most of the patients used as needed β_2 agonists, even in the group of patients with severe symptoms only 25% used inhaled steroids.[64] Both insufficient prescription and the unwillingness of patients to use the prescribed compounds are likely to contribute to the low use of steroids. Studies based on questionnaires as well as general practice records indicate that maintenance treatment is still insufficiently prescribed by physicians.[66–68] Data from a similarly designed Canadian study indicate that most patients do not understand the

Learning points

- Evaluation of the efficacy of treatment in asthma should be based on as wide a range of outcome measures as possible.
- Inhaled steroids remain the most effective form of asthma treatment currently available.
- Low doses of inhaled steroids are cost effective in the treatment of asthma.
- At present there are no data to indicate that combined treatment with long acting inhaled β_2 agonists and steroids increases asthma mortality.
- Most cases of fatal asthma are probably preventable.
- Recent surveys indicate that asthma management is still suboptimal throughout Europe.

rationale for using inhaled steroids and most of them have significant fears concerning their side effects.[69] In addition, the cost of steroids and resentment to the use of regular medication can further diminish patient adherence to inhaled steroids.[70 71] The study by Suissa *et al* further adds to the evidence that inhaled steroids, even at low doses, are cost effective at improving asthma control.[72] In addition, the safety of low to moderate doses of inhaled steroids, even when used over a long period, is increasingly being recognised.[73] Reiteration of this information to both physicians and patients would therefore seem very appropriate. It has been shown that specific education programmes focusing on the practical implementation of concepts introduced in the guidelines increase the prescription rate and adherence to steroids, improving the overall degree of asthma control.[74–77]

How do inhaled steroids reduce asthma mortality?

A final element that needs to be considered in relation to the study by Suissa *et al* is whether the observed effect on mortality is specific to the use of inhaled steroids. As already mentioned, it is unclear to what extent the observed effect is confounded by an increase in overall quality of asthma care. The initial report based on the Saskatchewan data indicates that the risk of fatal or near fatal asthma was lower in patients who had been prescribed more than one canister of inhaled steroids per month. The risk profile for asthma related mortality in this group was not lower in the number of patients who had been prescribed less than one canister per month, nor was there any difference in the number of specialist visits by the two groups.[23] Similarly, controlling for the rate of routine ambulatory care did not appreciably alter the reported protective effect of inhaled steroids on hospital admissions.[19] When aggregated, these and other observations seem to indicate that the effects obtained can be attributed to the pharmacological activities of inhaled steroids. Exactly how inhaled steroids reduce the likelihood of developing a life threatening asthma attack is unknown. Severe asthma exacerbations are thought to reflect excessive airway narrowing.[41] Inhaled steroids have been shown to reduce the degree of maximal airway narrowing in asthma[78–80] but the dose response characteristics of inhaled steroids on this aspect of airway physiology have not been fully established. In epidemiological studies the risk of asthma mortality has been shown to correlate with blood eosinophil counts and lung function variability.[35] The responsiveness of peak flow criteria and sputum eosinophil counts to low doses of inhaled steroids has been convincingly demonstrated.[81 82] The effect of inhaled steroids on hospital admissions also compares favourably with the effect of cromones or theophylline,[19 83] two medications that have some anti-inflammatory effects but less pronounced than those of inhaled steroids.[84 85] It is noteworthy with respect to the increased asthma mortality rate associated with smoking that smoking might reduce the anti-inflammatory effect of inhaled steroids.[86] Another potentially interfering element that needs to be considered is the concomitant use of β_2 agonists. There is consensus that the excessive use of short acting inhaled β_2 agonists is a marker of increased risk of an adverse asthma outcome. However, the causal association between short acting inhaled β_2 agonists and increased asthma mortality is a highly debated issue which we do not wish to develop further here.[87 88]

More importantly, in view of the increased use of combination products, is the potential influence on asthma mortality of prescribing long acting inhaled β_2 agonists with inhaled steroids. Currently available evidence indicates that combined treatment with inhaled steroids and long acting inhaled β_2 agonists, but not short acting inhaled β_2 agonists, improves asthma control and reduces the number of exacerbations.[7 89 90] In addition, treatment with long acting inhaled β_2 agonists does not seem to worsen the severity of the exacerbations[91] nor to mask progression of the underlying airway inflammation, judged by sputum eosinophil counts.[92] To what extent these observations can be extrapolated to more severe exacerbations that require hospital admission and mortality is at present unknown. Based on a recent case control study it would seem that the use of salmeterol by patients with chronic severe asthma is not associated with a significantly increased risk of developing a near fatal asthma attack.[93] Moreover, the introduction of fixed combinations of inhaled steroids with long acting inhaled β_2 agonists not only ascertains the concomitant use of inhaled steroids but should also increase compliance with them. The added benefit of the increased use of inhaled corticosteroids is likely to outweigh the hypothetical drawback associated with the use of long acting inhaled β_2 agonists on long term asthma control. Large scale surveillance data will undoubtedly clarify this issue further.

Conclusion

The data by Suissa *et al* once more underline the cost effectiveness of low doses of inhaled steroids on asthma control. Efforts should be continued to publicise this finding.

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PostScript

LETTERS TO THE EDITOR

BTS guidelines on CAP

The new BTS guidelines on the management of community acquired pneumonia (CAP) in adults[1] are welcome if they lead to improved diagnosis of pneumonia, better assessment of severity of illness, and thus more appropriate treatment according to clinical needs. It is widely accepted, however, that inappropriate implementation of the previous guideline contributed to large increases in unnecessary use of broad spectrum antibiotics with resultant increases in antibiotic resistance and *Clostridium difficile* infection. The authors acknowledge this, but the new guidelines seem likely to continue this unfortunate trend.

Firstly, there is no mention of the use of oral penicillin for treatment of mild cases of CAP. This is a first line choice in Scandinavian countries which have a commendably restrained history of antibiotic use (and consequently low rates of resistance).[2] The new BTS guideline recommendation for widespread use of the broader spectrum amoxicillin cannot help current antibiotic resistance problems. The pharmacodynamic arguments favouring amoxicillin may be important in those areas having problems with penicillin intermediate and resistant pneumococci, but in many areas of the UK—including much of Scotland—these strains are rare.[3] Did the authors consider oral penicillin as an option for mild cases?

Secondly, for treatment of severe pneumonia there is no mention of parenteral penicillin. The recommendation of co-amoxiclav or cefuroxime for this condition, while covering uncommon Gram negative pathogens and methicillin sensitive *Staphylococcus aureus* (MSSA), may lead to inadequate treatment of CAP due to penicillin resistant pneumococci. Surely benzyl penicillin is an option in young previously healthy people with severe CAP (the majority of whom will have pneumococcal infection).[4] Then, if there is a reasonable risk of infection with a pneumococcus with reduced susceptibility to penicillin, the dose of benzyl penicillin can be raised accordingly.

Thirdly, the recommendations for macrolide use in the first version of the guideline have probably been the main reason for the doubling of macrolide consumption in our local hospital since the previous guidelines were introduced (unpublished observation). If this observation is indicative of a more widespread trend, it may well be contributing to the current national problem with MRSA and other macrolide resistant organisms. To what benefit I wonder? Certainly, a laboratory diagnosis of atypical pneumonia is rare in our population. Isn't this another case for stratifying patients according to risk rather than treating all severely ill hospitalised patients with a macrolide?

I appreciate the huge body of evidence considered by the authors and the disappointing number of studies which were helpful in guiding best recommendations for treatment. Nevertheless, at a time when there is widespread concern about inappropriate antibiotic use, much of it with broad spectrum agents, it is crucial that new guidelines urge restrained prescribing unless the risks (inadequate spectrum) clearly outweigh the benefits (reduced ecological damage). At the same time, severe cases require the best treatment and this should not be compromised out of a desire to do the impossible and cover all conceivable (but unlikely) pathogens all of the time.

I M Gould
Department of Medical Microbiology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZN, UK; i.m.gould@abdn.ac.uk

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Transudates and exudates

Joseph *et al* have made a valuable contribution to the evaluation of pleural effusions.[1] However, we would like to sound a note of caution. Throughout all the literature, including the study by Joseph *et al*, one message remains the same: no single test is diagnostic for transudates or exudates.[2] Thus, overreliance on such a test can be very misleading and lead to either under or over-investigation.

Rarely in the literature is there any discussion regarding the *place* of pleural fluid protein or lactate dehydrogenase (LDH) estimation. Specifically, how does it alter management? Does the finding of a transudate obviate the need for further investigation? The main problem is that a significant number of malignant effusions are classified as transudates, whichever method is used.

The cause of a transudate is usually clinically obvious. If, however, there is no obvious underlying cause, surely cytological and/or histological examination should still be sought, as for an exudate?

Estimation of pleural fluid protein or LDH is also irrelevant if the fluid is bloodstained, as here further investigation for possible malignancy is warranted anyway.

We propose that the principal use for pleural fluid protein or LDH measurement is when a probable underlying cause for a transudative effusion is apparent, such as heart failure or hypoalbuminaemia, and the fluid is not bloodstained. In this situation the finding of a transudate may help to reassure that no further investigation is necessary except observation, and that a trial of treatment with, for example, diuretics may be of help.

S J Quantrill, L Dabal
Department of Cystic Fibrosis, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK; s.quantrill@ic.ac.uk

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Authors' reply

We appreciate the comments by Quantrill and Dabal on our recent paper[1] and would like to clarify the issues raised by them. By definition, when the pleural fluid is classified as a transudate, it indicates that a pathological process does not involve the pleural surface and that an effusion is formed because of a hydrostatic imbalance. If the pleural fluid is bloodstained, it therefore suggests disruption of the pleural membrane by an inflammatory or malignant process and hence cannot be classified as a transudate, which obviates the need for estimation of fluid LDH or protein estimation for diagnostic classification. However, as suggested by Quantrill and Dabal, an occasional malignancy may present as a transudate, in which case the mechanism is usually an effusion from collapse of a lobe causing an increase in the negative pleural pressure. Whatever the mechanism, if clinical suspicion for malignancy is high, further appropriate investigations need to be carried out.

Furthermore, Quantrill and Dabal state that hypoalbuminaemia is an apparent cause for transudative effusions.[2] However, recent literature shows that hypoalbuminaemia per se may not cause pleural effusions.[3] In our paper we have provided the positive likelihood ratios of the various tests so a clinician armed with the pretest probability for any individual patient and the positive likelihood ratio can work out the post-test probability using a standard nomogram.[4 5] In light of the above, we suggest that fluid LDH and total protein ratio are useful in the diagnostic separation of pleural effusions.

J Joseph, P Badrinath
Faculty of Medicine & Health Science, UAE University, Al Ain, UAE

G S Basran
Respiratory Unit, Rotherham General Trust Hospital, Rotherham, UK

S A Sahn
Division of Pulmonary & Critical Care Medicine, Medical University of South Carolina, Charleston, SC, USA

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Mycobacterium xenopi

We read with interest the report by Bachmeyer *et al* on *Mycobacterium xenopi* pulmonary infection manifesting in an HIV infected patient after receiving highly active antiretroviral treatment (HAART).[1] The diagnosis was made based on clinical, radiological, and histological findings of a granuloma in addition to one sputum specimen growing *M xenopi*. We think that the patient may meet the criteria set by the ATS for diagnosis and treatment of disease caused by non-tuberculous mycobacteria (NTM) but, according to this guideline, these recommendations fit best for *M avium* complex, *M kansasii*, and *M abscessus*. Too little is known about other NTM (such as *M xenopi*) and how applicable these criteria are to them.[2] This case may be one of those situations where it is difficult to make a definitive diagnosis.

M xenopi is usually a non-pathogenic coloniser of airways that has occasionally been associated with nosocomial outbreaks related to growth in hospital hot water systems.[3 4] A recent publication showed the incidence of *M xenopi* isolates in a large urban hospital and its pathogenicity to be low.[5] Tuberculosis would have the same clinical/radiological presentation and would have improved with the same treatment given to the patient.[6 7] The persistent negativity of tuberculin skin testing (TST) despite the increase in CD4 cell count cannot be used to exclude tuberculosis. TST has a high false negative rate even among non-HIV infected patients with confirmed tuberculosis.

While the management of this case would not have differed had the patient been treated as a presumed case of tuberculosis, it is important to keep in mind the need for contact investigation and appropriate public health interventions for tuberculosis cases.

J Salazar-Schicchi, S A Nachman
Department of Medicine, Columbia University College of Physicians & Surgeons, Division of Pulmonary and Critical Care Medicine, Harlem Hospital, 506 Lenox Avenue, New York, New York 10037, USA

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Authors' reply

We thank Drs Salazar-Schicchi and Nachman for their interest in our paper and their valuable comments. However, we consider that *Mycobacterium xenopi* was responsible for the patient's disease despite the fact that the microbiological diagnosis was not "definitive". Indeed, the criteria of the American Thoracic Society were not fulfilled.[1] These criteria do not seem to be applicable to *M xenopi* in HIV infected patients, in whom two positive cultures of *M xenopi* and no other cause of symptoms have been proposed as criteria for the diagnosis.[2] Our patient also did not fulfil these criteria. Indeed, we were concerned about the possible role of other pathogens—especially *M tuberculosis*—since coexistent pulmonary infections due to other pathogens had been reported.[3] However, no other pathogens were found and a search for *M tuberculosis* in the three sputum samples and bronchoalveolar lavage fluid was negative on direct microscopic examination and culture. This is rare in cavitatory tuberculosis and makes this diagnosis unlikely.

Mycobacterium xenopi may be found in hospital water taps, hot water storage tanks, and contaminated bronchoscopes.[4] Environmental contamination seemed unlikely since *M xenopi* was not isolated from samples in the microbiology laboratory during the period of management of our patient.

We conclude that *M xenopi* can be the cause of a lung disease in HIV infected patients that resembles tuberculosis and clinicians should not disregard the significance of this organism when isolated from respiratory specimen, even from only one.

C Bachmeyer
Département de Médecine Interne, Hôpital Laënnec, Creil Cedex, France

S Stelianides
Pneumologie, Centre Hospitalier du Vexin, Magny en Vexin, France

L Blum
Médecine Générale, Hôpital René Dubos, Pontoise, France

Correspondence to: Dr C Bachmeyer, Département de Médecine Interne, Hôpital Laënnec, Boulevard Laënnec, BP 72, F-60109 Creil Cedex, France; claude.bachmeyer@ch-creil.fr

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NOTICE

Pharmacology of Asthma

A course on the "Pharmacology of Asthma" suitable for physicians or scientists with an interest in the pharmacology and therapeutics of asthma organised by Professor Peter Barnes will be held on 25–28 November 2002. For futher details contact the Postgraduate Education Centre, National Heart & Lung Institute, Faculty of Medicine, Imperial College, Dovehouse Street, London SW3 6LY, UK. Telephone: 020 7351 8172. Fax: 020 7351 8246. E-mail: shortcourses.nhli@ic.ac.uk.

CORRECTIONS

Critical care training in Spain

In the review entitled "The pulmonary physician in critical care: towards comprehensive critical care?" by M J D Griffiths and T W Evans which appeared in the January issue of *Thorax* (2002;**57**:77–8), it was incorrectly stated that: "In Spain 4 years of training are required to achieve specialist status, 2 years of which are in intensive care medicine". This should have read: "In Spain **5** years of training are required to achieve specialist staatus, **3** years of which are in intensive care medicine".

Low dose of inhaled steroids and prevention of asthma death

In the paper by J C Kips and R A Pauwels entitled "Low dose inhaled corticosteroids and the prevention of death from asthma" which appeared in the 2001 Year in Review published as Supplement II in September 2001 (*Thorax* 2001;**56**(Suppl II):ii74–ii78), an error occurred in the abstract of the Introductory article by Suissa *et al* (*N Engl J Med* 2000;**343**:332–6). In the Results section it is stated that "... the rate of death from asthma decreased by 2% with each additional canister of inhaled corticosteroids used in the previous year ...". This should have read "... the rate of death from asthma decreased by **21%** with each additional canister of inhaled corticosteroids used in the previous year ...". The publishers apologise for this error.