ORIGINAL ARTICLE

# Respiratory medications and risk of asthma death

**S F Lanes, L A García Rodríguez, C Huerta**

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See end of article for authors' affiliations

Correspondence to: Dr S F Lanes, Boehringer Ingelheim Pharmaceuticals Inc, 900 Ridgebury Road, Ridgefield, CT 06877-0368, USA; slanes@rdg.boehringer-ingelheim.com

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**Background:** The effect of respiratory medications on risk of asthma death in the UK was studied using the General Practice Research Database.
**Methods:** A total of 96 258 individuals with a diagnosis of asthma were identified, 43 of whom had died as a result of their asthma. For each case 20 controls were selected. Relative risk (RR) estimates and 95% confidence intervals (CI) were computed for each respiratory drug category controlling for effects of age, sex, body mass index, smoking, frequency of visits to the GP, hospital admissions for asthma, and visits to a specialist.
**Results:** The strongest associations were found for at least 13 prescriptions of short acting β agonists during the previous year (RR=51.6, 95% CI 7.9 to 345) and 7–12 prescriptions of short acting β agonists (RR=16.2, 95% CI 2.6 to 101). Short acting β agonists and inhaled steroids tended to be prescribed most frequently to the same patients. In patients who received more than one prescription per month of short acting β agonists during the previous year, regular use of inhaled steroids was associated with a 60% reduced risk of asthma death (RR=0.4, 95% CI 0.2 to 1.0).
**Conclusions:** Regular use of inhaled steroids is associated with a decreased risk of asthma death, and excessive use of short acting β agonists is associated with a markedly increased risk of asthma death.

In recent years the asthma death rate has declined in the US, UK, and elsewhere.[1–3] It has been hypothesised that better care, particularly the use of inhaled steroids, may be at least partly responsible for this trend.[4] Studies have shown that prescribed inhaled steroids are associated with a lower rate of hospital admissions for asthma.[5 6] More recently, inhaled steroids were reported to be associated with a lower rate of asthma death.[7] The association between inhaled steroids and decreased risk of asthma death was confined to patients receiving at least six canisters of inhaled steroids per year, among whom there was only one asthma death.[7] This finding, if valid, may have important clinical implications. Whereas short acting β agonists constitute first line treatment, it is now suggested that inhaled steroids are "the most effective form of asthma treatment currently available".[8]

This study used the automated General Practice Research Database (GPRD) in the UK to evaluate further the relations between each of the major classes of respiratory drugs and asthma death.

## METHODS

### Data source

The GPRD contains computerised medical information entered systematically by general practitioners (GPs) and sent anonymously to the Medicine Control Agency (MCA).[9] The information recorded includes demographic data, clinical diagnoses from outpatient visits, consultant referrals and hospital admissions, and prescriptions. Prescriptions are generated directly from the GP's computer and entered into the patient's computerised file. More than 90% of all referrals present in the manual records in GPs' offices are entered into computer files with a code that reflects the clinical diagnosis.[10] A recent study has confirmed the validity of using the GPRD for respiratory epidemiological research.[11]

### Study population

The source population included patients 10–79 years old who were permanently registered with a GP between 1994 and 1998. From this source population we identified all patients with a physician diagnosis of asthma. All patients were required to have been enrolled with the GP for at least 2 years and to be free from any cancer diagnosis upon entry into the study. We followed the cohort from the first day in 1994 or when they met all the eligibility criteria until the earliest of the following: date of death, cancer diagnosis, or October 1998.

### Case ascertainment

Asthma deaths were identified in several steps. Firstly, all deaths were identified from automated patient records. The automated patient profiles (blinded to drug use) were then used to assign cause of death to categories of asthma, other respiratory disease, cardiovascular disease, and other causes. Based on the automated patient medical records, 77 deaths were assigned to asthma, 884 to other respiratory disease, 992 to cardiovascular disease, and 247 deaths to other causes. For 198 patients the cause of death could not be determined based on the computerised information and these deaths were classified as "unknown".

A copy of the death certificate for any death assigned to a cause of "asthma" or "unknown" was requested from the GP, as well as copies of the death certificates for a random sample of 64 deaths from the categories of "other respiratory" (n=21), cardiovascular (n=31), and "other causes" (n=12). Death certificate information was received for 297 (88%) of the requested patients.

To maintain confidentiality and avoid information bias, all patient personal identifiers were suppressed before reviewing computerised information as well as death certificates. Of the 77 deaths classified from automated data as asthma deaths, 34 were corroborated by death certificate as being due to asthma. Of the 198 deaths with an unknown cause of death based on automated data, four listed "asthma" as the underlying cause on the death certificate. In addition, five patients who were classified as asthma deaths and for whom we did not receive a death certificate were also included as asthma deaths, giving a total of 43. Among the deaths assigned to a specific cause other than asthma using the information recorded in the automated patient profiles, none was classified on the death certificate as being due to asthma.

### Analysis of data

We calculated the crude incidence rate for asthma mortality by dividing the number of asthma deaths by the corresponding

**Table 1** Incidence rate of asthma death by age and sex

| | Person years | Asthma deaths | Incidence per 100 000 person years (95% CI) |
|---|---|---|---|
| Age (years) | | | |
| 10–49 | 239 606 | 8 | 3.3 (1.7 to 6.6) |
| 50–79 | 105 824 | 35 | 33.1 (23.8 to 46.0) |
| Sex | | | |
| Male | 170 364 | 20 | 11.7 (7.6 to 18.1) |
| Female | 175 066 | 23 | 13.1 (8.8 to 19.7) |
| Total | 375 430 | 43 | 12.5 (9.2 to 16.8) |

number of person years at risk. Incidence rates were also calculated within strata of age and sex.

The 43 asthma deaths were analysed further in a nested case-control analysis. We sampled 860 controls (20 controls per case) from the study cohort, frequency matched to cases by age (within 1 year) and sex. For cases, the index date was assigned to be the date of death. In selecting controls, an index date was randomly assigned to each individual from their eligible person-time so that the likelihood of being selected as a control was proportional to the person-time at risk.

Respiratory drugs were classified according to number of prescriptions during the year before the index date. For most drugs the number of prescriptions was categorised as 0, 1–6, and 7+. Short acting β agonists were categorised as <3, 4–6, 7–12, and 13+ prescriptions per year. Only two cases and 165 controls received a prescription for cromoglycates, so these drugs were categorised as any prescriptions versus none.

During the year before the index date we also ascertained for cases and controls the number of GP visits, number of total hospital admissions and admissions for asthma, and whether or not there was a visit to a specialist. We also classified patients according to age, sex, body mass index (BMI), smoking, and certain co-morbidities (cardiovascular, diabetes, COPD).

Logistic regression was used to compute estimates of relative risk (RR) and 95% confidence intervals (CI) of asthma mortality associated with each respiratory drug. All variables were entered into logistic models using indicator terms to avoid restrictive modelling assumptions. For continuous variables we developed as many as five categories and collapsed across levels with similar effects. In addition, we conducted extensive cross-tabulations to support the logistic analyses. In this way the numbers of cases and controls available limited the number of variables entered into a model so that the modelling results would have a more reliable empirical basis.

## RESULTS

A total of 96 258 persons diagnosed with asthma were identified, who contributed 375 430 person years of observation and among whom we identified 43 deaths due to asthma (table 1). The overall asthma mortality rate in this population during the study period from 1994 to 1998 was 12.5 deaths per 100 000 person years; this increased with age and was similar for males and females.

Unadjusted RR estimates showed strong associations for all respiratory medications that increased with increasing prescription frequency (table 2). After adjustment for age, sex, BMI, smoking, prior hospital admissions for asthma, prior specialist visits, prior GP visits, and respiratory drugs, most of the RR estimates for respiratory drugs decreased substantially. The only RR estimates that did not decrease were for the intermediate categories of 3–6 and 7–12 prescriptions of short acting β agonists during the previous year which increased slightly. After adjustment, the largest RR estimates were for at least 13 prescriptions of short acting β agonists, followed by at least seven prescriptions of oral steroids, with weaker associations for at least seven prescriptions of long acting β agonists

**Table 2** Crude and adjusted relative risk (RR) estimates and 95% confidence intervals (CI) of asthma death by number of prescriptions (Rx) for respiratory drugs in the previous year

| | Cases (n=43) | Controls (n=860) | Crude RR (95% CI) | Adjusted RR (95% CI)* |
|---|---|---|---|---|
| Short acting β agonists | | | | |
| <3 Rx | 2 | 443 | Reference | Reference |
| 3–6 Rx | 2 | 188 | 2.4 (0.3 to 16.9) | 3.4 (0.4 to 29.1) |
| 7–12 Rx | 11 | 157 | 15.5 (3.4 to 70.8) | 16.2 (2.6 to 101.3) |
| 13+ Rx | 28 | 72 | 86.1 (20.1 to 369.5) | 51.6 (7.9 to 344.6) |
| Long acting β agonists | | | | |
| Non-use | 31 | 798 | Reference | Reference |
| 1–6 Rx | 6 | 44 | 3.5 (1.4 to 8.9) | 0.8 (0.2 to 3.3) |
| 7+ Rx | 6 | 18 | 8.6 (3.2 to 23.1) | 3.2 (0.7 to 14.1) |
| Antimuscarinics | | | | |
| Non-use | 16 | 765 | Reference | Reference |
| 1–6 Rx | 7 | 51 | 6.6 (2.6 to 16.7) | 2.3 (0.6 to 8.2) |
| 7+ Rx | 20 | 44 | 21.7 (10.5 to 44.8) | 3.2 (1.1 to 9.7) |
| Inhaled steroids | | | | |
| Non-use | 6 | 346 | Reference | Reference |
| 1–6 Rx | 15 | 340 | 2.5 (1.0 to 6.6) | 0.7 (0.2 to 2.9) |
| 7+ Rx | 22 | 174 | 7.3 (2.9 to 18.3) | 0.7 (0.2 to 2.8) |
| Oral steroids | | | | |
| Non-use | 15 | 693 | Reference | Reference |
| 1–6 Rx | 11 | 18 | 3.4 (1.5 to 7.6) | 1.4 (0.5 to 4.3) |
| 7+ Rx | 17 | 19 | 41.3 (18.0 to 94.9) | 10.1 (2.8 to 37.0) |
| Theophyllines | | | | |
| Non-use | 25 | 773 | Reference | Reference |
| 1–6 Rx | 8 | 42 | 5.9 (2.5 to 13.8) | 1.7 (0.5 to 6.6) |
| 7+ Rx | 10 | 45 | 6.9 (3.1 to 15.2) | 1.2 (0.4 to 3.8) |
| Cromoglycates | | | | |
| Non-use | 41 | 844 | Reference | Reference |
| 1+ Rx | 2 | 16 | 2.6 (0.6 to 11.6) | 0.5 (0.1 to 5.1) |

*Adjusted for age, sex, BMI, smoking, prior hospital admissions for asthma, prior specialist visits, frequency of visits to the GP, and all the drug variables shown in the table.

**Table 3** Distribution of controls according to frequency of use of short acting β agonists and inhaled steroids

| | Short acting β agonists | | | |
|---|---|---|---|---|
| Inhaled steroids | <3 Rx | 4–6 Rx | 7–12 Rx | 13+ Rx |
| None | 285 (64%) | 33 (18%) | 22 (14%) | 6 (8%) |
| 1–6 Rx | 128 (29%) | 134 (71%) | 63 (40%) | 15 (21%) |
| 7+ Rx | 30 (7%) | 21 (11%) | 72 (46%) | 51 (71%) |
| Total | 443 (100%) | 188 (100%) | 157 (100%) | 72 (100%) |

and antimuscarinic agents. RR estimates for theophyllines were close to the null value (RR=1.0), while inhaled steroids and cromoglycates were associated imprecisely with decreased mortality (RR <1.0).

Several factors related to medical care were also related to risk of asthma death after adjustment for respiratory medications and demographic factors including a previous admission to hospital for asthma (RR=2.0, 95% CI 0.8 to 5.3), more than 10 visits in the previous year to the GP (RR=0.41, 95% CI 0.2 to 1.1), and referral to a specialist (RR=1.5, 95% CI 0.6 to 3.5). Because asthma death is rare and many variables were controlled, none of the effect estimates was measured with great precision, as indicated by wide confidence intervals.

Besides the effect estimate for 13+ prescriptions per year of short acting β agonists (RR=51.6), the next largest effect estimate was for 7–12 prescriptions per year of short acting β agonists (RR=16.2). In addition, the effect estimates for 3–6 and 7–12 prescriptions per year of short acting β agonists were the only drug categories for which effect estimates did not decline after controlling for the confounding effects of other risk factors.

Because of the particularly strong association between excessive use of short acting β agonists and asthma death and the negative association between inhaled steroids and asthma death, we considered that high risk patients who overuse short acting β agonists might be at increased risk because they were less likely to receive inhaled steroids. In examining the relation between short acting β agonists and inhaled steroids in control subjects (representing the underlying asthma population), however, we found that increasing use of one of these drugs implied increasing use of the other (table 3). Thus, among people receiving 13+ prescriptions per year of short acting β agonists, 71% also received 7+ prescriptions per year of inhaled steroids. Inhaled steroids and short acting β agonists therefore each tended to be prescribed more frequently to the same patients.

Approximately 65% (28/43) of the cases and 8% of controls (72/860) received 13+ prescriptions of short acting β agonists. We estimated the effect of inhaled steroids within this high risk subgroup of patients. Because inhaled steroids were used so frequently in this group, patients receiving up to six prescriptions per year of inhaled steroids were used as a reference category. In those who used short acting β agonists excessively, we found that 7+ prescriptions for inhaled steroids (compared with less frequent use) were associated with a 60% reduction in risk of asthma death (RR=0.4, 95% CI 0.2 to 1.0). Effect estimates for other respiratory medications in this subgroup were similar to their effect estimates in the entire population, except for cromoglycates for which the RR estimate was 2.7 (95% CI 0.4 to 20.1). Effect estimates in the complementary subgroup of patients receiving fewer than 13 prescriptions of short acting β agonists during the previous year were similar to the adjusted effect estimates for the entire population.

The association with short acting β agonists was also apparent in individuals who received 7+ prescriptions for inhaled steroids during the previous year. Among these regular users of inhaled steroids, most patients also received multiple prescriptions for short acting β agonists during the previous year. Compared with patients who received fewer than seven prescriptions of short acting β agonists, increased risks were observed for individuals who received 7–12 prescriptions of short acting β agonists (RR=5.0, 95% CI 0.7 to 114) and those who received 13+ prescriptions of short acting β agonists (RR=14, 95% CI 2.3 to 304).

We considered the possibility that using death certificates to identify asthma deaths may be inaccurate, and that this subgroup may be unrepresentative of all asthma deaths in terms of drug use. To address this concern we repeated the analyses using as cases the larger group of 77 deaths classified as being due to asthma from the automated patient medical records. These cases tended to be older than the cases classified as asthma from the death certificate. The magnitude of the effect estimates tended to be slightly smaller with this larger group of deaths, although the pattern across drug classes was similar.

Finally, because previous research had suggested a potentially greater risk associated with fenoterol than with other short acting β agonists,[12] we conducted analyses in which short acting β agonists were subdivided into those with and those without fenoterol. Among high risk people with 13+ prescriptions of a short acting β agonist in the previous year, fenoterol was associated with a threefold increased risk of asthma death before adjusting for confounding. After adjustment for prior admission to hospital for asthma and prescribed oral steroids, however, there was no additional excess risk associated with fenoterol beyond the already increased risk of short acting β agonists as a class (RR=1.1, 95% CI 0.19 to 6.5).

## DISCUSSION

This study has evaluated the relations between major classes of respiratory medications and asthma death from 1994 to 1998 in a population of 96 258 patients in the UK diagnosed with asthma. During this period short acting β agonists and inhaled steroids were prescribed to most patients, antimuscarinic agents, theophyllines, and long acting β agonists were each prescribed to about 10% of patients, and oral steroids and cromoglycates were rarely prescribed. Leukotriene antagonists were introduced in the UK in 1998, too recent for inclusion in this analysis.

Asthma death is a rare outcome for which the rates have been declining.[1–4] Despite the variety of respiratory medications available, inhaled steroids constituted the only class of respiratory drug in this study which was consistently related to a decreased risk of asthma death. Inhaled steroids were most frequently prescribed to patients who were also prescribed short acting β agonists at least once per month and who were at greatly increased risk of asthma death. Nevertheless, even among this high risk subgroup of patients, regular use of inhaled steroids, defined as 7+ prescriptions per year, was associated with a 60% reduction in the risk of asthma death compared with less frequent use.

The only group of drugs for which the effect estimates for each category of prescribing frequency did not decrease after controlling for confounding was short acting β agonists. Specifically, the effect estimates for the intermediate categories of 3–6 and 7–12 prescriptions per year of short acting β agonists actually increased slightly after controlling for confounding. These results indicate little, if any, confounding of these associations by the risk factors controlled. The observed relation between short acting β agonists and increased risk of asthma death therefore appears to be less consistent with confounding than associations for other drugs.

Increased effect estimates for oral steroids, long acting β agonists, antimuscarinic agents, theophyllines, and cromoglycates are more consistent with confounding by disease severity. RR estimates for these drugs decreased markedly with control for other risk factors, and are less strongly related to risk of asthma death than are short acting β agonists. It is therefore conceivable that improved assessment and control of baseline risk could depress further and possibly eliminate the associations for these drugs.

One concern is that this study included elderly patients, among whom there is a greater incidence of chronic obstructive pulmonary disease (COPD), and there is a greater chance for diagnostic misclassification between asthma and COPD. An association could arise, for instance, between short acting β agonists and asthma death if COPD deaths were misclassified as asthma deaths because these patients use short acting β agonists excessively. Although some diagnostic misclassification probably occurred, several features of the design and analysis should be considered in evaluating this hypothesis. Firstly, entry criteria for the study required that all patients received from their physician a diagnosis of asthma. In addition, ipratropium is clearly associated with COPD, but the strong association with asthma death obtained for short acting β agonists was not obtained for ipratropium. Although diagnostic accuracy may be imperfect, adjustment for a concomitant diagnosis of COPD had no effect on the results. Finally, when we classified cause of death using automated medical records and blinded to drug use, the results were similar. These features mitigate the concern that patients were misclassified as asthma deaths because of their use of short acting β agonists, and that the strong association between the excessive use of short acting β agonists and asthma death is created by selective misdiagnosis of these patients.

At the population level, sales of short acting β agonists have been increasing while asthma deaths have declined; however, sales of inhaled steroids have also increased. Crude ecological correlations between drug sales and asthma mortality cannot at the same time support a positive association with short acting β agonists and a negative association with inhaled steroids. The ecological data appear to be more consistent with a beneficial effect of inhaled steroids. Possible explanations are that the association with inhaled steroids is observed at recommended doses used by a majority of patients, whereas the association with short acting β agonists is concentrated among excessive users who comprise <10% of the overall asthma population. In addition, crude ecological correlations are more susceptible to error from ecological bias and confounding. These considerations complicate comparisons between studies of populations and studies of individuals.

The results of this study are imprecise, but they replicate—with somewhat different methodologies in a different population—previously reported associations between excessive use of short acting β agonists and greatly increased risk of asthma death, and regular use of inhaled steroids and decreased risk of asthma death.[7 12] An increased risk associated with short acting β agonists has sometimes been regarded with scepticism because of an expected greater use of these drugs by high risk patients while the apparent protective effect of inhaled steroids is more often accepted as valid.[5–7] This study shows these medications to be highly correlated, so that preferential prescribing is operating in a similar fashion for inhaled steroids and for short acting β agonists. The relation between these drugs and asthma death, however, goes in opposite directions. To the extent that there is uncontrolled confounding by severity, then control for such confounding would decrease effect estimates for both classes of drugs. Consequently, if effect estimates for short acting β agonists are greatly overestimated due to confounding by severity, the true benefit of inhaled steroids would have to be much stronger than the already remarkable effect observed in epidemiological studies. However plausible or implausible this may be, there is no evidence to suggest that short acting β agonists have any beneficial effect on asthma death, while inhaled steroids appear to be considerably more effective at preventing asthma death than short acting β agonists.

It is encouraging that evidence is mounting to suggest that inhaled steroids prevent asthma death, and that increasing use of these medications may be responsible for international declines in asthma mortality. At the same time, it is disconcerting not to find evidence of a clinical benefit of short acting β agonists. This finding raises the question whether efficacy evaluations may be based too narrowly on certain aspects of lung function such as forced expiratory volume in 1 second ($FEV_1$). As the goal of asthma management moves from symptomatic relief towards long term preventive treatment, the evaluation of drugs used to treat this chronic disease should also evolve beyond their acute effects on $FEV_1$.

**Authors' affiliations**

**S F Lanes,** Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT 06877-0368, USA
**L A García Rodríguez, C Huerta,** Centro Español de Investigación Farmacoepidemiológica, Almirante 28-2, 28004 Madrid, Spain

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