

## LOW-DOSE INHALED CORTICOSTEROIDS AND THE PREVENTION OF DEATH FROM ASTHMA

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### ABSTRACT

**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 through 44 years of age who were using antiasthma drugs during the period from 1975 through 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 percent 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 21 percent with each additional canister of inhaled corticosteroids used in the previous year (adjusted rate ratio, 0.79; 95 percent 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.)

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**M**OST deaths from asthma are preventable, particularly those among young people. Nonetheless, the rate of death from asthma is between less than 1 and 4 per 100,000 per year among the general population worldwide and up to 10 per 10,000 per year among people with asthma in Canada who take medications.<sup>1,2</sup> The rate of death from asthma, which increases markedly with the severity of asthma,<sup>3</sup> nearly doubled in the United States during the 1980s.<sup>4</sup> The efficacy of inhaled corticosteroids in reducing airway inflammation and hyperresponsiveness has led to their widespread use as initial therapy in the treatment of moderate-to-severe asthma in adults. These drugs are very effective in reducing the frequency of days with symptoms, improving lung function, and reducing the frequency of hospitalization for asthma and the risk of a life-threatening attack.<sup>5-9</sup> However, information on whether inhaled corticosteroids prevent death from asthma is sparse and inconclusive.

Trends in several countries indicate that during the 1980s and 1990s, sales of inhaled corticosteroids increased as the yearly rates of death from asthma decreased.<sup>10-12</sup> Three case-control studies from New Zealand and a cohort study from Saskatchewan, Canada, which were designed to assess the effects of  $\beta$ -adrenergic agonists on death from asthma, found no association between the use of inhaled corticosteroids and death from asthma.<sup>2,13-16</sup> This may have been because of the low rates of use of inhaled corticosteroids during the 1980s. However, inhaled corticosteroids significantly reduced the combined risk of near-fatal and fatal asthma.<sup>5</sup> There have been no studies of the dose-response relation in inhaled corticosteroid therapy. Such studies are desirable because of the increasing doses used in many countries and the potential adverse effects associated with prolonged use of higher doses, especially ocular side effects in adults and decreased growth in children.<sup>17-20</sup>

We conducted a population-based epidemiologic study to determine whether and to what extent the use of inhaled corticosteroids prevents death from asthma.

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## METHODS

### Subjects and Source of Data

The cohort of patients with asthma whom we studied has been described in detail elsewhere.<sup>8,9</sup> Briefly, the computerized data bases of Saskatchewan Health formed the primary source of data on the cohort. These data bases were developed as a result of the universal health insurance provided to all residents of the province since 1975. Two million people have been covered by this program since it began. The data bases have been used extensively to study the effects of several prescription drugs at the population level.<sup>21</sup> We selected from this population all 30,569 beneficiaries 5 through 44 years of age who received at least three prescriptions for an antiasthma medication in any one-year period from September 1975 through December 1991. The medications included all antiasthma drugs that were covered by the health insurance plan during the study period, except for oral corticosteroids. These drugs were beclomethasone, budesonide, triamcinolone, flunisolide, cromolyn sodium, ketotifen, nedocromil, albuterol, fenoterol, terbutaline, isoproterenol, metaproterenol, procaterol, epinephrine bitartrate, ipratropium bromide, and any compound of theophylline. We initially omitted oral corticosteroids in order to exclude subjects with conditions other than asthma. However, we later obtained data on all prescriptions for oral corticosteroids for all selected subjects.

The subjects were followed until their 55th birthday, death, emigration from the province, the end of their coverage by the health insurance plan, or December 31, 1997, whichever occurred first.

### Outcome

All deaths from any cause that occurred during follow-up of the 30,569 members of the study cohort were identified, and the death certificates were obtained. Two pulmonary physicians, who were unaware of the drugs used by the patients, independently reviewed the death certificates to identify deaths due to asthma. The case patients were cohort members whose deaths were attributed primarily to asthma by both physicians. Deaths that occurred during or within a year after the 18-month period from July 1987 through December 1988 were excluded, because Saskatchewan Health did not collect data on medications during this period.

### Study Design

We used a nested case-control design within the cohort to allow precise assessment of the changes over time in the use of antiasthma drugs. Each patient who died of asthma was matched with all available controls within the cohort on the basis of several factors. First, all matched controls had to have been followed for at least as long as the corresponding case patient at the time of the date of death, which was designated the index date. Moreover, to control for trends over time in the use of inhaled corticosteroids, we required that the matched controls have entered the cohort on the same date ( $\pm 3$  months) as the case patient. Because we expected the case patients to be those with more severe disease, we used the following additional matching factors to control for the severity of disease: the occurrence of hospitalization for asthma during the two years before the index date and the number of canisters of  $\beta$ -adrenergic agonist dispensed (18 or fewer vs. more than 18), the use of theophylline, the use of nebulized  $\beta$ -adrenergic agonists, and the use of oral corticosteroids during the year before the index date. The 16 case patients who could not be matched with at least 2 controls who had entered the cohort on the same date ( $\pm 3$  months) were matched with additional controls who had entered the cohort during the 12 months (14 case patients) or 36 months (2 case patients) preceding or following the date of entry of the case patient.

### Exposure to Inhaled Corticosteroids

We determined the number of canisters dispensed in each prescription for inhaled corticosteroids to the case and control patients during the year before the index date. When two or more canisters were dispensed by the same prescription, the canisters were con-

sidered to have been used during successive months. Patients who had received at least one canister during each quarter of the previous year were considered to have used inhaled corticosteroids regularly and without interruption throughout that year.

### Statistical Analysis

To quantify the amount of exposure to inhaled corticosteroids, we determined the number of canisters dispensed to each case patient during the year before and during the six months before the index date. To assess the effect of discontinuation of inhaled corticosteroids, we divided the case patients into four groups: those who had used inhaled corticosteroids without interruption during the year before the index date, and those who had discontinued inhaled corticosteroids within three, six, and nine months before the index date.

Because controls were matched with case patients and the number of controls per case patient was variable, crude descriptive statistics for the characteristics of the controls could not be used. To allow unbiased comparisons with case patients, these statistics were weighted by the inverse of the number of controls in each matched set, a procedure equivalent to standardizing the number of controls to one control per case.

Conditional logistic regression for matched case-control data was used to estimate the adjusted rate ratios for death from asthma that were associated with the use of inhaled corticosteroids. To assess the dose-response effect, we first stratified inhaled-corticosteroid use as follows: no use, use of less than one-half canister per month, and use of one-half canister or more per month. To maximize the power of the analysis, we used conditional logistic regression to estimate the rate ratio for death from asthma as a function of the number of canisters of inhaled corticosteroids dispensed among users of these drugs, with the nonusers as the reference group. Both analyses were repeated for the one-year and six-month periods before the index date. To assess the effect of discontinuation of inhaled corticosteroids, we used conditional logistic regression to estimate the rate of death from asthma among subjects who discontinued inhaled corticosteroids within three, six, and nine months before the index date, relative to the rate among those who used inhaled corticosteroids without interruption during the entire year before the index date.

To control for any confounding that might remain after matching for the severity of asthma, we adjusted all estimates of rate ratios according to the quantities of prescribed antiasthma drugs. These quantities were expressed by the number of dispensed prescriptions for theophylline, nebulized and oral  $\beta$ -adrenergic agonists, and oral corticosteroids and by the number of canisters of inhaled  $\beta$ -adrenergic agonists dispensed in the year before the index date. We also adjusted for the number of hospitalizations for asthma during the two years before the index date and for the subject's age and sex.

## RESULTS

There were 562 deaths in the cohort, of which 77 were classified as being due to asthma. We excluded 11 of these deaths because they occurred during or up to a year after the 18-month period when Saskatchewan Health did not collect data on medications. The remaining 66 case patients were matched with 2681 controls from the cohort. The mean age of the case patients was 30 years (range, 9 to 54). Seventeen of the case patients were less than 18 years old. The case patients and their matched controls had severe asthma. Fifty-three percent had been hospitalized for asthma in the previous two years, and during the previous year, 48.5 percent had used oral corticosteroids, 57.6 percent had used more than 18 canisters of inhaled  $\beta$ -adrenergic agonists, 25.8 percent

had used nebulized  $\beta$ -adrenergic agonists, and 63.6 percent had used theophylline.

The case patients were older and more likely to be men than the controls (Table 1). Moreover, although case and control patients were matched according to the presence or absence of several markers of the severity of asthma, the frequency of these markers remained somewhat higher among case patients than among controls. As compared with controls, the case patients had more hospitalizations for asthma and more prescriptions for oral corticosteroids, inhaled  $\beta$ -adrenergic agonists, nebulized  $\beta$ -adrenergic agonists, oral  $\beta$ -adrenergic agonists, and theophylline. Ninety-three percent of the prescribed canisters of inhaled corticosteroids contained low-dose beclomethasone (200 puffs per canister, with 50  $\mu$ g of drug delivered per puff).

Table 2 presents the crude and adjusted matched rate ratios for death from asthma in relation to the use of inhaled corticosteroids during the previous year. The adjusted rate ratio for any use of inhaled corticosteroids during this period as compared with nonuse was essentially 1. However, the adjusted rate ratio for the use of six or more canisters of inhaled corticosteroids during this period was 0.15 (95 percent confidence interval, 0.02 to 1.22). Only one case patient had used six or more canisters during the previous year. From the continuous dose-response analysis, we calculated that the rate of death from asthma among users of inhaled corticosteroids decreased by 21 percent (rate ratio, 0.79; 95 percent confidence

TABLE 1. CHARACTERISTICS OF THE STUDY SUBJECTS.\*

CHARACTERISTIC	CASE PATIENTS (N=66)	CONTROLS (N=2681)†
Age (yr)	30.0±14.2	28.0±2.1
Male sex (%)	59.1	50.9
Indicators of severity of asthma in the previous year (no.)		
Hospitalizations for asthma‡	1.4±2.1	0.9±0.2
Prescriptions for oral corticosteroids	2.4±4.0	1.7±0.5
Prescriptions for $\beta$ -adrenergic-agonist metered-dose inhalers	25.7±23.4	20.8±2.6
Prescriptions for nebulized $\beta$ -adrenergic agonists	2.0±4.7	0.8±0.3
Prescriptions for oral $\beta$ -adrenergic agonists	1.7±3.1	1.1±0.4
Prescriptions for theophylline	6.5±7.8	3.8±0.8

\*Plus-minus values are means ±SD.

†To account for case-control matching, all means, standard deviations, and percentages for controls were weighted by the inverse of the number of controls in each matched case-control set.

‡Data are for the number of hospitalizations for asthma in the previous two years.

interval, 0.65 to 0.97) for every additional canister of inhaled corticosteroids used during the year. The rate was reduced by 54 percent (rate ratio, 0.46; 95 percent confidence interval, 0.26 to 0.79) for every additional canister of inhaled corticosteroids used during the previous six months.

Figure 1 shows the fitted dose-response curve for

TABLE 2. CRUDE AND ADJUSTED RATE RATIOS FOR DEATH FROM ASTHMA IN RELATION TO THE USE OF INHALED CORTICOSTEROIDS DURING THE ONE-YEAR AND SIX-MONTH PERIODS BEFORE THE INDEX DATE.\*

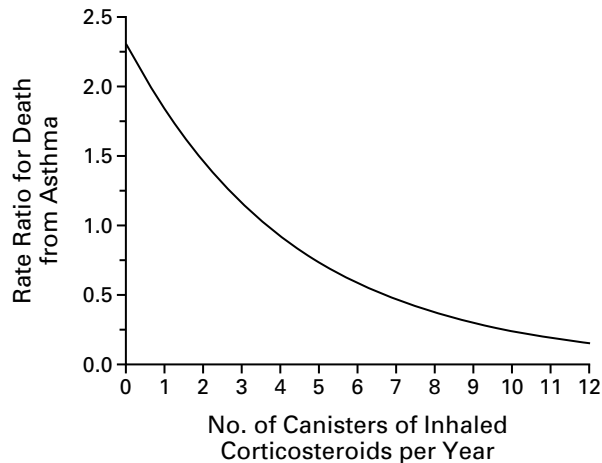
USE OF INHALED CORTICOSTEROIDS	CASE PATIENTS (N=66)	CONTROLS (N=2681)	CRUDE RATE RATIO	ADJUSTED RATE RATIO (95% CI)†
Previous 1 yr				
None (%)	47.0	53.8	1.0	1.0 (reference group)
Any use (%)	53.0	46.2	1.41	1.19 (0.66-2.14)
1-5 canisters	51.5	38.8	1.67	1.53 (0.83-2.80)
≥6 canisters	1.5	7.4	0.25	0.15 (0.02-1.22)
Mean no. of canisters	1.18	1.57	0.82‡	0.79 (0.65-0.97)‡
Previous 6 mo				
None (%)	56.1	65.7	1.0	1.0 (reference group)
Any use (%)	43.9	34.3	1.56	1.33 (0.74-2.37)
1 or 2 canisters	42.4	23.1	2.25	2.18 (1.18-4.02)
≥3 canisters	1.5	11.2	0.16	0.13 (0.02-0.97)
Mean no. of canisters	0.62	0.79	0.50‡	0.46 (0.26-0.79)§

\*The index date for case patients and matched controls was the date of the case patient's death from asthma. CI denotes confidence interval.

†All rate ratios are adjusted for the age and sex of the patient; the number of prescriptions for 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 dispensed in the year before the index date; and the number of hospitalizations for asthma during the two years before the index date.

‡The rate ratio per additional canister used during the year is given.

§The rate ratio per additional canister used during the six-month period is given.



**Figure 1.** Fitted Rate Ratio for Death from Asthma as a Function of the Number of Canisters of Inhaled Corticosteroids Used during the Year before the Index Date.

The index date for case patients and matched controls was the date of each case patient’s death from asthma. The rate ratio is adjusted for the age and sex of the patient; the number of prescriptions for 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 dispensed in the year before the index date; and the number of hospitalizations for asthma during the two years before the index date.

the one-year period. The rate of death from asthma among users of inhaled corticosteroids as compared with nonusers was reduced by about 50 percent with the use of more than six canisters per year. A similar curve (not shown) was found for the six-month period. Figure 1 also suggests that sporadic use of inhaled corticosteroids (fewer than four canisters per year) may be associated with higher rates of death from asthma.

As Table 3 shows, 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 (rate ratio, 4.6; 95 percent confidence interval, 1.1 to 19.1). The rate ratios after longer periods of interruption were also elevated, but not significantly so.

**DISCUSSION**

We found that the use of low-dose inhaled corticosteroids, such as several puffs of beclomethasone per day, is associated with a decreased risk of death from asthma. Our data also suggest that the discontinuation of inhaled corticosteroids can be detrimental.

The validity of our findings is strengthened by the increase in benefit observed with increased regularity of use and by the increase in risk with discontinuation of inhaled corticosteroids. The benefits occur at doses of corticosteroids that are lower than those associated with adverse ocular effects in adults and with decreased growth in children. Such doses are also associated with little or no biochemical evidence of systemic effects.<sup>22</sup> A prior study using the Saskatchewan data bases, although it suggested that inhaled corticosteroids had a beneficial effect in reducing the risk of life-threatening asthma, had insufficient power to examine death from asthma as the sole outcome.<sup>5</sup> Data on trends over time also suggest an association between declining death rates from asthma and increasing sales of inhaled corticosteroids, but the potential for bias makes such studies appropriate for generating hypotheses rather than proving them.<sup>12,23</sup>

Nonrandomized studies such as ours are susceptible to bias due to confounding by indication. Such bias would have occurred in the present study if patients with less severe asthma were more likely to have used inhaled corticosteroids. If there is any bias at all, it appears to have been in the reverse direction, since there was a slightly higher risk of death from

**TABLE 3.** CRUDE AND ADJUSTED RATE RATIOS FOR DEATH FROM ASTHMA IN RELATION TO DISCONTINUATION OF INHALED CORTICOSTEROID USE.\*

CORTICOSTEROID USE	CASE PATIENTS (N=66)	CONTROLS (N=2681)	CRUDE RATE RATIO	ADJUSTED RATE RATIO (95% CI)†
Uninterrupted (%)	4.6	7.9	1.0	1.0 (reference group)
Discontinued (%)				
1–3 mo before index date	19.7	9.0	3.9	4.6 (1.1–19.1)
4–6 mo before index date	4.6	6.3	1.3	1.8 (0.3–10.9)
7–9 mo before index date	4.6	5.3	1.7	1.6 (0.3–9.4)

\*The index date for case patients and matched controls was the date of the case patient’s death from asthma. CI denotes confidence interval.

†All rate ratios are adjusted for the age and sex of the patient; the number of prescriptions for 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 dispensed in the year before the index date; and the number of hospitalizations for asthma during the two years before the index date.

asthma among subjects who received at least one prescription for inhaled corticosteroids in the previous 12 months than among those who used no inhaled corticosteroids during that period. Furthermore, the greater benefit seen with increasing use and the high risk associated with discontinuation of therapy suggest that patients with more severe asthma may have been more likely to receive inhaled corticosteroids. Finally, we were able to adjust for many of the factors previously shown to be markers of the severity of asthma and the risk of death, such as prior hospitalization, use of oral corticosteroids, and excessive use of short-acting inhaled  $\beta$ -adrenergic agonists.

We believe that the most likely explanation of the excess risk of death from asthma shortly after the discontinuation of inhaled corticosteroid therapy is that such therapy was necessary to prevent death in these patients with asthma. The doses of inhaled corticosteroids used by most patients in this study were too low to result in adrenal insufficiency, a potential complication of the abrupt cessation of treatment with oral corticosteroids.

We excluded 11 deaths from consideration because they occurred during or within 1 year after an 18-month hiatus in the collection of information about drug prescriptions. There is no reason to believe that there was any significant difference between these 11 patients and the 66 patients whose deaths were included in the final analysis in terms of the severity of their asthma or the treatment they received. A strength of our study is that all deaths in this cohort of patients with asthma were identified, and that the cohort included all patients who were initially 5 through 44 years of age in the province of Saskatchewan to whom antiasthma drugs were dispensed on more than an occasional basis. We may have missed some deaths from asthma, because we included only deaths that two pulmonary physicians independently judged to have been due to asthma. There is no reason to believe, however, that missed case patients were more or less likely to have been prescribed inhaled corticosteroids, and therefore selection bias seems unlikely.

In conclusion, we found that the regular use of low-dose inhaled corticosteroids is associated with a decreased risk of death from asthma. This finding has important implications for the treatment of patients with asthma.

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Dr. Suissa is a consultant to Boehringer Ingelheim. Dr. Ernst is a consultant to Glaxo-Wellcome and Merck.

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**CORRECTION**

**Low-Dose Inhaled Corticosteroids and the Prevention of Death from Asthma**

Low-Dose Inhaled Corticosteroids and the Prevention of Death from Asthma . On page 335, in Figure 1, the curve should have started at 1, not at 0.