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Bronchospasm and cough as adverse reactions to the ACE inhibitors captopril, enalapril and lisinopril. A controlled retrospective cohort study

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1 We report a controlled retrospective cohort study of respiratory adverse reactions to ACE inhibitors. Bronchospasm and cough occurred at a higher rate in patients treated with ACE inhibitors, no links with sex, past history of bronchospasm, drug type or dose were found.

2 Cohorts of 1013 patients on angiotensin converting enzyme (ACE) inhibitors and 1017 patients on lipid lowering drugs (LLDs) were compared for the occurrence of new bronchospasm, relapse of previous bronchospasm, increase of current bronchospasm, and cough.

3 The prevalence of bronchospasm was 5.5% for patients on ACE inhibitors and 2.3% for patients on LLDs, $P < 0.001$. The relative risk of a bronchospasm adverse reaction for a patient on an ACE inhibitor compared with a patient on a LLD was 2.39, 95% confidence interval 1.47 to 3.90.

4 No ACE inhibitor specificity, or significant sex differences were found in the prevalence of bronchospasm or cough after correcting for bias implicit in the original cohorts. The bronchospastic reactions were not dose dependent.

5 The prevalence of a past history of bronchospasm in patients reporting ACE inhibitor-induced bronchospasm (16%) was not significantly different from the prevalence in patients on ACE inhibitors without an adverse reaction (13%), $P = 0.447$.

6 The prevalence of ACE inhibitor cohort cough was 12.3% and 2.7% in the patients on LLDs, $P < 0.0001$. Cough did not occur more commonly in patients on ACE inhibitors who had experienced any bronchospasm (28%) than in patients on LLDs with bronchospasm (27%).

Keywords angiotensin converting enzyme inhibitors adverse drug reactions bronchospasm cough cohort study

Introduction

Since the introduction of the first angiotensin converting enzyme (ACE) inhibitor captopril in the early 1980s, the ACE inhibitors have become widely prescribed for the treatment of hypertension and heart failure. The first three ACE inhibitors introduced into the New Zealand marketplace (captopril, enalapril and lisinopril) were included in the New Zealand Intensive Medicine Monitoring Programme (IMMP). This is a post-marketing event recording scheme which gathers information on all prescriptions of selected drugs and functions as an early warning system for adverse drug reactions. Captopril was monitored from April 1981 to December 1986, enalapril from June 1984 until January 1989 and lisinopril from February 1988 to March 1991.

By February 1992 the New Zealand Adverse Re-

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actions Centre had been notified of 596 respiratory adverse effects to the three ACE inhibitors monitored. Forty-eight percent of these were for enalapril, and 26% for both captopril and lisinopril; these proportions were not similar to the relative number of prescriptions recorded by the IMMP. Eight percent of the respiratory adverse reactions were for bronchospasm and dyspnoea, 86% were for cough and 6% were for less common reactions.

Post-marketing surveillance (PMS) and clinical trials have demonstrated a clear relationship between ACE inhibitor therapy and cough [1–4]. Estimates of the prevalence of this adverse reaction vary between 0.5% [5] and 27% [6].

Town *et al.* [7] in a study of ACE inhibitor associated cough which included patients with a history of obstructive airway disease, found some patients who had an increased nasal mucus production and one asthmatic who had increased sputum generation. This they proposed could lead to a cough from pharyngeal irritation.

Angiotensin converting enzyme is a zinc metalloenzyme dipeptidyl carboxypeptidase. Known active substrates include angiotensin I, bradykinin, enkephalins, chemotactic peptide, neurotensin, substance P and LHRH [8]. Many of these substrates are involved in bronchoconstriction and inflammation, their accumulation could lead to cough and/or asthma-like symptoms.

This paper describes a controlled cohort study which tests the hypothesis that there is an increased prevalence of bronchospasm and cough in patients taking one of the ACE inhibitors: captopril, enalapril or lisinopril.

Methods

Patient selection

Cohorts of patients on ACE inhibitors or lipid lowering drugs were compared for the occurrence of cough and new bronchospasm, relapse of previous bronchospasm, an increase in the symptoms of current bronchospasm, and cough.

The patients included were sourced from the New Zealand IMMP. The IMMP receives a copy of all prescriptions for monitored medicines. On the prescription form the prescribing doctor may indicate whether or not an adverse event has occurred. Adverse events include all clinical phenomena whether they seem associated to the drug treatment or not. The nature of the adverse event may be determined by further correspondence with the prescribing doctor. The prescription database for captopril consisted of 72 174 prescriptions, enalapril 89 017 prescriptions, lisinopril 41 776 prescriptions and the lipid lowering drugs (LLDs) 12 217 prescriptions.

The first prescription for each patient was selected. Duplications of patients due to variations (i.e. J. Horowitz and John Horowitz) in the data entered (name, address etc) were screened for and omitted. The captopril dataset consisted of 20 163 patients, enalapril 23 898 patients, lisinopril 11 235 patients and LLDs 4060 patients.

From the dataset of LLD patients, 3000 were randomly selected and matched on the characteristics of geographical area and age with patients from the combined captopril, enalapril and lisinopril dataset. The geographical area was known for all patients, age was known for only 39% of the ACE inhibitor cohort and 51% of the LLD cohort. Where age was unknown, patients of random age were used.

Questionnaires were sent by post to the prescribing doctors of the selected patients. Information about age, sex, smoking status, drug used, dosage of drug used, prior history of bronchospasm and changes in bronchospasm during ACE inhibitor therapy, occurrence of ACE inhibitor-induced cough, and post-nasal drip or increase in nasal mucus production was requested.

Patients were excluded if there was inadequate information to identify them or their prescribing doctor had died, retired or was unable to be traced. Of the initially selected 3000 patients in each cohort after exclusion these became; ACE inhibitor cohort n = 2441, LLD cohort n = 2205.

Analysis

Initial collation and analysis of the data was done using SAS/STAT release 6.03. Chi squared and Kolmogorov-Smirnov tests were done using Statview SE + Graphics for the Macintosh computer. Calculation of relative risk ratios and the corresponding 95% confidence intervals was carried out using the method of Morris & Gardner [9]. A relative risk of greater than one indicated a greater likelihood of patients on ACE inhibitors experiencing a bronchospasm reaction.

Verification of the responses to the questionnaire

As with any study which is reliant upon the return of questionnaires, it is important to consider what differences exist between those for whom a response was received and those for whom no response was received. We found no significant difference in the distributions of age, sex, and geographical location between the responders and non-responders.

Defining the valid study groups

A return period of 9 months was allowed for questionnaires to be accepted for analysis. The overall response rate was 58%. Sixty percent (1458 patients) for the ACE inhibitor cohort and 57% (1246 patients) for the LLD cohort.

After excluding patients whose records were no longer available, and those patients for whom grossly inadequate or contradictory information was supplied, only 41% (1013) of the 2441 patients on ACE inhibitors and 43% (1017) of the 2205 patients on LLDs were available for analysis.

Results

Demographic comparisons

The age ranges of the two cohorts were different, 53% of the ACE inhibitor cohort was over the age of 60 years compared with 42% of the LLD cohort (Kolmogorov-Smirnov test D(n) = 0.177, D(90:SS) = 0.062, D(n) > D(90:SS)).

The ACE inhibitor cohort consisted of 54% females and 46% males, whereas the LLD cohort consisted of 46% females and 54% males. This difference was significant; chi-squared statistic = 12.683, P = 0.0018. The gender proportions of both cohorts were statistically similar to the proportions found within the appropriate IMMP patient datafiles.

The patients in each cohort were geographically distributed throughout New Zealand in a similar fashion. The distribution reflected the normal demographic proportions of the entire population.

Prevalence of bronchospasm

Reported bronchospasm was grouped into four possible events (see Table 1); 1 – new onset bronchospasm after drug therapy, 2 – an increase in the symptoms of current bronchospasm, 3 – a relapse of prior bronchospasm, and 4 – prior history of bronchospasm unchanged after treatment. Chi-squared goodness of fit tests performed on the distributions showed a significant difference between the cohorts, chi-squared statistic = 45.702, P = 0.0001. Even when those with a prior history of bronchospasm are excluded from the bronchospasm adverse reaction group a significant difference between the cohorts still exists, chi-squared statistic = 9.156, P = 0.0025. The relative risks for the four groups of bronchospasm are shown in Figure 1.

The patients who were reported to have had their first episode of bronchospasm, an increase in current or a relapse of prior bronchospasm whilst on the investigated drug, were considered to have experienced a putative bronchospasm adverse reaction to the investigated drug, called for the purposes of this paper a bronchospasm reaction or putative bronchospasm reaction (Table 2).

Patients in the ACE inhibitor cohort had a 5.5% prevalence of bronchospasm reactions, compared with 2.3% of patients on LLDs, chi-squared statistic = 13.43, P = 0.0002.

The relative risk of a patient experiencing a bronchospasm reaction whilst on an ACE inhibitor compared with a patient on a LLD was 2.39 (95% confidence interval 1.47–3.90) see Figure 1.

Past history of bronchospasm

Patients on ACE inhibitors had a higher prevalence of a past history of bronchospasm (13%) than those on LLDs (5%). But those on ACE inhibitors with bronchospasm reactions did not have a significantly higher prevalence of past history of bronchospasm (16%) than those on ACE inhibitors without bronchospasm reactions (13%); (chi-squared statistic = 0.58, P = 0.447).

Indication for ACE inhibitor use

A significantly higher number of patients with putative bronchospasm reactions were receiving ACE inhibitors for heart failure or heart failure combined with hypertension; 39% compared with 23% in the overall cohort (chi-squared statistic = 7.5, P = 0.02). All of the remaining patients were receiving the ACE inhibitor for hypertension. If all heart failure patients are excluded from the putative bronchospasm group (i.e. all considered to be cardiac asthma) no significant increase in bronchospasm prevalence is measured (chi-squared statistic = 3.1, P = 0.0781), however, it would take only three of these 22 cases to be adverse reactions before a significant difference was noticed (chi-squared statistic = 4, P = 0.0458). No significant differences in the indication for use were seen in those patients experiencing ACE inhibitor-induced cough (chi-squared statistic = 1.8, P = 0.4031).

Gender effects (Table 3)

There was no significant difference in the prevalence of female patients experiencing a bronchospasm adverse reaction compared with male patients in either the ACE inhibitor cohort (chi-squared statistic = 0.43, P = 0.5104) or the LLD cohort (chi-squared statistic = 0.13, P = 0.7215).

ACE inhibitor specificity

Neither of the three drugs studied differed greatly in their ability to cause bronchospasm or cough adverse reactions, chi-squared statistic = 0.900, P = 0.6377.

Table 1 Comparison of bronchospasm events between cohorts

Cohort	*New onset*	*Increase current*	*Relapse prior*	*No change*	*No bronchospasm*	*Totals*
ACEI cohort	32 (4%)	11 (1%)	10 (1%)	108 (11%)	800 (83%)	961
LLD cohort	12 (1%)	3 (0%)	7 (1%)	44 (5%)	888 (93%)	954

Percentages are relative to the appropriate figure in the Totals column.
The rate of new onset, increased current and relapse of prior bronchospasm for the LLD cohort may be considered as a measure of the sporadic onset of bronchospasm expected in an age matched population.
Bronchospasm was unknown in 52 patients of the ACE inhibitor cohort and 63 patients of the LLD cohort.

Daily dosage of ACE inhibitor cohort

The mean daily dose of medicine for patients on ACE inhibitors with a bronchospasm reaction was 22 mg day^{-1} and for those without a bronchospasm reaction was 26 mg day^{-1}. These dosages are not significantly different, chi-squared statistic = 0.345, = 0.8417.

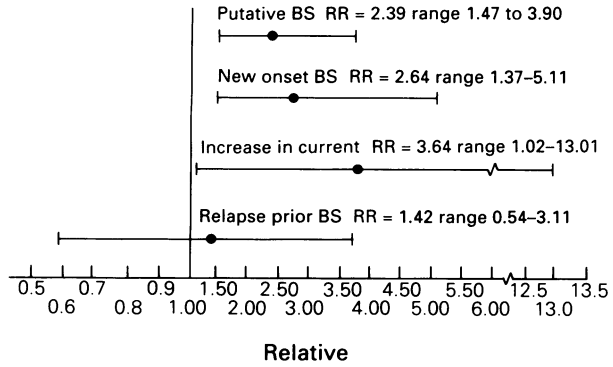

Figure 1 The relative risks (RR) (ACE inhibitor/LLD) for a patient to experience a bronchospasm adverse reaction and contributory bronchospastic events. If the Relative Risk = 1.00 there is no increased risk for the variable between the cohorts.

Table 2 Comparison of bronchospasm reactions between cohorts

Cohort	*Bronchospasm reaction*	*No bronchospasm reaction*	*Totals*
ACEI cohort	53 (5.5%)	908 (94.5%)	961
LLD	22 (2.3%)	932 (97.7%)	954

Percentages are relative to the appropriate figure in the Totals column.
Bronchospasm reaction is defined as new onset bronchospasm or an increase in current or relapsed prior bronchospasm. Bronchospasm was unknown in 52 patients of the ACE inhibitor cohort and 63 patients of the LLD cohort. These patients were excluded from analysis.

Occurrence of cough with putative bronchospasm adverse reactions (Figure 2)

Significantly more patients on ACE inhibitors (13%) experienced a cough reaction than did patients on LLDs (2%), (chi-squared statistic = 22.82, P = 0.0001).

To ascertain whether or not the bronchospasm reaction occurred more frequently in patients with ACE inhibitor-induced cough, those who had both bronchospasm reactions and cough reactions were compared with those who had only one of the two. Twenty-eight percent of those on ACE inhibitors with a bronchospasm reaction also experienced ACE inhibitor-induced cough, compared with a cough prevalence of 27% for those on LLDs with a bronchospasm reaction. This difference was not significant (chi-squared statistic = 0.1, P = 0.928). The 28% experiencing both cough and bronchospasm on ACE inhibitors is significantly different from the 12% of patients on ACE inhibitors who experienced cough but no bronchospasm (chi-squared statistic = 10.91, P = 0.001).

Of all patients on ACE inhibitors 13% experienced a putative ACE inhibitor-induced cough, compared with 4% of those on LLDs who did not experience a bronchospasm reaction (chi-squared statistic = 27.75, P = 0.0001).

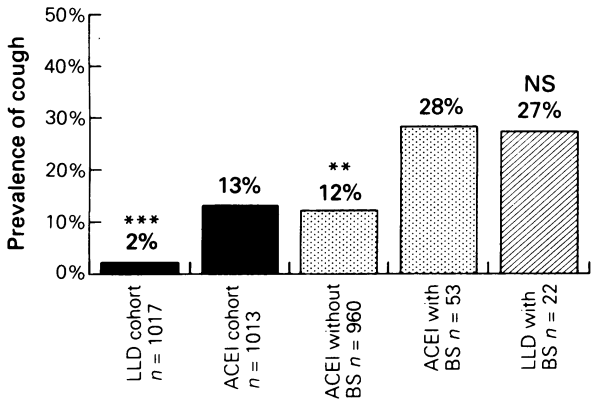

Figure 2 All figures are presented as a percentage of n. LLD = lipid lowering drug, ACEI = angiotensin converting enzyme inhibitor, BS = bronchospasm. $^{**}P < 0.01$, $^{***}P < 0.001$, NS not significant.

Table 3 Comparison of bronchospasm reactions between sexes

Group	*Bronchospasm reaction* *Female*	*Male*	*No bronchospasm reaction* *Female*	*Male*	*Totals*
ACEI	31 (58%)	22 (42%)	429 (54%)	370 (46%)	852
LLD	11 (50%)	11 (50%)	408 (46%)	479 (54%)	909

Gender was unknown for 161 patients in the ACE inhibitor cohort and 108 patients in the LLD cohort. These patients are excluded from analysis. Percentages are relative proportions of male and female within each reaction group.

Table 4 Gender comparison between bronchospasm and cough reactions and total cohort

Group	*Bronchospasm reaction*		*Cough reaction*		*Total cohort*	
	Female	*Male*	*Female*	*Male*	*Female*	*Male*
ACEI cohort	31 (58%)	22 (42%)	70 (59%)	49 (41%)	547 (54%)	464 (46%)

Percentages are relative proportions of male and female within each reaction group.

Gender proportions of the adverse reactions

Those who experienced ACE inhibitor cough and bronchospasm adverse reactions were divided into gender groups and the proportions were compared between the two adverse reactions and with the overall cohort (Table 4).

Contrary to the findings of Coulter & Edwards [1] the distributions of gender between the adverse reactions and the total cohort were similar (chi-squared statistic = 1.27, $P = 0.531$).

Post-nasal drip

There was a significant difference in the prevalence of post-nasal drip. Four percent of patients on ACE inhibitors reported an increase in nasal mucus production or post-nasal drip compared with 2% of patients on LLDs (chi-squared statistic = 12.43, $P = 0.0004$).

Discussion

In this retrospective controlled cohort study bronchospasm adverse reactions occurred 2.39 times more frequently in patients taking ACE inhibitors than in patients taking LLDs. The prevalence rate on ACE inhibitors was 5.5% and this was significantly greater ($P \leq 0.001$) than the 2.3% recorded in the control cohort. The prevalence of increased or new bronchospasm in the control cohort should be considered as a measure of the prevalence of new bronchospastic events in an age matched population.

Of the events which make up the bronchospasm reactions, new onset bronchospasm occurred 2.64 times more frequently in the ACE inhibitor patients than the LLD patients, increase in current bronchospasm 3.64 times more frequently and relapse of prior bronchospasm 1.42 times more frequently.

The term bronchospasm was not defined in the questionnaire. Bronchospasm was used in preference to the terms wheezing or bronchial hyper-responsiveness, this was because bronchospasm implies a narrowing of the airways but does not have defined limits to its clinical presentation. This 'terminology' allowed the questioned doctors the freedom to use their clinical judgement and report all cases of what they considered to be bronchospasm.

Considerably more patients on ACE inhibitors than LLDs had experienced bronchospasm previous to the drug therapy, this may reflect preferential prescribing of ACE inhibitors rather than β-adrenoceptor blockers to patients with a past history of bronchospasm. This source of potential confounding has been overcome by comparing past history of bronchospasm only between groups within each cohort; i.e. comparing past history of bronchospasm of those on ACE inhibitors without an adverse reaction with those on ACE inhibitors with an adverse reaction. This technique did not find past history of bronchospasm a risk factor for developing an ACE inhibitor-induced respiratory adverse reaction.

Twenty-eight percent of patients with ACE inhibitor-induced bronchospasm also coughed whereas only 12% of patients without ACE inhibitor-induced bronchospasm coughed. This may indicate that ACE inhibitor-induced cough contributes to or is associated with the ACE inhibitor-induced bronchospasm. Unfortunately the data we collected was unable to determine what proportion of the reported cough was aetiologically ACE inhibitor-induced and what proportion was aetiologically due to bronchospasm. Further consideration of linkages between the bronchospasm and cough are beyond the scope of this prevalence study and require elaboration by a case-comparison study.

Many of the clinical studies and post-marketing surveillance studies reported to date are uncontrolled or inappropriately controlled, and are subject to gender bias. This bias occurs because the studies rely on there being a similar prevalence of circulatory disease and self-reporting of drug-induced morbidity to doctors in both males and females. Both of these factors are proportionately higher in women [10].

Gender was not a matched variable for this study and the gender proportions of the two cohorts were opposite; Cooper *et al.* [11] found similar proportions. Gender differences (with females predominating) in the prevalence of the ACE inhibitor induced cough have been reported by several clinic based studies [4, 7, 12–14], and one PMS study [1]. In our study the prevalence of cough and bronchospasm reactions in females was not statistically different from the 54% predominance of women in the entire ACE inhibitor cohort.

No differences in the ability of each of the three ACE inhibitors to cause the adverse reaction were found. Neither the bronchospasm nor cough adverse reactions were dose dependent; a result similar to that found for the cough adverse reaction reported by McEwan [15].

In conclusion this controlled retrospective cohort study collected data from 1013 patients on ACE inhibitors and 1017 patients on the lipid lowering drug

bezafibrate. It was designed to measure the prevalence of bronchospasm adverse reactions. An increased rate of both cough and bronchospasm adverse reaction was found. Prior asthma or bronchospasm was not a risk factor, the two adverse reactions had similar demography and were not drug or gender specific.

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