ORIGINAL RESEARCH ARTICLE

Drug Safety 2001; 24 (6): 475-481
0114-5916/01/0006-0475/$22.00/0

Age- and Gender-Specific Asthma Death Rates in Patients Taking Long-Acting β_2-Agonists

Prescription Event Monitoring Pharmacosurveillance Studies

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Abstract

Objective: Prescription event monitoring is a national drug safety surveillance scheme in which prescribers are prompted to report events and deaths following prescription of newly marketed drugs. This paper presents age- and gender-specific asthma death rates in patients prescribed the long-acting β_2-agonists salmeterol and bambuterol.

Design and setting: Pharmacosurveillance cohort study of general practice patients in England.

Patients and participants: 15 406 patients prescribed salmeterol between December 1990 and May 1991, and 8098 patients prescribed bambuterol between February 1993 and December 1995.

Methods: Patients prescribed these drugs by general practitioners in England were identified using the national pharmacovigilance system of prescription event monitoring, in which details of all dispensed prescriptions were provided in confidence by the Prescription Pricing Authority. Questionnaires were sent to the prescriber asking for details of events occurring after the first prescription. In each study an attempt was made to establish the cause of all deaths reported on the questionnaires, via retrieval of the patients' medical notes or examination of death certificates.

Outcome measures and results: There was little evidence of heterogeneity in the drug-specific death rates and we therefore present the combined age- and gender-specific death rates for the 2 cohorts. Overall, there were 85 asthma deaths among people taking the long-acting β_2-agonists studied (bambuterol and salmeterol cohorts combined). The overall death rate was 2.33 [95% confidence interval (CI) 1.84 to 2.84] per 10 000 months of observation. There were 37 asthma deaths among male patients (rate 2.40 per 10 000 months of observation; 95% CI 1.74 to 3.40) and 48 asthma deaths among female patients (rate 3.08 per 10 000 months of observation; 95% CI 2.21 to 3.98). There was no difference in death rates when male and female patients were compared (rate ratio 0.78; 95% CI 0.49 to 1.22; $p = 0.26$).

Conclusion: Prescription event monitoring is a form of prompted surveillance allowing rapid, uniform, national and practical assessment of newly marketed

drugs on large cohorts of patients in England. These data provide benchmark rates from which to assess the performance of newly prescribed anti-asthma drugs and generate hypotheses for later analytical investigation in which confounding by indication and asthma severity can be controlled for. Any differences in these rates should be considered as a source of signal generation within the context of a surveillance programme, rather than as robust evidence of any mortality differential between drugs.

Concerns over the relationship between asthma-related deaths and drugs used for the treatment of symptomatic asthma were first raised as early as 1948.[1] An increase in asthma deaths in several countries followed the introduction in the 1960s of inhalers delivering a high dose formulation of the nonselective β-agonist isoprenaline (isoproterenol).[2] In the late 1970s a sharp rise in asthma deaths occurred in New Zealand following the introduction of the more selective β_2-agonist fenoterol,[3] and debate over reasons for these and other secular trends in asthma mortality has been conducted ever since.[4-9]

Since the late 1980s death rates from asthma in the general population declined significantly in England and Wales,[10] perhaps reflecting increased use of prophylactic treatment.[11] However, there are few data on death rates from asthma among patients prescribed anti-asthma drugs. In a study of 12 301 users of asthma drugs from Saskatchewan, Canada, the overall asthma mortality rate was 0.8 per 10 000 patient-months of observation.[9] Asthma mortality rates per 10 000 patient-months of observation were 1.6, 5.1 and 3.6 among patients exposed to oral β_2-agonists, the inhaled β_2-agonist fenoterol and nebulised β_2-agonists, respectively.

From a public health perspective it is essential that surveillance schemes involving large cohorts of patients are constructed with which to monitor newly marketed anti-asthma drugs. Voluntary reporting is a key component of drug safety surveillance in many countries, but there are a number of disadvantages.[12] First, surveillance is passive, waiting for the prescriber to report, and it is well known that there is significant under-reporting of even serious events. Secondly, the scheme is characterised by numerator data only, and the absence of a denominator makes comparisons between drugs difficult. Prescription event monitoring in England is a national form of pharmacosurveillance which is active, i.e. prescribers are prompted to report all events and deaths following the prescription of newly marketed drugs. In addition, the denominator is known. By closely monitoring crude and age- and gender-specific event rates, signals can be generated that lead to formal analytical epidemiological studies in which confounding by indication and severity, for example, can be controlled for.[13,14] However, some assessment of expected rates is required in order to generate signals for further enquiry, and such data are often lacking.

We conducted 2 surveillance studies in general practice in England among patients prescribed the long-acting inhaled β_2-agonist salmeterol[15] and patients prescribed the long-acting oral β_2-agonist bambuterol. As part of these studies we monitored age- and gender-specific asthma death rates. This paper presents the baseline results from this surveillance and discusses some of the difficulties encountered when interpreting pharmacosurveillance studies.

Methods

We analysed data from the prescription event monitoring database of the Drug Safety Research Unit, which has performed cohort studies on salmeterol and bambuterol prescribed by general practitioners (GPs) in England soon after their respective UK launch.[15-17] A total of 28 019 patients in England received at least 1 salmeterol prescription between December 1990 and May 1991, and a total of 18 013 patients received at least 1 bambuterol prescription between February 1993 and December 1995. Event data were obtained from questionnaires sent to prescribers asking for details of all new events

occurring after the first prescription. In the salmeterol cohort the questionnaires were sent out 12 months after the first prescription for each patient, and in the bambuterol cohort the questionnaires were sent out 6 months after the first prescription for each patient.

Deaths

In each study an attempt was made to establish the cause of all deaths reported on the questionnaires, whether or not the death was suspected to be related to drug exposure. In the salmeterol study, all patients who died during the observation period were followed up with a letter to the GP requesting permission to retrieve the patients' notes from the Family Health Services Authority.[15] These notes were used to identify the cause of death. If no cause of death was recorded in the patients' notes or if they were unobtainable, copies of death certificates were requested from the Office of Population Censuses and Surveys [now the Office for National Statistics (ONS)]. In the bambuterol study the death certificate was requested from the ONS for all asthma deaths. If any cause of death remained uncertain or the death was possibly drug-related, the GP was asked to give permission for the Drug Safety Research Unit to retrieve the patients' notes from the Health Authority. These notes were used to identify the cause of death. In both studies the final cause of death was established by consensus and was unblinded to exposure.

Analysis

We calculated age- and gender-specific asthma death rates for the 2 drug cohorts combined. In an initial drug-specific analysis we found no statistical evidence of heterogeneity in asthma death rates among males ($p = 0.3$) and only limited evidence of heterogeneity among females ($p = 0.03$) when bambuterol was compared with salmeterol. However, because absolute differences in asthma death rates were small and because uncontrolled confounding by indication and asthma severity could have explained the female-specific differences between bambuterol and salmeterol, further analysis was restricted to the combined cohorts. Rates were the numbers of deaths per 10 000 months of exposure during the first 12 months after the drug was first prescribed in the case of salmeterol and the first 6 months after the drug was first prescribed in the case of bambuterol. Person-months of exposure were calculated from the date the drug was first prescribed by the GP, with censoring at the date of death or the date the patient stopped the drug, or at the end of the 12- or 6-month follow-up period if the drug was not stopped. The date of death or the date the patient was no longer registered with the practice was used as the censoring time if these dates occurred before the end of follow-up and the drug had not been discontinued. Confidence intervals (CIs) for the age-specific rates were calculated by regarding each observed number of cases as a Poisson variable. Analysis was conducted using Stata statistical software.[18]

Results

The characteristics of the cohorts are given in table I. The salmeterol cohort consisted of 15 406 patients, 55.0% of the total of 28 019 patients in England who received at least 1 salmeterol prescription between December 1990 and May 1991. The bambuterol cohort consisted of 8098 patients, 45.0% of the total of 18 013 patients in England who received at least 1 bambuterol prescription between February 1993 and December 1995. The total number of patient-months of observation in the salmeterol and bambuterol cohorts was 280 982 and 84 465, respectively. The median number of months of observation was 17.0 (interquartile range 14.4 to 21.9) in the salmeterol cohort and 9.6 (7.9 to 12.3) in the bambuterol cohort. There was a higher proportion of male patients in the salmeterol cohort (7844; 51%) compared with the bambuterol cohort (3631; 45%). The median age of the salmeterol cohort (55 years; interquartile range 34 to 67 years) was lower than in the bambuterol cohort (60 years; interquartile range 38 to 72 years). The proportion of patients with a diagnosis of asthma/wheeze and chronic obstructive airways disease (COAD) was 70 and 12%, respectively, in the salmeterol cohort,

Table I. Characteristics of the cohorts

Characteristic	Salmeterol	Bambuterol
Dates of studies	December 1990 to May 1991	February 1993 to December 1995
Total number of questionnaires posted	28 019	18 013
Total number of questionnaires returned with usable data[a] [response rate (%)]	15 406 (55.0)	8098 (45.0)
Overall number of patient-months of observation	280 982	84 465
Median number of patient-months of observation (interquartile range)	17.0 (14.4 to 21.9)	9.6 (7.9 to 12.3)
Males (% of cohort)	7844 (50.9)	3631 (44.8)
Females (% of cohort)	7444 (48.3)	4400 (54.3)
Gender not known	118 (0.8)	67 (0.8)
Median age (years) [interquartile range]	55 (34 to 67)	60 (38 to 72)
Recorded indication for study drug (%)		
asthma/wheeze	10 820 (70.2)	4798 (59.2)
chronic obstructive airways disease	1816 (11.8)	1209 (14.9)
other[b]	424 (2.8)	879 (10.9)
unknown	2346 (15.2)	1212 (15.0)

a Final cohort.

b Other diagnoses (with n > 10) were, in the salmeterol cohort: dyspnoea (141), bronchitis (84), emphysema (81), cough (52), bronchiectasis (15) and cystic fibrosis (10); in the bambuterol cohort: bronchitis (271), dyspnoea (263), cough (206), chest infection (161), emphysema (42), bronchiectasis (13) and tight chest (12).

and 59 and 15% in the bambuterol cohort. GPs were more likely to record 'other' diagnoses in the bambuterol cohort (11%) compared with the salmeterol cohort (3%). This was attributable to greater use of nonspecific terms such as 'bronchitis', 'dyspnoea' and 'cough' in the bambuterol cohort.

There were a total of 1022 deaths in the salmeterol cohort (crude rate 36 per 10 000 patient-months of observation) and 472 deaths in the bambuterol cohort (crude rate 56 per 10 000 patient-months of observation). There were a total of 362 deaths from COAD in the salmeterol cohort (crude rate 13 per 10 000 patient-months of observation) and 104 deaths from COAD in the bambuterol cohort (crude rate 12 per 10 000 patient-months of observation).

Overall, there were 85 deaths from asthma during 365 447 patient-months of observation among people taking the long-acting β_2-agonists studied (bambuterol and salmeterol cohorts combined) [table II]. The overall death rate was 2.33 (95% CI 1.84 to 2.84) per 10 000 patient-months of observation. There were 37 asthma deaths among male patients (rate 2.40 per 10 000 patient-months of observation; 95% CI 1.74 to 3.40) and 48 asthma deaths among female patients (rate 3.08 per 10 000 patient-months of observation; 95% CI 2.21 to 3.98) prescribed the long-acting β_2-agonists in this study. There was no difference in death rates when males were compared with females (rate ratio 0.78; 95% CI 0.49 to 1.22; $p = 0.26$). Death rates were highest in people aged 60 to 69 years and 80 to 89 years for both men and women.

Discussion

The overall death rate from asthma among patients taking the long-acting β_2-agonists bambuterol and salmeterol combined was 2.33 (95% CI 1.84 to 2.84) per 10 000 patient-months of observation. In a cohort study of 12 301 patients with asthma on the computerised databases of the Saskatchewan health insurance plan,[9] the asthma mortality rate in patients exposed to oral β_2-agonists was 1.6 per 10 000 patient-months of observation. For patients who had any exposure to fenoterol by metered dose inhaler or to nebulised β_2-agonists, the asthma mortality rates were 5.1 and 3.6 per 10 000 patient-months of observation, respectively.

We emphasise that the 2 studies reported in this paper were national surveillance studies and not analytical epidemiological studies. Thus, our aim is not to provide best estimates of asthma death rates after controlling for all potential confounding factors, but rather to inform the otherwise limited evidence base for future postmarketing surveillance, early warning and signal generating studies of anti-asthma drugs. The methods of prescription event monitoring closely resemble those of surveillance routinely carried out to provide early warnings about patterns of communicable diseases. Surveillance has been defined as 'continuous analysis, interpretation, and feedback of systematically collected data, generally using methods distinguished by their practicality, uniformity and rapidity, rather than by accuracy or completeness.'[19] The main limitations of this study are therefore closely related to its strengths as a system of surveillance. The technique of prescription event monitoring may provide rapid signals of adverse events associated with newly marketed drugs that can be examined in hypothesis testing studies, or can confirm signals generated elsewhere, such as via the spontaneous reporting yellow-card scheme.[20]

It is important to discuss in detail the limitations of surveillance by prescription event monitoring. The data were derived from observational cohort studies carried out at different time periods. We have deliberately not compared asthma death rates between the 2 drugs since several differences in the patient population could explain any variation in rates. First, recent evidence suggests that since the late 1980s there has been a significant decline in asthma deaths in people aged 85 years or younger.[10] Secondly, there may have been differences in the patients selected to receive these different types of long-acting β_2-agonists in the different time periods studied. We were unable to control for potential differences in indication for treatment, severity of asthma, concurrent illness or concomitant medications. A clinical review of the patients who

Table II. Age- and gender-specific asthma death rates in patients taking long-acting β_2-agonists (bambuterol and salmeterol combined)

Age (years)[a]	No. of deaths	Patient-months of observation	Rate per 10 000 patient-months of observation	95% confidence interval of rate	
				lower limit	upper limit
Men					
20 to 29	1	9918.1	1.01	0.03	5.57
30 to 39	2	13 139.2	1.52	0.24	7.22
40 to 49	3	17 626.5	1.70	0.31	4.38
50 to 59	2	28 510.0	0.70	0.08	2.41
60 to 69	16	45 376.7	3.53	1.83	5.20
70 to 79	9	32 032.2	2.81	1.37	5.70
80 to 89	4	7589.4	5.27	1.09	10.24
All men	37	154 192.1	2.40	1.74	3.40
Women					
20 to 29	1	13 723.7	0.73	0.03	5.57
30 to 39	5	16 587.2	3.01	0.81	5.83
40 to 49	4	23 202.1	1.72	0.55	5.12
50 to 59	8	29 360.2	2.72	1.15	5.25
60 to 69	18	37 474.2	4.80	2.67	7.11
70 to 79	8	27 776.6	2.88	1.15	5.25
80 to 89	4	7815.0	5.12	1.09	10.24
All women	48	155 939.0	3.08	2.21	3.98
Gender unknown					
All ages	0	55 315.9	0		
Total	**85**	**365 447.0**	**2.33**	**1.84**	**2.84**

a Age at death.

died from asthma in the salmeterol cohort suggested that these patients were a frail elderly group.[15] Thirdly, there may have been differences in the use of prophylactic treatments, which we were also unable to control for. Fourthly, the accuracy of death certification for asthma is poor, particularly among the elderly where the differential diagnosis between COAD and asthma is often imprecise.[21] Fifthly, there was a low response rate to the questionnaires (55% for salmeterol and 45% for bambuterol), which would bias estimates if death rates differed in patients for whom a response was not obtained. However, this is a good response rate compared with the underreporting observed in voluntary reporting schemes and other surveillance schemes.[12] Finally, we computed death rates for the whole cohort, which included patients with asthma and COAD. The data on indications are weak in this study since they relied on the GP's reported diagnosis. Furthermore the high rate of 'unknown' indications and the differential use of 'other' diagnoses by GPs (such as cough, dyspnoea and bronchitis) could distort results stratified by indication because we do not know whether the true underlying diagnosis was asthma or COAD. Therefore, we have not attempted to stratify the results by indication. In more recent cohorts, the technique of prescription event monitoring has been developed to obtain better data on indication, severity and comorbidity,[22] but these data were not available for the current study.

Conclusions

These surveillance studies provide crude benchmark rates with which to monitor age- and gender-specific asthma deaths in large pragmatic post-marketing prescription event monitoring studies of newly launched anti-asthma drugs. However, any differences in these rates should be considered as a source of signal generation within the context of a surveillance programme, rather than as robust evidence of any mortality differential between drugs. Future prescription event monitoring studies will also need to take account of trends in background asthma mortality rates over time.

Acknowledgements

We would like to record our keen appreciation of the cooperation of the general practitioners and numerous other colleagues who have helped in this investigation. In addition we wish to thank the Prescription Pricing Authority, the Health Authorities of England and the Office for National Statistics for their important participation. Gilian Pearce managed the prescribing and analytical database. The Drug Safety Research Unit is an independent charity that works in association with the University of Southampton. It receives unconditional donations from pharmaceutical companies. The companies have no control of the conduct or the publication of the studies conducted by the Unit. The Unit has received such funds from Glaxo Wellcome and Astra Zeneca.

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