Prescribed fenoterol and death from asthma in New Zealand, 1981–7: a further case-control study

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Abstract

The association between inhaled fenoterol and death from asthma has been investigated further by studying 112 asthma deaths (cases) during 1981–7 in patients aged 5–45 years who had been admitted to a major hospital for asthma during the 12 months before death. Two age matched control groups were chosen. Control group A comprised 427 patients who had been admitted to hospital for asthma during the calendar year that the corresponding death occurred and who had also had a previous admission for asthma in the previous 12 months. Control group B comprised 448 patients admitted to hospital for asthma during the calendar year in which the admission of the corresponding case occurred. The inhaled fenoterol odds ratio was 2·11 (95% confidence interval (CI) 1·37–3·23, $p < 0·01$) when group A was used as the control (the approach used in previous studies), and 2·66 (95% CI 1·74–4·06, $p < 0·01$) with group B as the control (the approach recommended by critics of previous studies). Markers of chronic asthma severity were associated with asthma death when control group B was used, but not when control group A was used (which indicates that these markers were indirectly matched for when control group A was used). Information was also collected on various markers of acute asthma severity and prescription of psychotropic drugs, but it was found that these were not important confounders. These findings address the major criticisms of previous case-control studies of this issue, and add support to the hypothesis that inhaled fenoterol increases the risk of death in patients with severe asthma.

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Two recent New Zealand case-control studies,[1 2] conducted by our group, evaluated the hypothesis that the unsupervised self administration of fenoterol by inhalation increases the risk of death from asthma. The first national case-control study[1] compared the prescribed drug treatment of patients aged 5–45 years who died of asthma during August 1981–July 1983 with that of patients with severe asthma who did not die. The findings were consistent with the hypothesis that inhaled fenoterol increases the risk of death in patients with severe asthma. Some possible sources of bias were not excluded, however, particularly as information on prescribed drug treatment for asthma was obtained from different sources for cases and controls. The same hypothesis was evaluated in the second national case-control study,[2] which examined asthma deaths during January 1977–July 1981; information on prescribed medication for asthma was obtained from hospital notes for all cases and controls, and the findings were similar to those of the first national study.

We have now conducted a further case-control study of deaths in New Zealanders aged 5–45 years during August 1981–December 1987. The study includes some deaths (August 1981–July 1983) from the first national case-control study,[1] but uses a different study design and different data sources. The current study uses a design similar to that of the second national case-control study,[2] but with several refinements in response to criticisms.[3 4] In particular, a second control group has been added, and further information has been collected on markers of acute and chronic asthma severity and of psychosocial problems, to enable possible sources of bias to be assessed. This paper is primarily orientated to a discussion of methodological issues, rather than being a simple replication of previous studies.

Methods

SELECTION OF CASES

The study was based on 32 hospitals throughout New Zealand. The potential cases comprised all patients aged 5–45 years who died from asthma in New Zealand from August 1981 to December 1987, and who had been admitted to a major hospital for asthma during the 12 months before death. The study was again confined to the 5–45 year age group as death from asthma is a reasonably clearcut diagnosis in this age group.[5] Asthma deaths (ICD code 493) were identified from registrations at the National Health Statistics Centre. For each death the records of hospitals to which the patient was likely to have been admitted in an acute attack were then searched to identify any admission for asthma in the previous 12 months. If such an admission was identified the death was included in the study, and the admission closest to death was used as the index admission.

SELECTION OF CONTROLS

Control group A was selected in the same manner as in the second national case-control study.[2] Figure 1 illustrates this process (it shows the ideal situation in which the case and

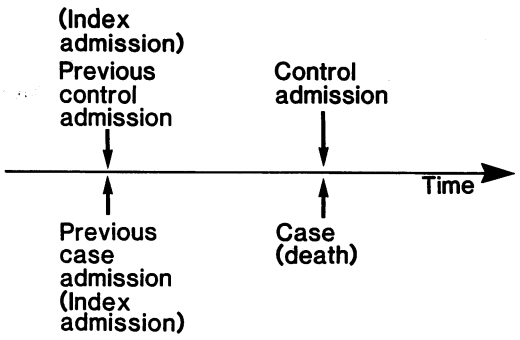

Figure 1 Selection of control group A.

control events took place on exactly the same dates but, as described below, the matching was less exact in practice). For each case potential controls were selected from patients discharged from the same hospital, with the diagnosis of asthma, in the calendar year in which the death occurred. The admission records for each potential control were then examined to determine whether the patient had had a previous hospital admission for asthma during the 12 months before the admission under consideration. If such an admission was found the patient was included as a control.

Control group B was selected in a more straightforward manner (fig 2). For each case potential controls were selected from all patients discharged from the same hospital with the diagnosis of asthma in the calendar year in which the case index admission occurred.

For each case four controls, matched by age within five years, were chosen for each control group. If sufficient controls could not be obtained then the acceptable age range was widened within the 5–45 year age range (four group A controls and three group B controls were aged 46–47 years) and the acceptable calendar period was widened within the period 1981–7. For 29 cases insufficient group A controls were available from the relevant hospital and 78 of their controls were selected from other hospitals in the same region. For 20 cases insufficient group B controls were available from the relevant hospital and 58 of their controls were selected from other hospitals in the same region. All cases and controls were considered to have been admitted primarily for asthma, as indicated by the discharge coding.

INFORMATION ON PRESCRIBED DRUG TREATMENT AND SEVERITY MARKERS

Information was extracted from records relating to the index admission (see fig 1 and 2). As in previous studies,[1 2] patients for whom an ethnic group was not recorded in the notes were assumed to be European (the proportion of patients whose ethnic group was not recorded was much greater in the current study and comprised about 28% of the cases and of each control group). Prescribed drug treatment at the time of the index admission was recorded from the case notes, the accident and emergency department notes, and the general practitioner's letter. Prescribed medication at time of discharge was recorded from the admitting officer's discharge notes, the discharge letter, and the discharge prescription. The data could not be recorded "blind," but the researchers were instructed to record all drug information from these sources. The data forms were copied and all information that identified cases and controls was deleted. Three members of the study team (CB, RB, and JC) then made a blind assessment of the drugs at admission and discharge. In some instances (five cases, six group A controls, and 11 group B controls) little information was available on the prescribed medication at the time of discharge, and we assumed that it was the same as the prescribed medication at the time of admission.

As in the previous study,[2] the possibility of confounding or effect modification by severity was assessed by considering various subgroups defined by markers of chronic severity: (1) prescription of three or more categories of asthma drugs at the time of the index admission; (2) a hospital admission for asthma during the 12 months before the index admission; (3) prescription of oral corticosteroids at the time of the index admission. Information was also collected on various markers of acute asthma severity at the time of the index admission, and (when available) for a previous admission during the 12 months before the index admission. These included: arterial carbon dioxide tension ($PaCO_2$), plasma potassium concentration (K^+), forced expiratory volume in one second (FEV_1), and peak expiratory flow (PEF). When it was stated in the notes that the peak flow rate was unrecordable or very low at the time of admission it was recorded as 50 l/min.

DATA ANALYSIS

The Mantel-Haenszel procedure[6] was used for calculation of odds ratios and of test based confidence intervals.[7] Logistic regression[8] was also used to calculate odds ratios adjusted for age, gender, date of index admission, and other potential confounders.

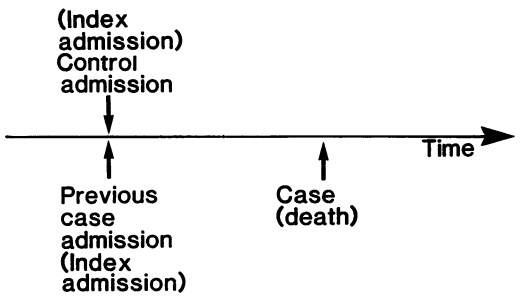

Figure 2 Selection of control group B.

Results

Identification of cases was conducted differently for the deaths that occurred during August 1981–July 1983 and during August 1983–December 1987 (table 1). There were 57 deaths in the first period with a record in the national asthma mortality survey[9] of a hospital admission for asthma during the 12 months before death[1]; 50 of these were eligible for the current study and the relevant notes were

Table 1 Identification of cases, exclusions, and final yield of cases

	No of cases	
	Aug 1981–July 1983	*Aug 1983–Dec 1987*
Potential cases	57	229
Ineligible		
Non-New Zealand resident	—	1
Name not clearly recorded	—	1
Address not recorded	—	3
No records found in major hospitals	5	66
Hospital records found but no admission for asthma in previous 12 months	2	75
Eligible cases	50	83
Hospital notes for index admission identified	46 (92%)	66 (88%)

found for 46 (92%). For the second period 229 asthma deaths were identified from national records; 83 of them were eligible for the current study, and the notes were found for 66 (88%). For each case four matched controls were selected for each group, with the exception of 17 cases for which sufficient group A controls could not be obtained. The study thus included 112 cases (32% of all deaths in the 5–45 age group during the study period), 427 group A controls, and 448 group B controls. Among the 112 cases, 21 patients had died in hospital, and these were treated as a separate group in some analyses (eight patients who died in an Accident and Emergency Department before an admission could be completed were included in the main group of 91 cases).

The case group was 51% male and 57% European, and had a mean age of 27·3 years. Control group A was 37% male and 70% European, and had a mean age of 25·6 years. Control group B was 34% male and 75% European, and had a mean age of 26·5 years. The mean time between the index admission and the next event (either death or the next admission) was 0·38 years for the cases and 0·37 years in the group A controls.

The relative risk of asthma death associated with prescription of inhaled fenoterol was 2·11 when group A was used as control and 2·66 with group B as control (table 2). The inhaled fenoterol relative risks tended to be lower for the 21 deaths that occurred after an admission to hospital (1·58 with group A controls and 1·97 with group B controls) than for the other 91 deaths (2·25 with group A controls and 2·86 with group B controls). The inhaled fenoterol relative risk was also greater for the 46 deaths that occurred from August 1981 to July 1983 (the group included in an earlier study[1]) than for the 66 deaths from the later period of August 1983–December 1987: when control group A was used the odds ratios were 2·92 (95% CI 1·49–5·73, $p < 0·01$) and 1·70 (95% CI 0·97–2·96, $p = 0·06$) and with control group B 3·07 (95% CI 1·58–5·98, $p < 0·01$) and 2·41 (95% CI 1·39–4·18, $p < 0·01$).

The inhaled fenoterol odds ratios were similar in males and females (2·52 and 1·98 when group A was used as control and 2·89 and 2·68 with group B as control). There were, however, differences in the relative risks in Europeans and non-Europeans (2·76 and 1·44 with group A controls and 3·54 and 1·71 with group B controls). There were smaller differences in the inhaled fenoterol odds ratios in patients aged less than 20 years and those aged 20 years or more (1·58 and 2·45 with control group A and 2·32 and 2·97 with control group B).

The inhaled fenoterol odds ratios tended to increase (but not substantially) when the analysis was restricted to subgroups defined by markers of chronic asthma severity (table 3). This pattern was not observed for other asthma

Table 2 Prescribed medication at discharge, markers of chronic severity, and the relative risk of death from asthma

	Cases		*Control group A*					*Control group B*				
	Yes	*No*	*Yes*	*No*	*Odds ratio*	*95% confidence interval*	*p*	*Yes*	*No*	*Odds ratio*	*95% confidence interval*	*p*
Prescribed medication at discharge												
Oral beta agonists	28	84	95	332	1·17	0·72–1·89	0·54	62	386	2·08	1·26–3·41	<0·01
Salbutamol	27	85	89	338	1·21	0·74–1·97	0·46	60	388	2·05	1·24–3·40	0·01
Beta agonists by metered dose inhaler	101	11	395	32	0·74	0·36–1·52	0·42	414	34	0·75	0·37–1·54	0·44
Fenoterol	67	45	196	231	1·76	1·15–2·67	0·01	179	269	2·24	1·48–3·40	<0·01
Salbutamol	37	75	200	227	0·56	0·36–0·87	0·01	230	218	0·47	0·30–0·72	<0·01
Beta agonists by nebuliser	18	94	33	394	2·29	1·25–4·18	<0·01	22	426	3·71	1·98–6·94	<0·01
Fenoterol	12	100	15	412	3·30	1·55–7·00	<0·01	10	438	5·26	2·39–11·6	<0·01
Salbutamol	7	105	18	409	1·52	0·62–3·70	0·36	12	436	2·42	0·96–6·14	0·06
All inhaled beta agonists	107	5	403	24	1·27	0·48–3·41	0·63	425	23	1·16	0·43–3·12	0·77
Fenoterol	73	39	201	226	2·11	1·37–3·23	<0·01	185	263	2·66	1·74–4·06	<0·01
Salbutamol	42	70	208	219	0·63	0·41–0·97	0·03	236	212	0·54	0·35–0·82	<0·01
Oral theophyllines	93	19	349	78	1·09	0·63–1·90	0·75	325	123	1·85	1·09–3·15	0·02
Sodium cromoglycate	15	97	73	354	0·75	0·41–1·36	0·35	83	365	0·68	0·38–1·23	0·20
Inhaled corticosteroids	75	37	286	141	1·00	0·64–1·56	1·00	275	173	1·28	0·82–1·97	0·28
Oral corticosteroids	94	18	335	92	1·43	0·83–2·49	0·20	329	119	1·89	1·10–3·24	0·02
Three or more categories of asthma drugs	95	17	370	57	0·86	0·48–1·55	0·62	346	102	1·65	0·94–2·88	0·08
Markers of chronic asthma severity												
Three or more categories of asthma drugs at admission	75	37	273	154	1·14	0·74–1·78	0·55	202	246	2·47	1·61–3·79	<0·01
Admission in previous 12 months	72	40	232	195	1·51	0·99–2·33	0·06	137	311	4·09	2·69–6·21	<0·01
Oral corticosteroids at admission	46	66	161	266	1·15	0·75–1·76	0·52	106	342	2·25	1·46–3·45	<0·01

Table 3 Prescribed inhaled fenoterol at discharge and the relative risk of death from asthma: findings in subgroups defined by markers of chronic severity

		Cases		Control group A					Control group B				
		Fenoterol		Fenoterol		Odds ratio	95% confidence interval	p	Fenoterol		Odds ratio	95% confidence interval	p
		Yes	No	Yes	No				Yes	No			
Three or more categories of prescribed asthma drugs at admission													
Yes		55	20	151	122	2·22	1·27–3·88	0·01	101	101	2·75	1·55–4·87	<0·01
No		18	19	50	104	1·97	0·96–4·06	0·07	84	162	1·83	0·92–3·65	0·09
Admission in previous 12 months													
Yes		49	23	108	124	2·45	1·41–4·24	<0·01	61	76	2·65	1·47–4·80	<0·01
No		24	16	93	102	1·65	0·83–3·28	0·16	124	187	2·26	1·17–4·38	0·02
Oral corticosteroids at admission													
Yes		37	9	91	70	3·16	1·47–6·82	<0·01	55	51	3·81	1·72–8·45	<0·01
No		36	30	110	156	1·70	0·99–2·92	0·05	130	212	1·96	1·16–3·31	0·01
Admission in previous 12 months	*Three or more categories of asthma drugs at admission*												
Yes	Yes	38	16	88	78	2·11	1·10–4·04	0·03	42	39	2·21	1·07–4·56	0·03
No	Yes	17	4	63	44	2·97	0·97–9·10	0·06	59	62	4·47	1·52–13·1	0·01
Yes	No	11	7	20	46	3·61	1·26–10·4	0·02	19	37	3·06	1·04–9·01	0·04
No	No	7	12	30	58	1·13	0·40–3·18	0·82	65	125	1·12	0·42–2·99	0·82
Admission in previous 12 months	*Oral corticosteroids at admission*												
Yes	Yes	27	7	57	41	2·77	1·12–6·86	0·03	21	22	4·04	1·48–11·0	0·01
No	Yes	10	2	34	29	4·27	0·94–19·3	0·06	34	29	4·27	0·94–19·3	0·06
Yes	No	22	16	51	83	2·24	1·08–4·62	0·03	40	54	1·86	0·87–3·97	0·11
No	No	14	14	59	73	1·24	0·55–2·80	0·61	90	158	1·76	0·81–3·83	0·16

Table 4 Prescribed medication at discharge and the relative risk of death from asthma: odds ratios (with 95% confidence intervals) in subgroups defined by markers of chronic severity

	Findings based on control group A				Findings based on control group B			
Prescribed medication at discharge	*Three or more categories of drugs at admission*	*Admission previous year*	*Oral corticosteroids at admission*	*Admission previous year and oral corticosteroids*	*Three or more categories of drugs at admission*	*Admission previous year*	*Oral corticosteroids at admission*	*Admission previous year and oral corticosteroids*
Oral beta agonists	1·33	1·29	2·23	2·73	1·98	1·53	2·76	2·30
	0·75–2·35	0·72–2·34	1·12–4·45	1·21–6·16	1·08–3·65	0·80–2·94	1·30–5·88	0·88–6·00
Salbutamol	1·27	1·24	2·04	2·42	1·99	1·43	2·52	2·04
	0·71–2·26	0·68–2·25	1·01–4·09	1·06–5·50	1·07–3·71	0·74–2·77	1·18–5·40	0·77–5·35
Inhaled beta agonists	3·11	1·70	2·05	2·15	3·85	0·87	3·18	1·61
	0·44–22·1	0·49–5·95	0·25–16·4	0·26–17·8	0·56–26·7	0·20–3·76	0·42–24·1	0·14–18·5
Fenoterol	2·22	2·45	3·16	2·77	2·75	2·65	3·81	4·04
	1·27–3·88	1·41–4·24	1·47–6·82	1·12–6·86	1·55–4·87	1·47–4·80	1·72–8·45	1·48–11·0
Salbutamol	0·69	0·66	0·51	0·67	0·63	0·56	0·53	0·46
	0·40–1·17	0·39–1·13	0·25–1·04	0·29–1·52	0·37–1·10	0·31–1·00	0·25–1·13	0·18–1·16
Oral theophyllines	1·16	1·12	1·23	0·76	2·01	2·40	1·68	1·22
	0·46–2·94	0·51–2·48	0·44–3·47	0·22–2·65	0·81–4·97	1·10–5·26	0·59–4·81	0·31–4·74
Sodium cromoglycate	1·09	0·88	1·72	2·35	1·04	0·68	1·48	1·36
	0·55–2·15	0·44–1·78	0·73–4·06	0·91–6·06	0·51–2·09	0·33–1·43	0·59–3·67	0·47–3·94
Inhaled corticosteroids	0·76	1·35	0·64	1·12	0·77	1·33	0·95	1·49
	0·42–1·38	0·74–2·46	0·31–1·32	0·43–2·92	0·42–1·44	0·70–2·53	0·44–2·01	0·51–4·35
Oral corticosteroids	2·03	1·58	1·15	0·51	2·01	1·74	1·09	0·00
	0·84–4·92	0·75–3·29	0·24–5·63	0·08–3·08	0·81–4·97	0·80–3·78	0·20–5·86	0·00–3·22

drugs, except for oral beta agonists, oral theophyllines, and prescribed oral corticosteroids at discharge when control group B was used (table 4).

When the case and control patients prescribed fenoterol were excluded, the relative risk of asthma death associated with prescription of three or more categories of asthma drugs at admission was 0·90 (95% CI 0·45–1·77) when control group A was used and 1·69 (95% CI 0·86–3·30) with control group B (not shown in table). The corresponding estimates for an admission in the previous 12 months were 1·18 (95% CI 0·59–2·36) with control group A and 3·54 (95% CI 1·82–6·87) with control group B, and those for oral corticosteroids prescribed at admission were 0·67 (95% CI 0·30–1·48) and 1·25 (95% CI 0·56–2·79) respectively. There was no change in the fenoterol relative risk with group A controls when it was adjusted for an admission in the previous 12 months and prescription of oral corticosteroids at admission; but the relative risk using group B controls fell from 2·66 to 2·34 when this adjustment was made, indicating weak confounding by these markers of chronic severity.

Table 5 shows measures of respiratory and

metabolic function for the controls, to help assessment of the potential for confounding by severity.[10] There was little evidence of systematic differences between the controls prescribed fenoterol and those prescribed other beta agonists. The only exception was in the group A controls, where the mean $PaCO_2$ was higher for the index admission (but not for previous admissions) in those prescribed fenoterol (47 *v* 41 mm Hg (6·3 *v* 5·5 kPa)).

Logistic regression was used to assess potential confounding further. When the risk associated with inhaled fenoterol was adjusted for age, gender, hospital, and date of index admission and for oral theophyllines and oral corticosteroids at discharge the odds ratio based on control group A increased to 2·74, and that based on control group B increased to 2·91. In the subgroup of patients for whom the $PaCO_2$ had been recorded the crude odds ratio based on control group A was 1·48; the estimate increased to 1·87 when the analysis was controlled for the above factors and it fell slightly to 1·71 when $PaCO_2$ was added to the model. The corresponding odds ratio estimates with control group B were 2·01, 2·74, and 2·59. These analyses suggest that confounding by these factors was relatively weak, and that the crude odds ratios are likely to be underestimates.

Psychotropic drugs were prescribed at the time of discharge (tranquillisers, neuroleptics, antidepressants, and anticonvulsants) in 11% of cases, 5% of group A controls (odds ratio 2·44, 95% CI 1·18–5·06) and 5% of group B controls (odds ratio 2·44, 95% CI 1·19–5·03). Prescription of these drugs was not, however, associated with prescription of fenoterol in either control group and adjustment for psychotropic drugs made little difference to the odds ratios for inhaled fenoterol: the crude and adjusted odds ratios were 2·11 and 2·13 respectively when control group A was used and 2·66 and 2·62 with control group B.

As a final check for possible bias, a further analysis was based only on the prescribed medication at admission (the index admission), with no account taken of prescribed medication at discharge. With control group A the inhaled fenoterol odds ratio was 2·08 overall, and 2·41, 2·31, 2·31, and 2·24 in the four subgroups of chronic severity defined in table 4. When control group B was used the inhaled fenoterol odds ratio was 2·71 overall and 2·74, 2·31, 2·66, and 3·05 in the four severity subgroups.

Discussion

The increased risk of death from asthma associated with inhalation of fenoterol in the current study is consistent with the previous findings.[1 2] The consistency and magnitude of the findings mean that chance can effectively be ruled out as an explanation for the association between fenoterol and death from asthma. Despite the consistency in overall findings between the various studies, there were some differences in the risk estimates for specific subgroups. In the previous studies[1 2] the relative risk associated with fenoterol increased substantially when the analysis was restricted to patients with chronic severe asthma, with a roughly 10 fold relative risk in the subgroup with the most severe asthma. In the current study the highest observed relative risks were about fourfold, and the tendency for the relative risk to be greater in the most severely affected subgroups was much weaker. Nevertheless, in terms of assessing the potential for confounding by asthma severity the most important point is that the relative risk associated with fenoterol did not decrease when the analysis was restricted in this manner. Furthermore, the confidence limits of the relative risks in the most severely affected subgroups are relatively wide, and the current findings are consistent with the stronger association seen in the previous studies.

There were also some differences in the findings for specific demographic subgroups between this and previous studies. The second national case-control study[2] found a higher relative risk associated with fenoterol in non-Europeans, whereas the current study found a lower relative risk in non-Europeans. Both previous national studies[1 2] have found a higher relative risk in patients aged less than 20 years, but this was not observed in the current study. In fact, the demographic differences in relative risk between the various studies are to some

Table 5 Measurements (mean (SD)) of respiratory and metabolic function in cases and controls

	Values at index admission				*Worst values at admission in previous 12 months*			
	Prescribed fenoterol *n*		*Not prescribed fenoterol* *n*		*Prescribed fenoterol* *n*		*Not prescribed fenoterol* *n*	
Group A controls								
$PaCO_2$ (mm Hg)	92	47 (22)	86	41 (17)	34	47 (18)	38	44 (16)
K^+ (mmol/l)	124	3·9 (0·5)	127	3·7 (0·5)	58	3·8 (0·6)	57	3·9 (0·7)
FEV_1 (l)	35	1·6 (0·8)	47	1·7 (0·8)	16	1·9 (1·1)	20	1·5 (0·7)
PEF (l/min)	162	132 (76)	169	147 (90)	82	152 (69)	77	141 (80)
Group B controls								
$PaCO_2$ (mm Hg)	70	47 (22)	89	44 (22)	17	43 (13)	24	45 (21)
K^+ (mmol/l)	121	3·8 (0·6)	138	3·8 (0·5)	37	4·0 (0·5)	32	3·8 (0·5)
FEV_1 (l)	34	1·7 (0·7)	45	2·0 (0·9)	13	1·7 (1·0)	12	1·3 (0·8)
PEF (l/min)	146	152 (77)	195	159 (83)	38	154 (89)	40	147 (81)

$PaCO_2$—arterial carbon dioxide tension; K^+—plasma potassium concentration; FEV_1—forced expiratory volume in one second; PEF—peak expiratory flow.
Conversion to SI units: 1 mm Hg = 0·133 kPa.

extent consistent with the course of the epidemic of fatal asthma, which was particularly severe in younger people and in Maori patients in the early years[9] but not subsequently.[11] Maori patients appear to have had a particularly high death rate during the early years of the epidemic[9] and a high relative risk associated with inhaling fenoterol,[2] but a lower death rate during the latter years of the epidemic[11] and a lower relative risk. These differences may simply reflect problems of ethnic classification (and the relatively large number of patients for whom ethnic group was not recorded in the current study) or the small numbers of patients in the subgroup analyses (the differences between subgroups in the current study do not reach conventional levels of significance). On the other hand, they might reflect changes in the management of asthma, and in the use of fenoterol, that followed the identification of the epidemic of fatal asthma in 1981.

Increased risk of death from asthma has been associated with some other asthma drugs, such as oral theophyllines and oral corticosteroids in some studies, but not consistently. In particular, oral beta agonists showed an increased relative risk when group B was used as the control in the current study but there was no evidence for this in previous studies.[1 2] These inconsistencies in risk estimates for other asthma drugs indicate that some of these findings may have been due to chance, though the possibility that they are due to changes in the form or use of these other asthma medications cannot be excluded.

The main importance of the current study is not in the replication of previous findings but in the assessment of possible sources of bias. In particular, two control groups have been used to enable us to address the main methodological criticisms advanced after the previous studies.[3 4]

The first methodological criticism related to our previous method of selection of controls.[2] The most straightforward approach would have been to select controls from all hospital admissions for asthma (fig 2). This simple example of a case-control study nested within a cohort study would have been the natural option had there been no concerns about confounding within the cohort (study base); a full cohort study would yield the same findings but would be much more expensive and time consuming.[12] To minimise confounding by severity, the additional criterion of an additional admission within 12 months (fig 1) was imposed in the second national case-control study,[2] and in control group A in the current study, to ensure that the controls and the cases had asthma of a similar chronic severity.[12] A criticism of this approach was that if prescription of fenoterol led to a decreased rate of hospital admission selection of controls by method A (fig 1) would underestimate the prescription of fenoterol in the study base.[3 4] Although there was no evidence that such a phenomenon was occurring, or was likely to occur, this was investigated by selecting further controls by method B in the current study (fig 2). In fact, this alternative control group yielded stronger relative risks than the control group selected by method A.

The second major criticism of the previous studies concerns the possibility of confounding by asthma severity.[3 4] We have investigated this hypothesis and can find no substantive evidence that fenoterol was marketed or prescribed specifically for patients with more severe asthma.[1 2 13] Furthermore, if the overall increased fenoterol odds ratio had been due to confounding by chronic severity, the odds ratio should have decreased when the analysis was increasingly restricted to those with chronic severe asthma[14 15]; but this did not occur.[1 2] In response to these findings, it has been argued that these markers "seem to classify baseline risk in the wrong direction" and are actually markers of good prognosis.[4] This suggestion was made because, in the second national case-control study,[2] these markers were actually less common in cases than in controls when those prescribed fenoterol were excluded (to remove the interaction between fenoterol and chronic severity). It was suggested that "the way to resolve the issue would be to use the same eligibility criteria for cases and controls,"[4] which is what we did by using control group B in the current study. When this approach was used, all three severity markers were associated with an increased risk of death. This was particularly true for hospital admission for asthma during the previous 12 months (which is consistent with the findings of the one previous study[16] that has collected information relevant to this issue). The increased risk associated with prescription of oral corticosteroids was relatively weak (possibly because this class of drugs may be beneficial in the high risk group of patients to whom it is prescribed), but the relative risk was still greater than 1·0, contradicting recent conjectures.[4] There was little difference in these severity markers between the cases and the group A controls, which again is consistent with the previous study by Rea *et al.*[16] Thus control selection by method A introduces indirect matching for these markers of chronic severity,[17] and in some instances produced a greater prevalence of these severity markers in the control subjects than in the cases.[18]

A further feature of the current study is that information was collected on various markers of acute asthma severity, which have been suggested as potential confounders.[3] Markers of acute as opposed to chronic severity are of doubtful relevance in studies of regular prescribed medication.[14] In particular, taking the severity of the final attack into account will lead to bias if fenoterol causes death by increasing the severity of acute asthma.[14] The findings of Trembath *et al*[19] are relevant in this context as they found that regular use of inhaled fenoterol led to a significant decrease in baseline FEV_1 and peak flow, in contrast to terbutaline, for which no such effect was observed. A further problem is that, for many patients, information on measures of respiratory and metabolic function were absent, and for most others it was considered to be of doubtful value because the

time of recording was not clear and there was no standardisation for factors such as time since admission or intensive therapy. Nevertheless, as the issue had been raised, information on markers of acute severity was collected when available. In general, the control patients prescribed fenoterol were very similar to those not prescribed fenoterol with respect to the markers of acute severity. The one exception was $Paco_2$ for the index admission, but this was only a weak confounder and did not explain the increased relative risk of death associated with fenoterol. A potential problem in comparisons of mean $Paco_2$ values is that $Paco_2$ may show a biphasic pattern as asthma becomes more severe, being low in the presence of mild to moderate airflow obstruction and then rising as asthma becomes more severe. The potential for bias from this phenomenon may, however, be assessed by examining the standard deviations of the mean $Paco_2$ values, and these were generally similar to those prescribed fenoterol and those not prescribed fenoterol (table 5).

A further feature of the current study is that prescription of psychotropic drugs was used to identify patients with potential psychosocial problems, which could affect the management of their asthma. A previous study found that such patients had a relative risk of death from asthma of 3·5,[16] and it has been suggested that this might be an important confounder in studies of fenoterol and asthma mortality.[20] In the current study prescription of psychotropic drugs was associated with death from asthma (odds ratio = 2·44), but not with prescription of fenoterol, and did not therefore confound the association between fenoterol and asthma death.

In summary, this study has addressed the major criticisms raised in response to previous New Zealand case-control studies of fenoterol and death from asthma. The use of two control groups has indicated that the association between fenoterol and asthma death was not due to the control selection procedure used in previous studies, and that the three major markers of chronic severity (particularly an admission in the previous 12 months) all identify patients at an increased risk of death from asthma. Furthermore, information on various markers of acute asthma severity and on the prescription of psychotropic drugs showed that these factors were not important confounders. Thus the current study addresses the major criticisms of previous studies, and adds support to the hypothesis that the unsupervised self administration of fenoterol by inhalation in patients with severe asthma increases the risk of death.

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