Prescribed drug therapy and near-fatal asthma attacks

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Prescribed drug therapy and near-fatal asthma attacks. C. Burgess, N. Pearce, R. Thiruchelvam, R. Wilkinson, C. Linaker, K. Woodman, J. Crane, R. Beasley. ©ERS Journals Ltd 1994.
ABSTRACT: Inhaled fenoterol has been associated with an increased risk of death in severe asthmatics, when compared to other adrenoceptor agonists. It is plausible that fenoterol may also increase the risk of near-fatal attacks. We have conducted a case-control study to investigate this hypothesis.

The cases comprised Intensive Care Unit (ICU) admissions for asthma in the Wellington region during 1977–1988. For each of these cases, two age-matched controls were selected from asthma admissions to the same hospital during the same period. For the 155 cases and 305 controls, information on prescribed drug therapy was collected from the hospital admission records.

The relative risk of a near-fatal asthma attack in patients prescribed inhaled fenoterol was 2.00 (95% confidence interval (CI) 1.35–2.97). An increased risk was also observed for oral theophylline (odds ratio (OR) = 1.88; 95% CI 1.26–2.79). For the 65 cases and 104 controls who had a previous admission for asthma in the previous 12 months, information relating to the previous admission was also collected; an increased risk was once again observed for inhaled fenoterol (OR = 2.18; 95% CI 1.10–4.33) and for oral theophylline (OR = 1.18; 95% CI 0.99–3.57). No other asthma drugs showed significantly increased risks. Although the ICU admission cases had generally been prescribed more asthma drugs than the hospital admission controls, and appeared to have more severe asthma, it is possible that the findings reported here are influenced by confounding by severity.

We nevertheless estimate that our findings are consistent with the hypothesis that fenoterol increases the risk of near-fatal asthma attacks, and that they complement previous findings on fatal asthma attacks. They also provide some support to previous concerns about the safety of oral theophyllines, although the evidence for this is less consistent.
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Three previous New Zealand case-control studies of asthma deaths in the 5–45 yrs age-group during 1977–1987 have found that inhaled fenoterol is associated with an increased risk of death in severe asthmatics [1–3]. These findings have been supported by a recent study in Saskatchewan [4], which also found an increased risk from inhaled fenoterol (compared with other beta-agonist, such as salbutamol) in the 200 μg dose in which it was marketed. This study also raised concerns about a general beta-agonist class effect, based on secondary analyses which suggested that the fenoterol and salbutamol risks may have been similar if fenoterol had been marketed in a lower dose; however, the interpretation of this theoretical extrapolation awaits further study [5].

It has not been possible from these epidemiological studies to determine the mechanism(s) whereby fenoterol increases the risk of death in comparison with salbutamol or terbutaline, which have not been incriminated in asthma mortality epidemics [6]. However, experimental studies which have compared the pharmacological properties of different beta-adrenoceptor-agonists, have identified important differences between these agents [7, 8]. These differences relate to adverse effects resulting both from their long-term use, and from their use in high doses in an acute attack, and may be relevant to their differing potential to increase the risk of death when used by patients with severe asthma. Long-term use of fenoterol has been shown to lead to worsening asthma and reduced lung function, when compared with terbutaline [9]. The repeated self-administered use of the high dose preparation of fenoterol could result in increased adverse cardiac affects [8], more marked hypokalaemia [10], and a greater delay in seeking medical advice, compared with salbutamol or terbutaline.

Whatever, the mechanism(s) by which fenoterol increases the risk of death, it might be expected that fenoterol may also increase the risk of near-fatal attacks. This hypothesis has been supported by findings from the Saskatchewan study [4], which found that fenoterol (in

the dose in which it was marketed) was associated with an increased risk of both fatal and near-fatal attacks of asthma, compared with the more commonly prescribed beta-agonist, salbutamol. This study also found that a number of other classes of asthma drugs, including oral theophylline, oral corticosteroids, inhaled corticosteroids and sodium cromoglycate, were also associated with an increased risk of fatal or near-fatal asthma. However, the lack of matching for asthma severity meant that their findings should be interpreted with caution, and certainly subsequent analyses have suggested a protective effect for inhaled corticosteroids [11].

To further investigate the possible role of different asthma therapies in the development of near-fatal asthma, we have conducted a case-control study of prescribed drug therapy and near-fatal asthma in New Zealand during 1977–1988, the period of the mortality epidemic.

Methods

A case-control design has been used to compare the regular prescribed drug therapy of asthmatic patients suffering near-fatal attacks of asthma and that of asthmatic patients suffering severe attacks requiring admission to hospital but in whom death was not imminent. As in previous studies, attention has been focused on the 5–45 yrs age-group, because death from asthma is a reasonably clear cut diagnosis in this group [12].

Selection of cases

The eligible cases comprised all persons aged 5–45 yrs who were admitted to the Intensive Care Units (ICUs) of Wellington or Hutt Hospital during the period 1977–1988 with a diagnosis of asthma.

Selection of controls

For each case, two controls were selected at random from hospital records of patients discharged from Wellington or Hutt Hospital with a diagnosis of asthma (but who were not admitted to the ICU) in the year in which the case was admitted. The controls were matched on hospital and on age (within 5 yrs). If sufficient controls could not be obtained, then the age-range was widened to 10 yrs; however, all controls were chosen from within the 5–45 yrs age range.

Information on prescribed drug therapy

For all cases and controls, hospital records were used as the information source for prescribed drug therapy at time of admission. Information was recorded from the case notes, Emergency Department notes, general practitioner letters, and other sources. It was not possible to perform the data extraction "blind", but the data extractors were instructed to record all drug information from these sources. When more than one record was available from a particular source (*e.g.* in the case notes), then the record with the most complete drug information was used. The data forms were copied, and all information which identified cases and controls was deleted. Two members of the study team (CB and JC) then made a blind assessment of the drugs on admission.

The drug therapy for those cases and controls with a hospital admission for asthma during the previous 12 months was also collected from that admission and assessed "blind". As in previous studies [1–3], the possibility of confounding or effect modification by severity was assessed by considering various subgroups defined by markers of chronic severity: 1) three or more prescribed categories of asthma drugs at time of admission; 2) a hospital admission for asthma during the previous 12 months (prior to the admission under consideration); and 3) prescribed oral corticosteroids at time of admission. These markers have been shown to identify patients with severe asthma at increased risk of hospital admission or death from asthma [13].

Data analysis

The MANTEL and HAENSZEL [14] procedure was used to calculate odds ratios (ORs) and test-based confidence intervals (CIs) [15]. Logistic regression [16] was also used to calculate ORs adjusted for potential confounders. This is analogous to a stratified analysis, but enables the control of additional confounders, simultaneously, in the model.

As in previous studies, the standard approach of considering each beta-agonist independently was used, and the small group of patients who were prescribed both fenoterol and salbutamol were considered to be "exposed" to both drugs.

Results

Identifying details were obtained from hospital records for 180 persons aged 5–45 yrs who were admitted to the ICU with asthma (International Classification of Disease (ICD) code 493) during the period 1977–1988. The search of hospital records actually identified personal records for 155 (86%) of these patients. Some records could not be found and may have been discarded, because in some instances the last admission had occurred more than 10 yrs previously. For each case, two matched controls were selected, although in a few instances only one control could be obtained. The study thus involved a total of 155 cases and 305 matched controls. Eighty four of the cases and 122 of the controls had had a previous admission for asthma (to any hospital) during the previous 12 months, and the relevant admission records were found at Wellington or Hutt Hospital for 65 (77%) of these cases and 104 (85%) of the controls.

The case group was 39% male, and had a mean age of 26 yrs; the control group was 40% male, and had a mean age of 26 yrs.

Table 1. – Prescribed drug therapy on admission, markers of chronic asthma severity, and the relative risk of admission to ICU

Prescribed drug therapy on admission	Cases		Controls		Odds	95% CI	p
	Yes	No	Yes	No	ratio		value
Oral beta-agonists	32	123	52	253	1.27	0.78–2.07	0.35
Salbutamol	29	126	47	258	1.26	0.76–2.10	0.37
Beta-agonists by MDI	139	16	289	16	0.48	0.24–0.98	0.04
Fenoterol	71	84	90	215	2.02	1.36–3.01	<0.01
Salbutamol	71	84	200	105	0.44	0.30–0.66	<0.01
Beta-agonists by nebulizer	11	144	18	287	1.22	0.56–2.65	0.62
Fenoterol	4	151	5	300	1.60	0.43–5.95	0.49
Salbutamol	7	148	14	291	0.98	0.39–2.49	0.97
All inhaled beta-agonists	141	14	291	14	0.49	0.23–1.03	0.06
Fenoterol	73	82	94	211	2.00	1.35–2.97	<0.01
Salbutamol	76	79	205	100	0.47	0.32–0.70	<0.01
Oral theophyllines	100	55	150	155	1.88	1.26–2.79	<0.01
Sodium cromoglycate	15	140	24	281	1.25	0.64–2.47	0.51
Inhaled corticosteroids	98	57	170	135	1.37	0.92–2.03	0.12
Markers of chronic asthma severity							
Three or more categories of asthma drugs on admission	87	68	129	176	1.75	1.18–2.58	0.01
Admission in previous 12 months	84	71	122	183	1.78	1.20–2.62	<0.01
Oral corticosteroids on admission	49	106	68	237	1.61	1.05–2.48	0.03

ICU: Intensive Care Unit; 95% CI: 95% confidence interval; MDI: metered dose inhaler.

Table 1 shows the relative risks of ICU admission associated with prescribed drug therapy at the time of admission. In many instances, it was difficult to determine from the hospital records whether oral corticosteroids had been prescribed as a continuous or short course. The data for oral corticosteroids, thus, refer to any prescribed oral corticosteroids (continuous, short course, or unknown regimen).

The relative risk for an ICU admission was 2.02 in patients prescribed fenoterol by metered dose inhaler (MDI), and 1.60 in patients prescribed fenoterol by nebulizer (the numbers were very small for this latter comparison). The overall relative risk for inhaled fenoterol was 2.00. Although most other asthma drugs (with the exception of salbutamol) also showed some positive association with ICU admissions the only other strong association was for oral theophyllines (OR=1.88).

All three markers of chronic asthma severity were associated with ICU admissions, (table 1), with ORs of 1.75 for three or more categories of asthma drugs on admission, 1.78 for an admission in the previous 12 months, and 1.61 for prescribed oral corticosteroids on admission.

The inhaled fenoterol relative risk generally tended to increase (but not substantially) when the analysis was restricted to subgroups defined by markers of chronic asthma severity: in those prescribed three or more categories of asthma drugs, the inhaled fenoterol relative risk was 1.61 (95% CI 0.93–2.78); in those with a hospital admission in the previous 12 months it was 2.58 (95% CI 1.46–2.55); in those prescribed oral corticosteroids it was 2.34 (95% CI 1.11–4.95); and in those with the most severe asthma (defined by an admission in the previous 12 months and prescribed oral corticosteroids at time of admission) it was 2.93 (95% CI

1.16–7.42). With the exception of oral theophyllines, other asthma drugs did not show the same elevation in risk when the analysis was restricted in this manner (table 2).

The analysis was also repeated (using records from the previous admission) for the 65 cases and 104 controls who had a previous hospital admission for asthma in the previous 12 months, in order to examine the regular prescribed medication prior to the near-fatal attack. As in previous studies which used a similar approach [2, 3], the prescribed drug therapy was assessed on discharge, with the exception of the markers of chronic asthma severity, which were assessed at time of admission. The findings (table 3) were generally similar to those in the overall analysis (table 1), with ORs of 2.18 for inhaled fenoterol and 1.88 for oral theophylline. Once again, some other asthma drugs showed minor elevations in risk, and cases were generally prescribed more asthma drugs than controls; however, for individual asthma drugs, only the findings for inhaled fenoterol and oral theophylline were markedly elevated.

The findings in table 1 and 2 were explored further by using logistic regression to adjust for a number of factors which showed positive association (inhaled fenoterol, oral theophylline, a hospital admission in the previous 12 months, and prescribed oral corticosteroids). When this was done, the overall OR for inhaled fenoterol decreased slightly to 1.79 (95% CI 1.19–2.64), but the oral theophylline ORs decreased to 1.44 (95% CI 0.92–2.25); the OR for inhaled steroids (OR=1.05; 95% CI 0.69–1.61) also decreased substantially, but that for sodium cromoglycate did not change (OR=1.25; 95% CI 0.63–2.50). The marked reduction for oral theophylline occurred because prescribing of this drug was associated with asthma severity: 52% of those prescribed oral

Table 2. – Prescribed drug therapy on admission and the relative risk of admission to ICU: odds ratios (and 95% CIs) in subgroups defined by markers of chronic asthma severity

Prescribed drug therapy on discharge	Three or more categories of drugs on admission	Admission in previous year	Admission previous year Oral corticosteroids on admission	and oral corticosteroids
Oral beta-agonist	0.93	0.96	1.17	0.93
	0.49–1.74	0.47–1.95	0.50–2.74	0.33–2.65
Inhaled beta-agonists	1.01	0.26	0.47	-
	0.17–6.21	0.06–1.26	0.08–2.80	-
Fenoterol	1.61	2.58	2.34	2.93
	0.93–2.78	1.46–4.55	1.11–4.95	1.16–7.42
Salbutamol	0.67	0.44	0.44	0.38
	0.38–1.16	0.25–0.77	0.21–0.92	0.15–0.96
Oral theophyllines	1.01	2.40	1.38	2.06
	0.35–2.96	1.25–4.59	0.47–4.04	0.48–8.82
Sodium cromoglycate	1.56	1.51	0.99	0.82
	0.67–3.64	0.57–3.60	0.29–3.34	0.20–3.37
Inhaled corticosteroids	0.78	0.84	1.03	0.93
	0.37–1.64	0.45–1.56	0.44–2.42	0.33–2.60
Oral corticosteroids	1.12	1.68	-	-
	0.65–1.94	0.94–2.98	-	-

95% CIs: 95% confidence intervals.

Table 3. – Prescribed drug therapy on discharge (from a previous admission in the previous 12 months), markers of chronic asthma severity, and the relative risk of admission to ICU

Exposure	Cases Yes	No	Controls Yes	No	Odds ratio	95% CI	p value
Prescribed drug therapy on discharge							
Oral beta-agonists	8	57	25	79	0.44	0.19–1.04	0.06
Salbutamol	8	57	24	80	0.47	0.20–1.10	0.08
Beta-agonists by MDI	50	15	78	26	1.11	0.54–2.31	0.78
Fenoterol	24	41	22	82	2.18	1.10–4.33	0.03
Salbutamol	28	37	56	48	0.65	0.35–1.21	0.17
Beta-agonists by							
Nebulizer	3	62	6	98	0.79	0.19–3.28	0.75
Fenoterol	1	64	1	103	1.61	0.10–25.7	0.74
Salbutamol	2	63	5	99	0.63	0.12–3.31	0.58
All inhaled beta-agonists	50	15	81	23	0.95	0.45–1.99	0.89
Fenoterol	24	41	22	82	2.18	1.10–4.33	0.03
Salbutamol	29	36	60	44	0.59	0.32–1.10	0.10
Oral theophyllines	43	22	53	51	1.88	0.99–3.57	0.05
Sodium cromoglycate	6	59	7	97	1.41	0.45–4.39	0.55
Inhaled corticosteroids	45	20	66	38	1.30	0.67–2.51	0.44
Oral corticosteroids	38	27	70	34	0.68	0.36–1.30	0.25
Three or more categories of asthma drugs	49	16	66	38	1.76	0.89–3.51	0.11
Markers of chronic asthma severity							
Three or more categories of asthma drugs on admission	45	20	53	51	2.17	1.13–4.14	0.02
Admission in previous 12 months	50	15	50	54	3.60	1.83–7.10	<0.01
Oral corticosteroids on admission	23	42	21	83	2.16	1.08–4.33	0.03

For abbreviations see legend to table 1.

theophylline had a previous hospital admission in the previous 12 months compared with 32% of those not prescribed oral theophylline (the corresponding figures for inhaled fenoterol were 44 and 41%).

Similar results were obtained for the analysis using data from previous admissions: the adjusted ORs were 1.99 (95% CI 0.95–4.17) for inhaled fenoterol, 1.85 (95% CI 0.93–3.70) for oral theophylline, 1.08 (95% CI 0.31–3.69) for sodium cromoglycate, and 1.27 (95% CI 0.57–2.85) for inhaled steroids.

Discussion

The findings presented here on prescribed drug therapy and near-fatal asthma attacks complement the previous studies of fatal asthma attacks [1–5], and are consistent with the hypothesis that inhaled fenoterol increases the risk of near-fatal attacks as well as fatal attacks. However, this finding, and those relating to other asthma drugs such as oral theophylline, should be interpreted cautiously, since there were significant differences in chronic asthma severity between cases and controls despite the use of hospital admission controls.

The study design was similar to that in our first case-control study of asthma deaths [1], where it was found that the use of hospital admission controls provided an adequate indirect match for chronic asthma severity, in that asthma deaths and hospital admission controls were similar with respect to recognized markers of chronic asthma severity [13]. However, in the current study, there were significant differences in chronic asthma severity between cases and controls. In the previous study [1], 32% of cases and 32% of controls (excluding those prescribed fenoterol) had a previous hospital admission for asthma in the previous 12 months; in the current study the corresponding estimates were 46 and 39%. Similarly, in the previous study, 42% of cases and 40% of controls (excluding those prescribed fenoterol) were prescribed three or more categories of asthma drugs, whereas the corresponding estimates in the current study were 50 and 36%. These differences between cases and controls in the current study were apparent not only at the time of the admission under study (the ICU admission for cases and the hospital admission for the controls), but also at the time of previous hospital admissions for asthma in the previous 12 months. Overall, the cases of near-fatal asthma attacks had chronic asthma severity which was not only greater than that of the hospital admission controls, but was also greater than that observed in previous studies involving asthma deaths [1–3]. Thus, whilst confounding by severity was not a major concern in the interpretation of the previous studies [17, 18], it cannot be excluded as an explanation for the findings of the current study, although it should be emphasized that there is little evidence of selective prescribing of fenoterol to more severe asthmatics in New Zealand [18].

Despite these reservations, the findings of the current study are of considerable interest. Fenoterol was associated with near-fatal asthma attacks; this association was slightly stronger within the subgroup of patients with more severe asthma, and was only slightly weakened when the findings were adjusted for oral theophylline and for markers of asthma severity, implying that the findings are unlikely to be due to confounding by severity. These findings are consistent with those in previous New Zealand case-control studies of fatal asthma attacks [1–3], and also with the findings of the Saskatchewan case-control study of fatal and near fatal attacks [4].

Prescribed oral theophylline was also associated with near-fatal attacks, but there was some evidence of selective prescribing of oral theophylline, and the association decreased when the findings were adjusted for fenoterol and for markers of chronic asthma severity (implying that confounding by severity may be more of a problem in the oral theophylline analyses). Previous New Zealand studies of fatal attacks [1–3] have found relative risks for oral theophylline of 1.44, 1.10, and 1.09, respectively, whereas the Saskatchewan case-control study found crude ORs of 3.7 for asthma deaths and 3.7 for asthma deaths and near-deaths combined. Thus, unlike the fenoterol findings, the oral theophylline findings are inconsistent across the various studies. The main positive findings for oral theophyllines are in the current study, and in the Saskatchewan study [4], and in both instances there is concern about the comparability of the cases and controls with respect to chronic asthma severity [19] (and, hence, about the possibility of confounding by severity). Nevertheless, the findings for oral theophylline are of interest, in light of concern about its safety, both alone and in combination with beta-adrenoceptor-agonists [20, 21].

The findings for other asthma drugs were generally unremarkable. Although cases were generally prescribed more asthma drugs than controls (presumably because of the differences in chronic asthma severity discussed above), the relative risks for drugs other than inhaled fenoterol and oral theophylline were not markedly or significantly elevated. Furthermore, the relative risks tended to decrease when the data were adjusted for fenoterol, oral theophylline and markers of chronic asthma severity. In particular, there was no increased risk found for salbutamol, or for the general class of inhaled beta-adrenoceptor-agonist drugs. This is consistent with the findings of previous New Zealand studies [1–3], and with the "crude" findings of the Saskatchewan study [4], and supports the view that the "adjusted" findings from the Saskatchewan study may reflect inadequate matching for asthma severity [19].

In summary, despite our reservations regarding possible differences in asthma severity between cases and controls, this study provides a useful complement to previous case-control studies of deaths and near-deaths from asthma [1–6]. It is consistent with previous evidence that fenoterol increases the risk of near-fatal [4], as well as fatal [1–4] asthma attacks. In addition, it provides some support to previous concerns about the safety of oral theophyllines [4], although the evidence in this regard is more limited and less consistent [1–4].

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