PRESCRIBED FENOTEROL AND DEATHS FROM ASTHMA IN NEW ZEALAND - SECOND REPORT

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A study relating prescribed fenoterol to death from asthma in New Zealand by Crane et al. was published in the Lancet on 29 April 1989 (1), and a second study has now been produced by this group (2) which so far has been published only as an abstract (3). In April 1989, Professor D C G Skegg and I reported to the New Zealand Department of Health on the first study (4). Following a further request from the Department of Health in September, I now present this second report, on the second study of the topic by the Wellington group, and other pertinent material made available to me through the Department of Health.

INDEX

		Page
PART A:	**Summary and conclusions**	
A1.	Summary of findings	4
A2.	Implications for clinical practice and public policy	8
A3.	Conclusions	10
A4.	Recommendations	11
PART B:	**Review of second study and comparison with other evidence.**	
B1.	Description of study	12
B2.	Results of second study and comparison with other results	16
PART C:	**Interpretation of the association between fenoterol prescription and asthma deaths**	
C1.	The design of the second study: choice of controls	23
C2.	Measurement of drug use, and observation bias	25
C3.	Confounding	30
C4.	Interaction between fenoterol and steroids	33
C5.	Chance variation	35
C6.	Summary of the interpretation of the second study	35
C7.	Other criteria for causality	36
PART D:	**Plausibility: the mechanism of the association**	38
PART E:	**Coherence: the relationship to time trends and international variation in asthma mortality.**	42
PART F:	**Implications for decision making.**	45
REFERENCES		47
FIGURES (2) and TABLES (7)		
APPENDIX 1:	**Misclassification of a confounder**	

PART A: SUMMARY AND CONCLUSIONS

A1. Summary of findings

The evidence implicating fenoterol with an increased risk of death from asthma is, in the light of this further study, considerably stronger than previously. Although it still falls short of a totally acceptable standard of scientific certainty, the evidence is strong enough to support clinical and public policy decisions, and there do not appear to be strong counter-balancing arguments for the benefits of this particular drug.

In our review of the first study (4,p34), we concluded that the association between fenoterol and asthma death could be causal, but also could be produced by "a combination of information basis, confounding, and chance". It is now possible to dismiss information bias as an explanation of the results, and given the consistency of the results between two large case control studies and a third small study, to reasonably dismiss chance variation. The main options are two:

(a) that the association is causal, and that the prescription of fenoterol rather than alternatives does result by some mechanism as yet not understood, in a higher risk of death in subjects who have severe underlying asthma.

A causal interpretation includes the possibilities both of pharmacological effects, and of non-pharmacological effects related to the method of use of the drug by patients and doctors. The implications of a causal relationship depend on the mechanism, and whether it is specific to fenoterol or is shared by other drugs.

(b) that the association between fenoterol and asthma deaths is due to confounding, in that patients who are prescribed fenoterol have a disease which is more severe or more unstable, and for that reason have a higher risk of death.

The main evidence in favour of the causal interpretation is as follows:

1. an association between the prescription of fenoterol and death from asthma in subjects aged 5-45 in New Zealand has been shown in two reasonably large case-control studies, and an earlier small study

2. the results of these two major studies are consistent

3. the association is statistically significant

4. in the second study, data were collected in an identical manner for all subjects.

5. the association becomes stronger when the comparisons are restricted to subjects who have characteristics which are likely to be markers of more severe asthma.

6. there is an association in time between the introduction of fenoterol in New Zealand and an abrupt, rapid, rise in the death rate from asthma.

Summary:

The evidence in favour of the causal hypothesis, (and against the confounding hypothesis), is empiric and from within the studies, rather than subjective and from general considerations. This evidence is based on the analysis of data on factors which have been taken as indicators of severity of underlying asthma; previous hospital admissions, multi-drug treatment, and prescription of oral steroids. Using these indicators it is clear that within the two major studies there is no strong association between these risk indicators and the prescription of fenoterol, and that controlling for these indicators makes no major difference to the overall association between fenoterol prescription and death. Stratification for these measures shows that the association becomes much stronger in the subjects who have one or more of these markers of severity. This finding shows unequivocally that confounding by these measures of severity cannot explain the observed association between fenoterol and asthma death. It has also been shown that random misclassification of the confounding effect, which would occur if these measures of severity were an unbiased but inaccurate guide to the underlying severity of asthma, cannot explain the observed results.

The main evidence in favour of the confounding hypothesis is as follows.

1. The difficulty in finding a mechanism for the observed relationship between fenoterol prescription and death from asthma.

2. The opinion of experienced physicians that fenoterol has tended to be used in patients with more severe asthma.

3. The data on prescribing of fenoterol suggesting that it has been used more often as a second line therapy and in conjunction with oral steroids, than alternative drugs.

4. The lack of concordance between recent decreases in asthma mortality and the continued high usage of fenoterol.

5. Consideration of case histories, suggesting that patients who die from asthma often have complex medical and social situations, and suggesting various alternative hypotheses, for example that fenoterol has been used in patients with severe unstable asthma when it is not an adequately powerful drug to deal with their condition.

Summary:

The evidence in favour of the confounding hypothesis is indirect, circumstantial, and considerably subjective; the hypothesis depends on the limitations of the studies done to date. Ideally, the main studies would be sufficiently detailed to allow a full description of all drug therapy prescribed to (and better, used by) the subjects in a defined period preceding death or the equivalent event in the controls, and would have extensive data on the severity of their asthma. The confounding hypothesis depends on this lack of detail. If the confounding hypothesis holds, it should be possible to demonstrate within the context of patients with severe asthma treated in New Zealand, that subjects who are treated with fenoterol do have more severe underlying disease than those treated with alternatives such as salbutamol, using

appropriate indices of severity of chronic asthma which have yet to be defined. There is insufficient information on what measures of severity in asthma are predictors of death.

The hypothesis that the associations seen are explained by confounding by severity of asthma is tenable only if four conditions are all met: (a) there are valid indicators of the severity of asthma other than those used in these studies, and (b) within the context of these or similar studies these indicators show major differences between deceased cases and living controls, and (c) between fenoterol treated patients and other patients, and (d) that such differences are more marked within those subjects who have the characteristics of previous admissions for asthma, multi-drug treatment, and prescription of oral steroids.

Conclusion: the balance of the available information is in favour of the causal rather than the confounding hypothesis.

There are several unresolved issues:

1. All the relevant data relate to drugs prescribed to patients over a variable time period; the relationships to drugs actually used, and to how and when they are used are unknown.

2. The association may be due to either a pharmacological or a medical care mediated mechanism; thus the relevance of the relationship to other, and to new and future drugs is unknown.

3. A particularly high risk in subjects who have been or are currently prescribed both oral steroids and fenoterol has been shown, and needs to be explained.

4. The association appears to be stronger in young subjects, under the age of 20, for unknown reasons; it is not however, restricted to such subjects.

A2. Implications for clinical practice and public policy

There are therefore two possible interpretations of the data in scientific terms; that the association is causal, or that the association is due to, as yet, unidentified and unexplained confounding factors. Two subtly different questions can be asked and have been asked, by different parties in relationship to these studies, and these have to be considered carefully as they directly impinge on decision making.

The first relevant question is:

1 *Do these results demonstrate an increased mortality risk due to fenoterol?*

The implication of this question is that the burden of proof is on the study to demonstrate an effect. This is the question which has been addressed by the panel convened by Boehringer Ingelheim (5), who have emphasised their findings in terms of whether the evidence provided can be interpreted unequivocally as demonstrating a cause and effect relationship between fenoterol use and asthma death.

(For example, the consensus report, page 11: "The alternative hypotheses of confounding by disease severity and bias in control selection require adequate testing before concluding that chronic fenoterol use increases the risk of asthma death." The corresponding proposition, which would read "The alternative hypotheses of confounding by disease severity and bias in control selection require adequate testing before concluding that the association between fenoterol and asthma death can be explained by these hypotheses" is not mentioned).

This question is relevant in the context of general scientific knowledge, for which an extremely high level of confidence is demanded before concluding that a cause and effect relationship exists, restricting it to situations in which all reasonable non-causal explanations have been tested and shown not to apply. The answer to the question as set in this way is 'no'; there remain a number of possibilities of non-causal explanations which have not been adequately tested and therefore cannot be confidently dismissed.

The second question is:

2. *Do these results show that the relationship between fenoterol and asthma death is due to confounding factors?*

In this question the burden of proof is put on the critics of the study to demonstrate that alternative mechanisms are responsible for the results produced. To answer this question in the affirmative requires empiric data rather than merely hypotheses, and such data are not available. Indeed, the data which are available and are relevant to the assessment of the confounding hypothesis within these two studies show that confounding does not explain the results seen; the answer to this question is also 'no'.

The clinical and public policy question is whether fenoterol should be used where an acceptable alternative exists, and in this context it is this second question which is the more relevant; the principle of 'primum non nocere' holds.

A3. Conclusions

A comparison of the weakness of the evidence which supports the non-causal possibility of confounding, with the consistency and strength of the evidence for an empiric relationship between fenoterol prescription and asthma death, leads to the conclusion that fenoterol prescription is likely to increase the risk of death from asthma. Clinical and policy decisions should be based on this assessment.

This does not preclude the continued search for new information or the acceptance that the evidence falls short of the standard desirable for a scientific conclusion to be firmly made.

The current evidence therefore gives strong reasons to minimise the use of fenoterol.

Clinical and policy decisions must be taken on the available evidence, even though the effects of these may depend on whether the causal relationship is specific to fenoterol or is shared by other drugs, and whether it is mediated by a pharmacological effect or an effect related to the way in which the drug has been used; conclusions on these matters cannot yet be reached.

Although it is not within the scope of this review, a related question is whether fenoterol has any essential advantages over alternative drugs. Patients with asthma are managed adequately in many other societies such as the United States without this drug, and there appears to be little evidence that it has any specific benefits over alternatives. There do not appear to be adequate comparative clinical trials demonstrating a benefit of fenoterol compared to alternatives in terms of clinically relevant outcome measures in the long-term management of asthma. It appears that the use of the drug cannot be justified by comparing the strength of the evidence relating its use to an increased risk of death, to the lack of strong evidence for a particular benefit.

A4. Recommendations

On the basis of the evidence reviewed here, the use of fenoterol should be minimised.

It is recommended that physicians avoid the use of fenoterol whenever possible, and use it only if there are particularly cogent reasons for its use in individual patients. The possibility that the risks seen with fenoterol may be related to the way the drug has been used, and may apply to some other drugs, has to be acknowledged.

It is recommended that the drug regulatory authorities should take steps to ensure that the use of fenoterol is minimised. This evidence presented here suggests that fenoterol prescribing should be restricted. If it is to be used, the situations in which fenoterol would be beneficial should be clearly and objectively defined. Again, the possibility that the risks seen with fenoterol may be related to the way the drug has been used, and may apply to other drugs including new drugs has to be recognised.

PART B: REVIEW OF SECOND STUDY AND COMPARISON WITH OTHER EVIDENCE

B1. Description of study

The second study is entitled "Prescribed fenoterol and death from asthma in New Zealand, 1977 - 1981; a further case control study" by N Pearce, J Grainger, M Atkinson, J Crane, C Burgess, C Culling, H Windom, and R Beasley, from the Departments of Community Health and of Medicine at the Wellington School of Medicine. The version used is dated June 1989 (2).

Stated objectives

In their introduction, the authors state that the prime objective of this second study is to assess the findings of the first study (1) by using a similar design on asthma deaths in an earlier time period 1977 - 1981, but avoiding the major problem that in the first study information on drug prescription was obtained from different sources for the cases and controls; the second study uses the same sources. The second study refers to an earlier time period (1977-81) than does the first study (1981-83).

The study design

The study design used is an original and interesting one, shown in figure 1. 'Cases' are subjects who have died from asthma and have had a hospital admission for asthma in the previous year; I shall refer to the death as the "outcome event" and this admission, which provides the drug therapy data, as the "reference admission". Controls have a non-fatal outcome event, an admission for asthma, and a corresponding reference admission in the previous year from which drug data are given. For both cases and controls the reference admission is the one closest to the time of the outcome event; they may have had earlier hospital admissions for asthma, prior to the reference admission. The mean interval between the outcome and reference admission was 4.1 months for the cases, and 2.8 months for the controls.

Case selection

To be eligible as cases, subjects had to have a death certified from asthma (ICD 493) between January 1977 and July 1981, been aged between 5 and 45 years, and have had a previous admission for asthma within the previous 12 months.

The selection of cases was however not straight forward (table 1). 366 asthma deaths were identified in the given age range and time period; of these 73 (20%) were excluded because they were in areas served by smaller hospitals which were not included in the study, or were in the Dunedin area, as the ethical committee for the Dunedin Hospital did not permit access to the records. This is regrettable and it is difficult to see the ethical justification for this decision. The investigators then restricted the study to those deaths in whom they could find some hospital record of an admission at any time; this they did for 214 patients. There were thus 79 patients excluded because no hospital admission could be found; this is 27 percent. This means that subjects who died of asthma but had no hospital record found are not included in this study; such patients dying presumably unexpectedly with no history of hospital investigation might be of particular interest.

From these 214 subjects, 30 were excluded from the study because their death occurred more than one hour after admission. The authors give the reason for this as being their concentration on self-prescribed medication. Some of these deaths may have occurred several days or more after admission. More detail on this would be helpful; in this I agree with the Boehringer Ingelheim consensus group (5). This leaves 184 subjects. Then come exclusions on the pre-set eligibility criteria, restricting the study to those subjects who had a previous hospital admission within the 12 months prior to death; records of such an admission were found for 67 patients, and were not found for 117, that is 64 percent of those eligible up to this point. A further 9 patients (13 percent) were excluded because although a previous admission was identified, appropriate records could not be found.

If ascertainment of previous admissions has been complete, the only non-protocol exclusions are the 9 cases for whom records could not be found, giving a participation rate of 58/67, 87%. It cannot be proven however that all previous hospital admissions were identified; the method used is rather indirect, involving searching the records of those hospitals to which subjects "were likely to have been admitted". In this study, of all deceased asthma patients, 214/293 (73%) had an

identified hospital admission at some time; 67/184 (36%) had an admission in the previous year. In the previous study (1), 52 of 117 cases (44%) had an admission in the previous year; as these deaths were studied very thoroughly by the Asthma Task Force those data may be more complete. The lower proportion with an admission in the previous year in the second study may be a real difference, but could suggest that some previous admissions were not detected.

The other major difference between this study and the previous one is that here deaths were accepted on the death certificate coding, whereas in the previous study they were only accepted after review by the Asthma Task Force; however this makes little difference as Sears et al. (6) reported that within the age group 0-44, 97 percent of deaths certified for asthma were accepted as such by the Asthma Task Force.

Control selection

There is less information given in the manuscript concerning the process of selection of controls. 227 controls, matched by hospital or area, and by age to within 5 or 10 years, who had had an admission for asthma in the previous year, were found by selection at random from asthma discharges. It is impossible to estimate the number of potential controls and the participation rate of controls. It would be useful to know, for example, what proportion of patients discharged with asthma had an earlier admission for asthma in the previous year, and if any potential controls were excluded because records were unobtainable or unsatisfactory.

As in the previous study, hospital records coded for asthma are taken to indicate an admission for asthma. This has been criticised as likely to allow inclusion of subjects not primarily admitted for asthma (e.g. 7), although the authors have defended their method, pointing out that asthma was coded as the cause of admission in all these subjects (8). If non-asthma admissions have been included, this will contribute to differences in severity between cases and controls and will be discussed under the heading of confounding.

Sex, age, ethnic origin

The case group in this study was 45 percent male, and 38 percent non-European, with corresponding figures of 44 percent male and 48 percent non-European in the first study. The controls for the current study were 36 percent male and 32 percent non-European, showing associations of asthma death with male sex and non-European

ethnic background, which are also seen in the first study. The mean age of cases in this study was 23.9 years, considerably lower than the average of 27 years in the first study; the main age of the control groups were similar to the case groups in each study. The considerable differences in sex and ethnic origin between cases and controls obviously must be carefully controlled in the analysis.

Information on prescribed drug therapy

In our first report (4), we commented extensively on the issue of defining the appropriate exposure data in these studies in that different definitions of the exposure data implied different hypotheses which were being tested. The issue is clearer in the second study, in that the authors have defined the relevant exposure as the prescribed drug therapy at the time of the prior "reference" hospital admission, in the 12 months before the death (case) or outcome admission (control). Drug therapy around that admission can be considered as the drugs used on admission, on discharge, or during the hospital stay; the authors collected both admission and discharge information. The medication was abstracted from case notes, Accident and Emergency department notes, the general practitioner's letter, and the discharge notes, discharge letter, and discharge prescription. It is not stated who performed this abstraction process, but it is stated that the "data extractors" were instructed to record all drug information, and to use the record with the most complete drug information where there was more than one record available. This abstraction process was not carried out in a blind fashion.

The assessment of these abstracted data were then made by two of the authors, from copies of the data forms in which information on case or control status was deleted; this therefore was done blind.

Indicators of severity

A major issue in the interpretation of the first study was whether the association between fenoterol prescription and asthma death was direct, or indirect because of confounding by severity of underlying asthma. The methods used by the authors in the first study to categorise severity of asthma have been considerably criticised as being insufficiently detailed and accurate to give a good measure of chronic severity (5,7,9-11), although there is no agreement on better measures which could be used in the context of retrospective studies based on medical records. In this second study the authors used exactly the same measures of severity, that is prescription of three or

more categories of asthma drugs, a hospital admission for asthma during 12 months prior to the 'reference' admission, and the prescription of oral corticosteroids; these factors being assessed at the time of admission to the 'reference' hospital episode (figure 1).

B2. Results of second study and comparison with other results.

Results; beta agonists

The data refer to drugs prescribed at discharge following the 'reference' hospital admission. The results of the two studies are shown in table 2. In comparing them, the second study relates to an earlier time period (1977-81, compared to 1981-83 in the first study) but for both cases and controls is restricted to subjects with a prior hospital admission for asthma, which means that they are likely to have in general more severe asthma.

The results of the two studies are generally consistent.

In each, the proportions of cases and controls using oral beta agonists (almost always salbutamol), were virtually identical.

Most subjects were prescribed a beta-agonist by MDI, although the risk of death was higher in those than in the small number of subjects who did not receive an MDI drug (OR 1.26 in the second study, 1.48 in the first). In the second study fenoterol by MDI was prescribed for 52 percent of cases compared to 36 percent of controls giving a relative risk of 1.93; in the first study the proportions were 51 percent in cases and 40 percent in controls giving an odds ratio of 1.55. A more direct comparison is possible with the first study restricted to subjects in that study who also had a previous hospital admission; here the proportions using MDI fenoterol were 65 percent in cases and 47 percent in controls, with an odds ratio of 2.16. In the first study (later time period) for a similar selection of cases and controls the usage of MDI fenoterol is greater than in the earlier time period study, which is in keeping with the increased general use of fenoterol.

In both studies, the use of MDI salbutamol, which is really a surrogate for the lack of use of MDI fenoterol, is associated with an odds ratio of 0.71.

The use of nebuliser drugs was very uncommon in the second study; the odds ratio for fenoterol by nebuliser is 1.97, similar to that of MDI fenoterol. The result for nebuliser fenoterol in each study is consistent with that for MDI fenoterol, but the numbers are inadequate for these results to be considered on their own.

Thus the main association between beta-agonist use and death is consistent in the two studies, both showing a positive association between death and the use of MDI fenoterol. It is also relevant to compare the results with those of Rea et al. (12). In this study, 47 patients resident in Auckland aged up to 60 who died from asthma in 1981-2 were compared to two sets of controls; one, patients who had been admitted with acute asthma, and the other patients known to have had asthma who consulted their general practitioners over a 4-week period (community controls). As presented by Crane et al. (1) re-analysis for the 32 cases and 27 hospital controls who were 4-45 years old gives an OR for fenoterol of 1.61 (95% limits 0.57-4.54), consistent with the larger studies.

Markers of severity of asthma; effect modification

In the previously published study, the most dramatic results were that although the overall association with fenoterol was 1.55, the association was stronger in subjects who had been prescribed three or more categories of asthma drugs (2.21), had an admission in the previous year (2.16), or who had been prescribed oral corticosteroids (odds ratio 6.45, table 3). The current study has already restricted cases and controls to those who have had an admission in the previous year, and the overall association with MDI fenoterol use is 1.93, very similar to the association of 2.16 in those with a previous admission in the first study. In the current study, the same three indicators are used as measures of the severity of underlying asthma; the odds ratio was 2.98 in subjects with three or more categories of asthma drugs, 3.91 in those with a hospital admission prior to the reference admission, and 5.83 in those with prescription of oral corticosteroids at the reference admission (table 3). All these associations are statistically significant, whereas none of the associations between fenoterol use and death in subjects without each of these three indicators considered separately is statistically significant. Joint tabulation of pairs of these three indicators, shows further increases in risk particularly in the group with oral corticosteroids on admission and a hospital admission in the previous 12 months, where the odds ratio is 9.82, but has confidence limits of 2.2 to 43.4.

This effect modification is similar to that seen in the first published study which used the same indicators. The effect modification seen in the first study was, as we emphasised (4), the most compelling result which made the non-causal interpretation of confounding unlikely. The consistency of these new results is therefore very important. The results within subgroups are also similar to those of the study of Rea et al. (12) as re-analysed by Crane et al. (1): table 3.

Markers of severity; confounding

Are these markers of severity confounders in the association between fenoterol and asthma death? To act as such they need to be associated independently with fenoterol use and with asthma death. The association between the risk indicators and fenoterol use is best assessed in the controls, and shows (second study) that the proportion of controls using fenoterol is higher in those with three or more categories of asthma drugs (42 compared to 32%), and in those with oral steroid use on admission (41% compared to 35%), but is lower in those with a prior admission (34 compared to 40%). The association between risk indicators and fenoterol is therefore mixed, positive for two of the three indicators. In the first study a similarly weak set of associations was seen. Thus within both of these studies, the severity of asthma appears generally similar in subjects prescribed fenoterol and in those prescribed other drugs.

The association between risk indicators and death is best assessed in those without fenoterol use, and in the second study shows a surprising pattern in that each of the risk indicators is negatively associated with asthma death. In cases without fenoterol, the percentages on three or more drugs, with a prior admission, and on steroids are 26, 41, and 11 percent respectively; the corresponding proportions for controls not using fenoterol are 44, 60, and 24 percent. Thus the relative risk of asthma death in subjects not using fenoterol associated with each of the three measures of severity are respectively 0.4, 0.5, and 0.4. The result of this in terms of confounding is a strong negative association between these risk indicators and death, which taken with the mixed association with fenoterol use, suggests that these risk

indicators are likely to have a mild or moderate negative confounding effect. This is confirmed by comparison of the crude odds ratio for fenoterol prescription, 1.99, with the Mantel Haenzsel odds ratios adjusted for the use of three or more drugs (2.1), for prior admission (2.0), and for oral steroid use (2.0). There is therefore no major confounding effect of these measures in this study.

However, the results are inconsistent that in for asthma patients not taking fenoterol, these three measures, chosen as measures of the severity of underlying disease, are negatively associated with the risk of death. This raises considerable questions about their relevance as measures of underlying severity. It may be that the matching of cases and controls by having one previous admission has achieved general compatibility, so that the actions of these other putative risk markers then become paradoxical. The expected positive associations of these risk markers were clearer in the first study, where matching on a previous admission was not done.

Sex, age, ethnic origin

In the current study, the association with fenoterol was greater in males than in females, although the difference is not significant (table 4). In the first study a slight difference in the other direction was found.

In the current study, the association with fenoterol was much stronger in non-Europeans (5.20), than in Europeans (1.20) and this difference is statistically significant (test of homogeneity gives P=0.02; extra data provided by Dr Pearce); however in the previously published study a slight difference in the other direction was found.

In both studies the association with fenoterol was stronger in subjects under the age of 20; in the current study the odds ratios were 4.02 and 1.33 in those under and over 20, and in the first study they were 2.08 and 1.34. The modification by age is not quite significant in the second study (P = 0.07), but the replication of the finding suggests that the concentration of risk with fenoterol in younger subjects may be real; it is worthy of further investigation, and had implications for the mechanism.

However it is more important to know if the major effect, the high risk with fenoterol in subjects with other risk markers such as oral steroid use, shows these modifications by age and ethnic origin. Such data are not published, and would be limited by small numbers.

Results: Other drugs

Again, the data refer to drugs prescribed at discharge following the 'reference' hospital admission (table 5).

Theophylline

In the second study the proportions of cases and controls prescribed oral theophylline are similar, giving no association with death, whereas in the first study (later period) the odds ratio was 1.44. This difference is not due to the selection on hospital admission, as in that subgroup in the first study the OR for theophylline was 1.65.

Cromoglycate

Sodium cromoglycate shows no association in either study.

Inhaled steroids

In the new study 45 percent of cases and 55 percent of controls have been given inhaled steroids, whereas in the first (later period) study the proportions were 50 percent for cases and 42 percent for controls. It is therefore a non-significant protective effect in the new study (OR 0.67) and a non-significant risk association (OR 1.34, and 1.44 with a previous admission) in the first study.

Oral steroids

In this new study the prescription of oral corticosteroids (on discharge after the reference admission) applied to 74 percent of cases and 56 percent of controls, giving a significant odds ratio of 2.30 (95 percent confidence limits 1.2 - 4.3). In the first study referring to the later time period the prescription of oral steroids was much less frequent, 28 percent in cases and 22 percent in controls, giving a non-significant odds ratio of 1.38. This changed only to 1.33 in those with a previous admission; 39 percent of such cases had been prescribed oral steroids, compared to 32 percent of controls.

The discrepancy may be due to different sources of information. The information in the new study is also given in terms of prescription of oral corticosteroids at admission on the reference hospital episode, which applied to 26 percent of cases and 26 percent of controls, somewhat similar to the results in the first study. The authors state in this study as they did in the one published earlier that they were unable from the records to distinguish the use of short term and long term corticosteroids. It

seems likely that the high rates of oral steroid prescription reported on discharge refer to short term usage, not reflected in the usage on admission. In the second study thus of the cases, 26% were on oral steroids at the reference admission, and 74% at discharge; 74-26 or 48% were put on steroids during the reference admission (table 6). For the controls, 26% were on steroids in admission, and 56% on discharge; 30% were put on steroids. This large difference suggests large differences in the management and the severity of the disease at that time, between cases and controls.

The interaction between steroids and fenoterol is discussed more fully below.

Multiple drugs

In the second study, 71 percent of cases and 68 percent of controls had 3 or more categories of asthma drugs on discharge (OR 1.14), whereas 38 percent and 49 percent respectively had three or more categories of asthma drugs on admission (OR 0.65). This difference in the change during that admission is presumably related to the steroid prescribing just noted. In the first study, the proportions of subjects with three or more categories of drugs were 58 percent of cases and 44 percent of controls (OR 1.78), and within those with a hospital admission they were respectively 78 and 61 % (OR 2.38).

Previous hospital admissions

In the new study, all cases and controls are defined by having had a reference hospital admission prior to the outcome event; before this reference admission 57 percent of both cases and controls had had at least one other admission in the previous 12 months. In the first published study, the proportions of cases and controls with a prior hospital admission were 44 percent and 35 percent respectively. This excess in the second study is explicable on the basis that the restriction in this study to the subjects with one prior hospital admission, is picking out subjects with more severe or more chronic asthma who are therefore more likely to have had other admissions.

Effect modification and other drugs

In the authors' table 3, they present data for the other major classes of drugs in terms of each of the three markers of severity, and in a group with two of the markers, admission in a previous year and oral corticosteroids on admission. The negative association with inhaled salbutamol is seen, and becomes stronger in those with more risk characteristics, as would be expected as this is reflecting the lack of use of

fenoterol. There is no clear pattern for inhaled beta agonists in total or for oral beta agonists. The association of death with oral theophyllines, which had an overall risk ratio of 1.10, increases with markers of severity (my table 3). There is no pattern seen for cromoglycate. Inhaled corticosteroids show an overall association of 0.68, and this protective effect becomes stronger in the groups with risk markers, reaching 0.35 in those with a previous admission and corticosteroids on admission.

The positive association with oral corticosteroids on discharge, which had the overall risk ratio of 2.30, is also more marked particularly in those subjects with three or more categories of drugs (8.24) and in those with corticosteroids on admission and admission in a previous year (3.42).

No drug other than fenoterol shows higher risks with each of these markers of severity. The information is difficult to interpret because of the relationships between drugs at discharge and drugs on admission, particularly as it applies to corticosteroids. Further, two of the three indicators of severity, the use of oral corticosteroids on admission, and the use of three or more categories of drugs on admission, are directly related to the use of corticosteroids on discharge. The authors point out in the text that when subjects prescribed inhaled fenoterol are omitted from the analysis, the relative risk for oral corticosteroids on discharge was 1.84 overall. This contrasts to the relative risk of 0.39 for steroid use on admission in subjects not using fenoterol. Again this relates to the large difference between cases and controls in the proportion of subjects who were put on oral steroids between admission and discharge, and suggests considerable differences in the severity of the asthma at the time of that reference hospitalisation.

PART C: INTERPRETATION OF THE ASSOCIATION BETWEEN FENOTEROL PRESCRIPTION AND ASTHMA DEATHS

C1 The design of the second study: choice of controls

The study architecture can be considered as in figure 2. Consider a source population of patients in New Zealand with a hospital admission for asthma, and consider their subsequent course in relationship to their drug therapy on discharge after that episode. There are four possible outcomes; death from asthma, further hospital admission for asthma, survival without a hospital admission, and other events such as death from other causes, emigration, and so on. In a prospective study one would attempt to compare patients with different discharge medications, controlling for measures of severity of the underlying asthma available at that time, and study the outcome probably simplified to death versus survival over a fixed time period after that discharge. The ideal method of achieving comparability in terms of severity of underlying asthma would be to randomise eligible patients between fenoterol and alternative drugs.

To achieve a case control design which would be comparable in architecture to such a prospective study, one could sample all deaths in this source population as the case events, and take a random sample of subjects in the source population who had not died by the end of an appropriate period as controls. With this design, the controls would be a representative sample of patients discharged with asthma who had not died. However, such a study would have to rely totally on the use of information on measures of severity to control confounding by severity, as it is likely that there would be great differences in underlying severity between all subjects who die and a random sample of those who do not.

The design the authors have used is rather than take a random sample of survivors as the controls, to use subjects who have had a further hospital admission for asthma. While the controls are not a representative sample of the source population, this design is likely to give a greater degree of comparability for severity of asthma. It is reasonable to assume that the severity of the underlying asthma in those with a further hospital admission for asthma is greater than in those with no such admission, and is more similar to the severity in those subjects who suffer death. Thus by this design, the authors have introduced some matching for severity in their choice of

controls. Assessment of how successful that has been, and whether the underlying severity is truly similar to that of the deceased cases, depends on the measures of severity available in the study.

This design is valid on the assumption that within the non-deceased subjects, fenoterol prescription itself does not influence hospital admission (that is as distinct from any relationship with fenoterol mediated by a true effect of differences in underlying severity of disease). If fenoterol had ill effects, or was an ineffective drug so that asthmatics treated by it would tend to get worse, it would be expected not only to increase the risk of death but also to increase the risk of hospital admission; thus the case control comparison made would under-estimate the true ill effect of fenoterol, by comparing a group with a severe ill effect of fenoterol (death) with a group with a less severe ill effect (hospital admission). On the same logic, if amongst patients who do not die, the prescription of fenoterol is negatively associated with hospital admission, which could occur if it were an effective drug which would allow more asthmatic patients to be treated outside hospital, the comparison could exaggerate any true effect of fenoterol, by comparing a group disadvantaged by fenoterol (deaths), with a group whose usage of fenoterol would be reduced because fenoterol use tends to prevent hospital admission.
The Boehringer Ingelheim consensus group (5) considered this issue and put considerable stress of the 'non-representativeness' of the controls, but take little account of the difficulties introduced by using a wider control group in terms of greater differences in severity of disease.

To explore these possibilities it is necessary to compare asthmatics who have a further hospital admission (analogous to the controls in this study), to asthmatic subjects who had kept out of hospital; such a comparison in terms of fenoterol use has the same difficulty as the main comparison in the current study, in that adequate control for the severity of underlying disease would be needed. There are few adequate data available on the use of fenoterol in asthmatic subjects who have stayed out of hospital, and to perform such a comparison with adequate control for severity is not likely to be easy. The study by Rea et al. (12) of 47 asthma deaths in Auckland in 1981-3 used two control series: one, patients admitted with acute asthma, and the other, asthma patients who had visited their general practitioners over a four week period. The differences in six measures of severity, and in five measures of medical management, were much greater between the cases and the community controls than between cases and hospital controls. This shows the greater problems of confounding which arise if the control group includes non-

hospitalised patients. We can make some relevant comparisons from the two main studies. In the first study, the proportion of controls prescribed fenoterol MDI was 46.7% for those with a previous hospital admission, i.e. with 2 admissions within 12 months; compared to 37.0% in those with only one admission. In the second study all controls had at least two admissions within 12 months; in those with an additional admission prior to the reference admission 33.8% were prescribed fenoterol, while in the rest the proportion was 40.2%. So in the first study the exposure to fenoterol in controls increased with more hospitalisations, while in the second it fell.

Summary:

On balance, the advantages of using hospital admissions as a comparison group in bringing in some degree of comparability for severity of underlying disease, would seem to outweigh the possibility that such comparison subjects are dramatically different in their use of drugs to subjects who had similar severities of asthma who had not been admitted. If the authors had made the comparison between deaths from asthma and a random sample of asthmatics in the community, the differences in severity of chronic asthma between cases and controls would probably have been much greater than in the current study.

C2 Measurement of drug use, and observation bias

The relevant question in this study is whether the drugs prescribed to and used by patients who subsequent die of asthma differ from those prescribed to and used by subjects with generally similar underlying asthma who do not die. The ideal would be to have histories covering a defined period before death or the admission in the comparison subjects, which would give all drugs prescribed, and ideally all drugs available for self administration, which might include those prescribed earlier. In a prospective study this would require repeated reviews of medications prescribed, available, and in use; but in a randomised trial, changes in drug use after the start of the trial would usually be ignored and analysis done on an 'intention to treat' basis. The analogy between a randomised trial with intention to treat analysis and the use of data on prescribed drug medication at one particular point in time in this case control study has been made (4). The primary reason for the intention to treat analysis is to preserve the randomisation in a prospective trial, not to deal with the effect of changes in drug medication. However there is a second reason behind intention to treat analysis; and that is on the logic that physicians do not control what drugs patients actually take, but only what drugs they are prescribed; therefore the

intention to treat analysis is relevant because clinical management plans are based on intention to treat, not on what the patient actually does. This has a clear analogy in these studies, in that it is the physician's prescription of drugs which can be controlled or changed and it is the empiric effect of different prescription plans which is important, even if these effects are mediated by the way patients use or do not use the drugs prescribed.

It is still not clear whether we are dealing with a chronic or acute drug effect in this relationship between fenoterol and death. The emphasis in the study, is on relationship between regular prescribed medication and outcome. An association between prescribed medication and death could be mediated either by a pharmacological effect of chronic medication, a pharmacological effect of medication available and used in the acute attack, or by indirect medical care mediated effects of the medication.

In this study the drug information used is based on the drugs prescribed to the patient at the time of discharge from the reference hospital admission. This will include drugs which are given with the intent of long term medication, and other drugs which are intended only for short term use. It would be ideal if such information could have been supplemented by information from follow-up visits and general practitioners' records, but this was not done. The issue of whether patients at the time of a further acute attack had access to other drugs, prescribed earlier or later than the reference admission, is also a relevant point on which we have no information.

Thus for both cases and controls, the information available on drugs is likely to be incomplete and there could be important differences between the drug information used in this study and what was actually available to or used by the patient.

However, the drug information for both cases and controls has certain major advantages. The information is obtained from identical sources and in an identical manner for both deceased cases and the comparison subjects. For both, an adequately careful and thorough method of abstracting drug information from all records relevant to the previous hospital admission appears to have been used. Although this was not done blind, for understandable practical reasons, it appears to have been done by persons other than the major investigators and to be done in an all-inclusive and non-judgemental fashion. The coding of such information and its summarisation, which is more open to subjective bias and clinical interpretation, has been carried out by the principal authors who are clinically experienced, and

importantly has been done blind using the abstracted data. This procedure of collecting drug information seems excellent and should be free of bias.

Thus although the drug information may be incomplete, and therefore the study may lose some power to detect real associations because of that, a difference in drugs recorded between cases and controls cannot logically be due to observer bias, and therefore is likely to represent a true difference in drugs prescribed at the time of discharge from the prior hospital admission. It is reasonable to assume that any such difference in medication also applied to the later time period. The Boehringer Ingelheim consensus group comment on the limitations of the drug data (5), using a one-sided argument: "Our main concern here is that fenoterol may have been added after hospital discharge to subjects who subsequently survived and are included as controls. If this is so, then fenoterol use may have been misclassified and underestimated in the control group, resulting in an overestimate of the odd ratio for the fenoterol/asthma death association." They do not mention the likelihood that fenoterol may have been added after discharge to the cases, resulting in an underestimate of the association. The usual assumption in these situations, in the absence of any evidence, is that the changes in medication apply to both groups, producing non-differential misclassification of exposure, which will tend to make the association seen conservative, that is, to underestimate any true difference.

A more difficult issue to judge is the contradictions in the information on the use of drugs for some of the deceased cases as assessed by O'Donnell et al. (7), Holst (12) and Rea (10) compared to the data in the first paper on drugs prescribed, and the rejoinder by the authors (8). A critical issue is that the methods of assessment must be applied similarly to cases and to controls; this indeed was the major weakness of the first study and the major improvement of the second. The re-assessments of drugs used have been made only for cases, and unless similar reviews are made for controls the dangers of information bias are increased by these further post-hoc assessments. Members of the Asthma Task Force worked with Crane et al. in the review of drugs prescribed (8); there seems reasonable consistency on this as reviewed earlier (4), but great difficulty in obtaining good data on drugs actually used. The inconsistencies in records of drugs shown by Rea (10) show that the quality of medical records is low, and the integration of hospital and general practitioner care is poor; the information given to the consensus group on "the high quality of hospital records in New Zealand" (5, page 8) is ill-founded.

Summary:

The major advantage of this study over the first one is that it avoids the serious question of observation bias which was present in the first study. Those criticisms of the first study which emphasised this likelihood of observation bias can therefore be dismissed, given the great similarity of results between the second and the first studies. It is reasonable to conclude not only that the results of this second study are unbiased, but that the results of the first study were not seriously affected by observation bias.

Is the drug information appropriate?

A critical issue in this study design is whether the authors have chosen the best data on drug prescribing. As no mechanism for any effect of fenoterol can be confirmed, the critical exposure period during which fenoterol would have to be prescribed and used to produce an effect on mortality cannot be defined.

In this study, there are two alternatives; to use the drug history at the time of the reference admission, or the drug history at the time of the discharge after that hospital admission. The authors have chosen the latter, on the basis presumably that is closer in time to the outcome event, and clearly there is an implication that drugs prescribed to the patient on discharge from hospital will be continued for a certain time. However it is unlikely that all drugs prescribed on discharge would be continued for a substantial time, as some are often given for a short time (e.g. oral steroids).

If a substantial proportion of drugs given to a patient on discharge from a hospital with asthma are intended only for short term use, then the better indicator of likely drug exposure prior to the outcome event (the fatal attack or hospital admission in the controls) may be the drugs prescribed at the time of the previous reference hospital admission, if we assume that the patients' general asthmatic condition has not changed dramatically in the interval between these two events. One would therefore be reassured if an effect seen in regard to drugs on discharge is also seen in regard to drugs prescribed at the time of the reference admission; because one would then assume that this drug was very likely to have been prescribed up to the time of the outcome event. Data on the use of beta agonists both at admission and at discharge at the reference admission are therefore useful. In the second study, results are given for inhaled fenoterol as assessed at the reference admission, giving an odds ratio of

1.72, rising to 3.57, 3.10, 16.59, and 14.00 in the four subgroups defined by severity markers shown in table 3. So in regard to fenoterol this issue has been dealt with.

The differences are considerable for oral steroids, as noted above and shown in table 6. Cases were much more frequently started on oral steroids at the referent admission; this suggests that the severity of asthma at that time was higher for the cases. More of the cases may have been on a short course of oral steroids, which are usually given in decreasing doses; this may be relevant to the mechanisms of the association.

A further method of analysis which might be helpful is to assess the relationships between the outcome event and drug histories in relation to the time interval between the outcome event and the reference admission, which has a range up to 12 months. If a result of the study was due to an incorrect classification issue in that a drug used at the time of the reference admission was in fact not used prior to the outcome event, one would expect that association to be weaker if the time interval between outcome event and the reference admission were greater. Consistency of effect, or an effect being seen as stronger when the interval between outcome event and reference admission was short, would protect against the error due to misclassification of the drug exposure.

Method of comparison

The authors, in both studies, present odds ratios comparing subjects using a particular drug to all subjects not using that drug. An argument can be made for comparing users of particular drugs to subjects using the alternatives within that class; thus given that users of MDI drugs in general have a higher death rate than non-users (perhaps because subjects not given any MDI drug have milder asthma), a better comparison may be between users of MDI fenoterol and the alternative of MDI salbutamol, as would be done in a clinical trial. This results in a slight reduction in the odds ratio: in the first study, the odds ratio given is 1.55; it is 1.50 comparing fenoterol to other MDI drugs. In the second study the odds ratio given is 1.99; it is 1.87 comparing fenoterol to other inhaled beta-agonists (ignoring 2 cases who had both fenoterol and salbutamol). In the further analyses, the drugs to all other subjects comparison has to be used as the data are given in that form. The two groups thus defined may differ in their use of other classes of drugs.

C3 Confounding

Review of the first study suggested that the results would be most likely to be explained by a causal relationship, observation bias or by confounding by the severity of the underlying asthma; that is patients receiving fenoterol had more severe underlying asthma and for that reason had a higher risk of death.

The way in which such confounding is dealt with in a case control study is to compare that cases compare to comparison subjects who have chronic asthma of similar severity. To achieve this it is necessary to have information on appropriate measures of severity of the chronic underlying asthma condition for all subjects, and to make the cases and controls comparable either by matching, or by stratified or multivariate analysis.

The measures of severity used in this study are identical to those used in the first study; the use of three or more types of drug, the prescription of oral corticosteroids, and a hospital admission for asthma in the year prior to the reference admission. If these measures are accurate and appropriate measures of underlying severity, the issue of confounding can be adequately dismissed. The data analysis for this second study shows that amongst the control population, those receiving fenoterol had a higher frequency of two of the markers, the use of three or more drugs and the use of oral steroids, and a lower frequency of prior admission, although none of these differences is very large, suggesting that the overall relationship between fenoterol prescription and severity of asthma is weak or non-existent. Adjustment for each of the measures of severity singly by standard methods shows that the association between death and fenoterol use is virtually unchanged. Thus on the basis of these confounders, there is no evidence that variations in severity explain the associations seen. The results of the first study were similar (4).

As in the first study, the fact that the odds ratio relating fenoterol use to asthma death is greater within subjects with one or more of these measures of severity argues strongly against the association being due to confounding. One possible alternative explanation which was raised in connection with discussions of the first study was that such apparent heterogeneity could possibly be produced by misclassification in these measures of severity, but we (Cox and Elwood) have explored that issue in detail and have dismissed it (see appendix). We have made analogous calculations in the data from the second study, with similar results.

Are the measures of severity used reasonable indicators? There is no independent information which substantiates (or, indeed, refutes) the claim that these indicators are adequate measures of the severity of underlying asthma. Even if these measures are not ideal indicators of severity, they are likely to have some validity and have been used in other studies (12). Although these measures of severity have been criticised, it is not easy to define better measures which would be readily available. Rea's study (12), from which these indicators are partially derived, suggest that they are indicators of severity: others suggested in that study are a previous life-threatening attack, an accident and emergency admission, or a previous respiratory arrest. The Boehringer Ingelheim consensus group suggest that information on symptoms such as night time wheezing and cough, time lost from school or work, and measures of lung function and blood gases could be used to develop a clinically relevant index of severity (5). Work to develop and validate such measures is of crucial importance to future studies, and is currently being undertaken. Some limited data have been provided by Pearce et al.(14): of 141 asthma admissions at Wellington hospital in 1977-87, arterial pCO_2 readings were obtained in 45; the readings were similar in the 17 patients prescribed fenoterol (mean 42.9, SD 10.0) as in 28 other patients (mean 40.2, SD 18.0).

The consensus report also states that "members of the New Zealand Task Force found further evidence to support the conclusion that the data are best explained by fenoterol being prescribed to patients with the more severe asthma." This has certainly been the conclusion given by members of the Task Force (7), but data to support that conclusion have not been presented. The reliance on opinion rather than empiric data in this issue comes through often. Although the data on blood gas measurements reported above are very limited, even data of this nature have not been presented to back up the arguments that simple alternative measures of severity exist, and if used would show major differences between fenoterol treated patients and others. The difficulty in assessing drug histories from records noted earlier also implies that estimates of severity will not be easily obtainable.

A difficulty in accepting these measures of severity as appropriate indicators is that within the data for the second study they do not show the expected relationship. If they are good indicators of severity of asthma, there should be an association between these indicators and the risk of death in subjects who were not prescribed fenoterol. (To look at the relationship within patients who were prescribed fenoterol is not helpful, as the main findings of the studies suggest that fenoterol is a risk factor

particularly within subjects with indicators of severity; thus a relationship between the indicators of severity and risk of death among subjects using fenoterol could be due to this interaction). However, analysis shows that each of the measures of severity is associated with a lower risk of death amongst the subjects not using fenoterol. This finding is difficult to explain. It is possible that the degree of matching achieved by the study design, as both cases and controls were restricted to those who had had a previous admission, is substantial giving comparability by severity of underlying asthma. In such a context, the behaviour of other indicators chosen on general grounds as markers of severity of asthma could be paradoxical.

It is important to emphasise that if the association seen in these two major case control studies between fenoterol prescription and asthma death is to be explained by confounding by the severity of asthma, the important issue is whether within these studies severity acts as a confounding factor, that is the patients prescribed fenoterol have more severe asthma than those not prescribed fenoterol, and the cases have more severe asthma than the controls. Using the measures of severity given, it is clear that confounding does not explain the association seen with fenoterol.

There are some data on the general association between the use of fenoterol and more severe asthma outside the context of these studies. An association is supported by comments of experienced physicians, by the drug company's marketing approach in advertising Berotec as "opening the airways for longer" (16), and by the data on prescribing contained in the recent Boehringer Ingelheim report (16). These data show that in general in New Zealand since 1983, prescriptions for fenoterol have more commonly represented a change in therapy than have prescriptions for salbutamol, and also show that oral steroids have been more frequently co-prescribed with fenoterol than they have with salbutamol. The conclusion that these data present "unequivocal" evidence (16, page 7) that fenoterol was used in more severe patients can be disputed as this evidence on prescribing to patients in general is indirect and does not give specific evidence on the therapy given to individual patients. However it does provide a general case that fenoterol may have been used in more severe asthmatics than salbutamol. The data presented from the Netherlands provide a similar viewpoint for that country. The relevance of this to the interpretation of the major case control studies is limited, however as the crucial issue is whether within these studies there are strong relationships between severity, fenoterol prescribing, and asthma death. The methods of analyses used by the authors of the case control studies are more specific and powerful than the indirect

evidence on populations outside the studies given in the Boehringer Ingelheim submission.

We commented in our earlier submission (4) that other confounding factors may require assessment, reviewing Rea's study (12) which showed associations of asthma mortality with below average medical care, patients' non-compliance, and psycho-social problems. The ability to control for these factors was very limited in the first case control study, and the same applies to the second study. The crucial issue is the strong relationship within the rather small group of patients who are using both fenoterol and steroids. It would be worthwhile, using both case control data sets, to summarise the cases and controls with exposure to both these drugs in terms of as many of these other factors as possible, and factors which may be associated with them such as age, sex, and ethnic status.

C4 Interaction between fenoterol and steroids

The assessment of this is made more difficult because of the lack of detail on oral steroids: the drugs prescribed, dosages, and duration of therapy are unknown. It is possible to look at the interaction between fenoterol on discharge (from the reference hospital episode) and oral steroids on admission, which has been taken as an indicator of disease severity, and may be a good indicator of the likelihood of continued steroid use a considerable time after the reference episode (table 7).

The data show a significant excess risk of fenoterol overall, both crude (OR = 1.99) and after adjustment for steroids (OR = 2.02); although the effect is considerably larger in those subjects also on steroids, (fenoterol OR = 5.83 with steroids, 1.46 without) the contrast, as assessed by the test for homogeneity, is not significant; that is, the difference in the association of fenoterol in those with and without steroids may be due to chance. In the first study, the situation is similar except that the difference in the association in steroid users (OR = 6.45) and non-users (OR = 0.96) is statistically significant. The consistency of the two studies is striking, although the data on steroids are not defined identically.

The results for risk in association with oral steroids are more complex (table 7). In the second study, steroids on admission at the reference hospital episode show no association with asthma death (OR = 0.99); this is 0.91 when adjusted for fenoterol use. However, the risk associated with oral steroids is reduced in subjects without fenoterol (OR = 0.39) and increased in those with fenoterol (OR = 1.55). The results

of the first study are similar to these. A combined analysis of the two studies is given in table 7. The conclusions are, statistically, clear. There is a significant interaction between oral steroids and fenoterol; the increased risk applies to subjects treated with both; fenoterol alone gives no significant increase in risk, and steroids alone are associated with a decrease in risk.

It would be useful to do a similar review using the data on oral steroids at discharge from the reference hospital episode in the second study. Oral steroids prescribed at that time are likely to represent a short course, particular in subjects without steroids at that admission. Unfortunately the data necessary for this comparison are not given. Some interaction is suggested in that the overall odds ratio for oral corticosteroids on discharge is 2.30, while the ratio in the absence of fenoterol prescription is 1.84; thus the odds ratio in the presence of fenoterol must be higher than 2.30. We are also told in the text that the overall fenoterol association of 1.99 is not substantially changed by standardisation for steroid use on discharge, becoming 1.85, which shows that there is not much confounding but does not address the question of effect modification.

How can this high risk of asthma death in subjects on both oral steroids and fenoterol be explained?

1. It may be that these patients have the most severe or unstable asthma, being prescribed the most powerful beta-agonist and the main therapy for severe asthma.

   Some further data would help. A comparison of patients on steroids and fenoterol, one only of these, and none, in terms of other drugs prescribed, age, sex, ethnic origin, and other characteristics of their disease would be useful. For example, it is important to know if subjects on steroids who are not prescribed fenoterol are given other drugs. If numbers permit, further analysis controlling for these factors in this high risk group would be useful. The two data sets could be combined for such analyses.

2. Such patients may have an undue concentration of other risk factors, such as poor compliance, difficult social circumstances, and so on (12). Further data from the studies or from new reviews could be helpful.

3. There may be a pharmacological interaction between oral steroids and fenoterol. Here the difficulty in distinguishing short from long-term steroids is important. Those subjects who were not prescribed oral steroids at the reference admission but were at discharge, that is, who were newly prescribed oral steroids, are worth examining specifically. A possibility worth considering is if the use of a short term, decreasing dose, oral steroid regime in severe asthma could produce at some point a period of bronchial hyper-responsiveness or in other ways lead to hyper-sensitivity to an asthma attack or to aberrant effects of beta-agonist therapy.

C5 Chance variation

The overall association between death and inhaled fenoterol is significant with a P value of 0.02 and 95 percent confidence limits of 1.12 - 3.55. Within sub-groups categorised by one or more of the "indicators of severity", the odds ratios and the lower 95 percent limits are correspondingly higher, despite the reduced numbers of subjects.

The results, despite the differences in the design from the first study are generally very consistent with those of the first study both in terms of the magnitude of the odds ratios and their significance. Chance variation is therefore a very unlikely explanation of the results.

C6 Summary of the interpretation of the second study

The main results of the study are consistent with those of the first case control study by Crane et al., and of the smaller case control study by Rea et al. This second case control study has a major advantage as compared to the first study in that the problem of observation bias can be dismissed. On the basis of the substantially raised and statistically significant increased risk particularly in high risk subgroups and the consistency of the three available studies, chance variation can be dismissed.

The remaining possibilities are two: either the results of these studies demonstrate an empiric causal relationship between the prescription of fenoterol and an increased risk of death from asthma, or the relationship is due to confounding, most likely by the severity of underlying asthma. The main evidence against the confounding hypothesis is the strengthening of the association between fenoterol and risk of death when the analysis is confined to subjects with indicators of greater severity of

underlying asthma, and also the fact that there is no strong association between fenoterol prescription and the risk indicators in either of the main studies. Confounding by severity of underlying asthma can be confidently dismissed if one can assume that the measures of severity used in the two case control studies adequately represent the severity of underlying asthma. However, this may not be so and further measures of severity are desirable.

C7 Other criteria for causality

Time relationship

The new results add little to the understanding of the time aspects of the relationship, and there is still no information which would distinguish long term effects related to the use of medication over a reasonable period leading up to death, from acute effects due to drugs available and presumably used during the severe pre-morbid attack.

Strength

The strength of the relationship in the second study is similar to that of the other studies, and as in the earlier studies it is the much higher risk ratios in the apparently more severe subgroups which are particularly important. The consistency of the three available studies adds to the evidence.

Dose response

As before, there is little useful evidence available on dose response as there is not adequate heterogeneity of dose within subjects in the study.

Consistency and specificity

A very important aspect of the current situation is that there are now three case control studies performed in New Zealand which show consistent results in terms of the overall association of deaths with fenoterol prescription, and the association within apparent high risk subgroups. Both the major studies show a concentration of the effect in younger subjects, aged under 20, and the consistency of this suggests that this modification of effect may be real, which raises several questions relating to the possible mechanism. The differences between the sexes, and the differences between European and non-European subjects, are not consistent between the two

studies. The most compelling evidence from the two major studies is the specificity of the effect within subjects with markers of more severe asthma, and particularly in subjects who are also prescribed corticosteroids.

PART D: PLAUSIBILITY: THE MECHANISM OF THE ASSOCIATION

Our comments on plausibility in the earlier report (4) still apply, and there have not been dramatic advances in this area. The possibilities of mechanisms remain as follows:

1 Pharmacological effects

(a) A specific ill effect of fenoterol used in the acute attack by a patient with severe asthma.

In this situation, the relationship between prescribed medication and risk of death arises because the prescribed medication indicates the drugs available and likely to be used by the patient in self medication for a severe acute asthmatic attack. There is considerable literature on the possibility of such acute ill effects, such as cardiac arrythmias and hypokalemia, and the detailed consideration of these reports is outside the scope of this review. However it should be emphasised that the critical issue is the effects of the drug when used in large and even excessive doses, under the conditions prevailing in an acute asthmatic attack. This implies anoxia and other metabolic changes, and very likely a panic situation. Thus studies which look at the effects of fenoterol in normal recommended dosages under normal conditions and which show no evidence of ill effect are not informative. There do not appear to be many studies which adequately test the hypothesis that fenoterol used in excess dosage under anoxic conditions may have particular effects which would not be shared by salbutamol used under similar conditions. This is a relevant place to mention the role of Adverse Reaction Reports; these "provide no evidence" for a causal role of fenoterol in asthma deaths, as concluded by Professor Buist (15). These reports, lacking any systematic method of assessment or any comparison group, are of very limited value, although they do argue against a sudden short-term or hypersensitivity type effect.

(b) A specific ill effect related to the longer term use of fenoterol.

It is possible that the long term use of fenoterol could have an ill effect, perhaps mediated by a change in bronchial sensitivity to beta-agonists or to other metabolic or cardiac effects.

(c) A specific pharmacological interaction between fenoterol and oral steroids.

The concentration of the effect in subjects with apparently more severe asthma has to be explained. The possibilities are that these risk indicators are acting to define a subset of patients with particularly severe asthma; or that the use of fenoterol is associated with risk particularly in subjects using oral steroids, due to some interaction between the drugs, perhaps specifically in the presence of anoxia. There is some evidence that the effects of fenoterol on hypokalemia and cardiac responsiveness may be increased in subjects on oral steroids. This is obviously a priority for further consideration.

2 Non-pharmacological effects

(c) We suggested in our first report that fenoterol or the fenoterol/steroid combination may be mis-applied, giving subjective relief in an acute attack but leading to a delay in seeking more effective medical help (4). This remains a major possibility. Professor Buist comments (15) "it is possible, even likely, that the fenoterol MDI provided temporary relief in individuals with a steadily deteriorating condition, giving the patients an inappropriate and inaccurate sense of improvement and security." The concentration of the effect in younger subjects seems more explicable on this basis. The specificity of the risk of death with fenoterol rather than salbutamol would therefore be explained on this basis by assuming that fenoterol when used in maximum or excessive dosages in an acute attack gives more symptomatic relief than does salbutamol used under the same circumstances. There does not seem to be any direct evidence which can support or refute this hypothesis. This suggests that if fenoterol were not used in these subjects and another powerful bronchodilating drug was used instead this same effect might apply (although the data still suggest salbutamol would be safer); however it also suggests possible means of controlling such an effect through patient education in the management of acute attacks, modifying the drug delivery apparatus to prevent over-use, or using regular medications to reduce reliance on acute relief.

(d) Again we suggested in the earlier report that fenoterol may be prescribed as part of an unsuitable therapy regimen, where more effective drugs or combination of drugs are needed by virtue of severity of the underlying disease. This could happen if physicians had an exaggerated opinion of the effectiveness of fenoterol in severe asthma. This mechanism (originally suggested by Sackett et al., 17) could possibly explain the particular association between fenoterol use and death in subjects with other indicators of severe asthma. Given that the data on oral steroid use in both the major studies are clearly incomplete and in particular do not distinguish between acute or long term use, a particular suggestion emerges that the patients on fenoterol who are also prescribed oral steroids have in fact had a short course of oral steroids in relation to previous acute attacks. There is evidence for this in the second case control study as reviewed above. If these patients have severe asthma which is unstable, but they are not on long term steroids, they may be being under-treated. This is supported by the review of case reports of patients who have died of asthma by Professor Buist, where she suggests that under-treatment and particularly the lack of adequate long term steroid treatment may be important; "the consistent theme is one of severe disease which was inadequately treated (15)". To explain the association of these conditions with fenoterol use rather than salbutamol use, implies that perhaps the real effectiveness of these two drugs is not greatly different but fenoterol has been marketed and has been regarded by physicians as the more powerful drug and therefore suitable for use in patients with more severe asthma, removing the need to prescribe other medications such as steroids. This seems an attractive hypothesis. The differences in severity would need to be subtle, not adequately described by the risk indicators used in the main studies. There does not seem to be any direct evidence which can clarify this idea further.

(e) Again we suggested in the earlier report that prescribed fenoterol could be linked to a high risk of death not because of the over-use of the drug in the acute attack, but because of under-use if there were any reason why effective therapy would not be used in subjects with fenoterol. This would imply that self administration of fenoterol would, in contradistinction to the above hypotheses, not produce adequate airway response and relief of acute symptoms as compared to use of salbutamol in the acute attack, or that some factor, perhaps the occurrence of side effects, would prevent patients from

using it adequately in an acute attack. There seems to be no evidence which can be used in relation to this hypothesis.

Is the association specific to fenoterol?

One important general question which has received too little attention is whether the observed association, and any of the above mechanisms, whether pharmacological or other, are specific to fenoterol, or whether they are merely characteristic of a potent high dosage bronchodilator drug. Fenoterol has been marketed at twice the effective dose per puff than salbutamol, and the marketing strategy of offering it as a more powerful drug, is a characteristic of the dose as well as the pharmacological preparation. The papers therefore in principle could have been written as a comparison of "inhaled beta agonists at 200 mg per puff compared to inhaled beta agonists at 100 mg per puff". The similarities between fenoterol and newer, and future, beta-agonist drugs need to be considered.

PART E: COHERENCE: THE RELATIONSHIP TO TIME TRENDS AND INTERNATIONAL VARIATION IN ASTHMA MORTALITY

Interpretation of information either on the time trends of asthma mortality or on international variations is a difficult issue. It must first be recognised that the analysis of time and geographical differences is a much less precise scientific method than that of an analytical study such as a case control study, in that the ability to control for other factors is extremely limited. Added to this there is the issue of the comparability of mortality data for asthma between countries, and also over time, although comparability across fairly short time intervals should be reasonable. The analyses have compared death rates with variations in the use of fenoterol, and here there is another difficulty, in that information on the use of fenoterol is obtained from indirect sources and is difficult to express in a comparable fashion to that of deaths. Death statistics are for example age specific, whereas the information on fenoterol is expressed either as sales of the drugs expressed as puffs divided by the entire all age population of the country, or as a market share, that is sales of the drug as a proportion of sales of all drugs of a comparable type.

If drug data are on the basis of units per population, one would expect this to relate to the frequency and intensity with which asthma is diagnosed and treated. Thus one would expect positive associations between the death rate from asthma and the frequency of use of any important drug in its therapy, if there are underlying variations in either the diagnosis of the condition, its real frequency, or the extent to which medical therapy is used. This consideration will apply primarily to international variations and to long term time trends. The data presented by Boehringer Ingelheim in their October submission (16) show this effect; there is a weak but generally positive association between death rates and the use expressed as puffs per person per year of fenoterol, beclomethasone, and salbutamol between countries. Of the countries noted, New Zealand has the highest mortality rate from asthma, and for fenoterol and beclomethasone, has also the highest utilisation rates; for salbutamol Australia has similar utilisation to New Zealand. This gives rise to a statistical problem; if there are a cluster of points with one outlier in terms of both the axes, a fitted regression line will readily give a high and often statistically significant correlation coefficient, which is dependent on the one outlying observation. The Boehringer Ingelheim submission shows that the relationship between mortality and most of these drugs is weak or non-existent if the New

Zealand outlier is ignored. It is clearly arbitrary and inaccurate to ignore one point; but at the same time the finding of a high correlation coefficient is indicating only that New Zealand has high asthma mortality and high drug utilisation, rather than any general trend over all the countries surveyed.

Asthma mortality has been higher in New Zealand than in most other countries for a considerable time. These international comparisons are too simplistic to be of much value. An assessment of international variation needs to be more subtle; designed to assess if the relationship between the mortality rates in New Zealand and other countries has changed over time in a way consistent with changes in the drugs prescribed for the treatment of asthma. The current data show that there is not a clearly specific relationship between fenoterol and asthma death internationally. Further analysis would also be better to use market share, or a measure which would look at total sales or use of the drug in relationship to the number of patients with moderate or severe asthma.

Time trends in New Zealand

The relationship between drug use and the trend in mortality in New Zealand is considerably more helpful, as variations in diagnostic and certification practices over a relatively short time period should not be major. Again there is the difficulty of comparing age specific mortality data with drug data which are based on total units sold or on total population. Boehringer Ingelheim have presented an interesting graph (16, figure 5) of asthma mortality in New Zealand from 1970-1986 divided into ages 5 to 20, and ages 20 to 45. This is appropriate as the two major case control studies have shown a concentration of the association in subjects under 20; however the data should be presented on a logarithmic scale to give directly the proportional change in the two mortality rates. Although the upward trend in the 20 to 45 age range looks much larger because it is on an arithmetic scale, comparison of rates around the early 1980s with rates in the pre-fenoterol period shows an approximate doubling of rates in both age groups. Similarly the decrease from the peak in the early 1980s is about 50 percent in both age groups. However, the 'epidemic' was approximately equal in the age range 5 to 20 and the age range 20 to 45, which does not fit with the results of the case control studies showing the concentration of effect in the under 20s. However, the drug data are not age specific; and the effect on the mortality rate in a particular age group, if the case control study results are correct, depends both on the relative risk associated with fenoterol use and on the exposure to fenoterol in that age group.

The overall relationship in time between the use of fenoterol and asthma deaths in the 5-34 or 5-44 age range has been discussed previously, and some points about this were discussed in correspondence between Beasley et al. (18) and Wilson (19). It is clear that as reviewed in the earlier document, asthma mortality in New Zealand rose from the early 1970s coincident with the introduction of fenoterol in 1976, to reach a peak in 1979, and thereafter mortality has dropped by about 50 percent, while sales of fenoterol on a population basis have continued to increase at least up to 1987.

The results of the case control studies show a concentration of effect in subjects with risk markers of severe asthma, therefore a more appropriate comparison could be with the extent of use of fenoterol in such subjects. It is tempting to speculate that the co-prescription data could be relevant, in that the Boehringher Ingelheim figure 3 (16) shows a considerable decrease in the co-prescription of Berotec and oral steroids from 1983 (the earliest data given) to 1985. Could this be related to the falling mortality rate during that same period? Thus to assess trends more carefully, information on the use of fenoterol, the use of other drugs, and the joint use of various combinations of drugs, within age groups of patients over the last 15 years or so is needed.

These considerations emphasise the weakness of making conclusions based on single factor comparisons of drug sales and asthma mortality. As stated in the first review, although these trend data and international data are of interest, they do not add greatly to the arguments for or against a causal relationship in the case control studies. The data show that fenoterol use is not a complete explanation for either the high death rate from asthma in New Zealand, or the mortality trends over the last 10 years.

PART F: IMPLICATIONS FOR DECISION MAKING

The several issues which have been discussed have a considerable effect on the interpretation of the empiric association between the prescription of fenoterol and the risk of death for asthma in New Zealand, and the actions which should be taken in response to it. If the effect is specific to fenoterol, the reduction in the use of the drug which has occurred and further reductions which would follow action to restrict or stop the use of the drug, should remove the problem and reduce the death rate. The extent of this reduction is hard to predict. The first case-control study includes an estimate of the proportion of asthma deaths at ages 5-45 due to fenoterol of around 18 %; as the second study is more restrictive in its control selection, it cannot furnish such an estimate. The death rate dropped from 1981-6 with no reduction in fenoterol prescribing; the proportion of asthma deaths now related to fenoterol could therefore be higher, unless there have also been changes in the way fenoterol is used which might reduce its risk. A reduction of 18%, from 55 deaths per year to 45 deaths (latest available figures, age 5-44), assuming total and complete effects of withdrawal, would not be unequivocally demonstrable; even ignoring variations in the recognition and certification of asthma deaths, the 95% confidence limits of 55 deaths are 43.4 to 68.9.

The ill-effect could be specific to fenoterol even if not pharmacological, that is, if one of the indirect mechanisms listed above applied only to fenoterol. Such a situation seems rather implausible, as it implies some characteristic of the drug or its delivery system which creates a specific association with difficulties in good medical care. If it were true, reduction of withdrawal of the drug would be beneficial, with the same arguments as apply to a specific pharmacological action.

The question of specificity is important. What features of this drug give these associations; the chemical structure, the delivery vehicle and method, the way it is used, or the doctors' and patients' perceptions of it? What other drugs, particularly new and future drugs, share these features? All we can say firmly is that the risk is related to the difference between fenoterol and salbutamol, as used in the 1977-1983 period.

If the effect is not specific to fenoterol but is merely the effect of a high dose bronchodilator, taking patients off fenoterol and replacing it with another powerful beta-agonist may not improve the situation. This could be because other drugs (but

not salbutamol) share the pharmacological dangers of fenoterol, or because fenoterol and other powerful drugs are prone to be mis-used. If fenoterol is the drug given to subjects whose risk of asthma death is increased by non-compliance, difficult patient-doctor relationships or other non-medical factors, the risk may remain even if another drug is substituted.

However, the restriction of fenoterol on the basis of the empiric evidence of risk may be justified even if other drugs may also be hazardous, as it would force a specific re-consideration of the therapy options in patients who have been using fenoterol. The whole issue has caused New Zealand respiratory physicians and general practitioners to address again the issues of the management of severe asthmatics, not simply the use of these drugs. For example, Professor Buist suggests that some of the patients currently managed with fenoterol should be given continuous courses of steroids (15). One assumption which must be avoided is the simplistic argument that observing the change in mortality following reduction in the use of fenoterol will give the final answer to this question; because of the current trends in asthma deaths which may be influenced by factors other than drugs, and the likelihood of non-specific drug effects, the interpretation of future trends in death rates will be no simpler than that of past trends. There emerges from this a strong argument for the continuance of studies of asthma deaths and suitable comparison groups to continue to assess the role of drugs and other aspects of therapy in the causation and prevention of death from asthma.

My conclusions and a summary of the findings are presented in the first section of this document.

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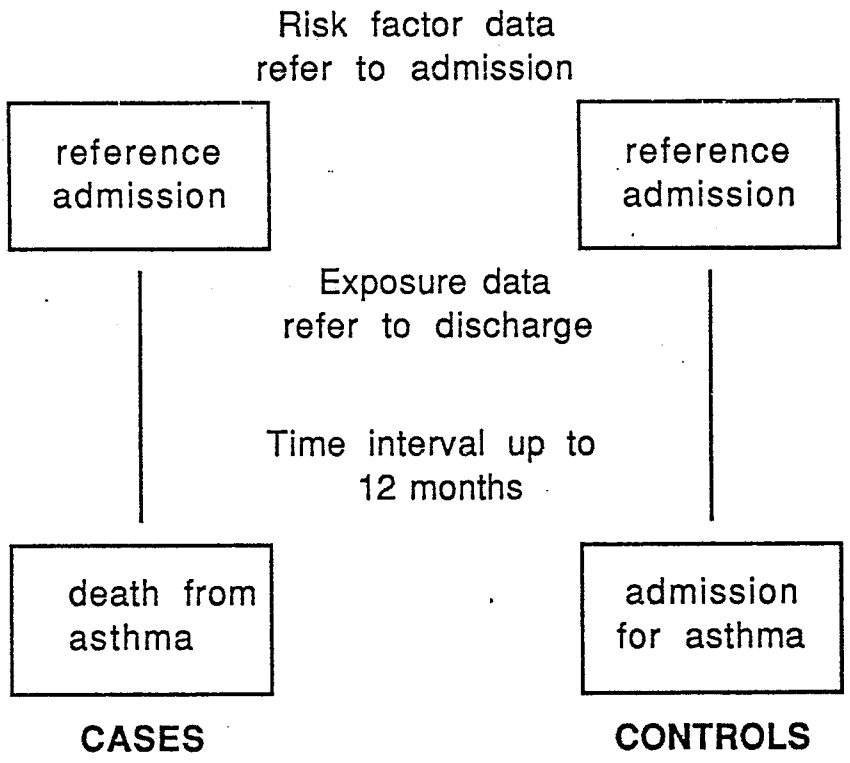

Figure 1: Design of the second case-control study (Pearce et al. 1989).

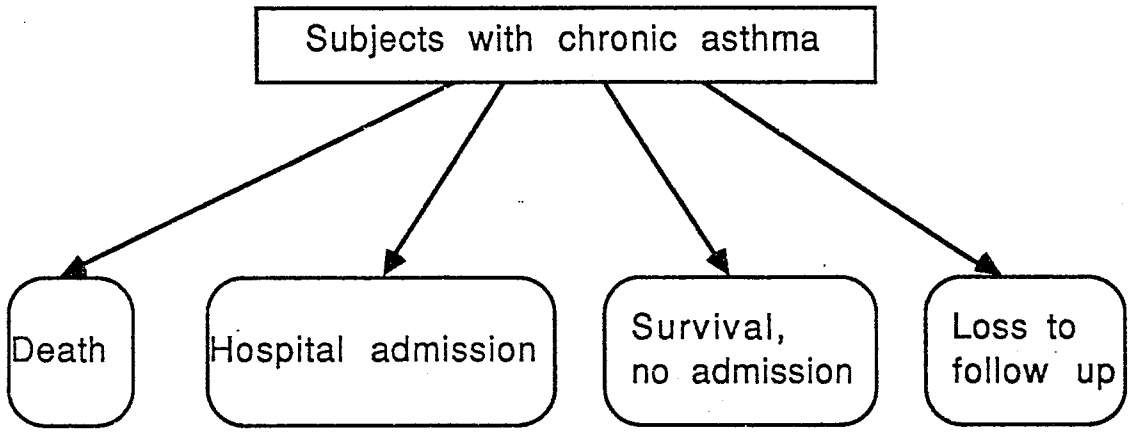

Figure 2 : Possible outcomes of asthma

Table 1: Case selection in second study

	numbers of asthma deaths: included	excluded	% loss
Deaths ICD 493 age 5-45 Jan 77-July 81	366		
Excluded : Dunedin area or small areas	293	73	19.9
Excluded: no hospital records found	214	79	27.0
Excluded: death >1 hour after admission	184	30	14.0
Excluded: no admission in previous 12 mo. fou	67	117	63.6
Excluded: notes not found	58	9	13.4

Table 2: Comparison of two studies: beta-agonists

	Second study % use cases	controls	OR	*First study* % use cases	controls	OR	*First study, subjects with previous admission* % use cases	controls	OR
oral beta-agonist	41.4	37.4	1.18	23.9	22.6	1.07			0.86
oral salbutamol	34.5	33.9	1.03	20.5	20.5	1.00			0.86
any MDI drug	86.2	83.3	1.26	91.5	87.8	1.48			
MDI fenoterol	51.7	35.7	1.93 *	51.3	40.4	1.55 *	65.4	46.6	2.16 *
MDI salbutamol	37.9	46.3	0.71	36.8	45.1	0.71			0.89
any nebuliser drug	3.4	4.8	0.70	20.5	8.8	2.69 *			1.94
nebuliser fenoterol	1.7	0.9	1.97	12.0	4.1	3.21 *			2.42
nebuliser salbutamol	1.7	4.0	0.42	8.5	4.5	1.99			1.34
any inhaled beta-agonist	89.7	86.8	1.32						
inhaled fenoterol	53.4	36.7	1.99 *						
inhaled salbutamol	39.7	49.8	0.66						

* Statistically significant: lower 95% confidence limit > 1.00
MDI = metered dose inhaler
OR = odds ratio

Table 3 : Modification of associations by markers of asthma severity

study	drug	*odds ratio: overall*	*in subjects with:* 3+ drugs	previous admission	oral steroids	admission + steroids
2	fenoterol	*1.99	*2.98	*3.91	*5.83	*9.82
1	fenoterol MDI	*1.55	*2.21	*2.16	*6.45	*13.29
Rea	fenoterol	1.61	2.20	3.00	14.1	-
2	theophylline	1.10	1.19	1.06	5.21	4.14
1	theophylline	1.44	0.88	1.65	1.50	1.19
2	oral steroids	2.30	*8.24	1.90	1.59	3.42
1	oral steroids	1.38	1.07	1.33	infin	infin
2	inhal. steroids	0.68	0.49	0.54	0.66	0.35
1	inhal. steroids	1.34	0.95	1.44	1.19	1.34

Study: 2 = second main study Pearce et al.
1 = first main study Crane et al.
Rea = Rea et al. (12) presented in (1)

* Statistically significant: lower 95% confidence limit > 1.00

Table 4: Modifying factors for fenoterol association

	Second study		*First study*	
	OR	*95% CI*	*OR*	*95% CI*
males	2.77	1.13-6.79	1.44	
females	1.53	0.71-3.31	1.65	
Europeans	1.20	0.58-2.5	1.72	
non-European	5.20	1.94-14.0	1.42	
age <20	4.02	1.57-10.3	2.08	1.01-4.29
age >20	1.33	0.64-2.78	1.34	0.82-2.19

OR = odds ratio
95% CI = 95% confidence interval

Table 5: Frequencies of use of other drugs in two studies

Drugs	*Second study* % use cases	controls	OR	*First study* % use cases	controls	OR	*First study, subjects with previous admission* % use cases	controls	OR
oral theophylline	63.8	61.7	1.09	64.1	55.3	1.44			1.65
cromoglycate	25.9	26.0	0.99	19.7	17.1	1.19			0.91
inhaled steroids	44.8	54.6	0.67	49.6	42.3	1.34			1.44
oral steroids	74.1	55.5	2.30 *	28.2	22.2	1.38	38.5	31.9	1.33
3+ drugs	70.7	67.8	1.14	58.1	43.8	1.78 *	78.8	61.3	2.35 *
Risk indicators (at reference admission)									
3+ drugs	37.9	48.5	0.65						
prev admission	56.9	57.3	0.98	44.4	34.8	1.50			
oral steroids	25.9	26.0	0.99						

* Statistically significant: lower 95% confidence limit > 1.00
OR = odds ratio

Table 6: prescription of oral steroids

Second study		% use of oral steroids Cases	Controls
at reference admission:	at admission	25.9	26.0
	at discharge	74.1	55.5
	net 'new' prescriptions	48.2	29.5
First study			
in period up to index event		28.2	22.2
same period, subjects with prior admission		38.5	31.7

Table 7: Combined analysis of two studies; fenoterol and oral steroids
(in second study, oral steroid data apply to the admission at the reference hospital episode)

		first study		second study		combined data		*test of homogen between studies*
drugs:		*OR*	*Con Int*	*OR*	*Con Int*	*OR*	*Con Int*	*chi-sq 1 df*
fenoterol	overall	1.55	1.04-2.33	1.99	1.12-3.55			
	with oral steroids	6.45	2.27-15.33	5.83	1.62-20.96	6.24	2.90-13.45	*0.04 NS*
	without oral steroids	0.96	0.59-1.56	1.46	0.74-2.89	1.10	0.74-1.64	*0.99 NS*
	adjusted for steroids	1.53	0.98-2.38	2.02	1.09-3.74	1.67	1.16-2.40	
oral steroids	overall	1.38	0.87-2.17	0.99	0.51-1.92			
	with fenoterol	3.04	1.65-5.58	1.55	0.65-3.69	2.39	1.43-4.00	*1.53 NS*
	without fenoterol	0.45	0.20-1.03	0.39	0.11-1.33	0.43	0.21-0.87	*0.01 NS*
	adjusted for fenoterol	1.35	0.75-2.43	0.91	0.41-2.02	1.18	0.74-1.90	
homogeneity test between drugs chi-sq 1 df		*12.53*	*P < 0.001*	*2.88 NS*				

Notes OR=odds ratio Con Int= 95% confidence interval test based

all results for combined data are adjusted for study

the homogeneity statistics test variation between the strata used;
thus there is no evidence of variation between the studies,
but there is statistically significant interaction between the drugs.