LETTERS TO THE EDITOR

Case-control study of prescribed fenoterol and death from asthma in New Zealand, 1977–81

Earlier this year we and others commented on a case-control study by Crane and others[1 2] suggesting that fenoterol was associated with risk of death in patients with severe asthma in New Zealand. We did not accept the validity of the first report because of several problems in methods and analysis. The most serious problems were: (1) ambiguity about the underlying clinical question; (2) poor standardisation of data gathering from cases and controls; and (3) inappropriate classifications of severity of asthma leading to inadequate adjustment for severity as a confounder. We now comment on a second case-control study by the same group (March 1990;45:170–5).

The second case-control study explores a possible relation between asthma medications and risk of death in asthmatic patients aged 5–45 years in New Zealand during the period 1977–81. The cases were 58 asthma deaths (ICD 493) of patients who had been admitted to hospital for asthma within 12 months of death. For each case four asthmatic controls discharged the same year were selected at random from the same hospital and matched on age. The key findings in this second study were that the odds ratio (relative risk) for asthma death in all patients prescribed inhaled fenoterol was 1·99; for patients prescribed three or more categories of asthma drugs 2·98; for patients with a previous admission for asthma in the past 12 months 3·91; and for patients prescribed oral corticosteroids at the time of admission 5·83. In a group of patients with the most severe asthma (defined by a previous admission for asthma during the past 12 months and prescribed oral corticosteroids at time of admission) the relative risk of death for those prescribed inhaled fenoterol was 9·82. Of particular note, the authors reported an odds ratio of 5·2 among non-Europeans, compared with 1·2 (NS) for caucasians only. Also of note, the risk was greater in men (2·77) than women (1·53) and higher in persons under 20 (4·0) than those over 20 (1·3). The investigators concluded that "These findings add further support to the hypothesis that inhaled fenoterol increases the risk of death in patients with severe asthma."

In the first case-control study the investigators confused the question of whether fenoterol has an acute toxic effect when used during an acute attack with the separate question of whether long term chronic use increases the risk of death. This confusion occurred in part because drug information for cases came from general practitioners but for the controls from hospital medical records. In the second study the investigators focused on the question of chronic use of fenoterol by collecting data on drug exposure for cases and controls from records pertaining to the hospital admission *before* an index event (death for cases, hospitalisation for controls). The improvement in data gathering methods does not offset the persisting principal conceptual, methodological, and execution problem of the original study—that is, inadequacy in the classification and adjustment for asthma severity and the likely confounding which probably results. They also repeated a serious error by dissociating the time when severity was measured from the time when exposure was classified. In this regard we do not agree that medications noted at admission or discharge are a valid proxy for "chronic drug usage."

The investigators have not addressed an important alternative explanation for their findings—namely, that sicker asthmatic patients tend to be switched from other medications to fenoterol and that sicker asthmatic patients are more likely to die than those with less severe disease. Fenoterol was marketed in New Zealand as a medication to be tried when control of the patient is otherwise difficult.

The contrasting relative risks for non-Europeans and Europeans, men and women, and those under age 20 and over age 20 deserve comment. An appropriate analogy might be the dilemma which faces investigators of aviation accidents. Does one impute the accident to the aircraft and its manufacturer or was it operator (pilot) error? The data of this case-control study (and the earlier one) do not allow us to set aside a second important competing hypothesis: fenoterol (or any inhaled bronchodilator) is risky when prescribed in the context of a substandard quality of care or when there is poor adherence to an appropriate therapeutic regimen. This may be the situation, for example, in the United States, where blacks have a death rate for asthma three to four times that of whites[3] and asthma mortality in the age group 5–34 is now primarily a problem of inner city ethnic minority populations. We now believe that in the United States this is primarily a reflection of poorer access to health care of high quality and poor adherence to therapeutic regimens.

The fact that two other well established pharmaceuticals, oral corticosteroids and theophylline, had increased risks was not adequately discussed by the authors. As they point out, both of these categories of drugs were prescribed at discharge to virtually all those with *severe* asthma, and the confidence limits for the relative risk estimates were therefore very wide. Why they choose to attribute the increased risks for theophyllines and oral corticosteroids to chance while choosing to accept the increased relative risk for fenoterol as a reflection of its toxicity is not at all clear.

We conclude that, for the second study as well as for the first, problems in the design of the study and the way in which the data were analysed make it impossible for us to agree with the authors' narrow interpretation pointing to only one primary explanation of the findings. As with the previous study, we believe that the results are consistent with several hypotheses which are equally tenable. The investigators have in our opinion failed to give due weight to these alternative hypotheses in their discussion and conclusions. They have nevertheless stimulated and challenged the scientific community to take a closer look at the disturbing possibility that good drugs when poorly used may be potentially harmful. This underscores the urgent need for better education of both health professionals and individuals with asthma about the principles and practice of treatment for this common condition.

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1 Crane J, Pearce N, Flatt A, *et al.* Prescribed fenoterol and death from asthma in New Zealand, 1981–1983: case-control study. *Lancet* 1989;i:917–22.
2 Buist AS, Burney PGJ, Feinstein AR, *et al.* Fenoterol and fatal asthma [letter]. *Lancet* 1989;i:1071.
3 National Heart Lung and Blood Institute. *Data fact sheet: asthma statistics.* Bethesda, Maryland: NHLBI Education Programs Information Center.

AUTHORS' REPLY The letter by Professors Spitzer and Buist consists almost entirely of a repetition of the criticisms, made by a larger group of Boehringer Ingelheim reviewers,[1] of our first New Zealand case-control study. These criticisms have already been answered at length.[2] It is surprising that the hypothesis that our findings are due to fenoterol being prescribed to those with more severe asthma has been raised once again, and even described as "equally tenable." No substantive evidence has been presented in support of the hypothesis. The evidence in fact is almost entirely against it. But as it has been raised again it is necessary for us to re-examine the available evidence.

We reviewed advertisements in clinical journals at the time of fenoterol's introduction into New Zealand, and can find no evidence that it was "marketed in New Zealand as a medication to be tried when control of the patient is difficult." Professors Spitzer and Buist provide no reference for this claim, and it is unlikely that fenoterol could have gained a 30% market share if it had been targeted at such a small and specific group. We can also find no substantive evidence that fenoterol was selectively prescribed to more severe asthmatic patients (within the population of recently hospitalised asthmatics on which our studies are based). Most importantly, the increase in the relative risk for fenoterol when our analyses are restricted to those with the most severe asthma effectively refutes the confounding by severity hypothesis. This point has already been made by one group of epidemiologists who were commissioned by Boehringer Ingelheim to review our first study, and who reached different conclusions from Professors Spitzer and Buist.[3]

Professors Spitzer and Buist have also suggested that "sicker patients tend to be switched from other medications to fenoterol", but provide no data to support this claim. This actually indicates that a hospital admission for asthma is a good marker of asthma which is perceived to be severe enough to require changes in medication. More importantly, it means that the confounding by severity hypothesis can be tested by examining changes in medication resulting from such an event.

We have tested this hypothesis with the data for the controls in our most recent case-control study.[4] Each of the controls had two hospital admissions for asthma over a 12 month period, and we have examined the 420 admissions in the 210 controls for which all the relevant data were available. There were

24 changes from another beta agonist to fenoterol as a result of the admission, and 46 changes in the other direction (most of the latter patients were switched to salbutamol). On the other hand, there were substantial changes for other classes of asthma drugs. In particular, as a result of the admission, the proportion of patients prescribed oral corticosteroids increased from 28% to 62%. Thus patients were often prescribed prophylactic medication as a result of their severe attack, but there is no evidence that sicker patients were switched to fenoterol.

The comment about substandard care in the United States among blacks is not relevant to our findings in the Maori. It is well known that Maori have a higher asthma death rate than non-Maori. We have shown something quite different: that the Maori who use fenoterol have a higher death rate than the Maori who do not use fenoterol. The implication that this finding is due to confounding by ethnicity is nonsense as the comparison was made within the one ethnic group.

More generally, are Professors Spitzer and Buist suggesting that the standard of medical care for New Zealand declined so rapidly in 1976 (when fenoterol was introduced) that this accounted for a doubling of the mortality in two years? If so, what evidence do they have for this? Do they also imply that the standard of medical care also declined suddenly in the six countries which had mortality epidemics in the 1960s when isoprenaline forte was introduced? Furthermore, if any bronchodilator can be harmful when prescribed in the context of poor medical care, why did New Zealand not see an epidemic when salbutamol was introduced?

Professors Spitzer and Buist suggest that we have challenged the scientific community with the possibility that good drugs when used poorly may be potentially harmful. We have not. The scientific community already knows this. Rather we have suggested that a poorly selective $beta_2$ agonist, which is more potent than salbutamol[5] but available by metered dose inhaler at twice the dose of salbutamol, may have been responsible for an epidemic of asthma deaths in young people with severe asthma in New Zealand.

Rather than repeatedly raising the same criticisms of our work, Professors Spitzer and Buist, or Boehringer Ingelheim, should inform the scientific community of the following: (1) Why was fenoterol marketed as a "forte preparation" (200 μg/puff compared with salbutamol at 100 μg/puff) when it was known to be more potent and to have greater cardiac effects than other commonly available beta agonists? (2) Why was the nebuliser formulation made available in New Zealand (5 mg/ml) five times the concentration used in Canada (1 mg/ml)? (3) Why was fenoterol never licensed in the United States? (4) Why was fenoterol marketed as a highly selective $beta_2$ agonist when Boehringer Ingelheim's own funded experiments had indicated that in the clinical situation it was no more selective than orciprenaline,[6] the poorly selective agent it was designed to replace?

In conclusion, we concur with the independent report commissioned by the New Zealand Health Department that the evidence proposed by the Boehringer Ingelheim reviewers in favour of the confounding hypothesis is indirect, circumstantial, and considerably subjective.[7] Although further research would clearly be valuable we also agree with the New Zealand Health Department's conclusion that the current balance of evidence is now in favour of a causal association between fenoterol use and asthma mortality. As a result, the New Zealand Minister of Health has moved to severely restrict the availability of fenoterol by removing it from the Drug Tariff, and a similar policy has now been adopted in Australia.

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1 Buist AS, Burney PGJ, Feinstein AR, *et al.* Fenoterol and fatal asthma [letter]. *Lancet* 1989;i:1071.
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Local anaesthesia for fibreoptic bronchoscopy

Dr AC Davidson and colleagues (March 1990;45:239) were impressed with the local anaesthesia produced by a transcricoid injection of 4–6 ml 5% cocaine (200–300 mg). They went on to state that they were unaware of a formal comparison of cocaine and lignocaine as local anaesthetics during bronchoscopy but recommended that other centres consider changing to the transcricoid instillation of cocaine for fibreoptic bronchoscopy.

In a double blind, randomised study of 60 patients we recently compared the local anaesthetic effects of intratracheal injections of lignocaine (4 ml of 4%: 160 mg) with cocaine (4 ml of 2·5%: 100 mg)[1]. Local anaesthesia was assessed by numbers of coughs, operator acceptability, and patient discomfort; in all areas cocaine scored only slightly better than lignocaine (for example, there was a mean of eight coughs per procedure with cocaine compared with 11 with lignocaine), none of the differences achieving statistical significance. The impression of Dr Davidson and colleagues of the superiority of cocaine may reflect their use of a dose two to three times higher than in our study. It has been recommended that no more than 1·0–1·5 mg/kg cocaine should be applied to mucous membranes in adults, while others have suggested a maximum dose as low as 50 mg[2]; the use of higher doses may increase the risks of toxicity.

We agree with Kinnear *et al*[3] that transcricoid injections of local anaesthetic are well tolerated and produce effective local anaesthesia for fibreoptic bronchoscopy. When used in the doses recommended above cocaine and lignocaine appear equally effective.

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1 Teale C, Gomes PJ, Muers MF, Pearson SB. Bronchoscopic local anaesthesia: intratracheal cocaine and lignocaine appear equally effective [abstract]. *Thorax* 1990;45:333P.
2 Reynolds JEF, ed. *Martindale. The extra pharmacopoia.* 29th ed. London: Pharmaceutical Press,1989:1213–5.
3 Kinnear WJM, Reynolds L, Gaskin D, Macfarlane JT. Comparison of transcricoid and bronchoscopic routes for administration of local anaesthesia before fibreoptic bronchoscopy [abstract]. *Thorax* 1988;34:805P.

AUTHOR'S REPLY We are grateful to Dr Teale and colleagues for drawing our attention to their study of local anaesthesia for bronchoscopy, which we had overlooked. The main point that we were making was that patient tolerance is dependent on the effectiveness of local anaesthesia and two studies now attest to the superiority of the transcricoid route.[1,2] Our impression of the greater effectiveness of cocaine may be the result of our use of a higher dose (200–300 mg) than that used by Dr Teale and colleagues in their study (100 mg); it is interesting that a trend towards a superiority of cocaine is apparent in their abstract. The question of the safe maximum dose of topical anaesthetic agents is controversial and surveys of practice in the UK suggest the use of more lignocaine at bronchoscopy than many authorities recommend. That this is safe practice is suggested by a study demonstrating serum concentrations well below the toxic range with topical doses in excess of 500 mg,[3] presumably because only a proportion of the administered dose is actually absorbed through mucus membranes. The recommended doses quoted by Dr Teale are unrealistically low and the *British National Formulary* recommends a maximum topical dose of 3 mg/kg for cocaine. We now aim to measure serum cocaine levels to ensure that the doses we employ do not produce toxicity. An internal audit of complications in nearly 1000 bronchoscopies has, however, shown no evidence of cocaine induced neurological or cardiac toxicity.

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BCG vaccination of schoolchildren in England and Wales

One aspect of discontinuing routine BCG not discussed by Drs V H Springett and I Sutherland (February 1990;45:83–8) is the possible increase in mortality which may result.

Using published data[1,2] from the Office