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 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 standards in the 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.1

The second case-control study explores a possible relation between asthma medications and risk of death in asthmatic patients aged 5–44 years in New Zealand during the period 1977–81. The investigators were asthmatics (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 greatest 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 attack with the 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 prescribed 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 are not equally possible and a competing alternative might be the dilemma which faces investigators of aviation accidents. Does one implicate the accident to the aircraft and its manufacturer or was it operator (pilot) error? The data of the first 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 poorly substantiated 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 non-blacks. 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 narrow. Why do 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’ main and 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’ main interpretation 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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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, as on which our studies are based). Most importantly, the important issue of 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.

Professors Spitzer and Buist have also suggested that “sicker patients tend to be shifted 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.3 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

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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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Local anaesthesia for fibroptic bronchoscopy
Dr AC Davidson and colleagues (March 1990;45:239) were impressed with the local anaesthesia produced by a trichloroether 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 assured us that others consider changing to the trichloroether instillation of cocaine for fibroptic 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). 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 our patients received. It has been recommended that no more than 1-4 mg/kg be used to abolish mucus membranes in adults, while others have suggested a dose of no more than 50 mg/kg; the use of higher doses may increase the risks of toxicity.

We agree with Kinneir et al that trichloroether instillation of lignocaine is well tolerated and produce effective local anaesthesia for fibroscopic bronchoscopy. When used in the doses recommended above cocaine and lignocaine appear equally effective.

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3 Kinneir WMJ, Reynolds L, Gaskin D, MacFarlane JT. Comparison of lignocaine and bronchoscopic routes for administration of local anaesthesia before fibroscopic 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, 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 trichloroether route. 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 (so: 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 is safe practice is suggested by a study demonstrating serum concentrations well below the toxic range with topical doses in excess of 500 mg, presumably because only a proportion of the administered dose is actually absorbed through mucous membranes. The recommended doses quoted by Dr Teale are unrealistically low and many anaesthetists would administer lignocaine or cocaine before bronchoscopy. 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 toxicological problems. A formal audit of complications in nearly 1000 bronchoscopies has, however, shown no evidence of cocaine induced neurological or cardiac toxicity.

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1 Kinneir WMJ, Reynolds L, Gaskin D, MacFarlane JT. Comparison of trichloroether and bronchoscopic routes for administration of local anaesthesia before fibroscopic bronchoscopy [abstract]. Thorax 1988;43:905P.

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 from the Office...
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Thorax 1990 45: 645-646
doi: 10.1136/thx.45.8.645