LETTERS TO THE EDITOR

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

The most recent case-control study of asthma death in New Zealand (February 1991;46: 105–11), by Dr J Grainger and others, improved on the methods of previous studies and reports increased risks in association with prescriptions for several asthma medications, including fenoterol. Although one explanation for these results is drug induced risk of death, another is risk induced use of drugs (that is, confounding by asthma severity).

The pivotal issue is the degree to which confounding by severity has been controlled. With its control group B, the new study 1 eliminates a source of control selection bias to which we previously drew attention, 2 thereby permitting an evaluation of all three of the authors' presumed severity markers. The results (table below) show that only one of them—recent hospitalisation for asthma—is a reasonably strong severity marker. With this factor taken into account, prescriptions for three or more asthma drug classes are much less strongly associated with baseline risk of asthma death, and oral corticosteroids prescriptions have no predictive validity at all.

The data therefore do not support the authors' use of oral corticosteroid prescriptions in defining the "most severe" subgroup of asthma patients. Instead, the patients at greatest baseline risk of asthma death are those with recent hospitalisations and prescriptions for three or more classes of asthma drug. Within this empirically defined high risk subgroup the relative risk (RR) estimate for inhaled fenoterol (2.21) is somewhat lower than in the study population as a whole (2.66). The RR standardised ("Indirectly" on the basis of data from table 4) for hospitalisation and multiple drug classes equals 2.37. This decrease in the RR after adjustment for severity markers indicates that, contrary to the authors' conclusion, some degree of confounding by severity was present.

We have suggested 1 that, in deciding whether or not to prescribe fenoterol (or any other drug), physicians consider many factors besides recent hospitalisation and drugs previously prescribed. Some of these factors, such as increasing frequency and severity of recent attacks, may be of prognostic significance. As asthma management is still guided largely by signs and symptoms, epidemiological studies should, as a minimum, include assessment of signs and symptoms in characterising baseline risk. The degree of confounding revealed by the secondary severity markers used thus far may be only the tip of the iceberg.

At face value, the authors' data (again using the valid control group B) seem to indicate that most asthma drugs are deadly. In addition to inhaled fenoterol, oral salbutamol (RR = 2.05), nebulised salbutamol (RR = 2.42), oral theophyllines (RR = 1.85), and oral corticosteroids (RR = 1.89) are all associated with an increased risk of death from asthma. A recent study of comparable design in Saskatchewan 2 also characterised baseline risk on the basis of data on prescribed drugs and hospitalisation history and produced similar results.

Do most asthma drugs cause life threatening asthma attacks? Perhaps, but to conclude only that fenoterol does so is to ignore the similar results for other drugs. The results are consistent with confounding by severity, and subsequent research should strive to characterise baseline risk more accurately. Building on the foundation of recent hospitalisation as a solid marker of asthma severity, further studies should strive to identify all clinical, functional, and biochemical measures that physicians are aware of at the time they prescribe asthma drugs and that have strong associations with baseline risk of death from asthma. In the absence of data on possibly the most important prognostic factors influencing treatment decisions, confounding by asthma severity remains a tenable explanation for the entire constellation of results in these studies. 3

Baseline relative risk of asthma death for markers of asthma severity

<table>
<thead>
<tr>
<th>Marker</th>
<th>Controlled for</th>
<th>RR estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral corticosteroids</td>
<td>Nothing (crude)</td>
<td>1.3 (0.6, 2.8)</td>
</tr>
<tr>
<td></td>
<td>Previous admission</td>
<td>1.0 (0.4, 2.3)</td>
</tr>
<tr>
<td>Previous hospital admission</td>
<td>Nothing (crude)</td>
<td>3.5 (1.8, 6.9)</td>
</tr>
<tr>
<td></td>
<td>Oral corticosteroids</td>
<td>3.7 (1.8, 7.5)</td>
</tr>
<tr>
<td></td>
<td>Three or more classes of asthma drug</td>
<td>3.8 (1.9, 7.7)</td>
</tr>
<tr>
<td>Three or more classes of asthma drug</td>
<td>Nothing (crude)</td>
<td>1.7 (0.9, 3.3)</td>
</tr>
<tr>
<td></td>
<td>Previous admission</td>
<td>1.5 (0.7, 3.1)</td>
</tr>
</tbody>
</table>

*Adjusted for a hospital admission in the previous 12 months and oral corticosteroids at admission. MDI-metered dose inhaler.

2 Poole C, Lanes SF, Walker AM. Fenoterol and fatal asthma (letter). Lancet. Nevertheless, it is important to check for confounding by severity, and we have done this repeatedly. 2 It is not possible to obtain "perfect" markers of asthma severity, but such markers are not required; it is only necessary that the severity markers "point in the right direction." Using such markers, we have shown that our findings are not due to confounding by severity, as the relative risk for fenoterol did not decrease when we examined the subgroups of patients with the most severe asthma. 3 Furthermore, our findings cannot be due to non-differential misclassification of severity provided that our severity markers do not "point in the wrong direction." This assumption is supported by four studies that have used these severity markers; these found relative risks in the ranges of 1.7–3.0 for three or more categories of asthma drug, 1.3–3.1 for oral corticosteroids, and 3.5–16.0 for a hospital admission in the last year. 4

In our previous studies we chose the control group (group A) in a manner that effectively matched for asthma severity. 5 In our most recent study 6 we used an additional, unmatched, control group (group B) in response to a criticism by Dr Lanes and his coworkers; this yielded stronger relative risks than the approach we had used previously. This additional control group was used solely to resolve this issue; its findings are unreliable in other respects because of the
potential for confounding by severity when an unmatched control group is used. A similar problem occurred in the Saskatchewan study, which also used an unmatched control group. When this problem is corrected, however, either by using an appropriate control group (group A) or by adjusting for markers of asthma severity (table, top of p 574), then the association of asthma drugs in general with deaths from asthma tends to disappear, whereas the findings for fenoterol remain firm (a similar pattern occurred in the Saskatchewan study). The table shows that control group A provides an adequate match for asthma severity, whereas some confounding exists in the unadjusted results for control group B. We drew this conclusion in the published paper, but Dr Lanes and co-workers have simply repeated our analysis but misrepresented our conclusions.

When the hazards of fenoterol are being considered it is important that all of the evidence should be considered. There is now a wealth of epidemiological, experimental, and clinical evidence that fenoterol is more hazardous than other commonly used β agonists. The peak of New Zealand mortality epidemic started when fenoterol was introduced in 1976, and continued until our first study was published in 1989; the death rate then fell by one half, and is now similar to that in other countries. It is important to search for alternative explanations, but the evidence increasingly indicates that confounding by severity is not a plausible explanation, and that the association between fenoterol and deaths from asthma is likely to be causal.

NEIL PEARCE
RICHARD BEASLEY
CARL BURGESS
RODDY JACKSON
Department of Community Health,
Auckland Medical School,
University of Auckland,
Auckland, New Zealand

4 Crane J, Pearce NE, Burgess C, et al. Markers of risk of asthma death or readmission in the 12 months following a hospital admission for asthma. Int J Epidemiol (in press).
6 Poole C, Lanes SF, Walker AM. Fenoterol and asthma mortality. Lancet 1990;320:

PLEURAL ABERRATION: A NEW METHOD OF PLEURODESIS

Pleural aberration, as a means of pleurodesis, is a new technique, as implied by the pioneer of Mr UT Nkere and others (August 1991;46:596-8). We and most thoracic surgeons in Australia have been performing transaxillary thoracotomies, apical bullae stapling, and ablative pleurodesis for at least 20 years. At the Prince Charles Hospital—a cardiothoracic hospital

serving Queensland—in the period January 1985-December 1990, 320 patients were operated on in our thoracic surgical service for spontaneous pneumothorax. The mean age was 28 years and M:F ratio was 1:1.41.

Surgery was performed via the following surgical approaches: transaxillary thoracotomy (TAT) 244 patients, bilateral TAT 12 patients, lateral thoracotomy 52 patients, anterior thoracotomy 6 patients, posterior lateral thoracotomy 6 patients. Pleurodesis was achieved thus: pleural abrasion 185 patients, talc with or without abrasion 42 patients, pleurodesy by 44 patients, talc with or without pleurodesy 4 patients, other or unknown 5 patients. The mean postoperative hospital stay was four days. There were recurrences requiring surgery in 20 patients and recurrences not requiring surgery in three patients.

I think you must agree that from our experience pleural abrasion is not a new method. We agree, however, with the authors that it is a highly suitable technique with good results. If combined with a transaxillary approach—often an incision no more than 2 inches (5 cm) wide—it is a cosmetically acceptable form of treatment for spontaneous pneumothorax, and we will continue to use this procedure.

P COLE
K S MATAR
Department of Thoracic Surgery, Prince Charles Hospital, Chermside, 4032 Queensland, Australia

AUTHORS' REPLY

We are grateful to Drs Cole and Matar for sharing their extensive experience of surgery for pneumothorax with us. It was with some misgivings that we accepted the editorial decision to change the original title of our paper from "A safe and effective method of pleurodesis" to "New method of pleurodesis". The one aspect of the technique which, as far as we are aware, has not been previously described is the use of a domestic pan scoucer to achieve pleural abrasion and even this is not our invention, as it was being used by Dr Ian MacArthur at King's College Hospital 20 years ago. Despite the fact, however, that pleural abrasion has been in widespread use in North America and, as we now know, in Australia for many years now many thoracotomists using the technique routinely have published their results, and in the United Kingdom there remains the belief outside a small circle of thoracic surgeons and enlightened chest physicians that surgery for pneumothorax calls for a full pleurectomy through a large and painful incision. Indeed, it was the inaccurate and sometimes alarming perception that many of our patients had appeared to receive that prompted us to put our experience together, and in that the subject seems now to have received a wider medical airing than before our principal objective has, in part, been fulfilled.


SHUNTING THROUGH A PATENT FORAMEN OVALE

The phenomenon of shunting through a patent foramen ovale, as recently reported by Dr L Berry and others (January 1992;47:60-1), has interested me for some time.

Those authors emphasised the important point that the shunt flow was detected by transoesophageal echocardiography but not by transthoracic echocardiography — this is not recognised by all echocardiographers. A characteristic feature of this syndrome is platypnoea and orthodeoxia — that is, more pronounced breathlessness and hypoxaemia in the upright than in the supine position. Thus the shunt measurements should probably be made with the patient in the upright position if possible.

The incidence of probe patent foramen ovale was about 22%, but so long as left atrial pressure exceeds right atrial pressure the valve leaflet acts as a closing flap. In the fetus the inferior vena cava empties anatomically and functionally into the right atrium, and is therefore directed into the left heart. In the adult a probe patent foramen ovale is most easily penetrated with a cardiac catheter passed from a femoral vein, not from the brachial vein. Unfortunately Dr Berry and her colleagues did not state which approach they used in their catheterisation.

For two reasons I doubt their explanation that the mechanism for the shunt is caused by mediastinal distortion caused by right pneumothorax. Firstly, this would not be the case if above, the normal anatomy favours blood flow from the inferior vena cava to the left heart where the flap is pressed open. Secondly, this may not represent shunting through a foramen ovale but rather through the patent foramen ovale and right ventricle, which is also more likely to persist following right to left shunting than the left to right.

In their paper Drs Berry and colleagues (1991;46:722-6) emphasised the specificity of the shape of the clearance curve by noting that none of their patients who did not have pneumocystis pneumonia had a bicuspid curve in both the upper and the lower zones of the lung.

We have observed three HIV infected homosexual men who did not have pneumocystis carinii pneumonia in whom the DTPA transfer time (mean SE) Tmn ranged from 3:1 to 4:6 (mean 4:3 minutes) and was bicuspid in the upper, mid and lower zones over a follow up period of four, 18, and 31 weeks. This compares with a mean SE Tmn transfer time in five HIV patients with pneumocystis pneumonia of 3:1 (range 1:8-9:6 minutes) and is significantly lower than transfer times in HIV positive patients with various non-pneumocystis pneumonia chest condi-

Persistent alveolar increased permeability to Macromolecules in pulmonary patients with advanced HIV infection

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