## Bronchodilator treatment in asthma

### Manufacturers underestimate mortality from asthma

EDITOR,—Win Castle and colleagues from Glaxo and Allen and Hanbury's describe the results of a large randomised clinical trial of their bronchodilator, salmeterol.[1] The title of their paper includes the phrase "nationwide surveillance study," which may give the impression that it is some form of postmarketing surveillance study. Their study is a postmarketing (phase IV) clinical trial and should not be regarded as any form of postmarketing surveillance study. The Drug Safety Research Unit is engaged in a postmarketing surveillance study of comparable size but longer duration. The preliminary results of this with regard to total mortality and mortality from asthma differ remarkably from those described by the authors.

In the Glaxo trial 16 787 patients treated with salmeterol were studied for 16 weeks. There were 54 deaths from all causes (0·32%), including 12 deaths from asthma (0·07%). In our prescription event monitoring study, which is not yet complete, we have followed up about 17 000 patients for more than one year. As this is three times the duration of the Glaxo study the authors' results would lead us to expect about 150 deaths from all causes and 30-40 from asthma if we assume that deaths are evenly distributed.

We have in fact recorded 1006 deaths (5·9%). Follow up is complete for only 572 of these deaths, but we have already identified 84 deaths due to asthma and others due to chronic obstructive airway disease. Our current prediction, which allows for deaths occurring more than one year after the start of treatment, is that the final total of deaths due to asthma is likely to be about 150, of which roughly 50 would have occurred in the first 16 weeks. We may thus record an overall death rate about six times and a death rate from asthma about four times the rates reported by Castle and colleagues.

It would be unwise to use the results of the Glaxo study to estimate the mortality from asthma.

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1 Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993;**306**:1034-7. (17 April.)

### Study too small to detect increase in deaths

EDITOR,—The *BMJ* encourages authors to include confidence intervals when reporting results to clarify their full significance. The recent study on the safety of salmeterol undertaken by the manufacturers shows the difficulty of full interpretation when confidence intervals are omitted.[1]

Despite the death rate from asthma in the group given salmeterol being three times that in the group given salbutamol the difference was not significant at $p<0·05$; it must therefore be concluded that there is no clinically relevant increase in risk. The total number of deaths (15) is "in line with that which would have been expected of a sample of patients with asthma of this size in the United Kingdom," but simple binomial tables show that with this small number the death rate from either regimen would need to be 4·33 times that of the other regimen to show significance at $p<0·05$. Even if either drug genuinely caused double the mortality of the other, three times as many subjects would be needed in the trial to show this at $p<0·05$.

Thus despite the large numbers recruited to this randomised double blind trial the predictably low death rate ensures that the power of the trial was inadequate to detect even a fourfold increase in death from either drug at $p<0·05$.

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1 Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993;**306**:1034-7. (17 April.)

### Regular treatment with β agonists remains unevaluated

EDITOR,—Win Castle and colleagues' stated objective was to compare the safety of salmeterol and salbutamol in treating asthma.[1] The increased number of deaths in the group of patients treated with salmeterol must be of concern despite statistical manipulations to indicate that there were no significant differences in the number of deaths between the groups treated with salbutamol and salmeterol. The fact that fewer of those treated with salmeterol withdrew because of asthma is only superficially reassuring as salmeterol is considerably more potent than salbutamol[2] and might therefore be expected to prevent more exacerbations. Possibly the episodes of asthma that broke through salmeterol treatment were more severe than those in the patients treated with salbutamol, and unless this was assessed simple comparison of numbers is irrelevant. One could postulate that the increased number of deaths in the patients treated with salmeterol, although not significant, was due to the increased severity of breakthrough exacerbations.

The authors indicate that the data generated from this large surveillance study are not consistent with the conclusions of previous, much smaller studies, which suggested an apparent deterioration in asthma during prolonged regular treatment with β agonists.[3,4] The comparison of salmeterol with salbutamol was not designed to address this problem, and a direct comparison of two regularly administered active drug regimens could never provide this information. In retrospect it is unfortunate that the Glaxo study was not designed to investigate whether regular treatment with a β agonist has any adverse effects. Until the results of studies that have been so designed are available we must avoid regular treatment with β agonists whenever possible.

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1 Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993;**306**:1034-7. (17 April.)
2 Smyth ET, Pavord ID, Wong CS, Wisniewski ASZ, Williams J, Tattersfield AE. Interaction and dose equivalence of salbutamol and salmeterol in patients with asthma. *BMJ* 1993;**306**:543-5. (27 February.)
3 Sears MR, Taylor DR, Print CG, Lake DC, Qingqing L, Flannery EM, *et al.* Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990;**336**:1391-6.
4 Van Schayck CP, Dompeling E, van Herwaarden CLA, Folgering H, Veerback ALM, van der Hoogen HJM, *et al.* Bronchodilator treatment in moderate asthma or chronic bronchitis: continuous or on demand? A randomised controlled study. *BMJ* 1991;**303**:1426-31.

### Increase in deaths during salmeterol treatment unexplained

EDITOR,—The authors of the postmarketing study comparing the safety of regular salmeterol and salbutamol in asthma predicted 10 deaths during treatment with salmeterol and five during treatment with salbutamol.[1] Most deaths due to asthma occur in patients not under regular supervision or when disease is unstable; such patients are unlikely to have been part of the study group as they would either not have been seen for enrolment or have been excluded as having "serious uncontrolled pulmonary disease." Hence those entered were at low risk of death due to asthma, as shown by the lower than predicted number of deaths during salbutamol treatment (two rather than five). The same low risk should apply to both treatment groups, hence only four deaths should be expected during salmeterol treatment rather than the 10 predicted from national statistics. On the contrary, 12 deaths occurred, suggesting a threefold increased risk of death due to asthma associated with regular use of salmeterol.

The report lacks critical information on age at death. Recent case reports suggest that salmeterol may put young people at risk,[2] as did high dose isoprenaline and fenoterol.[3] Increased age specific mortality may be masked if deaths are related only to total population figures. Information on age at death is essential for a proper understanding of these data.

The place for salmeterol remains in doubt. It is arguable whether long acting bronchodilators are appropriate in mild asthma, especially in those not using inhaled corticosteroids.[4] Patients with severe asthma needing high dose corticosteroids might benefit from salmeterol, but studies have not yet been reported in such patients. Furthermore, the postmarketing study suggests that this group may be at higher risk of death while taking salmeterol.[1] Surprisingly, five of 14 deaths due to asthma occurred in hospital. No data are given regarding these deaths: were these attacks resistant to usual intensive treatment?

The authors reiterate the concept that "high use of β agonists merely reflects severity of asthma, and that these patients with more severe asthma are at greater risk of death." We have shown, however, that the severity of disease is itself increased by frequent use of a potent β agonist when every other variable is kept constant.[5] Regular use of

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