LETTERS

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.)
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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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salmeterol, although relieving symptoms, may mask or even increase the severity of the underlying disease.[2] The mortality data provided by Win Castle and colleagues do not alleviate current concerns that the frequent or regular use of β agonist drugs may be contributing to morbidity due to and 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.)
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5 Sears MR, Taylor DR, Print CG, Lake DC, Li Q, Flannery EM, *et al.* Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990;**336**:1391-6.

Authors' reply

EDITOR,—William H W Inman presents data from prescription event monitoring and suggests that they are at variance with ours. These differences emphasise the importance of performing a controlled randomised study such as the Serevent nationwide surveillance study. The differences are, firstly, the speed with which our study was completed and, secondly, that we have a well defined population of patients in whom severity was characterised at the outset of the study. Thus it is possible in our study to put the adverse events into context. In Inman's continuing study it is not possible to define accurately post hoc whether the patients treated with salmeterol had asthma or chronic bronchitis. It is also uncertain whether the deaths were truly due to asthma as they were not audited by independent physicians, as they were in our study. In addition, Inman includes a very elderly population compared with ours. It is also noteworthy that, as Inman collected data from the launch of the drug, his population will have much more severe asthma than the general population with asthma. Although Inman's data are of interest, lack of an adequate control group limits their usefulness.

Robert Bunney comments on the power of our study to detect a true difference in the death rate and a lack of confidence intervals. In fact, confidence intervals were quoted in the paper. We agree that a much larger study would be required to detect a difference in death rate, but the purpose of this study was to examine the overall profile of serious adverse events with salmeterol compared with salbutamol. Such events were significantly fewer with salmeterol. It would not have been feasible to mount a larger study without the timescale being inappropriately long to have been of any benefit.

Graham K Crompton makes several points. Firstly, he states that as the patients in both groups were treated with a regular β agonist it is not possible to compare the data with those from previous studies. Both twice daily salmeterol and four times daily salbutamol have been compared favourably with placebo in a well controlled clinical study by Perlman *et al.*[1] Secondly, he raises the issue of the relative potency of salmeterol compared with salbutamol. We have addressed this point previously.[2] Finally, he notes that salmeterol may mask exacerbations and that, although it may reduce the total number of exacerbations, the remaining exacerbations could be more severe. We have conducted two 12 month studies comparing salmeterol with salbutamol in which we have collected information on exacerbations and admission to hospital.[3,4] The table gives the data and shows that there is an overall reduction in both exacerbations and admissions in those treated with salmeterol and that the ratio of the two is lower with salmeterol than with salbutamol.

Numbers of exacerbations of asthma and admissions to hospital in patients given salmeterol 50 μg twice daily and in patients given salbutamol 200 μg four times daily or 400 μg twice daily

	Salmeterol 50 μg twice daily	Salbutamol 200 μg four times daily or 400 μg twice daily
Patients	576	586
Exacerbations	421	560
Admission to hospital	23	37
Admissions/100 exacerbations	5·5	6·6

M R Sears and D R Taylor request further data on the deaths due to asthma. The ages of the patients who died while taking salmeterol were 14, 33, 38, 44, 45, 48, 59, 60, 63, 68, 70, and 80 and of those taking salbutamol 20 and 62. Given the range, the most appropriate statistic to use is overall mortality, and our predictions were calculated after age standardisation to the population of the Serevent nationwide surveillance study. No age group was particularly at risk. Sears and Taylor also extrapolate from the small number of deaths in the salmeterol group to suggest that the death rate from asthma in the United Kingdom should have risen threefold. We would reassure them that, in the first two years after the launch of salmeterol, the death rate from asthma in the United Kingdom was unchanged. The five patients who died in hospital were not found to have had unusual features in the specialist audit.

Finally, we would draw Sears and Taylor's attention to a recent three month comparison of salmeterol 50 μg and 100 μg twice daily in severe asthma.[5] No deterioration in asthma was noted, even in patients not taking a concomitant steroid.

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Treatment of streptococcal sore throat

Beware glandular fever trap

EDITOR,—P Shvartzman and colleagues suggest that amoxycillin once daily is as effective as phenoxymethylpenicillin in the treatment of group A β haemolytic streptococcal pharyngitis.[1] Continued treatment with amoxycillin was based on positive culture of β haemolytic streptococci from throat swabbing; however, it is known that this organism can be grown from throats of asymptomatic patients—with no rise in antistreptolysin O titres (and, conversely, the titres can rise with no symptoms).[2] The diagnosis of streptococcal pharyngitis is notoriously difficult—Shvartzman and colleagues established a laboratory diagnosis in 157 out of 393 clinically diagnosed subjects, some 40%.

Broad spectrum antibiotics—such as amoxycillin—are contraindicated in blind treatment of sore throats,[3] because of the risk of rash in cases of glandular fever. All sore throats should be regarded as potential cases of glandular fever, even after laboratory investigation—which may be unreliable or misleading, and in any case is little used in British general practice.[4]

If penicillin was replaced with amoxycillin in the treatment of presumed streptococcal pharyngitis the incidence of rashes with glandular fever would rise—with attendant medicolegal implications.

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1 Shvartzman P, Tabenkin H, Rosentzwaig A, Dolginov F. Treatment of streptococcal pharyngitis with amoxycillin once a day. *BMJ* 1993;**306**:1170-2. (1 May.)
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4 Tompkins D, Shannon A. Clinical value of microbiological investigations in general practice. *Br J Gen Pract* 1993;**369**: 155-8.

Stick to penicillin or nothing

EDITOR—P Shvartzman and colleagues suggest that amoxycillin once daily is as effective as phenoxymethylpenicillin in treating β haemolytic streptococcal pharyngitis, and they emphasise the importance of adequate treatment of streptococcal pharyngitis in preventing rheumatic fever.[1] We question the choice of patients studied, the inequality of the treatment groups, and the authors' assumptions about the prevention of rheumatic fever.

The authors studied patients with suspected streptococcal pharyngitis in whom throat cultures yielded positive results. Unfortunately, a diagnosis of streptococcal pharyngitis on clinical grounds alone is known to be unreliable, and the throat swab has a low sensitivity and specificity (26-30% and 73-80% respectively[2]). Thus the patients will have included only a minority of those at risk of developing rheumatic fever. Furhermore, given that three patients in the amoxycillin group also received phenoxymethylpenicillin after 24 hours, it is not clear that amoxycillin was responsible for the "much better eradication after 14 days."

A fundamental problem with prescribing antibiotics for sore throat is that only a minority of patients (possibly only 1 in 18) with sore throat ever attend their doctor.[3] Thus for there to be any appreciable difference in the outcome in the community either general practice surgeries would need to be overwhelmed with patients or antibiotics would have to be freely available in the community. Thus to treat streptococcal pharyngitis in the community effectively would entail considerable costs. There is also evidence to suggest that patients who have antibiotics are as likely to develop rheumatic fever as those not taking antibiotics.[4]

The paper encourages use of antibiotics to a self limiting condition—which would increase patients' expectation of being prescribed an antibiotic and increase their likelihood of consulting their doctor —without good evidence that any difference will