Eur Respir J, 1995, 8, 673–678
DOI: 10.1183/09031936.95.08050673
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European Respiratory Journal
ISSN 0903 - 1936

EDITORIAL

Present state of the controversy about regular inhaled β-agonists in asthma

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The use of inhaled beta-agonists in the treatment of asthma has, on occasions, been postulated to be associated with asthma mortality and/or with deleterious effects on asthma control.

Asthma mortality

Ecological studies

A possible association between the use of β-agonists and mortality from asthma was postulated for the first time during the so-called epidemic of asthma deaths, which was observed in England and Wales in the 1960s [1]. With reference to this epidemic, INMAN and ADELSTEIN [2] reported a rise and fall of asthma mortality paralleling an increase and decrease, respectively, in the use of pressurized aerosols. However, SPEIZER *et al*. [1], the authors of the first report, pointed out that "Accounts of the excess use of aerosols have been obtained in some cases, but decisive evidence to incriminate them is lacking". Other studies based on the same approach have yielded different results. In New Zealand, from 1979 to 1987, asthma mortality showed a trend to decline, whereas fenoterol and salbutamol use had a further increase [3]. In Sweden, asthma mortality remained quite stable from the beginning of the 1960s, whereas there was a marked increase in the use of inhaled β-agonists [4]. In the UK, prescription of β-agonists increased threefold during the 1980s, without any appreciable change of asthma mortality in this decade [4]. In Italy, no correlation was apparent between asthma mortality in three age classes (5–34, 35–54, and more than 55 yrs) and the number of β-agonist canisters sold in the period 1980–1989, since against an increase in the sale of metered-dose inhalers there was a trend for asthma mortality firstly to level-off and then to decline [5]. Ecological studies of this type, which are based on correlations, at a regional level, between rates of asthma death and sales of inhaled β-agonist bronchodilators, may be used only to generate or support cause-effect hypotheses, which then require other methodological approaches to be tested [6].

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Case-control studies

Concerning the type of investigations required to test this cause-effect hypothesis between inhaled beta-agonists and asthma mortality, it should be pointed out that a randomized controlled clinical trial is not practical, since asthma death may affect too few people to have a chance to be adequately observed in this type of study. On the other hand, a case-control study may be applied to test this hypothesis, even though there may be problems with the selection of appropriate controls. The existing case-control studies have examined the use of beta-agonists among asthmatic patients who died and asthmatic patients who did not die [7–12]. The effects of patient sample age and mode of delivery (oral, metered-dose inhaler (MDI), and nebulizer) have also been examined.

A meta-analytic integration of these case-control studies, performed by MULLEN *et al*. [13], has revealed a significant, although extremely weak relationship between beta-agonist use and death from asthma (z=3.996; p=0.000075; mean r=0.055). This relationship emerged only when beta-agonists were administered with a nebulizer (z=4.481; p=0.000038; mean r=0.103). There was no association between beta-agonist use and death when beta-agonists were administered by MDI (z=1.194; p=0.11; mean r=0.031) or orally (z=1.247; p=0.1; mean r=0.031). Adults were more likely than adolescents to indicate the association between beta-agonist use and death. In conclusion, the authors of the meta-analysis interpret these results as documenting the extremely small magnitude of the relationship between beta-agonist use and death from asthma. The validity of this conclusion, on the other hand, depends to a large extent on the selection of controls who match closely the asthma severity of the cases. Since the possibility of obtaining appropriate controls of the cases with respect to asthma severity is much debated [14–16], it appears that even the extremely small magnitude of the relationship between beta-agonist use and death from asthma should be taken with caution.

Cohort studies

A close scrutiny of the results of the six case-control studies included in the meta-analysis indicates that only one of them reports a particularly positive association

between the use of all the inhaled beta-agonists and the risk of asthma death (or near death) [12]. This study is based on a nested case-control sample of 129 cases and 655 control subjects selected from a cohort of 12,301 users of asthma drugs. Although the nested case-control design may be considered an efficient means of analysing a cohort, it has certain limitations. Because of this, the same authors of the original study have reanalysed their data from the entire cohort, taking into consideration all the deaths (but excluding the near deaths), both asthma-related and non-asthma-related, and following all of the 12,301 asthmatics (actually users of asthma drugs) over 7 yrs [17]. Absolute and excess risks for asthma death associated with the use of inhaled β-agonists (fenoterol and albuterol) were estimated. Accurate dose-response models of risk were computed. Using these models, the threshold above which the associated risks start to increase markedly was also estimated. Finally, the association between β-agonist use and non-asthma death was assessed.

A few relevant results were obtained. The asthma death rate in Saskatchewan from 1980 to 1987 - the calendar period of the study - decreased steadily and significantly from 18 to 5 per 10,000 asthmatics annually. The non-asthma death rate did not change significantly, oscillating around the mean value of 28 per 10,000 asthmatics annually. The absolute death rate associated to fenoterol and albuterol by MDI was 61.5 and 9.8, respectively, and the adjusted excess death rate 58.3 and 6.1, respectively. These adjusted excess death rates were reduced to 36.2 and 3.6, respectively, for fenoterol and albuterol when they were further adjusted for oral corticosteroid use and the number of asthma hospitalizations in the prior 24 months. The adjusted excess death rate associated to oral corticosteroid use and to number of asthma hospitalizations in the previous 24 months was 15.6 and 7.7, respectively. It is evident, according to the analytical approach of this study, that a significant excess risk for asthma death is also associated with the use of oral corticosteroids.

The authors admit that they "did not have additional data on asthma severity with which to make further adjustments" [17]. If they had additional data on asthma severity (*e.g.* number of episodes of respiratory viral infection, exposure to allergens, individual susceptibility, *etc.*), it may be hypothesized that the adjusted excess death rate associated to fenoterol and albuterol (and oral corticosteroids) would be further reduced (perhaps to the point of becoming insignificant).

At first sight, this cohort analysis, based simply on the use/non-use classification for beta-agonists, demonstrated a much higher risk for fenoterol than for albuterol. The results derived from a more precise analysis, using the extent of exposure to these drugs, reveal a significant dose-response relationship both for fenoterol and albuterol. Fenoterol was associated with a much higher risk of death than was albuterol, but only in the subgroup of excessive users of these beta-agonists (*i.e.* users of 25 or more canisters per year). This difference between the two β-agonists could, in part be explained by the higher average use in the number of dose-equivalent canisters (of 20,000 µg each) among excessive users of fenoterol as compared with albuterol [17]. However, the authors of the cohort analysis suggest that the disparity between the fenoterol and albuterol risk among the excessive users could be real or, more plausibly, the result of the differential indications of the two products, fenoterol being considered a more potent drug and, consequently, prescribed to patients with more severe asthma not responding to albuterol [18]. Depending on the model selected to describe the dose-response curve, and keeping in mind that the amount of medication prescribed and dispensed to the individual subjects may differ from the amount actually self-administered, it appears that the risks of asthma death associated with the use of inhaled β-agonists by MDI are extremely high in users of two or more canisters (of 20,000 µg each) per month (more than 13 puffs of 100 µg each daily). In fact, the predicted asthma death rates are 9.7 and 18.8 per 10,000 asthmatics annually, respectively, for one and two canisters per month, and increase markedly to 54.3 and 93.1 deaths per 10,000 asthmatics annually for three and four canisters [17].

Finally, non-asthma death was not associated with the use of either of the inhaled β-agonists investigated in this study. Using the words of the authors, the cohort analysis has still not shown whether the very strong association between the dispensing of large amounts of inhaled β-agonists and the risk of fatal asthma is causal, *i.e.* due to toxic effects of the medications or their vehicles, or whether excess β-agonist use is, instead, a marker of severe, poorly controlled asthma, itself the cause of the high risks observed [17]. The authors favour the latter explanation, in part because they were unable to demonstrate an excess of non-asthma deaths, even among the excessive users of beta-agonists, which might have been expected if cardiotoxic effects of beta-agonists were at fault. In any case, the use of two or more canisters of β-agonists per month is a very powerful marker of increased risk of fatal asthma and deserves particular attention.

In conclusion, the quoted ecological studies of association between asthma mortality and β-agonist sales [2–5] show diverging results, especially during the declining phase of the irregular cyclic course that characterize asthma mortality in different countries. Case-control studies, up to now, have been essentially inconclusive in establishing a causal link between bronchodilator use and death from asthma due to the difficulty in selecting a suitable control group of severe asthmatics who survived [7–13]. In fact, they have been unable to avoid the so called susceptibility bias [19], that occurs when a treatment administered to patients with a given prognosis is compared with another treatment (or no treatment) administered to patients with a different prognosis. It is probable that controls do not use beta-agonists the way cases do because the former have less severe asthma than cases. Concerning the study based on a cohort analysis [17], limitations derive from the possibility that not all the important factors of asthma severity could be included in the analysis. Moreover, it appears extremely difficult to use predictors of fatal asthma especially when we consider that it may be precipitated, for instance, by a

respiratory viral infection or exposure to allergens. Even in this type of study, the susceptibility bias may distort association with asthma mortality. In fact, in this cohort analysis [17], not only asthma hospitalization in the previous 24 months but also oral corticosteroid use appears a significant risk factor for fatal asthma.

Asthma control

When reviewing the controversy about inhaled beta-agonists in asthma treatment, it is necessary to consider not only the possibility of an acute toxic effect of the beta-agonist when used during an acute attack of asthma, but also any chronic long-term effect, associated to regular inhaled beta-agonists, that might exacerbate the natural course of the disease. In the latter case, increased asthma severity may become an important risk factor for fatal asthma. In a double-blind, placebo-controlled, randomized, cross-over study of the effects of regular *versus* on-demand inhaled fenoterol for 24 weeks in 89 subjects with stable asthma, SEARS *et al*. [20] reported that regular inhalation of a beta-sympathomimetic agent was associated with deterioration of asthma control (judged by daily morning and evening peak expiratory flow rates (PEFR), symptom diaries, use of additional inhaled bronchodilator, and requirement for short courses of prednisone) in the majority of subjects. These authors concluded that the increasing use of beta-sympathomimetic drugs is possibly contributing to the worldwide increase in morbidity (especially severity) and perhaps mortality from asthma. It should be remarked, however, that the deleterious effects of fenoterol on asthma control, reported by SEARS *et al*. [20], appear of small magnitude [21].

Somewhat at variance with the paper by SEARS *et al*. [20], in a 4 week, randomized, cross-over trial of regular salbutamol (2 puffs, 200 µg, *q.i.d*.) for 2 weeks and as-needed for 2 weeks in 341 people with stable asthma of moderate severity, CHAPMAN *et al*. [21] observed no significant differences in morning and evening peak flow rates between treatments but report that asthma symptoms and supplementary bronchodilator use were significantly less frequent when salbutamol was given regularly. These authors conclude that, in asthma of moderate severity, regularly administered salbutamol does not produce lower peak flow rates than as needed salbutamol, and is associated with less frequent asthma symptoms. Furthermore, they comment that concerns about loss of asthma control with regular inhaled $beta_2$-agonist may be overstated.

Some mechanisms have been proposed to explain the possible adverse effect of chronic regular treatment with beta-agonists in asthma. The first hypothesis is the reduction in the administration of inhaled steroids due to the regular long-term treatment with beta-agonists: the control of asthma symptoms by regular bronchodilator therapy may cause an inadequate chronic regular treatment with anti-inflammatory drugs, and may induce an increase in the underlying airway inflammation which can eventually overcome the effects of beta-agonists and determine a deterioration of asthma. Some studies have reported changes in bronchial hyperresponsiveness to methacholine or histamine in asthmatic subjects treated regularly with beta-agonists only. In 15 patients with chronic asthma, 400 µg of salbutamol, *q.i.d*. for 1 year, induced a significant decrease in the provocative concentration of histamine causing a 20% decrease in forced expiratory volume in one second ($PC_{20}FEV_1$) with respect to the pretreatment value, in comparison with a control group treated with anticholinergic drugs [22]. Previous non-controlled studies had not shown such an effect [23]. On the other hand, studies to assess the efficacy of long-term inhaled steroids on bronchial hyperresponsiveness used subjects treated with beta-agonists only as control groups. In most evaluations over a number of years, bronchial hyperresponsiveness did not significantly change, but the high cumulative percentage of withdrawals in these groups suggested a deterioration of asthma, and probably of the underlying airway inflammation [24–26].

Although studies confirming the increase in airway inflammation by bronchial lavage, induced sputum, or bronchial biopsy after long-term treatment with beta-agonists alone are lacking, this hypothesis is pertinent. However, considering that the guidelines of asthma treatment suggest that beta-agonists should not be used as the sole long-term treatment of asthma, this hypothesis should not explain the supposed increase in the deterioration of asthma control due to beta-agonists. Furthermore, the deterioration of asthma observed during short-term treatment with $beta_2$-agonists alone cannot necessarily be ascribed to an impairment of airway inflammation. In a double-blind cross-over study, bronchial responsiveness to histamine after 14 days of regular treatment with 500 or 2,000 µg of terbutaline *t.i.d*. was significantly higher than after one day of terbutaline treatment [27]. Recently, some authors have reported that regular treatment with salbutamol 200 µg *t.i.d*. for 3 weeks was associated with an increase in peak expiratory flow (PEF) variability and, after cessation of treatment, a fall in FEV_1 and increased bronchial reactivity that persisted for 59 h [28]. This short-term effect should not be ascribed to a lack of anti-inflammatory treatment, and other possible mechanisms could be involved.

Treatment with traditional short-acting beta-agonists, or with the new long-lasting beta-agonists, has been shown to cause a tolerance to the protective effect of these drugs on bronchoconstriction induced by non-specific and specific stimuli. This effect can be observed after only 1–2 weeks of regular beta-agonist treatment, and was greater for allergen or adenosine challenge [29, 30] than for methacholine responsiveness [31], suggesting that the downregulation of $beta_2$-receptors by chronic $beta_2$-agonist treatment can be greater on airway inflammatory cells than on airway smooth muscle. Thus, regular $beta_2$-agonist therapy can induce the airways of atopic subjects to be more sensitive to the effects of inhaled allergen and less amenable to protection from this adverse effect by further $beta_2$-agonist therapy. Although this hypothesis is suggestive, the magnitude of these effects is mild, and it is not yet established how important the effect of $beta_2$-agonist tolerance is in clinical practice.

Other mechanisms underlying possible adverse effects of β-agonists on asthma morbidity and mortality seem related to concurrent steroid therapy. In a recent study, regular exposure to terbutaline abolished the beneficial effects of budesonide therapy on lung function and protection against the early response to antigen [32]. In a study examining the effects of adding terbutaline to budesonide in 16 subjects with mild asthma, there was a greater rise in evening PEF during combined treatment, but budesonide alone caused a greater decrease in nocturnal symptoms scores and a greater increase of FEV_1 after treatment [33]. There were no significant differences between treatments in the protection against histamine and adenosine monophosphate (AMP) challenge. This study [33], like that of WONG *et al*. [32], suggests that PEF is higher during treatment with a combination of inhaled steroid and β-agonist, but that the beneficial effect of budesonide on lung function after cessation of treatment is reduced by the addition of terbutaline. There is some evidence, therefore, to suggest that β-agonists reduce the response to corticosteroids, although this was not seen with the reactivity measurements [33]. In connection with these observations, it may be mentioned that, in preparations of human lung parenchyma, salbutamol has been shown to interfere with the binding of the steroid-receptor complex to specific deoxyribonucleic acid (DNA) sequences, thus inhibiting gene transcription [34]. By this mechanism, high-dose β_2-agonists may inhibit the anti-inflammatory response of asthmatic lung both to endogenous and exogenous glucocorticosteroids [34]. To what extent, however, this effect may contribute to the possible adverse influence that high doses of β_2-agonists can exert on morbidity and mortality in asthma is not known.

One additional problem concerns long-acting inhaled bronchodilators, such as salmeterol and formoterol, in the treatment of asthma. Such β-agonists are now available in several nations and are under clinical evaluation. These bronchodilators should be reserved for patients with chronic symptomatic asthma requiring daily therapy or, according to BONE [35], for patients already taking step 2 anti-inflammatory therapy. A few studies reporting on relatively long-term use of salmeterol have already been made available [36–39].

In a double-blind, randomized, clinical trial in parallel groups over 16 weeks, designed to compare safety of salmeterol and salbutamol in treating asthma, 25,180 patients with asthma considered to require regular treatment with bronchodilators were recruited by their general practitioners (n=3,516) [38]. Treatment over 16 weeks with either salmeterol or salbutamol was not associated with an incidence of death related to asthma (n=14) in excess of that predicted (n=15). In fact, if mortality and admissions to hospital were as expected, there was a small but nonsignificant excess mortality in the group taking salmeterol, and a significant excess of asthma events including deaths in patients with severe asthma on entry. Overall control of asthma was better in patients allocated to salmeterol. Use of more than two canisters of bronchodilator a month was particularly associated with the occurrence of an adverse asthma event. The authors of this study conclude that serious adverse events occurred in patients most at risk on entry, and were probably due to the disease rather than treatment [38]. It should be mentioned, however, that if asthma deaths were no more than expected they were no less either. Thus, if we take as main outcome measure of the study the asthma fatality rate, which was 18 per 10,000 asthmatics annually in these patients who were over the age of 12 yrs, had a clinical requirement for regular bronchodilator treatment, and were distributed in 3,516 general practices throughout the UK, we should conclude that salmeterol and salbutamol had no effect.

By taking surrogate outcome measures, such as overall control of asthma, which may bear on the quality of life, then it appears that patients allocated to salmeterol performed better. In a randomized, double-blind, placebo-controlled, parallel-group study over 12 weeks, designed to compare the efficacy and safety of inhaled salmeterol with that of albuterol, a total of 322 male and female patients at least 12 yrs of age with chronic symptomatic asthma requiring daily therapy were included [39]. FEV_1, PEF, asthma symptoms, nocturnal awakenings due to asthma, episodes of asthma exacerbations, and electrocardiographic (ECG) findings were taken as outcome measures. The authors of this study concluded that salmeterol inhaled *b.i.d.* is more effective than albuterol inhaled *q.i.d.* (or as-needed) in patients with asthma requiring maintenance therapy. No deterioration of asthma control was observed with the use of salmeterol over a 3 month period [39]. It should be mentioned, however, that no main outcome measure, such as asthma fatality rate, was considered (nor could have been considered, given the number of the patients observed), that the period of observation was fairly short, and that the size of the patient sample was too small for this type of study.

In a study of 426 adult asthmatic patients who still had symptoms despite maintenance treatment with 200 µg *b.i.d.* inhaled beclomethasone dipropionate (BDP), 220 were assigned salmeterol xinafoate (50 µg *b.i.d.*) plus BDP and 206 were assigned higher dose BDP (500 µg *b.i.d.*) for 6 months [40]. Morning PEF increased more in the salmeterol/BDP group than in the higher dose BDP group at all treatment weeks, and evening PEF increased with salmeterol/BDP but not with higher dose BDP. There were significant differences in favour of salmeterol/BDP, in diurnal variation of PEF (all treatment weeks), and in use of rescue bronchodilator (salbutamol) and daytime and night-time symptoms (some treatment weeks). There was no significant difference between the groups in adverse effects or exacerbations of asthma, indicating that in this group of patients regular β_2-agonist therapy was not associated with any risk of deteriorating asthma control over 6 months. GREENING *et al*. [40] concluded that their study suggested a need for a flexible approach to asthma management. Moreover, the findings of this study support the suggestion by BONE [35] that salmeterol should be reserved for patients already taking step 2 anti-inflammatory therapy.

In conclusion, all the analyses so far performed on the reported association between asthma mortality and use of inhaled β-agonists have not shown whether this link is causal. It appears that the irregular cyclic course of

asthma mortality, that has been observed over the last decade in countries such as the USA and Italy which did not experience an "epidemic", is independent of the use of inhaled β-agonists [5]. In the UK, the Committee on Safety of Medicines recently reviewed trends in β-agonist sales and in asthma mortality rates in England and Wales [41], and concluded that there was no association, since β-agonist sales rose threefold over 10 yrs whilst mortality changed little, with irregular cyclic course. In the serevent nationwide surveillance study [38], treatment of 25,180 asthmatics over 16 weeks with either salmeterol or salbutamol was not associated with an incidence of death related to asthma in excess of that predicted. It should, thus, be investigated whether "epidemics" and irregular cyclic course of asthma death can be explained by some other risk factors (*e.g.* episodes of viral respiratory infections [42], exposure to allergens [43], *etc.*). Studies of morbidity, natural course, and overall control of asthma may also help to understand "epidemics" and irregular cyclic course of fatal asthma, and to assess the efficacy and safety of the various treatments. Although clinical studies have suggested a deleterious effect of regular β_2-agonist administration on bronchial hyperresponsiveness and a negative interaction between β_2-agonists and corticosteroids, the clinical relevance of these effects seems minor and large long-term follow-up studies are required. A recent paper reported decreasing trends in hospital admission rates for asthma in East Anglia and Wales, reflecting recently published trends for mortality from asthma in England [44]. Another recent paper described trends in prevalence and severity of childhood asthma diverging, with prevalence increasing and severity decreasing, possibly due to an improvement in treatment received by wheezy children [45]. To assess the criticism that β-agonists may pose significant risks if used regularly over a period of time [46], future studies should include long-term trials on large population samples, with hospitalization and other health care utilization measures as outcome variables [47].

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