

Beta-agonists and asthma research: an international consultation

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Sarasota, January 19-21st, 1992

The McGill Pharmacoepidemiology Programme invited academics from around the globe to Sarasota, Florida, in order to discuss recent research on beta-agonist bronchodilators in the treatment of asthma. The purpose of the meeting was the development of a research agenda to deal with unanswered questions in the medium and long term. The meeting was sponsored by AB Astra, Boehringer Ingelheim GmbH, Fisons Pharmaceuticals (Canada), and Glaxo Group Research.

The opinions and recommendations expressed herein are those of the authors and do not necessarily reflect a consensus of all the conference participants

Background

Asthma mortality has been increasing in many countries [1]. The increase has been gradual, with superimposed epidemics. The most serious epidemic for which documentation is available appears to have occurred in England and Wales in the 1960s. This epidemic of asthma deaths occurred concurrently with increasing sales of the beta-agonist isoproterenol [2]. This ecological association was used to suggest that use, and more probably overuse, of beta-agonist inhalers, was at the origin of this epidemic of asthma deaths [3].

A subsequent epidemic of asthma death in New Zealand in the late 1970s led to studies which identified recent hospitalizations for asthma, emergency room visits, severe disease, and discontinuity of medical care, as clinically important risk factors for fatal asthma [4, 5].

The New Zealand epidemic of asthma deaths occurred concurrently with the introduction of the inhaled beta-agonist fenoterol. This ecological association led to a case-control study by CRANE *et al.* [6], who reported an increased risk of death from asthma in subjects taking fenoterol by metered dose inhaler, as

compared to subjects prescribed salbutamol. Because all subjects had been prescribed one or the other inhaled bronchodilator, only the risk of one beta-agonist as compared to the other could be evaluated.

The possibility that fenoterol may be more hazardous as compared to salbutamol has been attributed, at least in part, to the greater cardiovascular effects of fenoterol, as demonstrated by greater increases in heart rate and electrocardiographic Q-Tc intervals, as well as a more pronounced reduction in serum potassium per inhalation [7]. The differences observed in non-respiratory effects may be related to the fact that fenoterol is dispensed at a higher dose per actuation than other beta-agonists. The relevance of these cardiac and hypokalaemic effects to death from asthma has yet to be demonstrated. In contrast, MOLFINO *et al.* [8] recently established that among cases of near-fatal asthma patients who survived long enough to get to the emergency room, the principal abnormality is severe respiratory acidosis from severe airways obstruction.

There are several respiratory mechanisms by which beta-agonists might increase the risk of major adverse events due to asthma. Specifically, the study by SEARS *et al.* [9] suggests the possibility that regular use of beta-agonists may actually worsen asthma control. Evidence of this possibility had previously been reported by KRAAN *et al.* [10], as well as by KERREBIJN *et al.* [11], who describe an increase in airways hyperresponsiveness with regular use of inhaled beta-agonists, while the converse was true among subjects taking inhaled corticosteroids. BEL *et al.* [12] recently demonstrated that while beta-agonists shift the dose response curve to the right, so that more bronchoconstricting agent is required to initiate bronchospasm, the maximal degree of airway narrowing attained is not reduced, and the actual rate of decrease in forced expiratory volume in one second (FEV₁) may be increased. VAN SCHAYCK *et al.* [13] have reported longitudinal data suggesting that, over a two year period, regular use of bronchodilators without the concomitant use of inhaled corticosteroids might be associated with a more rapid decline in lung function.

In the first study from the Saskatchewan Asthma Epidemiology Project (SAEP), based on linked

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computerized databases [14], there was a strong association between beta-agonist use, especially when used above recommended doses, and the risk of fatal and near-fatal asthma. The study was consistent with this being a class effect of beta-agonists, although at very high doses the odds ratios for fenoterol fatality were appreciably higher than for salbutamol. However, by its nature the study did not permit conclusions to be drawn as to whether the association between beta-agonist use and asthma death and near-fatal asthma was causal. An alternative explanation is that the more severe patients, who are more likely to die of asthma, are also more likely to use high doses of beta-agonists. In an attempt to resolve this question, field data were gathered by the SAEP in order to categorize case patients and their matched controls, as to indicators of asthma severity. Several factors were found to be associated with an increased risk of death from asthma in this population (over and above the factors for which the cases and controls were matched, particularly prior hospitalization for asthma). These were prior loss of consciousness, prior respiratory acidosis, and a history of attacks precipitated by the ingestion of food [15]. When these were included in a model assessing the association between beta-agonist use and risk of asthma death and near-death, the direction and strength of the association did not change.

A recent addition to our armamentarium for the treatment of asthma are the long-acting beta-agonists. These agents are certainly efficacious in achieving prolonged bronchodilatation and in reducing symptoms [16]. They are not thought to substantially affect the primary abnormality of asthma, *i.e.* airway inflammation. The place of these agents in the treatment of asthma remains to be clearly defined [17].

Discussion of related issues

Sears presented further data related to the study by SEARS *et al.* [9] published in December 1990. The FEV₁ remained higher amongst subjects on placebo, as opposed to regular beta-agonist therapy. Furthermore, there was minimal tachyphylaxis, based upon the response of FEV₁ to bronchodilator. Among subjects on regular beta-agonist therapy, the first asthma exacerbation, after treatment was initiated, occurred significantly sooner when compared to subjects on placebo. In an open study among 32 of the 64 previously reported patients, an increase in the dose of inhaled corticosteroids resulted in better control of asthma, thus providing a validation of the measures of asthma control used in the published study.

Fuller from the Glaxo research group presented data from the salmeterol research programme. In several large multicentre studies, there was no deterioration found in FEV₁ over a 12 month period, and no increase in the number of exacerbations, with regular salmeterol or regular salbutamol therapy, regardless of whether or not patients were receiving corticosteroids.

Exacerbations were actually reduced with salmeterol use, when compared both to regular salbutamol and placebo.

Lofdahl commented that the results as far as he was aware with formoterol, were very similar.

Clark questioned whether monotherapy with bronchodilators should be phased out, and indicated that bronchodilator therapy without anti-inflammatory therapy remained the most common mode of treatment throughout industrialized countries. Therefore, such therapy was thought to be efficacious both by patients and their physicians. Convincing information would be required to change this habit. He further felt that it might be of interest to study what terminates an epidemic, since this might shed light on what initiates it.

Suissa presented the statistical methodology used in the Saskatchewan Asthma Epidemiology Project, and illustrated specifically the issues of confounding and effect modification. To emphasize that, in this study, the crude analyses were misleading, he showed that the risk of asthma death for salbutamol is strongly confounded by the use of fenoterol, principally because subjects using salbutamol are much less likely to use fenoterol and *vice versa*. This explains how the crude odds ratio of 0.9 of asthma death for salbutamol becomes 2.8 when the subjects are stratified for the concurrent use of fenoterol. With respect to effect modification which essentially requires the analysis of small subgroups of the study population to estimate heterogeneous odds ratios, he submitted that, while the question was of great interest to all, the study was not designed *a priori* for such subgroup analyses as the sample size did not permit it. He recognized that the conditional logistic regression technique, used to estimate odds ratios, was based on several assumptions, one of which is precisely this homogeneity of odds ratios. This was tested despite the small sample size and assumed to be true in the Saskatchewan data. He further described the goodness of fit approach, used to verify the log-linearity assumption of the dose response curves, and the data augmentation technique, used to assess the stability of the models.

Mechanisms

There is no doubt as to the efficacy of inhaled beta₂-agonists as bronchodilators, and explanations for possible adverse effects are sought elsewhere.

Tattersfield listed the mechanisms proposed to explain the association of beta-agonists with worsening asthma morbidity and mortality: failure to use anti-inflammatory drugs; cardiac arrhythmias; increased asthma severity due to beta-receptor down-regulation; increased inhalation of allergen; a decrease in mast cell heparin; or a change in the quantity and the characteristics of airway mucus.

The study by VATHENEN *et al.* [18] showed a rebound increase in bronchial responsiveness following two weeks of therapy with regular beta-agonists,

which was maximal 23 h following cessation of treatment. A follow-up study by Wahedna and colleagues (submitted for publication) found a similar rebound increase in bronchial responsiveness following three weeks of regular therapy with salbutamol, which was maximum 59 h following cessation of treatment, and was associated with a 10% fall in FEV₁. Such increases in airways responsiveness might explain the worsening of asthma control after stopping beta-agonists. The possibility of beta-receptor dysfunction is suggested by the decreased relaxant response to beta-adrenoceptor agonists in severe disease, including fatal asthma [19] despite an increase in the number of beta-agonist receptors [20]. This might be due to uncoupling of the receptor, thus providing a signal to the beta-receptor gene to increase production. While beta-receptor desensitization is well-described *in vitro*, the bronchodilator response to beta-agonist has not been lost with regular therapy in most studies of patients with asthma.

Barnes presented recently completed studies comparing the effects of asthma medications on induced bronchoconstriction which demonstrate that corticosteroids and beta-agonists provide greater protection against bronchoconstriction induced by adenosine 5'-monophosphate (AMP), which acts indirectly *via* the release of mediators from mast cells, as compared to bronchoconstriction induced by methacholine (MCH), which acts directly on smooth muscle, and metabisulphite (MBS) which stimulates nerve endings [21, 22]. Tachyphylaxis to the protective effect of beta-agonists on AMP-induced bronchoconstriction is apparent [23]. Loss of such a protective effect might be a mechanism for worsening of asthma control with regular beta-agonist use because it leaves the airways susceptible to potentially catastrophic bronchoconstriction. This is felt to relate to beta-receptor down-regulation on mast cells, which (like other inflammatory cells) occurs more easily than on smooth muscle. This might be especially relevant to the airway response to allergen. Further evidence of a dissociation between the bronchodilator effects of beta-agonists and the protection against induced bronchoconstriction has been reported for salmeterol; after 8 weeks of therapy, the increase in FEV₁ was maintained, while the protective effect against methacholine was diminished [24].

The potential significance of cardiac arrhythmias caused by excessive beta-agonist use was discussed, but there was no consensus as to the importance of this mechanism for an increase in asthma mortality. It was felt unlikely, however, to be the predominant mechanism of death in most cases.

Beta-agonists shift the dose response curve to induced bronchoconstriction to the right, without diminishing maximal bronchoconstriction [12]. The position of the dose response curve, as reflected in the provocative concentration producing a 20% fall in FEV₁ (PC₂₀), is a measure of the ease of bronchoconstriction but carries little information as to its potential extent. As asthma is a disease characterized by ex-

cessive airway narrowing, a test which assesses this may be more useful than PC₂₀.

Macklem pointed out that there appears to be two types of asthmatics. Firstly, there is a group that responds to bronchoconstrictive agents with a drop in vital capacity (and an increase in residual volume), while maintaining a relatively normal FEV₁/forced vital capacity (FVC). He feels that the dose-dependent decrease in vital capacity (VC) is a measure of excessive bronchoconstriction. Among subjects who respond by decreasing FEV₁/FVC, the position of the dose response curve is likely to be more important, since they will tend to maintain a plateau to the maximal bronchoconstrictive response [25]. Some studies indicate that regular corticosteroid use may diminish the extent of bronchoconstriction in asthma, while beta-agonists do not [12, 26].

Further distinctions between the effects of beta-agonists and corticosteroids were discussed. While beta-agonists influence acute inflammatory events, it is the chronic inflammatory events that are of importance in asthma, those responding primarily to corticosteroids. Concerning the interactions between beta-agonists and corticosteroids, *in vitro* studies suggest that corticosteroids may increase the responsiveness of β -receptors and decrease tachyphylaxis, possibly by increasing receptor density and decreasing down-regulation. The mechanism appears to be increased beta-receptor gene transcription [27].

Epidemiology

Mortality rates for asthma have been increasing in several parts of the world, although they may now be in decline in some countries. In the United States, morbidity in the 5–34 yr age group has been increasing, as reflected in increased hospitalizations for asthma. Prevalence of both asthma and atopy appears to be increasing also. Uncertainty remains as to whether beta-agonists are responsible for worsening of asthma morbidity and mortality, or whether their pattern of use is a marker for severe or poorly controlled asthma. The influence of corticosteroid use on the association between beta-agonists and worsening of asthma remains to be determined.

Leeder believes that the experience of cardiovascular disease epidemiology may shed light on what can be expected from population-based studies of factors that influence the natural history of asthma. Despite extensive epidemiological studies, substantial uncertainty remains about the determinants of cardiovascular disease frequency. Thus, observational studies of asthma were thought unlikely to unravel the very close association between the severity of disease and the use of medications. Such studies may provide empirical estimates of risk, their relative importance, and whether adverse effects of beta-agonists are generalized within the population, or limited to various susceptible subgroups. Other potential gains include information on interactions between risk factors, the

risk benefit of various therapies and its modification according to dose, long-term effects, and the effects of discontinuing therapy.

A promising approach would be to identify a geographically defined concurrent cohort of asthmatic subjects covering the whole range of severity of disease, rather than a general population sample among whom the number of affected individuals would be small. Such a cohort study would collect data on factors, other than medication use, which might contribute to the risk of death (see table 1). Such extensive data collection appears necessary because of the uncertainties surrounding the assessment of asthma severity, as well as the very limited information currently available from population-based studies on the importance of various risk factors. Furthermore, agreement must be achieved as to defined outcomes, other than fatal and near-fatal asthma which remain rare events. Advantage should also be taken of recent innovations in the management of large data sets and in analysis of longitudinal data. Finally, such studies must have clearly defined objectives to allow hypothesis testing. Possible strategies for the identification of asthmatics to be included in such a cohort include an asthma registry.

Weiss suggested that potential sources of patients include asthmatics identified through the third National Health and Nutritional Examination Survey (NHANES) or members of health maintenance organizations.

Table 1. — Factors which might contribute to the risk of fatal asthma to be included in cohort studies

Educational	Knowledge, understanding
Behavioural	Attitude, compliance
Historical	Childhood respiratory illness, parental asthma
Environmental	Aero-allergens, smoking, air pollution, occupation
Socio-economic	Nutrition, housing conditions
Asthma severity	Symptoms, peak flow variability, exercise tolerance, lung function, bronchial responsiveness

Asthmatics with new or recent onset of disease need to be preferentially recruited, in order to minimize the influence of prior therapy on studies of natural history and its modification by various interventions.

Samet expressed concern regarding the feasibility of an asthma patient registry, with regard to the lack of a good operational definition for asthma, as well as the multiplicity of potential risk factors, which may affect asthma morbidity and mortality.

Schlesselman thought that the uncertainty surrounding the benefits of regular beta-agonist therapy appear somewhat analogous to the controversy surrounding treatment of juvenile diabetes, where close and loose control of blood sugar have been proposed as alternative treatment strategies.

Faich thought large multicentre trials might be required to resolve such questions. The potential lack of representativeness of patients participating in drug trials was discussed; specifically the frequent absence of women of child-bearing age. One strategy to counter such selection biases is through improved post-marketing surveillance of medications.

Concerning studies of ecological associations between mortality and drug sales, linkages are made between aggregates of persons and not individuals. The secular trends observed do not establish temporal precedence, and the increase in death is often most marked in one age group, while sales figures are only available for the total population. For these reasons, ecological associations may be used to suggest a study hypothesis, but should not be used to argue against more valid designs of observational studies.

Saskatchewan Asthma Epidemiology Project; future contributions

The Saskatchewan databases will continue to be used to answer questions about the treatment of asthma. The risk of non-asthma death is currently being examined in a full cohort analysis of all 12,301 subjects. This may shed light on the possibility of adverse cardiovascular effects from asthma medications. The full cohort analysis will also permit calculation of absolute and excess risks, with potentially the most useful information emanating from the estimates of risk of death and near-fatal asthma attributable to excess use of beta-agonists; specifically, more than two inhalers per month. Whether the combined risks associated with the various asthma medications are additive or multiplicative will be directly assessed by the analyses. Patterns of drug use will be examined; looking for dominating treatment profiles, particularly involving combinations of beta-agonists and inhaled corticosteroids, and their changes over time, and relating them to adverse events. Finally, asthma hospitalization will be used as an end-point, and its risk will be assessed in relation to the use of beta-agonists and other asthma drugs. The use of this more frequent outcome measure of morbidity will increase power and, therefore, permit the subgroup analyses necessary to assess the effect modification role of drugs, which was not possible for fatal and near-fatal asthma.

Concluding remarks

Inhaled beta-agonist bronchodilators remain the mainstay for the immediate treatment of acute bronchospasm, and may be life-saving in this situation. However, the uncertainties surrounding the exact role of inhaled beta₂-agonist therapy in the regular treatment of asthma need to be resolved expeditiously.

Do some or all of the short-acting preparations have adverse effects on the clinical course of asthma

and, if so, is this modified by the frequency of use and the dose inhaled? Can such adverse effects, if present, be prevented by the concomitant use of inhaled corticosteroids? While the benefits of sustained use of long-acting beta₂-agonists are established, with little evidence of change in asthma severity, research into this class of drugs continues to determine whether there are any potential hazards of such sustained use. These, and other unanswered questions concerning the treatment of asthma, require the clinician to keep an open mind as to the nature of optimal management of this common disorder.

Directions for research

1. To test the current model in the treatment of moderate asthma, namely that inhaled corticosteroids should be used as first-line therapy, with inhaled beta₂-agonists as a back-up, to be used when needed.
2. To determine the feasibility of setting up a population-based registry of asthma patients in order to: a) recruit new representative cases of asthma to study the natural history of the disorder at the onset of interventions and in relationship to these interventions; and b) develop and validate measures of outcome and of asthma severity, which would allow identification both of high and low risk groups of patients, and the study both of the benefits and of the potential hazards of therapy.
3. To study further the molecular mechanisms of drug actions, including the potential for tachyphylaxis, and the interactions of beta-agonists and corticosteroids.
4. To examine the earliest stages in the pathogenesis of asthma, in order to identify particular events which might be prevented or reversed.
5. To assess the cost-effectiveness of the competing treatment plans.

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