Eur Respir J
1992, 5, 773–775

EDITORIAL

Study designs of adverse events in asthma treatment

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The possibility that the use of beta-agonist medications increases the risk of death from asthma was first suspected during an epidemic of asthma deaths in England and Wales in the 1960s. The evidence was the synchronous increases in asthma death rates in young people and in the sales of inhaled beta-agonist bronchodilators [1]. Such associations, called ecological correlations, remain weak evidence by epidemiological standards. The observed associations are between areas and not individuals and there are, therefore, no guarantees that the people buying the drugs in question are among those dying from asthma. Whilst investigating a similar epidemic in Australia, GANDEVIA [2] re-examined the association between beta-agonist sales and rates of death from asthma within smaller regions and found that the association had disappeared. Ecological associations are, thus, useful for generating hypotheses but cannot be used to argue against evidence obtained from stronger study designs [3].

To decisively study the relationship between fatalities due to asthma and the medications used to treat this condition would require a randomized, controlled trial. Death from asthma is fortunately a rare event. This implies, however, that such a trial would necessitate a large number of asthmatics followed for a prolonged time, in order to provide a sufficient number of adverse events to reach confident conclusions. Observational designs such as the cohort and the case-control study are powerful alternatives to these lengthy and expensive trials. The case-control design is particularly valuable in determining factors which might be associated with an increase in rare events such as dying from asthma. The case-control design is very efficient in the use of information and resources in that it utilises all the rare cases but only requires one to study a limited number of the much more common non-cases or controls, that is the individuals who form the comparison group without the outcome in question. This was the methodology utilized by investigators in New Zealand in their reports of an increase in the risk of asthma death among subjects prescribed fenoterol [4–6].

Case-control studies are retrospective in logic, in that they start with the outcome, in this instance death from asthma, and look backwards in time for the factors such as the type of medication used, to identify whether they occurred more frequently in the cases as compared to their controls. The results of this type of observational study may be contradictory and controversial, however, because they are subject to bias. Information bias may result because the outcome is known when the information on exposure is being gathered. Selection bias occurs when only a proportion of the subjects are included in the study and/or if the controls did not have the same opportunity of exposure as the cases (or vice versa). In the original report from New Zealand, the likelihood of information bias could not be ruled out, since the information on exposure in cases and controls was gathered using different methods [4]. The comparability of cases and controls was also in doubt because the diagnosis of asthma had been confirmed by an expert panel for all the asthma deaths, whilst this was not done for the controls. The two subsequent studies from New Zealand [5, 6] in large part rectified these sources of bias. However, both studies were confined to subjects taking either inhaled fenoterol or salbutamol and, therefore, only the relative risk of one *versus* the other, and not the risk of each, could be examined. An apparent protective effect of salbutamol was, thus, a design artifact. The question remained as to whether an increase in risk of fatal asthma was limited to subjects prescribed fenoterol or whether the risk increased with the use of most commonly used beta-agonists.

The first study to be reported from the Saskatchewan Asthma Epidemiology Project (SAEP) is a historical cohort study of 12,301 residents of the province of Saskatchewan who had been dispensed 10 or more prescriptions for asthma medications from 1978–1987 [7]. The logic of the study, as behoves a cohort study, is prospective; the information on exposure is collected prior to the outcomes, asthma death and near fatal asthma. Our study is also historical (not retrospective) in that the information on both exposure and outcome was analysed several years after their occurrence. This distinction, which is often not made [8], is crucial because the historical cohort study is not subject to some of the important information and selection biases inherent in the retrospective case control design.

To address the high costs of analysing such large cohorts with rare events, an innovation in the analysis of cohort studies, which has become common in the past 10 yrs, is to use all subjects with the event and a sample of the remaining subjects, as is done in

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the design of case-control studies. An essential feature of this nested case-control analysis of cohort data is that follow-up is completed before all of the cases can be determined. As indicated by LIDDELL [9], "there is a radical difference from the traditional case-control study, in which cases are determined as the first stage of the research, and referents are selected in a second stage, both independent of any cohort study". Such an analysis was first used in respiratory disease to examine the health of asbestos workers in the mines and mills of Quebec [10]. The resulting cost saving was large, since exposure needed to be measured only in a sample of the cohort. This method of analysis is efficient and is considered to be empirically and theoretically correct [11]. In the Saskatchewan study, this approach was dictated by the very large size of the cohort in terms of numbers of subjects, length of follow-up and detailed daily exposure information available. The matching of cases and controls as to the period of observation (and, therefore, the period at risk of an adverse outcome) also allowed one to account for the changes in the patterns of drug utilization over the time period of the study.

The Saskatchewan study demonstrated a clear association between all inhaled beta-agonists in use at the time of the study and the risk of asthma death and near fatal asthma. The excess risk was greater for fenoterol as compared to salbutamol, and this was especially so when considering asthma deaths alone. The greater risk for fenoterol may result from its formulation at a higher dose (200 μg per inhalation) despite its greater potency [12]. The risk associated with either beta-agonist was similar when they were compared on a weight per weight basis. Both salbutamol and fenoterol were associated with a greatly increased risk of asthma death and near death, almost 30 times greater, when an average of two or more inhalers per month were dispensed in the year prior to the major adverse event. Such a dose-response relationship is usually considered a strong argument for causality, for example, in the relationship between cigarette smoking and lung cancer [13]. The situation here, however, is more complex because the exposure of interest, *i.e.* beta-agonists, is actually used in an attempt to avoid the outcome, *i.e.* asthma death and near fatal asthma. This is an example of susceptibility bias [3], which allows for an alternative explanation of the Saskatchewan findings; *i.e.* that more severe asthmatics, or those at greater risk of dying, are more likely to use and abuse inhaled beta-agonist bronchodilators.

It may not be possible, using observational studies, to determine whether beta-agonist use is a marker for, or cause of, life-threatening asthma because of the complexity of the relationships involved. In theory, an experimental design such as a randomized clinical trial would result, on average, in the allocation of subjects of similar severity and at similar risk of dying into different treatment groups. Such a trial would measure the risk of beta-agonists independently of severity but could not assess the role of severity on this risk. If potential markers of severity of asthma or risk of asthma death could be defined and measured at the start, such trials might then also provide a better understanding of the factors other than treatment that are associated with an increased risk of asthma death or near fatal asthma.

What is the clinician to do whilst these uncertainties are being resolved? Firstly, whether beta-agonist use is a cause of increased asthma deaths or a marker of severe disease, the Saskatchewan study clearly indicates that patients using two or more inhalers per month are at greatly increased risk and, therefore, merit particular attention on the part of their physician. Secondly, there is increasing evidence that use of anti-inflammatory medications may favourably alter the natural history of asthma [14] and, therefore, much may be gained by following current guidelines, which suggest their early and regular use [15–17].

Acknowledgements: The authors would like to thank M. Becklake and N. Colman for their advice and comments. The authors are Research Scholars of the Fonds de Recherche en Santé de Québec.

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