

## Mortality and $\beta$ -agonists, or the Risk of Statistical Inference

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Since the end of the 1960s, when Inman and Adelstein<sup>1</sup> first reported the risk of severe complications arising from asthma rescue medication, the risk–benefit ratio for these drugs has been periodically called into question. Forty years ago, at a time when there were very few treatment options for asthma, the complications were attributed to the excessive doses taken by some patients and to the use of isoprenaline, which was less selective for  $\beta_2$  receptors. In 1989, a case–control study carried out in New Zealand suggested that the use of fenoterol, a short-acting  $\beta$ -agonist no longer in use, was associated with increased risk of death in asthmatic patients<sup>2</sup>; the association was not observed for salbutamol (albuterol). That study was later heavily criticized due to marked bias resulting from the design, but 2 later studies whose methodology was more rigorous also showed an increased risk of death associated with fenoterol, although not in patients taking salbutamol.<sup>3,4</sup> In 1992, Spitzer et al<sup>5</sup> observed an increased risk of death associated with  $\beta$ -agonists (fenoterol and salbutamol), although the risk was noticeably greater with fenoterol. The study did not clarify whether  $\beta$ -agonists were directly responsible for the deaths or whether more  $\beta$ -agonists were used by the most severely ill patients. Despite these results, neither the medical literature nor medical practice has advised against  $\beta$ -agonists in the treatment of asthma. International guidelines have simply attempted to classify them appropriately.

During the early 1990s, a new generation of  $\beta$ -agonists became available. These new drugs were interesting in that they could maintain the effect of therapy for 10 to 12 hours, unlike the old drugs, whose bronchodilator effect only lasted 4 to 6 hours. They were known as the long-acting  $\beta$ -agonists and all guidelines agreed that they should be used in patients with moderate or severe asthma that could not be sufficiently controlled with inhaled corticosteroids.

Doubts over the safety profile of these new  $\beta$ -agonists became apparent as soon as they came onto the market. The Serevent Nationwide Surveillance Study,<sup>6</sup> published in 1993, was a randomized, double-blind trial that aimed to compare the safety profile of salmeterol with that of salbutamol: it lasted only 16 weeks and enrolled 25 180 patients, of whom only 69% were receiving inhaled corticosteroids, an indispensable condition for prescribing long-acting  $\beta$ -agonists according to international guidelines. The percentage of deaths attributable to asthma or airway disease was 0.07% (12/16 787 patients) for salmeterol and 0.02% (2/8393 patients) for salbutamol. Despite the fact that, by today's standards, the statistical evaluation could be open to question,<sup>7</sup> the study concluded that there were more deaths in the group treated with salmeterol than with salbutamol, although the difference was not significant. The United States Food and Drug Administration later proposed a new pharmacovigilance study, known as SMART,<sup>8</sup> which aimed to include 60 000 patients and perform an intermediate analysis when 50% of the patients had been enrolled and certain statistical criteria had been fulfilled. The primary outcome was a combination of the mortality rate and the incidence of life-threatening respiratory events; the secondary outcomes included among others the evaluation of the incidence of asthma-related deaths. From a methodological viewpoint, the study characteristics were, to say the least, debatable. There were 2 distinct recruitment phases: in the first (1996-1999), patients were recruited through media such as television and radio commercials; in the second (2000-2003), the study researchers themselves were responsible for enrolling the patients. The protocol required a single face-to-face visit, telephone check-ups every 4 weeks, and a 28-week follow-up. The use of short-acting  $\beta$ -agonists was only recorded during that visit. Two treatment groups were established and patients received salmeterol or placebo blindly. They were specifically told to continue taking their habitual medication without changing it. We know that 49% of the Caucasian patients were receiving inhaled corticosteroids compared with only 38% of the African Americans. The study was interrupted before 50% of the patients had been included (the final study population was 26 355 patients) and without fulfilling the criteria established in the study

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design for the inclusion of new cases, the reason given being ethical problems. True, the study did not find statistically significant differences in the proposed primary outcome, but it did find small though statistically significant differences in the secondary ones, mainly a greater incidence of asthma-related deaths in the salmeterol group. A post-hoc analysis that was reasonable, although not always sound, showed that these differences were not observed in the Caucasian group. In other words, this study used a methodology that is worthy of criticism, it did not fulfill the established design criteria, the main outcome evaluated did not show statistically significant differences between the groups, and an increased risk of asthma-related death was only observed in the group treated with salmeterol when the cohort evaluation included African American patients, who in turn presented a lower prevalence of therapy with inhaled corticosteroids.

Experience with formoterol is more limited. A study by Wolfe et al<sup>9</sup>—a double-blind, placebo-controlled trial of 2 doses of formoterol (12 and 24  $\mu\text{g}/12$  h), lasting 16 weeks and enrolling 2085 patients—found a slightly lower percentage of exacerbations requiring admission to hospital in the placebo group, although the number of severe exacerbations requiring oral corticosteroids was the same for all the groups. The study concluded that high-dose formoterol is not associated with a greater risk of exacerbations due to asthma (primary endpoint) than in the other 2 groups. The same conclusion was reached in a first study by Bensch et al<sup>10</sup> in 541 patients aged between 12 and 75 years who were followed for 12 weeks. The groups formed were similar to those of the study by Wolfe et al.<sup>9</sup> In a second study, Bensch and colleagues<sup>11</sup> followed a cohort of 518 patients aged between 5 and 12 years for 1 year. There were no deaths, and in the 3 study groups—formoterol 24  $\mu\text{g}/12$  h; formoterol 12  $\mu\text{g}/12$  h; and placebo—43%, 42%, and 45% of patients, respectively, presented acute asthma exacerbations (serious and nonserious). With regard to serious acute exacerbations, the authors observed 11 cases (6%) in the first group and 8 (5%) in the second, leading to 10 admissions with 7 premature discontinuations in the first group and 8 admissions with 5 premature discontinuations in the second group. Curiously, there were no admissions in the placebo group, although there were 7 premature discontinuations. The authors do provide a welcome posthoc analysis, in which they stress their surprise that in a cohort of 174 patients who received placebo there were no admissions, when a correct standardization of the data would lead us to expect 5.4 admissions. The authors offer as a possible source of bias the greater monitoring of both physicians and parents over the patients (normal in this type of protocol). Such monitoring would lead to a lower risk of hospitalization and a greater rate of premature discontinuation in the placebo group, which in turn would lead to an underestimation or reduction in the number of patients with a greater risk of requiring hospitalization.

Salpeter et al<sup>12</sup> recently published a meta-analysis to evaluate the increased risk of admissions due to asthma, severe asthma exacerbations, and deaths due to asthma in patients treated with long-acting  $\beta$ -agonists. An analysis

of the figure referring to the first outcome mentioned shows that, of the 12 studies included, only one—that of Bensch et al<sup>11</sup>—found statistically significant differences that were unfavorable for formoterol. The limitations and considerations of possible biases in this study, which makes up 26.35% of the meta-analysis, have been mentioned above. For the second variable—the risk of severe exacerbations—the authors examined 7 studies including SMART,<sup>8</sup> the only one to find a greater risk of severe exacerbations in the group treated with long-acting  $\beta$ -agonists and which provides 79.9% of the sample. The situation is almost the same for mortality. We have already mentioned the serious defects of the SMART study, and, given the enormous weight of this study in the meta-analysis by Salpeter et al, those authors do little more than reproduce its conclusions. Obviously a metaanalysis cannot discuss the biases of studies it includes, but we do miss a certain amount of self-criticism by the authors when they interpret their results.

Short-acting  $\beta$ -agonists clearly have specific pharmacological properties, such as the ability to increase electrical conduction across the atrioventricular node<sup>13,14</sup> or to reduce potassium levels in blood. Depending on the patient's clinical status, these may be considered side effects, since they increase the risk of arrhythmias in patients with asthma or chronic obstructive pulmonary disease,<sup>13-15</sup> or they may be therapeutic effects if increasing the conduction rate in a patient with atrioventricular block is desirable or if intravenous salbutamol is used to quickly reduce dangerously high levels of potassium in blood. Nevertheless, international guidelines have not removed short-acting  $\beta$ -agonists from the therapeutic arsenal. Why should we not expect long-acting  $\beta$ -agonists to have adverse effects, if both drugs are from the same family? Why should we withdraw them from the therapeutic arsenal for the treatment of asthma if we do not even consider withdrawing their older brothers? As Hasford and Virchow<sup>7</sup> point out, what we must do is use them appropriately as recommended in international guidelines, ie, in patients whose condition is not properly controlled after correct and appropriate administration of inhaled corticosteroids.<sup>16</sup> Such a cautious attitude was not the rule in most of the studies mentioned here.

In the discussion section of their meta-analysis, Salpeter et al<sup>12</sup> use their results to suggest that salmeterol could cause 1 death per 1000 patient-years of treatment. This calculation refers to the United States of America and estimates that in 3.5 million people treated with salmeterol there could be approximately 4000 salmeterol-related deaths per year. If we extrapolate these data to Spain, it could mean 400 deaths per year due to salmeterol, a figure which is indeed difficult to accept. It is unlikely that such an important occurrence would have escaped the attention of epidemiologists. Therefore, when reviewing the medical literature, we must take particular care to critically evaluate the method (design and statistical analysis) and come to a clinical interpretation of the results. For Poincaré, statistics were a measure of our ignorance: let inference not be a measure of our arrogance.

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