Drug Safety and Salmeterol: The Controversy Continues

Since their introduction in the 1960s, inhaled β-agonists have been celebrated for their ability to offer dramatic relief of symptoms for persons with asthma. However, they have engendered considerable controversy. Early indications suggested that higher doses of some of the short-acting β-agonists were associated with higher fatal and near-fatal asthma-related events (1). Further research suggested that overuse of even moderate doses of inhaled short-acting β-agonists was associated with a small but definite increase in fatal and near-fatal events (2).

The 1990s provided a major milestone in the advancement of β-agonist therapy—the introduction of long-acting β-agonists (3, 4). These drugs were much more convenient to use, led to even better control of asthma symptoms, and improved quality of life. However, and perhaps not unexpectedly, controversy soon erupted about the safety of long-acting β-agonists (5, 6).

As early as 2003, the concerns about the safety of long-acting β-agonists led the U.S. Food and Drug Administration to require GlaxoSmithKline (Research Triangle Park, North Carolina) to conduct a very large (>26,000 persons), postmarketing, randomized, controlled trial to examine drug safety (7). The SMART (Salmeterol Multicenter Asthma Research Trial) was a randomized, double-blind, placebo-controlled study of drug safety under a “real-world,” effectiveness study design based in the United States. The study allowed concomitant use of inhaled corticosteroids. GlaxoSmithKline ended the study because of preliminary findings and difficulties in reaching target enrollment and published the results in 2006. The trial found no statistically significant differences between treatments in the combined end point that included respiratory-related deaths and life-threatening experiences. However, the individual clinical end points of respiratory-related and asthma-related deaths were statistically significantly increased in persons receiving salmeterol, and the time to first serious event was slightly shorter (8). Moreover, a post hoc subgroup analysis strongly suggested that the risk may be greater in African Americans.

In an additional post hoc analysis, the increased mortality rate seemed to persist regardless of whether participants were receiving inhaled corticosteroids at baseline. However, the study lacked sufficient power to make any statistically valid inferences from these subanalyses. The authors speculated that the treatment effect might be related to a physiologic treatment effect, genetic factors, or patient behaviors. Ultimately, data from this study combined with other previous reports led the U.S. Food and Drug Administration to continue its warnings about long-acting β-agonists.

In 2006, Salpeter and coworkers (9) reported the results of a meta-analysis that examined questions about the safety of long-acting β-agonists. By reviewing the pooled results from 19 trials, including those in SMART, the investigators found that long-acting β-agonists statistically significantly increased asthma-related hospital exacerbations, life-threatening exacerbations, and asthma deaths. This study further supported concerns about long-acting β-agonist safety.

Patients clearly prefer the symptom relief and convenience of long-acting β-agonists; however, rare but important safety concerns and clinical guidelines that recommend using long-acting β-agonists only as add-on therapy (and not initial therapy) in poorly controlled asthma pose an important question in asthma care (10): Does the use of long-acting β-agonists combined with inhaled corticosteroids enhance treatment efficacy and reduce adverse event rates?

The article by Bateman and colleagues (11) in this issue reports the most recent findings to try to answer this question and resolve the ongoing controversy about the safety of long-acting β-agonists. Combining patient data from many randomized clinical trials conducted by GlaxoSmithKline, the authors asked whether incidence of severe asthma-related events differs in persons receiving salmeterol plus inhaled corticosteroids compared with inhaled corticosteroids alone. They found no clinically significant effect of salmeterol on asthma-related hospitalizations. In a subgroup of trials that provided information on severe asthma exacerbations, this outcome was less frequent by a statistically significant—albeit small—amount in patients taking salmeterol. Asthma-related death in either group was too infrequent to provide useful guidance.

Although the study is well executed and uses sound methods, the source of the data—randomized efficacy trials—limits its ability to answer the question. The SMART was designed as a prospective, real-world clinical trial with adequate power to measure the frequency of an uncommon serious adverse event. Bateman and colleagues (11) had the same intent when conducting their meta-analysis, but they used safety information from several, mostly small, trials that were designed and powered to test clinical efficacy in patients receiving closely supervised care in a clinical trial environment. Furthermore, the major adverse event rates in SMART were higher than those in Bateman and colleagues’ meta-analysis, suggesting that the study samples differed, a different level of attention was given to measuring adverse events accurately, or both. Finally, Bateman and colleagues (11) did not address the apparently higher mortality rates in African Americans in SMART. Bateman and colleagues ultimately helped answer the question about safety when long-acting β-agonists are used with inhaled corticosteroids in an idealized clinical environment, but they did not resolve the controversy about the safety of long-acting β-agonists (with or without steroids) in an environment that more closely reflects actual clinical practice.
Combination therapy in severe asthma is an important consideration. With more than $6 billion in worldwide sales (12), GlaxoSmithKline’s product, which combines long-acting $\beta$-agonists with an inhaled corticosteroid, is well accepted as a clinical tool for improving asthma symptoms and quality of life, with what may be a very small but important drug safety concern. Other similar combinations in this class of drugs now compete in the market. The number of patients receiving the combined product exceeds the number of patients with moderate to severe asthma, making it likely that physicians are prescribing it for patients who do not fit the guideline-recommended indication of moderate asthma (that is, asthma not controlled by anti-inflammatory medications alone). Physicians recognize the benefits of this therapy as part of their asthma management strategies. Because severe adverse events are rare, patients are not likely to experience a major adverse event that would put them on guard to avoid another. A prospective, real-world, randomized trial that directly addresses the safety of this highly popular combination versus inhaled steroids alone is very unlikely. For all practical purposes, physicians should learn to live with uncertainty about the dangers of this combined therapy.

Because we cannot expect any more new data, how should physicians and patients use combination therapy? Perhaps the best advice is to consider using combination therapy only for indications that accord with nationally accepted clinical guidelines (10). Specifically, long-acting $\beta$-agonists with or without inhaled corticosteroids should not be used as first-line treatment and especially not for persons with mild asthma. In addition, the prudent course would be to use this treatment only when the physician is confident that the patient will adhere to close monitoring and instructions to seek care when asthma is out of control. Moreover, physicians should consider alternative therapy for patients at high risk for severe exacerbations, including those who have difficulty accessing health care in an emergency (because of lack of health insurance or other sociobehavioral factors that may affect ability to adhere to treatment recommendations).

Ultimately, nearly all drugs have therapeutic windows within which physicians and patients must function. Like insulin and oral anticoagulation, long-acting $\beta$-agonists have a narrow therapeutic window. They deserve the same caution and meticulous attention to detail that physicians expect of themselves when they prescribe potentially harmful drugs.

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References