

# Chapter 136

## Safety of Long-Acting Beta-Agonists

**SP RAI**

Beta<sub>2</sub>-adrenoceptor agonists have been used as bronchodilators in the management of bronchial asthma and chronic obstructive pulmonary disease (COPD); however, there is evidence suggesting that beta<sub>2</sub>-adrenoceptor agonist use may increase morbidity and mortality<sup>1</sup>. The long term beta-agonists, salmeterol and formoterol were introduced at the time of heightened concern about safety of beta<sub>2</sub> agonist drugs. There have been occasional reports of deterioration in asthma control, and even respiratory arrest, following the commencement of a long-acting beta-agonist<sup>2-8</sup>.

### **BETA-ADRENERGIC SYSTEM**

The beta-adrenergic system contains beta<sub>1</sub> and beta<sub>2</sub> receptors that are found in varying concentrations in the heart and lung, as well as in peripheral tissues throughout the body<sup>9</sup>. Beta<sub>1</sub> and beta<sub>2</sub>-adrenergic receptors coexist in the heart, generally in a ratio of 3:1. Beta<sub>2</sub> receptors are also present on adrenergic nerve terminals in the heart, where they facilitate norepinephrine release. The stimulation of either receptor results in positive inotropic and chronotropic responses, cardiac myocyte growth, and cardiac toxicity. Beta<sub>2</sub> receptors are found predominantly in bronchial and vascular smooth muscle, peripheral leukocytes, and adrenergic nerves. Beta<sub>2</sub>-agonists, such as salbutamol, salmeterol and formoterol are widely used as bronchodilators in the treatment of asthma and COPD.

### **CARDIOVASCULAR EFFECTS OF BETA-AGONISTS**

The use of betablockers has been shown to reduce morbidity and mortality in patients with ischemic heart disease, myocardial infarction, congestive heart failure, cardiac arrhythmias and hypertension as well as in the perioperative period. Beta-agonists exert physiologic effects that are opposite of those of betablockers and may

be expected to have deleterious cardiovascular effects. Doubts have gradually been emerging concerning the cardiovascular safety of beta<sub>2</sub>-agonist use, especially in patients who are at risk for heart disease. Case-control studies have demonstrated an association between beta<sub>2</sub>-agonist use and an increased risk for myocardial infarction, congestive heart failure, cardiac arrest, and acute cardiac death, with odds ratios ranging from 1.3 to 3.4<sup>9</sup>.

A meta-analysis including 13 single-dose trials and 20 longer duration trials showed that beta<sub>2</sub>-agonist use in patients with obstructive airway disease increases the risk for adverse cardiovascular events. The initiations of treatment increases heart rate and reduces potassium concentrations compared to placebo. A single dose of beta-agonist increased the heart rate by 9.12 beats/min (95% confidence interval (CI), 5.32 to 12.92) and reduced the potassium concentration by 0.36 mmol/L (95% CI, 0.18 to 0.54), compared to placebo. For trials lasting from 3 days to 1 year, beta<sub>2</sub>-agonist treatment significantly increased the risk for a cardiovascular event (relative risk (RR), 2.54; 95% CI, 1.59 to 4.05) compared to placebo. The RR for sinus tachycardia alone was 3.06 (95% CI, 1.70 to 5.50) and for all other events it was 1.66 (95% CI, 0.76 to 3.6)<sup>10</sup>.

### **BETA-AGONISTS IN BRONCHIAL ASTHMA**

Currently, inhaled corticosteroids are the most effective treatment for the symptoms of persistent asthma. However, in patients with severe disease, these drugs often fail to control asthma symptoms fully, necessitating additional treatment with inhaled bronchodilators. Until the early 1990s, the only effective inhaled bronchodilators available were short-acting beta<sub>2</sub>-adrenergic agonists such as salbutamol. Since these agents have durations of action of four to six hours, patients whose asthma symptom were not controlled by inhaled corticosteroids

needed to use them several times a day to obtain continuous relief.

To decrease the treatment burden, inhaled beta<sub>2</sub>-agonists with duration of action of 10 to 16 hours were developed. These long-acting beta-agonists, which include salmeterol and formeterol, were shown to be effective in improving symptom control and lung function for 12 hours or more when added to inhaled corticosteroid therapy<sup>11</sup>. Eleven years after the introduction of first long-acting beta-agonist, salmeterol the Food and Drug Administration (FDA) in USA issued a stern public warning that these medicines may increase the chance of severe asthma episodes, and death when those episodes occur<sup>2</sup>.

A large randomized, double-blind study was undertaken in UK to compare salmeterol with ablutolol (salbutamol) as daily therapy supplementing the usual treatment for asthma<sup>10</sup>. The study enrolled more than 25,000 patients and lasted 16 weeks. Patients receiving salmeterol were three times as likely to die from asthma during the trial as those treated with albuterol (12 to 16,787 patients vs, 2 to 8393 patients). There was one death attributable to salmeterol for every 650 patient-years of treatment. Another trial Salmeterol Multicenter Asthma Research Trial (SMART) was carried out, in which patients with asthma were randomly assigned to receive either salmeterol or placebo for 28 weeks in addition to their usual therapy<sup>12</sup>. An interim analysis, performed after approximately 26,000 patients had been enrolled, showed that asthma-related death was 44.4 times as likely in salmeterol group as in the placebo group (95 percent confidence interval, 1.3 to 15.3; P=0.02). One death was attributable to salmeterol for every 700 patient-years of treatment, a result strikingly similar to that in the UK study. At this point, the manufacturer halted the study.

No studies similar to SMART are available for formeterol, however data provided for the FDA advisory committee by Novartis showed an increased incidence of serious asthma-related events in patients taking formeterol – a trend found among both patients who were using inhaled corticosteroids concomitantly and those who were not<sup>2</sup>. Both these studies were not designed to test the hypothesis that salmeterol would increase the risk of death regardless of concomitant treatment with inhaled corticosteroids. Taken together, the evidence indicates that regular treatment with long-acting beta-agonists is associated with increased risk of severe exacerbations of asthma and of death from asthma in a small but not inconsequential subgroup of patients.

### SAFETY OF BETA-AGONIST USE IN COPD

The Cornell and Stanford universities did statistical analysis of 22 trials with 15,276 participants. They found

that anticholinergic bronchodilators (tiotropium and ipratropium) reduced severe respiratory events by 33 percent and respiratory-related deaths by 73 percent, compared with a placebo. However, the same meta-analysis found that regularly inhaled beta-agonists (metaproterenol, formeterol, salmeterol and ablutolol) increased the risk of respiratory death more than two fold, compared with a placebo. Edwin Salpeter concluded that “When patients used the anticholinergics, they experienced fewer severe exacerbations requiring hospitalization and fewer respiratory deaths than those taking only a placebo. With the beta-agonists, it’s the other way around, where the number of respiratory deaths increased when compared with those who took on the the placebo”<sup>13</sup>. These results suggest that anticholinergics should be the bronchodilator of choice in COPD.

### POSSIBLE MECHANISMS FOR IMPAIRMENT OF ASTHMA CONTROL

1. **Paradoxical bronchospasm**—may occur in association with all inhaled medication, and its incidence is said to be as high as 4% of subjects while regular long-acting beta-agonists do not enhance bronchial hyperresponsiveness (BHR) in most patients<sup>14</sup>, the possibility of increased BHR occurring in the individual cases, as a result of drug use, can not be exclude<sup>15</sup>.
2. **Tolerance**—Tolerance implies that with regular or high dose usage, the response to supplementary short-acting beta-agonist use may be blunted or absent. Previous studies have shown that patients with asthma and COPD build up tolerance to beta-agonists bronchodilator and bronchoprotective effects after regular treatment compared with the first dose<sup>16</sup>. While beta-agonists may reduce symptoms through bronchodilation, the researchers believe they also promote bronchial inflammation and sensitivity by reducing bronchial protection without any warning of increased symptoms, which can then lead to a life-threatening response. Two aspects require consideration.
  - i. Tolerance to the bronchodilator actions of short-acting beta-agonists (used as “relievers”) when long-acting beta-agonists are being inhaled regularly.
  - ii. Tolerance to the protective effects of short-acting beta-agonists e.g. against exercise or allergen challenges.

### CLINICAL STRATEGY

How do we reconcile in clinical practice to the established beneficial effects of long-acting beta-agonists on asthma control with their rare potential for contributing

to severe illness or death? In patients with mild-to-moderate asthma, inhaled corticosteroids should be used in sufficient amounts to control symptoms. Patients of severe persistent asthma needs addition of other bronchodilators. In a perspective article Martinez recommended addition of leukotriene - receptor antagonists or low dose theophylline to therapy for asthma that is not controlled with the use of inhaled corticosteroids which is completely opposite to that of the National Asthma Education and Prevention Program expert panel, prefers the addition of long-acting beta-agonists, instead of leukotriene modifiers, to the treatment of asthma not controlled by inhaled corticosteroids. It should prevent one exacerbation for every 38 patients treated<sup>18</sup>.

No study has shown that the combination of inhaled corticosteroids and long-acting beta-agonists results in increased deaths from asthma, and the data from the SMART trial showed to increased risk of death from asthma with salmeterol, as compared with placebo, in patients taking inhaled corticosteroids. Overstating the risks of long-acting beta-agonists is irresponsible, because it may lead to the use by patients of suboptimal therapy, noncompliance with a regimen, or both. Reconciling the benefit with the potential harm of long-acting beta-agonists is simple: these drugs should not be used alone but, rather should be added to therapy with inhaled corticosteroids for moderate-to-severe asthma, as recommended by current guidelines.

Since we still do not know whether long-acting beta-agonists pose a risk when used appropriately in such patients, close medical monitoring is necessary, and users should be cautioned to continue taking all their asthma medications and to seek medical care should their symptoms remain uncontrolled or worsen despite this dual treatment. Until the manufacturers of these drugs undertake the appropriate studies needed to clear the air, the safety of long-acting beta-agonists will remain uncertain.

## CONCLUSION

Practitioners ought to be aware of the potential for deterioration in COPD and asthma control following the introduction of long acting beta-agonists, albeit rarely. This often occurs within the first six weeks of therapy, hence careful monitoring of patients at this time is advised. Peak flow monitoring, at least in the short term, should be encouraged. Patients should be advised to seek advice if they perceive a lack of benefit from using reliever medication.

Compliance with inhaled steroids- which may be less if the long-acting beta-agonist initially improves symptoms-should be emphasized. The long-acting agent ought to be withdrawn in the event of deteriorating asthma

control in the absence of other explanations for the adverse clinical events.

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