Case Report

Cardiorespiratory Arrest Associated with Recent Initiation of Salmeterol Therapy

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The introduction of the long acting B_2-agonists has offered a new class of therapeutic agents for the management of asthma.[1-3] While efficacious in that role, a number of toxicities have been reported.[2,4,5] We present a case of cardiorespiratory arrest associated with the use of one of these agents, salmeterol.

CASE

A 54 year-old male, with a 20-year history of COPD requiring home oxygen therapy, presented to the emergency department with a sudden onset of shortness of breath. At that time his vital signs were a blood pressure of 120/88 mmHg, heart rate of 143 bpm, and a respiratory rate of 28/min. Blood gases obtained at that time revealed a PaO_2 of 32 mmHg [70-100], pH of 7.14 [7.35-7.45], a $PaCO_2$ of 119 mmHg [35-45], a HCO_3^- of 39 mmol/L [21-28] and an oxygen saturation of 47%. Shortly after arrival the patient progressed to a cardiorespiratory arrest, was intubated, and transferred to the Intensive Care Unit where he was noted to be in electromechanical dissociation (EMD). He was resuscitated with a single injection of epinephrine, 1 mg. Although initial blood work on admission was sparse due to the acuity of this patient's presentation, all post resuscitation laboratory data including electrolytes were unremarkable with the exception of an elevated serum bicarbonate (40 mmol/L).

Over the past year the patient had noted a progressive decline in pulmonary function to the point where he was dyspneic most of the time and required frequent administration of salbutamol. Recent pulmonary function tests revealed an FEV_1 of 0.45L (.20L predicted) and a FEV_1/FVC value of 28% (normal 66-88%). He had quit smoking three months prior, having smoked three packs per day for 35 years.

Pharmacologic management of his condition prior to admission included a regimen of salbutamol 200mcg inhaled every 2-3 hours as needed, ipratropium bromide 40mcg qid, and salmeterol 50mcg bid. The salmeterol was a recent addition, being started only nine days prior to this admission. In response to initiating salmeterol, the patient noted a marked subjective improvement in his dyspnea, accompanied by a marked decrease in his salbutamol use as documented in clinic records from a follow-up appointment seven days after the initiation of salmeterol.

The patient's past medical history consisted of his ongoing COPD, a 10-year history of well controlled hypertension, and a self-reported history of alcohol intake of approximately 6 oz per day. No other significant medical problems were noted. This patient claimed to have no known drug allergies.

His medications on admission included nifedipine (Adalat XL®) 30mg bid, furosemide 40mg bid, ranitidine 150mg bid, and 20mmol potassium chloride daily in addition to his inhalers. The patient indicated excellent compliance with this regimen.

Physical examination was unremarkable. An initial suspicion of decompensating cor pulmonale as a cause of this event was ruled out by a 2D echocardiogram which showed normal right ventricular size and motion. Global hypokinesis of the left ventricle and severe left ventricular systolic dysfunction suspected to be due to alcoholic cardiomyopathy were noted at this time.

Within 24 hours the patient was extubated and a day later was transferred to the floor: all medications, except salmeterol, were continued. Given the temporal relationship of this event with regard to starting salmeterol, and the marked improvement in pulmonary symptoms after starting salmeterol, it was hypothesised that an arrhythmia associated with initiation of salmeterol in a patient with existing cardiomyopathy had led to the cardiorespiratory arrest.

DISCUSSION

While the etiology of the arrest is not clear, the temporal relationship would support salmeterol as playing a role; particularly in view of the patient's stated improvement in symptoms prior to the arrest. This

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does not rule out an underlying deterioration in the pulmonary disease and indeed many of the deaths associated with the use of salmeterol have been associated with respiratory failure.[5-10] In addition, there were several other potential causes which could have explained the scenario including the use of salmeterol to treat an acute exacerbation, beta agonist overdose, an arrhythmia resulting from an electrolyte abnormality, or an arrhythmia resulting from hypoxia. None of these seemed to be probable in our case for the following reasons. In terms of an acute exacerbation and beta agonist overdose the patient indicated that his "as needed" use of salbutamol had actually decreased since starting salmeterol and that he had not exceeded the prescribed salmeterol dose of two puffs twice daily. No marked electrolyte or metabolic abnormalities other than hypoxia would support an arrhythmic event. The fact that the patient's dyspnea had improved up until the morning of this arrest suggests that hypoxia was not likely a factor. Due to the lack of evidence for other causes, it was felt that a cardiorespiratory event secondary to salmeterol use in a patient with known left ventricular dysfunction should be considered. This was further supported by the rapid recovery of the patient and his early extubation which would be compatible with a sudden cardiac event. Because of the uncertainty and the lack of objective information prior to the arrest we were not able to conclusively prove the role of salmeterol. The role of B-receptor subsensitivity to acute bronchodilator use following salmeterol therapy has recently been reported and this would render rescue bronchodilator therapy less effective.[11] It is unknown if this played any role in our case.

The reporting of 48 deaths in the first two years of salmeterol availability in the U.K. lead to a warning issued by the Committee on Safety of Medicines regarding the use of this agent.[6] Subsequently, these warnings have been included in the Canadian monograph.[12] These warnings emphasize that salmeterol should not be considered as a substitute for inhaled corticosteroids, should not be used to treat acute symptoms, and should not be initiated for a significantly worsening asthmatic condition that could be deemed life threatening.

Although an extensive literature evaluation by Devoy et al[13] concluded that there was no significant evidence to claim that the long acting B_2-agonists were associated with an increased morbidity and mortality, potential serious adverse effects should not be overlooked. Following the introduction of the long acting B_2-agonist, salmeterol, in the United Kingdom in 1990, the group of Castle et al[7] under the authority of the Glaxo Research Institute completed an extensive evaluation of salmeterol compared to salbutamol in a study involving over 25,000 asthmatic patients. They showed a non-significant, threefold increase in risk of death from asthma related respiratory failure and a 1.45 fold increase in risk of cardiovascular death in the salmeterol group. Concern has been expressed over these results despite the lack of statistical significance.[14] It should be noted that the patient in this report did not have a history of asthma, but rather COPD. While not currently indicated for non-asthmatic conditions, recent studies have shown promise with the use of salmeterol in these settings.[15]

Although it is impossible to determine whether the arrest was triggered by a cardiac or respiratory event, this patient was likely at increased risk for cardiac toxicity due to his left ventricular dysfunction. However, his subjective improvement since initiation of salmeterol and lack of warning symptoms prior to his acute decompensation made this sudden event difficult to foresee. In conclusion, this case suggests that salmeterol should be used with caution, if at all, in patients with significant risk factors for arrhythmias.

REFERENCES

1. Boulet LP. Long- versus short-acting B_2-agonists. *Drugs* 1994;47:207-22.
2. Brogden RN, Faulds D. Salmeterol xinafoate - A review of its pharmacologic properties and therapeutic potential in reversible obstructive airways disease. *Drugs* 1991;42:895-912.
3. Kamada AK, Spahn JD, Blake KV. Salmeterol: Its place in asthma management. *Ann Pharmacother* 1994;28:1100-2.
4. Bennett JA, Smyth ET, Pavord ID, et al. Systemic effects of salbutamol and salmeterol in patients with asthma. *Thorax* 1994;49:771-4.
5. Finkelstein FN. Risks of salmeterol? [letter]. *N Engl J Med* 1994;331:1314.
6. Anon. ADR news: CSM Serevent warning. 92/02/03
7. Castle W, Fuller R, Hall J, et al. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993;306:1034-7.
8. Inman WHW. Manufacturers underestimate mortality from asthma (letter). *BMJ* 1993;306:1610.
9. Clark CE, Ferguson AD, Siddon JA. Respiratory arrests in young asthmatics in salmeterol. *Respir Med* 1993;87:227-8.
10. Mann RD, Kobota K, Pearce G, et al. Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients [letter]. *BMJ* 1994;309:1018.
11. Grove A, Lipworth BJ. Bronchodilator subsensitivity to salbutamol after twice daily salmeterol in asthmatic patients. *Lancet* 1995;346:201-6.
12. Glaxo Canada. Serevent Product Monograph. Mississauga;1994.
13. Devoy MAB, Fuller RW, Palmer JBD. Are there any detrimental effects of the use of inhaled long-acting B_2-agonists in the treatment of asthma? *Chest* 1995;107:1116-24.
14. Sears MR, Taylor DR. Bronchodilator treatment in asthma [letter]. *BMJ* 1993;307:446.
15. Ulrick CS. Efficacy of inhaled salmeterol in the management of smokers with chronic obstructive pulmonary disease: A single centre randomized double blind placebo controlled, crossover trial. *Thorax* 1995;50:750-4.