Paradoxical Response to Levalbuterol

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Asthma is a common condition that can substantially affect patients’ quality of life. Although several drugs, most commonly β-adrenergic agonists, alleviate symptoms of asthma, they may cause paradoxical bronchospasm or paradoxical bronchoconstriction. Levalbuterol hydrochloride—a pure form of the (R)-stereoisomer in racemic albuterol—eliminates the adrenergic properties that can cause such adverse effects. However, we report a case of paradoxical bronchoconstriction in a 36-year-old man who was recently diagnosed as having new-onset asthma and was treated with levalbuterol.

In 2005, 15.7 million noninstitutionalized adults (7.2%) and 6.8 million adolescents (9.4%) in the United States had asthma.1 In the same year, asthma visits accounted for 12.8 million visits to office-based physicians.1 For more than a century, β-adrenergic agonists, which provide rapid relief for hyperresponsive airways, have been an integral component of asthma therapy for both adults and adolescents. Currently, the most common β-agonist used is racemic albuterol, a 50:50 combination of the (R) and (S)-stereoisomers.2 Racemic albuterol has been shown to cause paradoxical bronchoconstriction, thought to be a result of constrictive action of the (S)-stereoisomer.3 A pure form of (R)-albuterol—referred to as levalbuterol—is now clinically available. Currently, two forms of levalbuterol exist: (1) levalbuterol tartrate, which is administered by an inhaler, and (2) levalbuterol hydrochloride, which is administered by a nebulizer.

Levalbuterol has been reported to have a greater affinity for the β-receptor and less sympathetic irritation than the racemic form, therefore decreasing the incidence of paradoxical bronchospasm.5 Although paradoxical bronchospasm is listed in levalbuterol’s drug label and is associated with new inhalation canisters,6 few published studies document this adverse effect.7 We report a case of paradoxical bronchoconstriction in a man recently diagnosed as having new-onset asthma.

Report of Case

A 36-year-old white man sought care at an emergency department (ED) for intense wheezing that was diagnosed as new-onset asthma. The patient was treated with oral steroids and levalbuterol administered by a metered-dose inhaler (MDI) and then discharged. Because the patient had persistent symptoms, he visited the Pulmonary Clinic at the Naval Medical Center San Diego in San Diego, Calif, the next day for a follow-up examination.

On presentation at the clinic, the patient’s blood pressure was 128/85 mm Hg; heart rate, 80 beats per minute; respiratory rate, 14 breaths per minute; body temperature, 98.3°F; and oxygen saturation, 97%. He was in no acute distress without evidence of conversational dyspnea or respiratory distress.

The patient reported 3 months of progressive dyspnea on exertion, periodic coughing, wheezing, and nocturnal dyspnea without sputum production or hemoptysis. The patient denied having a history of childhood asthma but did note a hypersensitivity to cat dander and some grasses until the age of 8 years. However, his childhood hypersensitivities were never evaluated further. The patient was a nonsmoker and until the previous day had never had any steroids or bronchodilators administered or prescribed. He reported no history of asthma or eczema and denied any recent exposure to dusts, molds, or danders. The patient had been using over-the-counter nebulized epinephrine (Primatene mist) with minimal relief of symptoms.

Physical examination revealed diffuse wheezing throughout the lung fields with adequate air flow. Findings from a chest radiograph taken the previous day at the ED were normal. At the clinic, a spirometry test—measuring forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio—was performed before and 15 minutes after administration of two puffs of levalbuterol (90 µg) via an MDI. Standard spirometry (ie, three forced respiratory maneuvers before and after medication) revealed decreased pulmonary function (Figure 1 and Figure 2).
indicating bronchoconstriction. For example, the FEV$_1$ decreased by 460 mL (14%). Spirometry was discontinued, and the patient was advised to complete his oral steroid therapy as prescribed at the ED and was started on combination therapy with salmeterol xinafoate, 50 μg, and fluticasone propionate, 250 μg, twice daily.

The patient returned to the clinic 1 month later for a repeated bronchodilator study using nebulized levalbuterol (1.25 mg, repeated testing performed 15 minutes after administration of levalbuterol), and his results again showed a significant paradoxical decrease in airflow after drug administration. The patient was continued on combination salmeterol and fluticasone for treatment of his mild, persistent asthma, and he has since reported substantial improvement of his symptoms.

Discussion

Endogenous epinephrine, a potent β-agonist, is an (R)-isomer compound that results in airway bronchodilation in the setting of increased sympathetic activity. Modification of the β$_2$ molecules resulted in a class of β$_2$-agonists, a 50:50 combination of both (R)- and (S)-isomers known as albuterol. The most recent member of this class, levalbuterol, is a pure (R)-isomer. Research has demonstrated that the racemic formulas (albuterol, fenoterol, formoterol fumarate, salmeterol, and terbutaline sulfate) exhibit both bronchoconstricting and bronchodilating properties, which have led to paradoxical bronchoconstriction in some patients with reactive airway disease. The (R)-isomer binds to the β$_2$ receptor, resulting in decreased intracellular calcium and decreased airway reactivity. Comparatively, the (S)-isomer has been shown to function as an adrenergic antagonist with pro-inflammatory effects in both in vitro and in vivo experimental models and may be harmful, particularly in patients who have asthma. Recent data suggest that the (S)-isomer is metabolized 10 times slower than the bronchodilating (R)-isomer, and therefore may remain in the body at higher levels and for a longer time with possible detrimental airway effects. Because levalbuterol does not have this adrenergic antagonist, it is not expected to cause paradoxical bronchoconstriction.

In the present case, the prebronchodilator spirometry demonstrated a decreased FEV$_1$/FVC ratio (67; normal >70) as well as a decreased percent predicted FEV$_1$ (80%; normal >80%). These values indicate a mild obstructive abnormality before levalbuterol administration. According to the American Thoracic Society guidelines, a positive response to bronchodilators—indicating reversible airway disease—is defined as a 12% and 200-mL increase in either the FEV$_1$ or the FVC. In our patient, 90 μg of levalbuterol via an MDI produced a 460-mL (14%) decrease in FEV$_1$ and a 220-mL (4%) decrease in FVC, thereby qualifying as a paradoxical response to levalbuterol.

In the previously reported case of paradoxical bronchospasm, the patient had several comorbidities and was treated in an acute setting. In addition, medications such as β-blockers, diuretics, digoxin, monoamine oxidase inhibitors, and tricyclic antidepressants are known to interact harmfully in some patients using levalbuterol and racemic albuterol. However, the patient in the present report did not have comorbidities and was not taking interfering medications, yet his pulmonary function documentation revealed the untoward effects. The bronchoconstrictive response to nebulized levalbuterol upon repeated spirometry suggests that the first paradoxical response was not a reaction to an adulterant in the hydrofluoroalkane product. Therefore, we are confident that our findings of decreased pulmonary function within minutes of levalbuterol inhalation in our patient were a paradoxical response to the drug.
Figure 2. Comparison of forced expiratory volume in 1 second (FEV1) before and after administration of levalbuterol via a metered-dose inhaler. Although the patient performed three respiratory maneuvers, the best effort data are represented.

Conclusion
The current report demonstrates paradoxical bronchoconstriction in a patient who had recently diagnosed asthma without comorbidities. Physicians must be aware of this possibility when treating a patient who is nonresponsive to levalbuterol or has worsening symptoms after drug administration.

References

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