

Suicidal Ideation and Thought Disorder Associated With the Formoterol Component of Combined Asthma Medication

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Summary. Combination inhaled asthma medications containing corticosteroids and long-acting beta-adrenergic (LABA) agents are generally well tolerated, although a small minority of children receiving them may develop side-effects. Herein is reported a case of a 9-year-old boy who developed insomnia, pressured speech, agitation, and suicidal ideation within the 1st month after initiating formoterol + budesonide. He had not received oral glucocorticoids for >90 days. All symptoms resolved within 48 hr upon discontinuing formoterol while continuing budesonide. To our knowledge, this is the first report of childhood suicidal ideation strongly associated with use of a combination inhaled corticosteroid/LABA. **Pediatr Pulmonol.**

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INTRODUCTION

Although long-acting beta-agonists (LABA) are effective bronchodilators, their role in asthma treatment has been controversial. LABAs can provide symptom control and lung function improvement in combination with a low-dose inhaled corticosteroid (ICS) with efficacy comparable to that provided by moderate (double) dose ICS.¹ However, LABAs may cause untoward effects and, therefore, not be suitable for treatment of all childhood asthmatics.

CASE REPORT

HJ was a non-atopic 9-year-old white male who presented with 48 hr of pressured speech and suicidal ideation. He was treated multiple times for bronchiolitis during the first 3 years of life, having had a first episode of RSV infection at age 3 weeks after uncomplicated term birth. His care at this institution began at age 4 years. From that time, he was routinely treated with inhaled corticosteroids and albuterol for asthma. In addition, he had annual exacerbations requiring oral glucocorticoids for 1–3 weeks. He had frequent symptoms of productive cough, relative exercise intolerance at altitude, and weight gain. His pulmonary function tests showed reversible airways obstruction compatible with American Thoracic Society criteria for asthma. He had previously undergone Nissen fundoplication for gastroesophageal reflux at 6.5 years old. In addition, he had undergone tonsillectomy and adenoidectomy for

obstructive sleep apnea (age 7.5 years), with resolution. Past evaluations for other causes of airways obstruction (e.g., cystic fibrosis, oral aspiration, ABPA, bronchiectasis, etc.) had provided no additional diagnosis besides asthma. He did have 5T/7T variant (heterozygous presence of 5T variant in intron 8 of the CFTR gene). He had not received oral glucocorticoids for >90 days. His controller was changed from budesonide 180 µg/puff, 2 puffs, twice daily (Pulmicort Flexhaler) to budesonide (160 µg/puff) plus formoterol (4.5 µg/puff; Symbicort), two puffs twice daily. Supplemental short-acting β₂ adrenergic agents were not used. Within 14 days of this change, mood changes accompanied by “yelling, screaming, crying, and episodes of anger” directed at family members occurred. Within 28 days, symptoms

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deteriorated, with statements such as: “I hate you. I hate my life. Everything is unfair. I’d rather be dead.” Lifelong, he had never mentioned suicide, nor previously shown sustained pressured speech nor agitation. Insomnia began about 10 days before onset of suicidal thoughts (20 days after the medication was changed to budesonide + formoterol). Changing the timing of medication did not alleviate insomnia.

After 30 days of budesonide + formoterol treatment, his medication was changed to budesonide 180 µg/puff, two puffs in the morning and one in the evening. Within 48 hr, no further mentions of suicide were made and pressured speech abated. The patient stated that he felt “less anxious,” and indicated: “I have a lot more control of my emotions.” He remains free of suicidal ideation after >6 months of follow-up. Insomnia also resolved within 48 hr. Re-challenge with budesonide + formoterol was felt to be unethical.

DISCUSSION

This is the first case report of budesonide + formoterol use associated with suicidal ideation in a pediatric patient. Although causality was not proven, it was postulated that budesonide + formoterol most likely caused both the suicidal ideation and thought disorder, given their onset shortly after initiation of the medication, and the abrupt resolution of symptoms upon discontinuation.

Although corticosteroids can cause neuropsychiatric side effects² use of both inhaled and systemic steroids predated mood changes and sleep disturbances. The child had received budesonide for many years. Post-marketing events for budesonide + formoterol included behavior and sleep disturbances, nervousness, agitation, depression, and restlessness, although none were reported in earlier randomized trials of this combination. Despite low incidences (approximately 3%), these can be clinically significant.^{1,3} β_2 -agonists have the propensity to potentiate acute anxiety by stimulating β_2 -receptors in the brain, since they are structurally similar to catecholamines.⁴ Agitation and tremulousness have accompanied childhood poisonings due to albuterol.^{5,6}

Profound thought disorders, including albuterol-induced exacerbations of psychosis and new-onset psychiatric disturbance, were reported in patients with pre-existing disease and those with no history of mental illness.^{7,8} Altered mood and/or thought disorders can occur with acute and habitual overuse of asthma medication. Hallucinations or psychoses can occur with

abuse of an albuterol inhaler.⁹ In our patient, medication use was strictly monitored by the mother, and there was no use of albuterol, nor overuse of formoterol. Asthma, independent of medication, increases risks of psychological disturbances.¹⁰ Thought and behavior disturbances may have been augmented by sleep deprivation.

CONCLUSIONS

The child’s mood, thought and behavior disturbances, as well as his insomnia, began within two weeks after addition of formoterol, and showed prompt, complete resolution when formoterol was discontinued, indicating a strong association between use of this agent and his psychiatric symptoms. Careful monitoring of both sleep and mood changes in young children receiving LABA for asthma, especially during early treatment, is recommended.

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