



Case report: Paradoxical responses to short acting beta-agonists in a pediatric patient

Alexandra Graden, Sonia Gandhi & Avni Y. Joshi

To cite this article: Alexandra Graden, Sonia Gandhi & Avni Y. Joshi (2019): Case report: Paradoxical responses to short acting beta-agonists in a pediatric patient, Journal of Asthma, DOI: [10.1080/02770903.2019.1668009](https://doi.org/10.1080/02770903.2019.1668009)

To link to this article: <https://doi.org/10.1080/02770903.2019.1668009>



Published online: 01 Oct 2019.



Submit your article to this journal [↗](#)



Article views: 5



View related articles [↗](#)



View Crossmark data [↗](#)

CASE REPORT



Case report: Paradoxical responses to short acting beta-agonists in a pediatric patient

Alexandra Graden, MD, Sonia Gandhi, MD, and Avni Y. Joshi, MD

Department of Allergic Diseases, Mayo Clinic, Rochester, Minnesota, USA

ABSTRACT

Introduction: Asthma is one of the most common airway diseases that nearly all pediatricians will encounter in their clinical practice. Using spirometry to compare a patient's forced expiratory volume in one second (FEV1) both pre- and post-bronchodilator administration is the ideal way to document a paradoxical bronchodilator response.

Case Study: Here, we present a patient who experienced paradoxical responses to short acting beta-2 agonists (SABAs; albuterol and levalbuterol).

Results: This patient responded to an anti-cholinergic agent (ipratropium bromide) with both subjective as well as objective response.

Conclusion: This case highlights the need to include paradoxical response to SABAs in the differential of a patient with poorly controlled asthma. It also provides an example of successful treatment of a pediatric patient with a class of medications previously reserved for adults with chronic obstructive pulmonary disease.

ARTICLE HISTORY

Received 1 May 2019

Accepted 10 September 2019

KEYWORDS

Case Reports;
Pediatrics; Treatment

Introduction

Asthma is one of the most common airway diseases that nearly all pediatricians will encounter in their clinical practice. Establishing a diagnosis of asthma involves a careful process of history taking, physical examination, and diagnostic studies, especially spirometry which can provide proof of a bronchodilator response in school-age children and adolescents. The forced expiratory volume in one second (FEV1) is the most effective measurement of bronchodilation and bronchospasm. This is due in part to its sensitivity to changes compared with the forced vital capacity and has less variation with changes in effort (1). Using spirometry to compare a patient's FEV1 both pre- and post-bronchodilator administration is the ideal way to document a paradoxical bronchodilator response. Classically, albuterol is used for evaluating a post-bronchodilator response; in less than 10% of asthmatic patients, it causes paradoxical bronchospasm (2).

Albuterol is the prototype of short acting beta-2 agonists (SABAs), which are the cornerstone of rescue treatment in asthma. It acts by stimulating bronchial smooth muscle relaxation. The beta-2 receptor is a G protein-coupled transmembrane receptor that activates the enzyme adenyllyl cyclase (3). Variations in the

molecular structure of beta-agonists effect their onset and duration of bronchodilation. There is heterogeneity in individual responses to SABAs, which may be related to multiple factors, including the underlying airway pathophysiology and potential triggers for bronchoconstriction. Albuterol is a racemic mixture of isomers: R isomer (the active form) and S isomer (the inert form). Racemic albuterol has been shown to cause paradoxical bronchoconstriction. This is thought to be the result of constrictive action of the (S)-stereoisomer (4). A pure form of (R)-albuterol, also known as levalbuterol, eliminates the adrenergic properties and has greater affinity for beta-adrenergic reception (5,6). However, its clinical superiority has not been conclusively established in children (7–9).

Case report

A 11-year-old biracial female was referred to the Pediatric Allergy and Immunology Clinic for management of asthma. The patient had a history of shortness of breath and had undergone a methacholine challenge test at age 8 years and was subsequently diagnosed with mild intermittent asthma. The patient was treated with albuterol on an as needed basis,

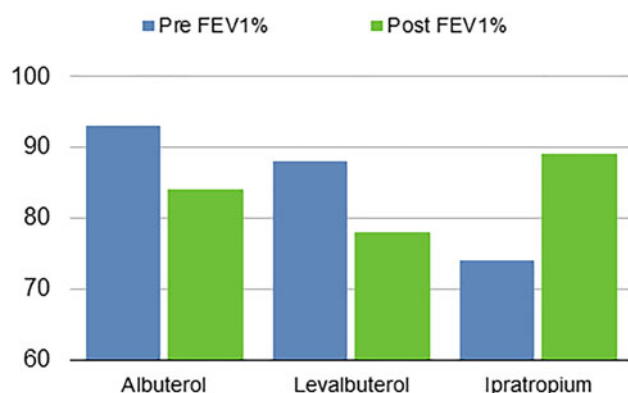


Figure 1. Treatment with albuterol and levalbuterol demonstrated a reduction in FEV1 of approximately 10%. Treatment with ipratropium demonstrated a sustained increase in FEV1 of approximately 15%.

however, the patient and her family noted a change in her behavior with the development of delusions, paranoia, and mood changes after the use of albuterol. Hence, the patient was switched from albuterol to levalbuterol.

In the subsequent months, monteleukast was added to the patient's regimen as she was having more exercise-induced symptoms. Almost one year later, the patient experienced an exacerbation of her asthma in which she experienced chest tightness and productive cough with yellow-colored sputum. The patient tried levalbuterol without any significant improvement in her symptoms. When the patient was seen for follow up, she expressed significant discontent with her rescue inhaler regimen.

Objective measures of the patient's response (or lack thereof) to bronchodilators was achieved by performing two pulmonary function tests, each with a different bronchodilator, spaced two weeks apart. The patient's subjective assessment was confirmed with pulmonary function testing that failed to show any bronchodilator response to levalbuterol. (Figure 1) Ipratropium bromide, on the other hand, was associated with a significant bronchodilator response, as well as a sustained increase in the forced expiratory volume in one second (FEV1) percentage from 73.6% to 89.0%.

At present, the patient continues to use ipratropium bromide as needed, and has reported immediate relief of her symptoms.

Discussion

The patient mentioned above experienced, in addition to paradoxical bronchoconstriction, anxiety and a change in her behavior as a result of SABA use.

Beyond underlying patient characteristics that may predict a paradoxical response to albuterol, the chemical composition may trigger an irritant reaction. Benzalkonium Chloride (BAC), sulfites, and chlorobutanol are often added to albuterol to prevent bacterial growth. These additives, depending on their concentration, can trigger bronchospasm. BAC-induced bronchoconstriction occurs over prolonged accumulative periods and may in fact, blunt the bronchodilator response of albuterol (10–12). This can be overcome by using a preservative-free product.

In comparison to SABAs, anticholinergics are mainly used to treat chronic obstructive pulmonary disease in adults and are rarely used for acute asthma in children. Most published studies show that beta-agonists are superior to atropine for acute asthma exacerbations in children (13). Both levalbuterol and ipratropium tend to induce a higher degree of bronchodilation and fewer episodes of paradoxical bronchospasm. In contrast, African Americans, like the patient mentioned above, are more likely to exhibit mutations in the ADRB2 gene which codes for the beta-2 adrenergic receptor. As a result, they are more likely to exhibit therapeutic failure with inhaled beta-agonists (14–16).

As a result of our experience with the patient mentioned above, we propose that a paradoxical response to SABA be considered in the differential diagnosis of a patient who presents with poorly controlled asthma. In addition to this, other upper airway disorders including paradoxical vocal cord motion (vocal cord dysfunction), should also be considered. Testing for a paradoxical response to albuterol or levalbuterol can be detected with spirometry with bronchodilator response.

Conclusion

Here, we present a patient who experienced paradoxical responses to short acting beta-2 agonists (SABAs; albuterol and levalbuterol), and who responded to an anti-cholinergic agent (ipratropium bromide) with both subjective as well as objective response.

Disclosure statement

The authors report no conflicts of interest.

References

1. Tepper RS, Wise RS, Covar R, Irvin CG, Kercsmar CM, Kraft M, Liu MC, O'Connor GT, Peters SP, Sorkness R, et al. Asthma outcomes: Pulmonary

- physiology. *J Allergy Clin Immunol.* 2012;129:S65–S87. doi:[10.1016/j.jaci.2011.12.986](https://doi.org/10.1016/j.jaci.2011.12.986).
2. Mirsadraee M, Kabolie M, Boskabady MH. Best drugs for avoiding paradoxical bronchospasm during spirometry. *Tanaffos* 2009;8:58–64.
 3. Barisione G, Baroffio M, Crimi E, Brusasco V. Beta-adrenergic agonists. *Pharmaceuticals (Basel)* 2010;3: 1016–1044. doi:[10.3390/ph3041016](https://doi.org/10.3390/ph3041016).
 4. Broski SE, Amundson DE. Paradoxical response to levalbuterol. *J Am Osteopathic Assoc.* 2008;108: 211–213.
 5. Magee JS, Pittman LM, Jette-Kelly LA. Paradoxical bronchoconstriction with short-acting beta agonist. *Am J Case Rep.* 2018;19:1204–1207. doi:[10.12659/AJCR.910888](https://doi.org/10.12659/AJCR.910888).
 6. Berger WE. Levalbuterol: pharmacologic properties and use in the treatment of pediatric and adult asthma. *Ann Allergy Asthma Immunol.* 2003;90: 583–592. doi:[10.1016/S1081-1206\(10\)61859-5](https://doi.org/10.1016/S1081-1206(10)61859-5).
 7. Hardasmalani HD, DeBari V, Bithoney WG, Gold N. Levalbuterol versus racemic albuterol in the treatment of acute exacerbation of asthma in children. *Pediatr Emerg Care.* 2005;21:415–419. doi:[10.1097/01.pec.0000169433.91196.6a](https://doi.org/10.1097/01.pec.0000169433.91196.6a).
 8. Qureshi F, Zaritsky A, Welch C, Meadows T, Burke BL. Clinical efficacy of racemic albuterol versus levalbuterol for the treatment of acute pediatric asthma. *Ann Emerg Med.* 2005;46:29–36. doi:[10.1016/j.annemergmed.2005.02.001](https://doi.org/10.1016/j.annemergmed.2005.02.001).
 9. Andrews T, McGintee E, Mittal MK, Tyler L, Chew A, Zhang X, Pawlowski N, Zorc JJ. High-dose continuous nebulizer levalbuterol for pediatric status asthmaticus: a randomized trial. *J Pediatr* 2009;155: 205–210. doi:[10.1016/j.jpeds.2009.01.073](https://doi.org/10.1016/j.jpeds.2009.01.073).
 10. George M, Joshi SV, Concepcion E, Lee H. Paradoxical bronchospasm from benzalkonium chloride (BAC) preservative in albuterol nebulizer solution in a patient with acute severe asthma. A case report and literature review of airway effects of BAC. *Resp. Med. Case Rep.* 2017;21:39–41. doi:[10.1016/j.rmcr.2017.03.005](https://doi.org/10.1016/j.rmcr.2017.03.005).
 11. Prabhakaran S, Abu-Hasan M, Hendeles L. Benzalkonium chloride: A bronchoconstricting preservative in continuous albuterol nebulizer solutions. *Pharmacother.* 2017;37:607. doi:[10.1002/phar.1929](https://doi.org/10.1002/phar.1929).
 12. Camus P, Rosenow EC. Drug-induced and iatrogenic respiratory disease. Boca Raton (FL): CRC Press; 2010.
 13. Teoh L, Cates CJ, Hurwitz M, Acworth JP, van Asperen P, Chang AB. Anticholinergic therapy for acute asthma in children (Review). *The Cochrane Library* 2012.
 14. Finkelstein Y, Bournissen FG, Hutson JR, Shannon M. Polymorphism of the ADRB2 gene and response to inhaled beta-agonists in children with asthma: a meta-analysis. *J Asthma.* 2009;46:900–905. doi:[10.3109/02770900903199961](https://doi.org/10.3109/02770900903199961).
 15. Maitland-van der Zee AH, Daly AK. Pharmacogenetics and individualized therapy. Hoboken: John Wiley & Sons, Inc., 2012.
 16. Adkinson NF, Bochner BS, Burks AW, Busse WW, Holgate ST, Lemanske RF Jr, O’Hehir RE. Middleton’s allergy e-book: Principles and practice. Amsterdam: Elsevier Publishing; 2013.