Paradoxical bronchospasm: a rare adverse effect of fenoterol use
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Abstract
Paradoxical bronchospasm refers to the constriction of the airways after treatment with a sympathomimetic bronchodilator. Theoretically, bronchodilators, such as beta-agonist inhalers, act to ease asthma symptoms by relaxing the muscles surrounding the walls of the bronchial tubes, which relieve bronchial constriction. However, in rare instances, some patients develop respiratory distress or even respiratory failure after inhaled bronchodilator use, although the exact mechanism for this adverse effect is unknown. We report a male, with a known asthma history diagnosed for more than one decade, receiving fenoterol (Berotec®) for wheezing control and the worsening of his clinical condition immediately after bronchodilator administration.

Introduction
Paradoxical bronchospasm means a constriction of the airways after treatment with a sympathomimetic bronchodilator. Selective beta 2-agonist inhalers are the most potent bronchodilators currently approved for clinical use in asthma and obstructive lung disease. Theoretically, bronchodilators act to ease symptoms by relaxing the muscles surrounding the walls of the bronchial tubes, which relieve bronchial constriction [1–3]. However, in rare cases, some patients develop aggravating ordinary respiratory discomforts, even respiratory distress or acute respiratory failure events, after bronchodilator use. Be that as it may, the exact mechanism for this adverse effect remains unclear. Here, we report a man, with a known asthma history diagnosed for over one decade, receiving fenoterol (Berotec®, Boehringer-Ingelheim, Taiwan) for wheezing control and the worsening of his clinical condition, including being intubated twice due to acute respiratory failure, which occurred less than 5 min immediately after one puff of fenoterol (Berotec) inhalation.

Case Report
The 50-year-old gentlemen had a previous history of type 2 diabetes mellitus (DM) and bronchial asthma, both of which had been diagnosed for over one decade. Drug allergy to penicillin was also documented in his previous medical records. In mid-June of 2013, he had one common cold event took one puff of fenoterol (Berotec) due to dyspnoea. However, his dyspnoea worsened, and his wheezing sound became more prominent after fenoterol (Berotec) inhalation. He was sent to the emergency department of a regional hospital in Kaohsiung for treatment. The symptoms were relieved after ipratropium and terbutaline inhalation, and he was discharged via the emergency room on the same day. One week later in late June, he suffered another wheezing attack and had one puff of fenoterol (Berotec) inhalation for symptoms relief at home; however, his dyspnoea worsened. He was sent to the hospital again, and this time, received intubation due to acute respiratory failure. The patient was extubated and discharged in early July after a good recovery. A similar event also happened once in early August, but he did not receive invasive mechanical ventilation therapy because it presented as a milder clinical condition. The patient reported that he had had one puff of fenoterol (Berotec) inhalation before wheezing worsened.

He was admitted to one regional hospital in Kaohsiung in early September 2013 due to acute respiratory failure. Common cold-associated symptoms, such as productive
cough and dyspnoea, were noted for one week before he was sent to the hospital. On the same day, he was admitted to the hospital, and dyspnoea with a wheezing breathing sound developed in the morning. He received one puff inhalation of fenoterol (Berotec) at home, yet dyspnoea was aggravated instead of being relieved. He was sent to the hospital by ambulance, and intubation was performed immediately after his arrival at the emergency room due to his poor respiratory pattern. After 30 min of intubation, he was extubated as his clinical condition improved. Upon going to our pulmonology outpatient department for further evaluation, the chest X-ray showed no obvious lung lesion. The blood eosinophil count was 354/μL and the IgE level was 564 IU/mL. We noticed he had a prior intubation episode mentioned above due to acute respiratory failure in late June 2013. Coincidentally, one puff of fenoterol (Berotec) had been inhaled by the gentleman before each intubation episode, according to his statements.

Tracing back his medical records, his occupation was an office worker in a factory (screw manufacturer) and was rarely exposed to the raw materials. He had been diagnosed as having DM for more than two decades and was under regular follow-ups at the outpatient department of family medicine at National Cheng Kung University Hospital (NCKUH). He took metformin, vildagliptin, and glimepiride for DM control. As for his asthma history, he was diagnosed as having asthma when he was 40 years old at a regional hospital in Kaohsiung. However, there is no known asthma history for any of his family members. Fluticasone/salmeterol has been prescribed as the controller since the asthma was diagnosed and it was well tolerated. The asthma was under good control since hardly did he have acute exacerbation, as he reported. Although fenoterol (Berotec) had been prescribed for wheezing control in the prior decade, not until the June 2013 event did he receive inhaled fenoterol (Berotec) therapy for a wheezing attack.

Considering his clinical presentations, paradoxical bronchospasm was suspected. We reported this case and made bronchodilator adjustments at our pulmonology clinic later. After discussing with the patient, bronchodilator (fenoterol) test was performed in mid-September of 2013 under close monitoring and informed consent, which reported negative impact on both forced expiratory volume in 1 sec (FEV1) and forced vital capacity (FVC) (Fig. 1). He previously had fluticasone/salmeterol (Seretide® Accuhaler, GSK, Taiwan) as the controller for asthma treatment. The controller was switched to fluticasone/vilanterol (Relvar 92/22®, GSK, Taiwan), and umeclidinium (Incruse®, GSK, Taiwan) was added consecutively. Symbicort®, Astrazeneca, Taiwan, as the reliever, was administered once and no paradoxical bronchospasm event developed. He is now under regular outpatient department follow-up at NCKUH.
Discussion

Paradoxical bronchospasm is defined as the sudden onset of an unanticipated contraction of smooth muscle in the walls of the bronchi occurring soon after the administration of an aerosolized bronchodilator. Rare, but not isolated, transient reductions of FEV₁ have been observed in previously healthy subjects after inhalation in two phase I trials [4].

Several mechanisms have been proposed to account for the paradoxical bronchoconstriction observed with beta 2-agonist metered-dose inhaler (MDI), including an IgE-mediated reaction to excipients in the MDI (e.g. soya bean lecithin) [5], as well as secondary irritation to propellants, preservatives, or turbulence of airflow due to inappropriate inhaler technique [6]. Hypotheses have been proposed to account for the paradoxical bronchospasm that has occurred with nebulized beta 2-agonists, including bronchial irritation caused by the hyper-/hypo-osmolality and acidity [7] of the solution as well as preservatives (e.g. sodium metabisulphite, benzalkonium chloride, and ethylenediaminetetraacetic acid (EDTA)) [8,9] (Table 1). Zhong et al. demonstrated a case that did not induce paradoxical bronchospasm from the same inhaler by removing the preservatives [11]. Moreover, the same major content with different excipients or preservatives led to a different impact on FEV₁ [10,13]. Several previous retrospective studies have revealed that the statistical incidence of paradoxical bronchospasm was <1%.

We reviewed the literature concerning paradoxical bronchospasm, the published case reports of which are shown in Table 1 and the prevalence of paradoxical bronchospasm for SABA, LABA, and long-acting muscarinic antagonist (LAMA) are listed in Table 2. We reviewed the literature on the PubMed®, using “paradoxical bronchospasm/bronchoconstriction” as the key word and 63 results were searched. The results narrowed down to 18 if we add “case report” as the key word. The literature was limited to studies that have open access to the full text and in English (or English translations), which resulted in

Table 1. Cases of paradoxical bronchospasm from 1986 to 2018.

| Reference                     | Number of cases/Age and Sex or details | Diagnosis     | Medication          | Possible aetiology      | Final medication |
|-------------------------------|----------------------------------------|---------------|---------------------|-------------------------|-----------------|
| Magee and Pittman, 2018 [10]  | 1/25 M                                 | Asthma        | Albuterol           | Excipient               | Ipratropium     |
| George et al., 2017 [8]       | 1/17 F                                 | Asthma        | Albuterol           | BAC                     | Levabuterol/BAC free |
| Zhong et al., 2014 [11]       | 1/68 F                                 | Asthma        | Salbutamol         | Enantiomer              | Not mentioned   |
| Broski and Amundson, 2008 [12]| 1/36 M                                 | Asthma        | Levalbuterol        | At least not HFA        | Salmeterol and fluticasone |
| Spooner and Olin, 2005 [13]   | 1/92 M                                 | COPD          | Albuterol           | Not mentioned           | Not mentioned   |
| Mutlu et al., 2000 [9]        | 1/22 F                                 | Asthma        | Albuterol/metaproterenol | EDTA                   | ICS, theophylline |
| Facchini et al., 1996 [18]    | 1/age not reported F                   | Asthma        | Not mentioned       | Soya-derived excipients | Not mentioned   |
| Jorup et al., 2014 [4]        | 5/3 COPD and 2 healthy                 | COPD/healthy  | COPD/healthy FEV₁↓  | LAMA AZD9164            | Not mentioned   |
| O’Callaghan et al., 1986 [7]  | 17/Infants                             | Wheezing/asthma | Salbutamol         | High osmolality and acidity | Not mentioned   |

BAC, benzalkonium chloride; COPD, chronic obstructive pulmonary disease; EDTA, ethylenediaminetetraacetic acid; FEV₁, forced expiratory volume in 1 sec; HFA, hydrofluoroalkane; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist.

Table 2. Prevalence of paradoxical bronchospasm for SABA, LABA, and LAMA.

| Medication          | Prevalence (%) | Reference |
|---------------------|----------------|-----------|
| Albuterol/salbutamol| 1–8            | 14, 15    |
| Salmeterol (Seretide Eviholer) | <0.01 | 16 |
| Tiotropium          | <1             | 17 |

LABA, long-acting beta2 agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta2 agonist.
exclusion of 4 studies. The time of publication is not limited. Eight studies were excluded because the broncho-
spasm is not bronchodilator-induced. The phenomenon
was more prevalent in asthma subjects than in those with
chronic obstructive pulmonary disease (COPD), indicating
that asthma sufferers might be more susceptible to the
development of paradoxical bronchospasm. Within the six
reported paradoxical bronchospasm cases, four patients
were using albuterol, while the other two cases were using
salbutamol. The speculated aetiology of paradoxical bron-
chospasm varied, including excipient, preservatives (benz-
alkonium chloride), and enantiomer.

In this brief study, we presented a case with a rarely
seen adverse effect after fenoterol inhalation. Paradoxical
bronchospasm is one of the adverse effect listed on the
package insert of fenoterol (Berotec®) but it is rarely
reported. Bronchodilator test using fenoterol as the bron-
chodiater was performed on this patient and showed
reductions of FEV₁ and FVC, compatible with the
fenoterol-induced paradoxical bronchospasm. It is crucial
that clinicians are aware of this unexpected adverse event
to provide prompt monitoring of patients to improve
outcomes.

Disclosed Statement

Appropriate written informed consent was obtained for
publication of this case report and accompanying images.

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References

1. Sorkness CA. 2009. Beta-adrenergic agonists. Pp. 1485–
1503 in N. F. Adkinson, B. S. Bochner, W. W. Busse, et al.,
eds. Middleton’s allergy: principles and practice, 7th ed.
Mosby, Philadelphia, PA, USA.
2. Johnson M. 2001. Beta 2-adrenoceptors: mechanisms of
action of beta2-agonists. Paediatr. Respir. Rev. 2:57.
3. Johnson M. 2006. Molecular mechanisms of beta 2-
adrenergic receptor function, response, and regulation.
J. Allergy Clin. Immunol. 117:18.
4. Jorup C, Bengtsson T, and Strandgården K. 2014. Transient
paradoxical bronchospasm associated with inhalation of the
LAMA AZD9164: analysis of two phase I, randomised, double-
blind, placebo-controlled studies. BMC Pulm. Med. 14:52.
5. Facchini G, Antonicelli L, Cinti B, et al. 1996. Paradoxical
bronchospasm and cutaneous rash after metered-dose
inhaled bronchodilators. Monaldi Arch. Chest Dis. 51:
201–203.
6. Nicklas RA. 1990. Paradoxical bronchospasm associated
with the use of inhaled beta agonists. J. Allergy Clin. Immunol.
85:959–964.
7. O’Callaghan C, Milner AD, and Swarbrick A. 1986. Parado-
xical deterioration in lung function after nebulized sal-
butamol in wheezy infants. Lancet 2(8521–22):1424–1425.
8. George M, Joshi SV, and Concepcion E. 2017. Paradoxical
bronchospasm from benzalkonium chloride (BAC) preser-
native in albuterol nebulizer solution in a patient with acute
severe asthma. A case report and literature review of airway
effects of BAC. Respir. Med. Case Rep. 6(21):39–41.
9. Mutlu GM, Moonjelly E, Chan L, et al. 2000. Laryngospasm
and paradoxical bronchoconstriction after repeated doses of
beta 2-agonists containing edetate disodium. Mayo Clin.
Proc. 75:285–287.
10. Magee JS, and Pittman LM. 2018. Paradoxical broncho-
constriction with short-acting beta agonist. Am. J. Case Rep.
19:1204–1207.
11. Zhong G, Shen NY, and Sammut J. 2014. Nebulised sal-
butamol challenge confirming life-threatening paradoxical
bronchospasm. Emerg. Med. Australas. 26(2):202–203.
12. Broski SE, and Amundson DE. 2008. Paradoxical response
to levalbuterol. J. Am. Osteopath. Assoc. 108(4):211–213.
13. Spooner LM, and Olin JL. 2005. Paradoxical broncho-
constriction with albuterol administered by metered-dose
inhaled and nebulizer solution. Ann. Pharmacother. 39(11):
1924–1927.
14. DailyMed. 2009. Albuterol sulfate inhalation solution,
0.083% 2.5 mg*/3 ml. Nephron Pharmaceuticals Corpora-
tion, Orlando, FL, USA. Available at: https://dailymed.nlm.
nih.gov/dailymed/drugInfo.cfm?setid=574824f3-51cc-4b94-
9c10-e3204d819f8. Accessed on March 01, 2019.
15. Shaheen MZ, Ayres JG, and Benincasa C. 1994. Incidence of
acute decreases in peak expiratory flow following the use of
metered-dose inhalers in asthmatic patients. Eur. Respir. J. 7:
2160–2164.
16. Perrio MJ, Wilton LV, and Shakir SA. 2007. A modified
prescription-event monitoring study to assess the introduc-
tion of Seretide Evohaler in England: an example of study-
ing risk monitoring in pharmacovigilance. Drug Saf. 30(8):
681–695.
17. Hodder R, Pavia D, Lee A, et al. 2011. Lack of paradoxical
bronchoconstriction after administration of tiotropium via
Respimat® Soft Mist™ Inhaler in COPD. Int. J. Chron.
Obstruct. Pulmon. Dis. 6:245–251.
18. Facchini G, Antonicelli L, and Cinti B. Paradoxical broncho-
spasms and cutaneous rash after metered-dose inhaled bron-
chodilators. Monaldi. Arch. Chest. Dis. 1996;51(3):201–203.