Annals of Case Reports
Zhang Y, et al. Ann Case Rep: 8: 101500
www.doi.org/10.29011/2574-7754.101500
www.gavinpublishers.com

Case Report

A Case Study of an Adverse Reaction to Inhaled Terbutaline-Causing Tremor in Both Hands

Yuexin Zhang[1], Zhen Zhang[2], Honggang Ma[1*]

[1]Department of Clinical Laboratory, Shenyang Children's Hospital, Liaoning Provincial Children's Hospital, Liaoning Province, China.

[2]School of Pharmacy, China Medical University, Liaoning Province, China.

[*]**Corresponding author:** Honggang Ma, Department of Clinical Laboratory, Shenyang Children's Hospital, Liaoning Provincial Children's Hospital, Liaoning Province, China.

Citation: Zhang Y, Zhang Z, Ma H (2023) A Case Study of an Adverse Reaction to Inhaled Terbutaline-Causing Tremor in Both Hands. Ann Case Report 08: 1500. DOI: 10.29011/2574-7754.101500.

Received Date: 31 October 2023; **Accepted Date:** 03 November2023; **Published Date:** 06 November 2023

Introduction

Terbutaline is a β2-adrenergic agonist, which has strong and fast diastolic flat bronchial smooth muscle, enhances ciliary movement to clear respiratory tract secretions, and also reduces microvascular exudation, regulates the release of inflammatory mediators from mast cells and eosinophils [1]. It can also reduce microvascular exudation and regulate the release of inflammatory mediators from mast cells and eosinophils, thus having anti-inflammatory and anti-airway hyperreactivity effects [2]. It is a commonly used drug to relieve symptoms of dyspnoea in acute exacerbation of COPD, and its adverse effects include muscle tremor (usually hand tremor), headache, and diaphoresis [3], tachycardia, hypokalaemia, abnormal behaviour, etc. [4,5]. This paper discusses and analyses the case of inhalation of terbutaline resulting in tremor of both hands.

Summary of medical history

A patient surnamed Tang, male, 71 years old, 170 cm tall, 70 kg weight, BMI 24.22kg/m2, was admitted to hospital due to "cough, phlegm and shortness of breath aggravated for 1 day". The patient complained of asthma at a young age, and then self-alleviated. In 2017, there was no obvious incentive to cough, cough a small amount of white mucus sputum, aggravated in the morning, obvious in winter and spring, accompanied by shortness of breath and discomfort, obvious after activities. In the past hospitalization diagnosis, "acute aggravation of chronic obstructive pulmonary disease" was considered, and symptoms were relieved after symptomatic support treatment. On March 13, 2023, there was no obvious cause for coughing again, coughing an equal amount of yellow and white pus sputum, obvious in the morning, accompanied by chest tightness and shortness of breath, obvious after exercise, no fever, no headache, chest pain, no hemoptysis, night sweats, abdominal pain, diarrhea and other special discomfort. For further diagnosis and treatment, he came to our respiratory department. Since the onset of the illness, good spirit, poor food and sleep, normal bowel and urine, no significant weight gain. He had a history of "hypertension" for more than 20 years, and his symptoms could be controlled. He had a history of "coronary heart disease" for more than 3 years, and was not given special treatment. Deny "diabetes"; Denial of "hepatitis" and other infectious history. No history of trauma, blood transfusion, food or drug allergy. The patient had a history of smoking (20 cigarettes/day, 35 years), no history of alcohol consumption, and no history of dust exposure.

Physical examination: T: 36.7°C, P: 97 beats/min, R:21 beats/min, BP: 125/74 MMHG, clear mind, no cyanosis of lips, barrel-like chest, increased respiratory movement of both lungs, weak tongue tremble, silent percussion, a few wet rales wheezing in both lungs, no pleural rubs. The heart rate was 109 beats/min, the rhythm was normal, the heart sound was good, there was no murmur or pericardial rub, the abdomen was soft, there was no tenderness or rebound, and there was mild edema of the lower limbs.

Auxiliary examination: (Emergency department of our hospital on March. 13, 2023)

1. Blood routine: white blood cell count 14.46 × 109/L; The ratio of neutrophils was 75.2%. Neutrophil count 10.87X10^9/L; Lymphocyte count 0.28 × 109/L;
2. Blood gas: pH 7.443; The partial pressure of carbon dioxide was 40.3 mmHg; Partial pressure of oxygen was 97.8 mmHg; The oxygen saturation was 96.8%.

3. Electrocardiogram showed sinus tachycardia with right axis deviation.
4. Chest CT: 1. Chronic bronchitis and emphysema were considered. 2. Old lesions in bilateral upper lobes; Blood biochemistry, coagulation function, 2019-COVID nucleic acid test: negative.

Admission diagnosis: 1. Chronic obstructive pulmonary disease with acute lower respiratory tract infection 2. Bronchial asthma 3. Hypertension grade III 4. Coronary atherosclerotic heart disease (1. Angina pectoris 2. The heart function was grade II)

Discharge diagnosis: 1. Chronic obstructive pulmonary disease with acute lower respiratory tract infection 2. Bronchial asthma 3. Hypertension grade III 4. Coronary atherosclerotic heart disease (1. Angina pectoris 2. The heart function was grade II) 5. Fatty liver 6. Hyperlipidemia 7. Renal cysts 8. Bilateral kidney stones

Treatment

On the 1st day of admission, the patient was initially diagnosed with acute exacerbation of Chronic Obstructive Pulmonary disease (COPD), and three major routine tests, blood biochemistry, electrocardiogram, sputum bacteriology, procalcitonin, C-reactive protein, tuberculosis antibody, blood gases, and immunoglobulin lgE were perfected, and he was immediately given transnasal catheter oxygen therapy, and was empirically treated with Levofloxacin Sodium Chloride Injection (0.5 g iv gtt qd) to fight infections, 0.9% Sodium Chloride Injection 50ml + sodium methylprednisolone succinate for injection (40 mg iv gtt qd) anti-airway inflammation, 5% glucose injection 100ml + doxophylline injection 0.3g relaxes the smooth muscle of the airway, antispasmodic and asthma symptomatic supportive treatment. 100% glucose injection 100ml + bromhexine 4mg for injection, and acetylcysteine (0.2 g po tid), phlegm fever clearing capsules (1.2 g po tid) to reduce phlegm and stop the symptoms of the disease. g po tid) to reduce phlegm and relieve cough, (11:43 pm) to be given terbutaline sulphate nebulised inhalation solution 5mg + beclomethasone propionate suspension for inhalation (2ml nebulised inhalation bid) to dilate the bronchial tubes to alleviate the symptoms of dyspnoea. Dyspnoea was relieved by bronchodilatation. At 10:00 a.m. on the fourth day of admission, the patient was given terbutaline sulphate nebulised inhalation solution 5 mg + beclomethasone propionate suspension (2 ml nebulised inhalation bid) for bronchodilation and relief of respiratory symptoms. At 10:00 a.m. on the fourth day of admission, the patient was given terbutaline sulphate 5mg solution for nebulised inhalation and beclomethasone propionate 2ml suspension for inhalation (2ml for nebulised inhalation bid). At 17:10 pm, after nebulisation again, tremor in both hands appeared, and the patient informed the physician, who, taking into account the patient's current condition, considered that there was a high likelihood of an adverse reaction to the medication, and discontinued it. On the fifth day (17 March 2022), at 9 a.m., the patient's hands trembled again after nebulisation. On the fifth day (17 March 2022), the patient complained of relief of tremor in both hands at 9:00 a.m., and was discharged from the hospital on 24 March without recurrence of tremor in both hands after stopping the medication.

Analysis and discussion

For this patient, the following points of analysis and discussion are highlighted:

Adverse drug reaction relevance evaluation

According to the national standards for the evaluation of the association of adverse drug reactions [6], the association of adverse reactions in this case was evaluated: (1) The patient on March 13, 2023 The patient started to use terbutaline sulfate solution for nebulized inhalation 5 mg + beclomethasone propionate suspension for inhalation (2 ml nebulized inhalation bid) on March 16th morning and 5:10 pm. After using terbutaline sulfate nebulized inhalation solution 5mg + beclomethasone propionate suspension for inhalation (2ml nebulized inhalation bid) at 10 am and 5:10 pm on March 16, both patients developed muscle problems in both upper limbs and hands. Both of them showed muscle tremor of upper limbs and hands, suggesting that there is a temporal correlation between drug use and the occurrence of adverse drug reactions; (2) terbutaline sulfate nebulized inhalation solution has a description of the effects on muscle tremor. (2) The instructions for terbutaline sulfate nebulized inhalation solution contain a description of muscle tremor, which is a known type of adverse reaction; (3) the patient stopped the terbutaline sulfate nebulized inhalation solution at 9:00 a.m. the next day. At 9:00 a.m. the next day after the patient stopped taking terbutaline sulfate nebulized inhalation solution, the symptoms of muscle tremor in both upper limbs and hands improved; (4) the patient did not use terbutaline sulfate nebulized inhalation solution again, and similar symptoms did not recur; (5) the patient's symptoms did not recur [5].

The patient has had hypertension for more than 20 years and has been taking amlodipine regularly to lower blood pressure, which is similar to the intravenous levofloxacin sodium chloride injection that was used after the patient was admitted to the hospital. The patient has been taking amlodipine regularly for more than 20 years to lower his blood pressure, and he was treated with levofloxacin sodium chloride injection and doxophylline injection, which were used intravenously after his admission to the hospital. However, the patient experienced hand tremor on both occasions while using the terbutaline sulfate nebulized inhalation solution group of medications, and the remaining

treatment regimen remained unchanged when the terbutaline sulfate nebulized inhalation solution group of medications was discontinued. When the remaining treatment program was unchanged, similar symptoms did not recur, and we can tentatively rule out levofloxacin, doxorubicin injection, and amlodipine tablets as the cause of these symptoms. Therefore, it is not clear whether such symptoms are due to the effects of the condition. In conclusion, it is considered that terbutaline sulfate solution for nebulized inhalation was the trigger for bilateral upper limb and hand muscle tremor. The association between the patient's adverse reaction of tremor of both upper limbs and hand muscles and terbutaline sulfate nebulized inhalation solution was evaluated as "probable".

Analysis of the possible causes of muscle tremor caused by terbutaline sulfate nebulized inhalation solution

Physiopathology: studies have shown that the incidence of adverse reactions caused by terbutaline sulfate nebulized inhalation solution in airflow obstruction patients in the fasting state is significantly higher than that of non-fasting patients, probably due to the increased sensitivity of the body to the reaction to the drug in fasting, on the one hand, it may be that the body's metabolism in the fasting state is weaker, and the outside world stimuli to give the body anawakening [7, 8]. The role of the stressor, which triggers a series of physiological changes; coupled with the patient's advanced age and poor physical condition, it is very easy to cause muscle tremor and other discomforts. Adverse drug reactions occur; confusion with changes in the disease itself increases the difficulty of diagnosis and treatment [9, 10].

Drugs: β2 agonists agonize receptors in slow contractile fibers of skeletal muscle, which ultimately leads to a decrease in intracytoplasmic calcium concentration, affecting the excitatory-contractile coupling of skeletal muscle, inhibiting contractile tone, and separating contractile fusion, resulting in muscle tremor, which is prevalent in the limbs, face, and neck [11]. Among the adverse effects of terbutaline, tremor, tonic spasms, and palpitations are attributed to sympathomimetic amines. Although terbutaline is a selective β2 agonist, it also excites β receptors in skeletal muscle and the heart, causing skeletal muscle tremor and increased heart rate. These adverse reactions are more likely to occur in patients with cardiovascular disease, hyperthyroidism, history of seizures, hepatic and renal insufficiency, and the elderly [12]. Patients have coronary atherosclerotic heart disease, which may also be an important factor in the occurrence of adverse reactions. Literature reports that terbutaline increases the probability of adverse reactions such as theophylline-induced tremor; the effect of terbutaline cannot be excluded in the case of tetrapanic tremor caused by doxophylline. The clinician and the clinical pharmacist analyzed and concluded that the patient had a tremor in both upper limbs and hand muscles at 10 a.m. on March 16 when he applied terbutaline sulfate solution 5 mg for nebulized inhalation and beclomethasone propionate suspension for inhalation (2 ml for nebulized inhalation bid). On March 16 at 5:00 p.m., tremor of both upper limbs and hand muscles reappeared after the use of this group of drugs, and it did not recur on March 17 after stopping the use of this group of drugs. Therefore, the tremor of both upper limbs and hand muscles was considered to be an adverse reaction caused by terbutaline sulfate solution for nebulized inhalation.

How to avoid the risk of tremor in patients using terbutaline

Some studies have shown that beta 2 agonist adverse effects are dose-related, with smaller starting doses being associated with fewer adverse effects. The instruction manual recommends that the adult dose of terbutaline be 5 mg per inhalation via a nebulizer, but the patient is an elderly person with cardiovascular disease, and the dose of terbutaline can be adjusted to a low dose of 2.5 mg for high-risk patients who may develop muscle tremor in clinical practice, and the combination of doxophylline and terbutaline increases the probability of adverse reactions of tremor, so the doxophylline injection should be used in conjunction with the nebulized solution of terbutaline, so it should be used as a starting dose [13]. When the nebulized solution is used in combination, the dosage of doxophylline should be adjusted appropriately according to the blood concentration, and the blood concentration of the drug should be controlled at 8.38 ± 2.19 μg/ml through the monitoring of doxophylline blood concentration to improve the therapeutic efficacy as well as to improve the safety of the combined use of the drug, and to minimize the occurrence of adverse reactions. It can also be replaced with nebulized canister mask inhalation to improve the safety of drug administration [14]. For patients with tremor of both hands, patients can be instructed to move their limbs slowly, perform limb massage, and avoid maintaining the same position for a long time. The use of β2 receptor desensitizers has been documented to reduce the incidence of adverse reactions. The clinical pharmacist analyzed the relevance of the drugs used and their adverse reactions, and suggested stopping the inhalation of terbutaline nebulizer and observing the changes in the condition if the tremor of the limbs did not decrease, then consider stopping the use of other drugs (such as doxophylline injections), which was adopted by the clinician. After stopping the inhalation of terbutaline nebulizer on March 17. The clinical pharmacist analyzed that the tremor in both upper extremities and hand muscles was probably caused by inhalation of terbutaline nebulizer and recommended discontinuing the drug. Therefore, the clinical pharmacist analyzed that the tremor in both upper limbs and hands was probably due to the inhalation of terbutaline nebulizer and recommended discontinuing the drug.

The choice of inhalant for this patient

The patient is a chronic obstructive pulmonary disease, bronchial asthma patients, inhaled glucocorticoids are the most effective drugs for the treatment of asthma, regardless of the severity of the disease, they are the first line of treatment for all patients with persistent disease, fluticasone propionate is a relatively new inhaled glucocorticoid, which has better efficacy on the lung function of patients with chronic stabilized bronchial asthma, and tiotropium bromide is a new long-acting anti-choline Tiotropium bromide is a new type of long-acting anticholinergic, and its bronchodilator effect is better than ipratropium bromide, which is currently used as the first-line drug for the treatment of COPD in the clinic, and has been recommended by the Global Initiative for the Prevention and Control of COPD as the basic drug for stable COPD [15,16]. The patient's lung function: severe mixed pulmonary ventilation dysfunction, and the doctor has given him budesofrine inhalation aerosol, which contains the β2 agonist formoterol, and if it is intolerable, the literature suggests that AZD3101 can be used [17]. The literature suggests the use of AZD3199 (inhaled ultra-long-acting β_2-adrenoceptor agonist), which has a higher safety profile than formoterol, with a very low incidence of adverse effects that may be related to its lower level of systemic side effects, as well as in combination with fluticasone propionate inhalation aerosol and tiotropium bromide powdered inhalation or with other glucocorticosteroid inhalers and M-receptor blocking agents [18]. Glucocorticoid inhalers inhibit the release of inflammatory mediators from the airway, suppressing the body's inflammatory response and improving airway function, and M receptor blockers reversibly inhibit M cholinergic receptors, causing smooth muscle relaxation [19, 20]. The M receptor blocker reversibly inhibits the M cholinergic receptor, causing smooth muscle relaxation. It greatly relieves the fatigue of bronchial smooth muscle, thus improving pulmonary ventilation [21, 22].

Conclusions

This patient was an elderly patient with chronic obstructive pulmonary disease with acute exacerbation combined with hypertension and coronary artery disease who had tremors in both hands caused by the use of terbutaline. In this case the clinical pharmacist utilized his knowledge of pharmacology and reviewed the relevant literature to report the adverse reaction in a timely manner. The occurrence of adverse drug reactions the occurrence of adverse drug reactions may be related to a number of factors (age, comorbidities, dosage, relevance of adverse reactions to different medications, etc.), and should be monitored with care when administering medications. As a member of the medical team, the clinical pharmacist should actively participate in the treatment of the patient, assist the physician to analyze and study the condition, actively consult the information, and participate in the adjustment of the medication regimen according to his or her own expertise. As a member of the medical team, the clinical pharmacist should actively participate in the treatment of the patient, assist the physician in analyzing and studying the condition, actively review the information, participate in the adjustment of the medication plan based on his/her professional knowledge, provide reference for the physician in the use of drugs, drug interactions, adverse reactions, etc., and guide the patient to rationally use drugs. They should contribute to the rational use of medication for patients, and give full play to their professional expertise in the field of pharmacy.

Disclosure

Author Contributions: methodology and software, Yuexin Zhang and Zhen Zhang; investigation and resources, Yuexin Zhang and Honggang Ma; data curation, Zhen Zhang; writing—original draft preparation, Yuexin Zhang and Zhen Zhang; writing—review and editing, Yuexin Zhang and Honggang Ma; supervision, Yuexin Zhang and Zhen Zhang.

Funding: This research received no external funding.

Institutional Review Board Statement: All experimental procedures were approved by the Human Research Ethics Committee of the Federal University of São Paulo and conformed to the principles outlined in the Declaration of Helsinki (approval number approval number 4.354.386). This study was guided by ethical standards and national and international laws. All athletes signed the consent form after receiving instructions regarding the possible risks and benefits and were granted privacy, confidentiality, and anonymity rights. The participants were free to stop participating any stage of the experiment without giving reasons for their decision.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: Data supporting the study results can be provided followed by request sent to the corresponding author's e-mail.

Acknowledgments: We thank all patients who took the time to contribute to this research

Conflicts of Interest: None.

References

1. 2006. Terbutaline. In Drugs and Lactation Database (LactMed(R)). Bethesda (MD). Number of.

2. Abd Elhaleem SM, Elsebaei F, Shalan S, Belal F (2023) Investigating the Effect of Silver Nanoparticles on the Fluorescence Intensity of Bambuterol and its Active Metabolite Terbutaline Using FRET. J Fluoresc 33:1717-25

3. Aboushady D, Hanafi RS, Parr MK (2022) Quality by design approach for enantioseparation of terbutaline and its sulfate conjugate metabolite for bioanalytical application using supercritical fluid chromatography. J Chromatogr A 1676: 463285

4. Adair E, Dibaba D, Fowke JH, Snider M (2022) The Impact of Terbutaline as Adjuvant Therapy in the Treatment of Severe Asthma in the Pediatric Emergency Department. Pediatr Emerg Care 38: e292-e4

5. Alotaibi NH, Sarwar M, Alamgeer, Jabbar Z, Munir MU, et al. (2022) Pharmacological exploration of anti-arthritic potential of terbutaline through in-vitro and in-vivo experimental models. Pak J Pharm Sci 35: 253-7

6. Bagwan NUS, Sheokand S, Kaur A, Dubey G, Puri V, et al. (2021) Role of surface molecular environment and amorphous content in moisture sorption behavior of milled Terbutaline Sulphate. Eur J Pharm Sci 161: 105782

7. Gross M, Iruretagoyena JI, Srinivasan S, Karnowski J, Adams J (2022) Terbutaline-triggered fetal arrhythmia prior to neonatal diagnosis of Wolff-Parkinson-White syndrome: A case report. Case Rep Womens Health 33: e00382

8. Khammy MM, Truong CKH, Wright CE, Angus JA (2020) The beta(2)-adrenoceptor agonist bronchodilators terbutaline and orciprenaline are also weak alpha(1)-adrenoceptor antagonists. Eur J Pharmacol 882: 173304.

9. Kittiarpornpon V, Siripattanapipong P, Bowornkitiwong W, Kitsommart R, Ngerncham S, et al. (2021) Association of Antenatal Terbutaline and Respiratory Support Requirements in Preterm Neonates. Am J Perinatol.

10. Li Y, Xu Z, Qing C, Zhang H, Wu X, Yang J (2021) Clinical efficacy of glucocorticoid and terbutaline in the treatment of acute exacerbation of chronic obstructive pulmonary disease. Am J Transl Res 13: 7029-34.

11. Loureiro JA, Andrade S, Ramalho MJ, Oliveira N, Pereira MC (2021) The interaction of a beta2 adrenoceptor agonist drug with biomimetic cell membrane models: The case of terbutaline sulphate. Life Sci 285:119992.

12. Luo Q, Peng X, Zhang H (2021) Effect of terbutaline plus doxofylline on chronic obstructive pulmonary disease. Am J Transl Res 13: 6959-65.

13. Ma CY, Nguyen TTH, Gajjar P, Styliari ID, Hammond RB, et al. (2023) Predicting the Strength of Cohesive and Adhesive Interparticle Interactions for Dry Powder Inhalation Blends of Terbutaline Sulfate with alpha-Lactose Monohydrate. Mol Pharm 20: 5019-31.

14. Maxa JL (2020) Serotonin Syndrome Following Terbutaline Administration in a Heart Transplant Patient on Multiple Inotropic Agents: A Case Report. Transplant Proc 52: 2817-9.

15. Barna T, Szucs KF, Schaffer A, Mirdamadi M, Hajagos-Toth J, et al. (2023) Combined uterorelaxant effect of magnesium sulfate and terbutaline: Studies on late pregnant rat uteri in vitro and in vivo. Acta Obstet Gynecol Scand 102: 457-64.

16. Carvajal Gonczi CM, Hajiaghayi M, Gholizadeh F, Xavier Soares MA, Touma F, et al. (2023) The beta2-adrenergic receptor agonist terbutaline upregulates T helper-17 cells in a protein kinase A-dependent manner. Hum Immunol 84: 515-24.

17. Chaoui M, Chevrel S, Perinel-Ragey S, Prevot N, Pourchez J (2022) Assessment of High-Power Electronic Nicotine Delivery System as an Alternative Aerosol Device for Terbutaline Delivery. Pharm Res 39: 587-97.

18. Chen Y, Du S, Zhang Z, He W, Lu E, et al. (2020) Compatible Stability and Aerosol Characteristics of Atrovent((R)) (Ipratropium Bromide) Mixed with Salbutamol Sulfate, Terbutaline Sulfate, Budesonide, and Acetylcysteine. Pharmaceutics 12: 776.

19. Duan X, Yang Y, Yang A, Zhao Y, Fan F, et al. (2022) Terbutaline attenuates LPS-induced injury of pulmonary microvascular endothelial cells by cAMP/Epac signaling. Drug Dev Res 83: 699-707.

20. Elkomy MH, El Menshawe SF, Kharshoum RM, Abdeltwab AM, Hussein RRS, et al. (2022) Innovative pulmonary targeting of terbutaline sulfate-laded novasomes for non-invasive tackling of asthma: statistical optimization and comparative in vitro/in vivo evaluation. Drug Deliv 29: 2058-71.

21. Ge Y, Liu P, Xu L, Qu M, Hao W, et al. (2022) A portable wireless intelligent electrochemical sensor based on layer-by-layer sandwiched nanohybrid for terbutaline in meat products. Food Chem 371: 131140.

22. Gogolashvili A, Chankvetadze L, Takaishvili N, Salgado A, Chankvetadze B (2020) Separation of terbutaline enantiomers in capillary electrophoresis with neutral cyclodextrin-type chiral selectors and investigation of the structure of selector-selectand complexes using nuclear magnetic resonance spectroscopy. Electrophoresis 41: 1023-30.