Received: 28 February 2024 | Revised: 3 June 2024 | Accepted: 23 June 2024

DOI: 10.1002/ccr3.9137

CASE REPORT

Clinical Case Reports Open Access WILEY

A severe tremor caused by a beta2 agonist in a patient with asthma-chronic obstructive pulmonary disease overlap

Kota Nakajima[1,2] | **Kenji Momo**[2]

[1]Department of Pharmacy, Izumi Memorial Hospital, Tokyo, Japan

[2]Department of Hospital Pharmaceutics, School of Pharmacy, Showa University, Tokyo, Japan

Correspondence
Kenji Momo, Department of Hospital Pharmaceutics, School of Pharmacy, Showa University, Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142-8555, Japan.
Email: k.momo@pharm.showa-u.ac.jp

Key Clinical Message

A 46-year-old male developed respiratory distress due to asthma-chronic obstructive pulmonary disease overlap and experienced severe tremor caused by beta2 agonist inhalant. We present our successful experience with tizanidine administration.

KEYWORDS

asthma-chronic obstructive pulmonary disease overlap, tizanidine, tremor, β2 agonist

1 | INTRODUCTION

Beta2 agonists are widely used bronchodilators to treat bronchial asthma and chronic obstructive pulmonary disease (COPD). Patients can select from among several options, such as inhaled formulations or transdermal or oral drugs, depending on their lifestyle. Inhalers are primarily used because they are less likely to induce side effects, given the administration of lower doses than those taken orally[1] and their efficacy in preventing attacks. Nevertheless, some patients using inhalation beta2 agonists develop palpitations (0.4%), headaches (2.5%), or tremors (6.4%).[2] In most cases, these side effects are transient and not severe and may thus get easily overlooked by medical staff.[3–5] Therefore, it is important to obtain detailed knowledge regarding symptoms experienced by patients taking beta2 agonists and their management to improve the quality of life for these patients.

Here, we report a case of a male subject with asthma-COPD overlap (ACO) who developed severe and persistent tremors.

2 | CASE HISTORY

The patient was a 46-year-old Japanese male (height: 172 cm, weight: 51.0 kg) with no history of smoking and allergy. An interview conducted during hospitalization confirmed a history of bronchial asthma and bronchiectasis for at least several years. Bronchial asthma was managed with once-daily inhaled vilanterol 25 μg/fluticasone furoate 200 μg, one inhalation at a time. The patient was unable to provide a history of childhood asthma. The patient did not show any neurological findings suggestive of sensory disturbance or anxiety. Additionally, the patient had no history of thyroid disease. Liver function markers (aspartate aminotransferase, alanine aminotransferase, and total bilirubin) and kidney function markers (serum creatinine and blood urea nitrogen) were within normal range. The patient had no history of regular alcohol consumption. In February 2021, he underwent a medical examination at a general practitioner's clinic owing to respiratory distress. His symptoms were under control after administering 20 mg oral prednisolone for 7 days, along with tiotropium/olodaterol (5/5 μg) once daily via

an inhaler. On March 31, he was emergently brought to Izumi Memorial Hospital following the recurrence of respiratory distress.

3 | METHODS

A diagnosis of ACO was reached, and following the recommendations of the "Asthma Prevention and Management Guidelines 2021",[6] we administered steroid injections for treatment in the emergency outpatient department (Figure 1). However, the patient was hospitalized owing to symptom persistence, and the date of hospitalization was set as day 1. Although the acute phase was subsequently subdued, the patient continued to experience respiratory distress. During hospitalization, oral steroids were administered and gradually tapered. The treatment plan shifted towards discharge, transitioning to inhaled steroids (salbutamol 2.5 mg and bromhexine 4 mg administered via nebulizer three times a day) according to our hospital's treatment protocol. Subsequently, the BGF inhaler (containing budesonide 160 μg, glycopyrronium 7.2 μg, and formoterol 4.8 μg per inhalation) was prescribed, with two inhalations administered twice daily. Laboratory test results, obtained 26 days before and 20 days after initiating the BGF inhaler, were as follows: O_2 saturation,

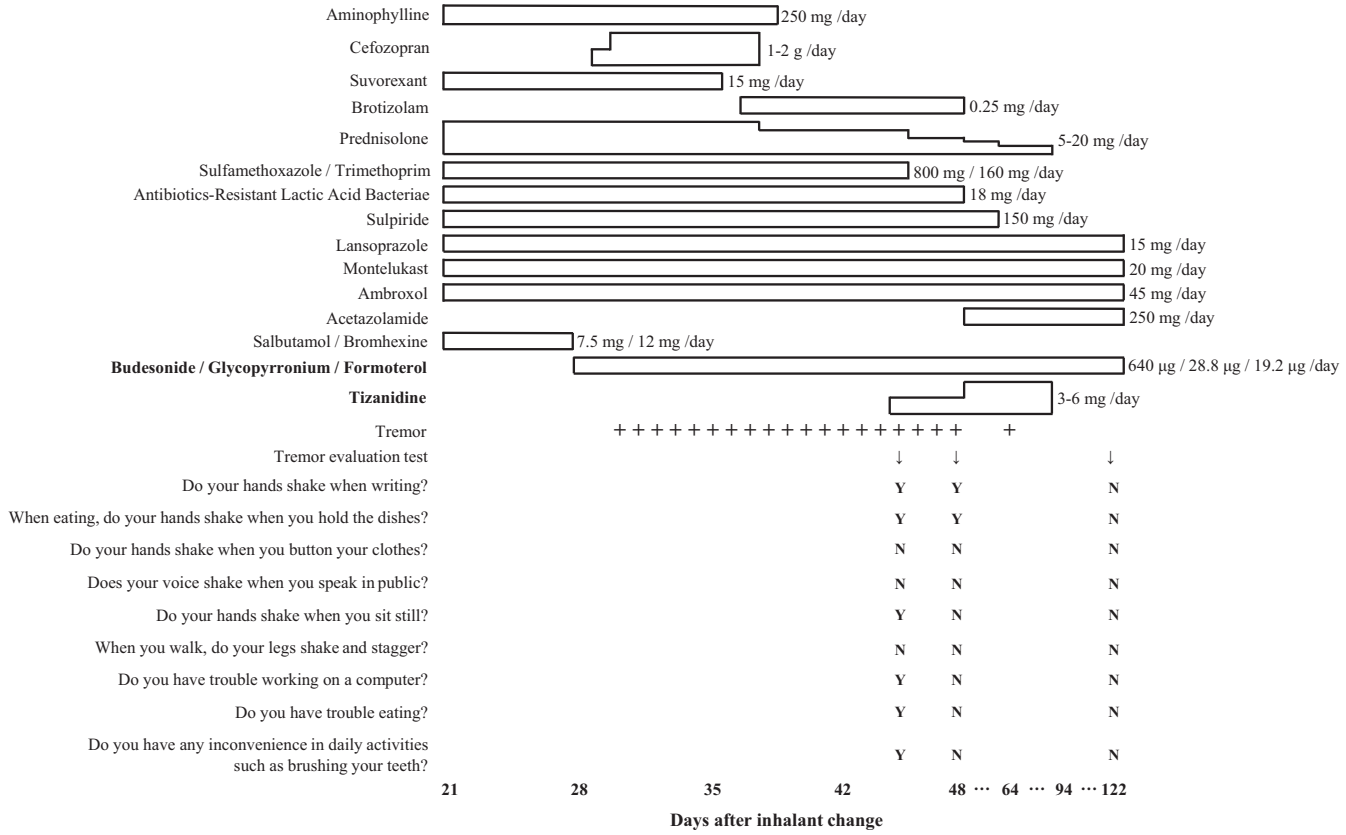

FIGURE 1 Clinical course of the present case.

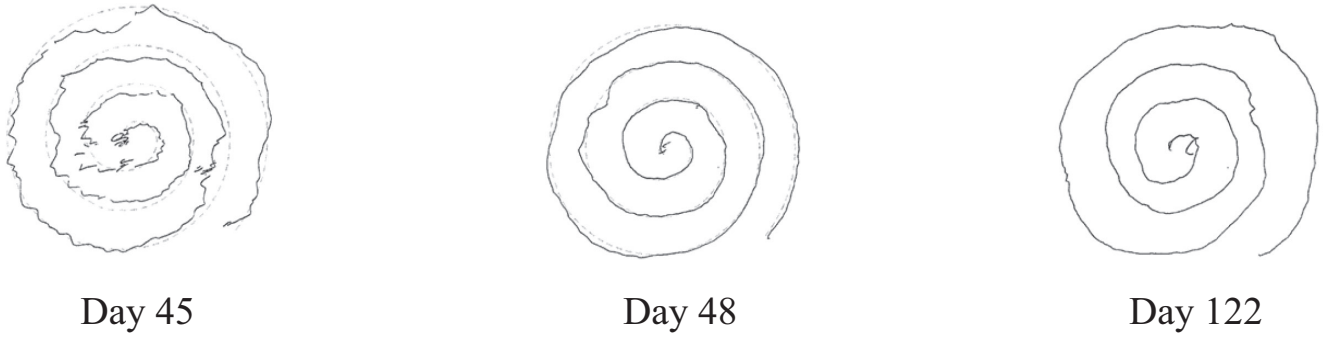

FIGURE 2 Eddy writing test result for tremor evaluation in the present case.

98.3% versus 97.6%; arterial blood gas pH, 7.399 versus 7.402; pCO_2, 51.9 versus 43.7 mmHg; pO_2, 120.4 versus 100.3 mmHg. Cefozopran was administered for infection treatment (positive sputum culture results). The patient developed tremors 2 days after initiating BGF inhaler use. The tremors commenced immediately after initiating inhalation medication and persisted throughout the day. Notably, symptoms worsened shortly after inhalation and then gradually decreased over time. Additionally, our patient did not exhibit tremors prior to initiating the inhalation medication and did not have any medical history related to tremors. As symptoms failed to improve by Day 38, we decided to continue monitoring tremors up to Day 45, given that beta2 agonist-induced tremors are transient and last for a maximum of 2 weeks. On Day 45, the tremors worsened, and the patient experienced difficulty in performing activities of daily living. For example, considerable shaking was observed during the Eddy writing test (Figure 2).[7] Therefore, tizanidine 3 mg/day was initiated after verbal consent was obtained for off-label use.

4 | CONCLUSION AND RESULTS

On Day 48, his writing test results improved, along with his performance in terms of completing activities of daily living (Figure 2). By Day 49, tremors had stopped affecting the patient while performing daily life activities. Hence, he was discharged with a prescription of tizanidine 6 mg/day. The patient visited our outpatient department on Day 94; tizanidine was discontinued on that day because his tremors had disappeared. A repeat Eddy writing testing conducted on Day 122, i.e., after tizanidine discontinuation, revealed no problems despite the continued use of the BGF inhaler.

5 | DISCUSSION

We describe a case in which persistent severe tremors were observed after the use of a beta2 agonist. We were eventually successful in controlling the tremors by administering tizanidine. Despite limited evidence supporting the use of tizanidine for tremors, we opted for its treatment owing to the following reasons: (1) alternative inhalation formulations could not be used owing to the patient's symptoms and treatment history, (2) the central alpha2 agonist mechanism of action of tizanidine is applicable in patients with bronchial asthma, and (3) the reported mechanism of tremors involves an imbalance between the contraction and relaxation of skeletal muscles.[5,8] Based on our literature review, we hypothesized that the patient's tremors were partially stimulated by beta2 receptors in muscle spindles, leading to an enhancement of physiological tremors.[5,8] Consequently, we decided that the administration of tizanidine represented a reasonable risk–benefit balance. Tizanidine has been shown to indirectly reduce muscle spindle sensitivity by inhibiting gamma motor neurons in the spinal cord.[9] In the current case, the potential pharmacological effect mediated by beta-agonists in terms of alleviating the indirect activation of muscle spindles may have contributed to tremor improvement.

The reported incidence of tremors associated with inhaled formoterol is approximately 6%, which is slightly higher than that associated with salmeterol.[10] Typically, tremors induced by beta2 agonists cease within a few weeks without intensive treatment.[4,5] Nonselective beta-blockers, commonly used for tremor treatment, are contraindicated in patients with bronchial asthma. Additionally, treatment options such as anxiolytics and antiepileptic drugs pose a higher risk in these patients owing to potential adverse effects.[11] In the current case, considering safety, we initiated tizanidine at the lower limit of the recommended dose, which is 3 mg/day. However, the dose was increased to 6 mg/day owing to insufficient effectiveness. The dose increase led to improvements, eventually allowing discontinuation from Day 93. Given the absence of previous reports on the use of tizanidine for tremors induced by inhalation medications with beta-stimulating effects, we selected a conservative strategy. Ultimately, the treatment was successful, and tizanidine exhibited good safety. Moreover, initiating tizanidine at 6 mg/day may not have posed a problem unless concomitantly administered with known cytochrome P450 (CYP) 1A2 inhibitors (as mentioned in the package insert). Additionally, tizanidine was administered from Day 45 to 93, and improvement in symptoms was confirmed on Day 94. Therefore, we deemed further administration unnecessary and discontinued tizanidine. To assess the recurrence of tremors after stopping tizanidine, we conducted a spiral writing test on Day 122. Considering the half-life of tizanidine is ~1.5 h,[12] we believe that the effects of tizanidine completely disappeared by Day 122, which was 29 days after drug discontinuation, and there was no recurrence of symptoms. Therefore, we did not conduct further evaluations in the current case.

Despite inhalation formulations generally being administered at lower doses than nebulizer formulations, it is debatable why tremors develop after switching to inhalers. Tremors could be attributed to drug-induced parkinsonism due to sulpiride.[13] However, characteristic symptoms of drug-induced parkinsonism, such as mask-like facies or difficulty in walking,[14] were not observed during sulpiride administration in this case. Therefore, although the tremors observed in the current case are likely attributable to the inhaled medication, the contribution of

sulpiride cannot be completely overlooked. One explanation could be the patients' poor self-administration techniques with nebulizers. However, pharmacists provided instructions on the inhalation technique when the patient started using the inhaler. Other potential reasons for severe tremors include the initiation of anticholinergics and steroids upon hospitalization.

The limitations of the current case report need to be addressed. First, evidence supporting the use of tizanidine administration for tremor control was not identified in our literature survey. Second, considering the method of tremor measurement, we did not apply objective evaluation scales and rigorously measure tremors.

In conclusion, our case highlights the benefits of administering tizanidine. However, it is essential to note that tizanidine is metabolized solely by the drug-metabolizing CYP1A2 enzyme, posing a potential risk for severe drug–drug interactions, especially in polypharmacy patients.[12,15–19] The use of tizanidine for the management of tremors requires further investigation and careful consideration. We have previously reported a case demonstrating severe symptoms resulting from the combination of tizanidine[16,17] and a CYP1A2 inhibitor. As tizanidine is predominantly metabolized by CYP1A2,[20] it is crucial to avoid administering tizanidine to patients concurrently taking drugs with CYP1A2 inhibitory effects. On the other hand, we underscore the challenges associated with the management of severe tremors when limited alternative treatment options are available.

AUTHOR CONTRIBUTIONS

Kota Nakajima: Conceptualization; data curation; visualization; writing – original draft; writing – review and editing. **Kenji Momo:** Conceptualization; project administration; visualization; writing – original draft; writing – review and editing.

ACKNOWLEDGMENTS

None.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

The Department of Hospital Pharmaceutics received a contracted research fee for other research from Ono. KM received honorarium fees for presentations from Abbvie, Eisai, Sawai, and Nippon-Kayaku and received travel fee from Abbvie to participate in a conference held by them. The Department of Hospital Pharmaceutics, School of Pharmacy, Showa University received research grants from Nippon-Kayaku, Ono, Shionogi, Daiichi Sankyo, Eisai, Mochida, and Taiho.

DATA AVAILABILITY STATEMENT

All information pertaining to this case is included in this published article.

ETHICS STATEMENT

None.

CONSENT

We obtained written informed consent from the patient for publication of this report.

ORCID

Kenji Momo https://orcid.org/0000-0001-9856-0097

REFERENCES

1. Faulds D, Hollingshead LM, Goa KL. Formoterol. A review of its pharmacological properties and therapeutic potential in reversible obstructive airways disease. *Drugs*. 1991;42(1):115-137. doi:10.2165/00003495-199142010-00007
2. Schultze-Werninghaus G. Multicenter 1-year trial on formoterol, a new long-acting beta 2-agonist, in chronic obstructive airway disease. *Lung*. 1990;168:83-89. doi:10.1007/BF02718118
3. Bartow RA, Brogden RN. Formoterol. An update of its pharmacological properties and therapeutic efficacy in the management of asthma. *Drugs*. 1998;55(2):303-322. doi:10.2165/00003495-199855020-00016
4. Bengtsson B. Plasma concentration and side-effects of terbutaline. *Eur J Respir Dis Suppl*. 1984;134:231-235.
5. Cazzola M, Matera MG. Tremor and β(2)-adrenergic agents: is it a real clinical problem? *Pulm Pharmacol Ther*. 2012;25(1):4-10. doi:10.1016/j.pupt.2011.12.004
6. Japanese Society of Allergology. *Asthma Prevention and Management Guidelines 2021*. Japanese Society of Allergology; 2021.
7. Japanese Society of Neurological Therapeutics. Standard neurotherapy: essential tremor. *Shinkei Chiryogaku*. 2011;28(3):295-325. Hyoujunteki shinkei chiryo: hontaisei shinsen (in Japanese).
8. Waldeck B. Beta-adrenoceptor agonists and asthma—100 years of development. *Eur J Pharmacol*. 2002;445(1–2):1-12. doi:10.1016/s0014-2999(02)01728-4
9. Ono H, Matsumoto K, Kato K, et al. Effects of tizanidine, a centrally acting muscle relaxant, on motor systems. *Gen Pharmacol*. 1986;17(2):137-142. doi:10.1016/0306-3623(86)90130-8
10. Stålenheim G, Wegener T, Grettve L, et al. Efficacy and tolerance of a 12-week treatment with inhaled formoterol in patients with reversible obstructive lung disease. *Respiration*. 1994;61(6):305-309. doi:10.1159/000196360
11. Zesiewicz TA, Elble R, Louis ED, et al. Practice parameter: therapies for essential tremor: report of the quality standards Subcommittee of the American Academy of Neurology. *Neurology*. 2005;64(12):2008-2020. doi:10.1212/01.WNL.0000163769.28552.CD
12. Momo K, Homma M, Osaka Y, Inomata S, Tanaka M, Kohda Y. Effects of mexiletine, a CYP1A2 inhibitor, on tizanidine pharmacokinetics and pharmacodynamics. *J Clin Pharmacol*. 2010;50(3):331-337. doi:10.1177/0091270009341961

13. Tarsy D. Neuroleptic-induced extrapyramidal reactions: classification, description, and diagnosis. *Clin Neuropharmacol*. 1983;6(Suppl 1):S9-S26.
14. Hayes MT. Parkinson's disease and parkinsonism. *Am J Med*. 2019;132(7):802-807. doi:10.1016/j.amjmed.2019.03.001
15. Momo K, Doki K, Hosono H, Homma M, Kohda Y. Drug interaction of tizanidine and fluvoxamine. *Clin Pharmacol Ther*. 2004;76(5):509-510. doi:10.1016/j.clpt.2004.08.003
16. Momo K, Homma M, Kohda Y, Ohkoshi N, Yoshizawa T, Tamaoka A. Drug interaction of tizanidine and ciprofloxacin: case report. *Clin Pharmacol Ther*. 2006;80(6):717-719. doi:10.1016/j.clpt.2006.08.017
17. Momo K, Homma M, Abei M, Hyodo I, Kohda Y. Tizanidine-induced hypotension in patients with liver cirrhosis. *Eur J Clin Pharmacol*. 2008;64(6):647-648. doi:10.1007/s00228-008-0469-7
18. Momo K, Homma M, Matsumoto S, Sasaki T, Kohda Y. Clinical survey of tizanidine-induced adverse effects—impact of concomitant drugs providing cytochrome P450 1A2 modification. *Yakugaku Zasshi*. 2013;133(2):275-281. doi:10.1248/yakushi.12-00222
19. Momo K, Homma M, Kohda Y. Lower metabolic clearance of tizanidine in Japanese subjects. *Int J Clin Pharmacol Ther*. 2013;51(12):986-988. doi:10.5414/CP201964
20. Granfors MT, Backman JT, Laitila J, Neuvonen PJ. Tizanidine is mainly metabolized by cytochrome p450 1A2 in vitro. *Br J Clin Pharmacol*. 2004;57(3):349-353. doi:10.1046/j.1365-2125.2003.02028.x

How to cite this article: Nakajima K, Momo K. A severe tremor caused by a beta2 agonist in a patient with asthma-chronic obstructive pulmonary disease overlap. *Clin Case Rep*. 2024;12:e9137. doi:10.1002/ccr3.9137