International Medical Case Reports Journal

Dovepress
Taylor & Francis Group

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CASE REPORT

Urticaria-Like Hypersensitivity Reaction Following Botulinum Toxin Injection: A Case Report of Possible Interaction with β-Lactam Antibiotics

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Abstract: Botulinum toxin serotype A (BTX-A) is commonly used for treating facial dynamic wrinkles. The clinical safety of BTX-A has been proven, and it has few side effects; despite this, BTX-A has the potential to cause an allergic reaction. This case raises concerns about a possible interaction between botulinum toxin serotype A (CBTX-A) and β-lactam antibiotics, contributing to the limited literature on hypersensitivity reactions. Herein, we described the case of a 35-year-old woman who was injected with Chinese botulinum toxin serotype A (CBTX-A) to treat crow's feet. The treatment was performed after the patient had taken cefprozil for an upper respiratory tract infection. Subsequently, the patient developed urticaria-like symptoms that completely resolved within 24 hours after administration of antihistamines. This case emphasises the need for careful medication history review before botulinum toxin administration, especially in patients receiving β-lactam antibiotics, as hypersensitivity reactions may occur.

Keywords: botulinum toxin, β-lactam, hypersensitivity

Introduction

Botulinum toxin serotype A (BTX-A) has become the most popular non-surgical cosmetic treatment owing to its controllable side effects and satisfactory treatment outcomes. In rhytidectomy, BTX-A can be used to treat dynamic wrinkles on the upper face. The most frequently observed adverse reactions are systemic symptoms, followed by headache and local cutaneous reactions. Other side effects include sensory disturbances, muscular abnormalities, edema, facial paralysis, dizziness, and dysphagia.[1] Allergic reactions to BTX-A are occasionally reported.[2] After the outbreak of COVID-19, the number of allergy cases has increased.[3,4] However, no allergic reactions have been reported when BTX-A is used concomitantly with β-lactam.

We report a case of an urticaria-like reaction caused by the administration of the Chinese botulinum toxin serotype A (CBTX-A, named Prosigne in Brazil; Lanzhou Institute of Biological Products Co., Ltd., China) for the treatment of crow's feet. The patient was taking cefprozil, which was permissible according to the package insert for CBTX-A.

Case Presentation

A 35-year-old woman experienced urticaria-like symptoms after receiving a CBTX-A injection in lateral orbital orbicularis muscle. Other than allergic rhinitis, the patient had no history of allergic reactions or allergic reactions to cephalosporins. Moreover, the patient was not in her menstrual period, and no anaesthesia was administered before the injection. She had been suffering from an upper respiratory tract infection for a week; thus, the patient took cefprozil (0.25g, Yangtze River Pharmaceutical Co., Ltd., China) 0.5g orally, 5 hours before the injection.

Received: 29 December 2024
Accepted: 18 March 2025
Published: 20 March 2025

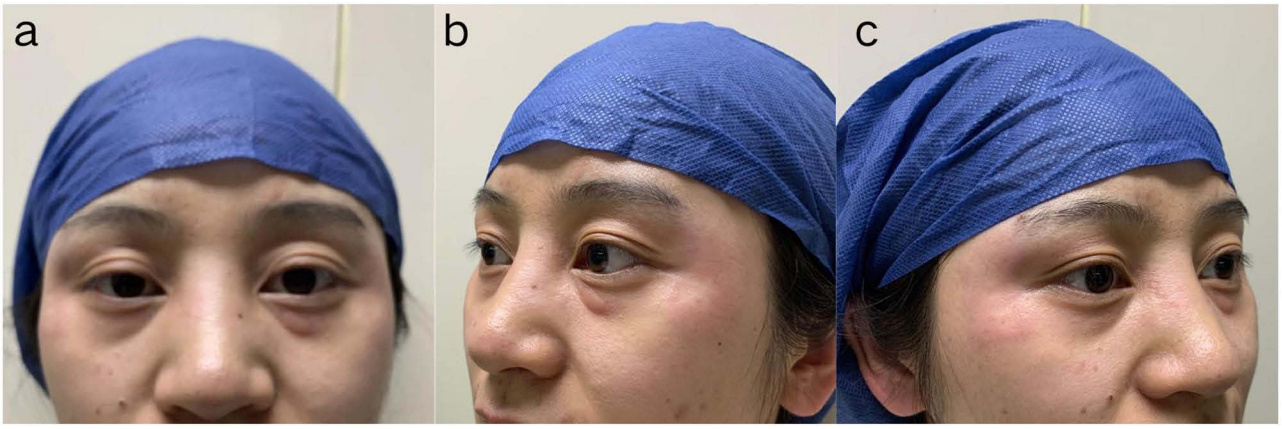

Figure 1 (**a–c**) After injection, urticaria-like manifestations occurred on the upper face, with redness, swelling, and wheal formation.

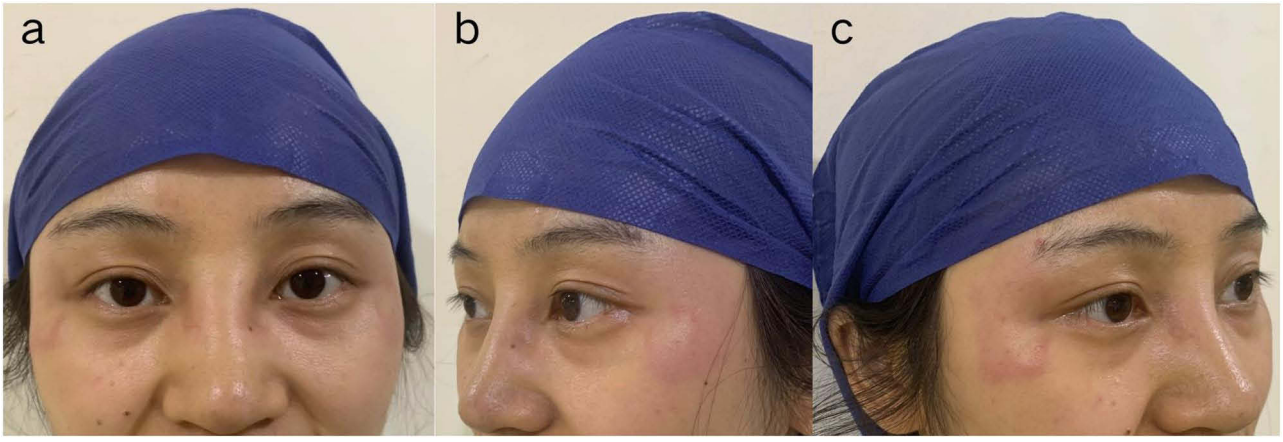

Figure 2 (**a–c**) 2 hours later, the urticaria-like manifestations were mitigated.

CBTX-A was diluted in 2.5 mL saline and was injected bilaterally subcutaneously into the orbicularis oculi muscle at the lateral orbital area of the eyes. Three sites were injected, on each orbicularis oculi (2 U per site; 12 U in total).

One hour after injection, urticaria-like manifestations occurred on the patient's upper face, with redness, swelling, and wheal formation. No other symptoms, such as pruritus and pain, were noticed (Figure 1a–c). The patient was treated immediately with 10 mg of oral loratadine tablets (Clarityne, Bayer, Leverkusen, Germany) and topical skin-icing. Two hours later, the symptoms were mitigated (Figure 2a–c). As the patient had no fatal symptoms, she was not willing to undergo examinations, which included vital signs, blood tests, and skin tests.

The following day, the patient reported that all symptoms had subsided. The wrinkles were less noticeable within a week. This effect lasted approximately three months.

Discussion

BTX-A can inhibit the release of acetylcholine by acting on the motor endplate, temporarily paralyzing muscles and impairing motor functions. In cosmetic treatment, BTX-A is commonly used for treating facial dynamic wrinkles. The occurrence of common complications usually can be predicted,[5] but rare side effects are still reported. Skin rash,[6] death,[7] exantema,[8] erythema,[9] swelling,[10] urticarial plaques,[11] angio-oedema,[12] and drug eruption[13] have been reported as hypersensitive reactions.

CBTX-A was approved for marketing by the China Food and Drug Administration (CFDA) in 1997, and it was officially approved as a treatment in cosmetic surgery in 2009. Careta et al[11] reported a case of urticarial plaques

following injection with CBTX-A in the forehead. Intradermal testing was performed on the forearm and erythema to detect allergies, and it resulted in the occurrence of edema. CBTX-A contains bovine gelatin as an excipient, which may increase the incidence of allergic reactions.[14]

Guo et al[3] described two cases of subacute hypersensitivity reactions to CBTX-A following the administration of an inactivated COVID-19 vaccine. Similarly, Fabio et al[4] reported 12 cases of temporary, delayed hypersensitivity reactions associated with BTX-A following COVID-19 vaccination, suggesting that the BTX-A injection in the post-vaccination period may trigger a transient immune response that leads to such reactions.

Zari et al[15] reported a case in which a herpes zoster outbreak occurred following BTX-A injections. They hypothesized that the quantity of BTX-A complex proteins internalized by dendritic cells from the BTX-A formulation—and subsequently presented to T cells via their specific T-cell receptors—plays a critical role in determining antigenicity.

In our case, the patient had previously received CBTX-A with no significant discomfort or allergic reactions noted. The injection procedures were identical and performed by the same surgeon. Importantly, she had not received a COVID-19 vaccination. Six months later, after a mutual decision between the patient and the clinicians, she underwent another CBTX-A injection and again experienced no allergic reaction. These findings suggest that the allergic reaction observed in the current episode is unlikely to be attributable solely to CBTX-A. Based on the rapid onset of her clinical symptoms, we speculate that her reaction represents an immediate hypersensitivity mediated by IgE antibodies (a Gell–Coombs type I reaction). Due to the mild nature of the symptoms and their swift resolution, the patient declined further hypersensitivity tests.

Cefprozil is a second-generation cephalosporin belonging to the β-lactam group and is commonly used for the treatment of respiratory tract and soft tissue infections. β-lactam agents can induce IgE-mediated type I hypersensitivity reactions, which account for 60–70% of acute adverse responses, whereas T cell-mediated type IV reactions are frequently observed in delayed responses.[16] The metabolic products of cefprozil form hapten–protein complexes that retain the immunogenic R1 side chain, thereby potentially activating IgE responses.[17]

Botulinum toxin protein, comprising two heavy chains and one light chain, exhibits immunogenic potential through its structural components.[18] Li et al[19] documented three cases of acute hypersensitivity reactions associated with BTX-A, manifesting at systemic sites distal to the injection area. They hypothesized that the heavy chain may serve as a B cell-activating antigen, potentially driving immunoglobulin E (IgE)-mediated type I hypersensitivity reactions.

Choi et al[20] suggest that subcutaneous injection of BTX-A reduces rosacea-associated skin inflammation by directly inhibiting mast cell degranulation, as evidenced by a decrease in the cleavage of SNAP-25 and VAMP2. In contrast, Blas et al[21] observed an initial increase in mast cell numbers during the first 24 hours following intramuscular administration of BTX-A, with counts stabilizing at 7 and 15 days and then rising again at 30 days. These observations indicate that the route of injection may influence mast cell behavior. Consequently, when BTX-A is administered for the treatment of crow's feet, the injection's proximity to the skin may promote an increased mast cell response.

In this case, the patient received cefprozil a few days before the CBTX-A treatment without any allergic manifestations. Given that BTX-A does not contain transpeptidases—the enzymatic targets of β-lactams—it is unlikely that a direct pharmacological interaction between cefprozil and botulinum toxin is responsible for the reaction. We hypothesize that a synergistic effect may have occurred: the cefprozil metabolites, acting as haptens, might have activated IgE and induced a state of immune priming. Consequently, the subsequent BTX-A injection, with its protein constituents, could have provided an additional immunostimulatory signal under specific conditions, while also modulating higher mast cell metabolism to lower the threshold for an allergic response. BTX-A's neuromodulatory actions may also disrupt immune tolerance to cephalosporin metabolites. This combined effect may have culminated in an urticaria-like reaction.[22] The interactions between BTX-A and β-lactam require further investigation.

Our report of urticaria-like symptoms after CBTX-A injection indicated that concomitant use of CBTX-A with β-lactam could be the cause. There was no life-threatening danger possibly because the administered dose was low. The danger was that symptoms could appear an hour after injection, which was longer than the clinically required observation time. In consideration of botulinum toxin injections being a convenient and rapid therapeutic option with a low incidence of severe adverse events, we suspect that clinicians might sometimes overlook critical aspects of a patient's medication history and comorbidities. By presenting this seemingly unspectacular case, we aim to emphasize the importance of

a detailed pre-injection evaluation of the patient's recent health status. For individuals with potential risk factors, it may be advisable to postpone the injection or to inform them of the possible risk of adverse reactions and to extend the observation period, thereby reducing post-injection anxiety and tension arising.

Conclusion

We report a case of urticaria-like anaphylaxis following the injection of CBTX-A after the oral administration of a β-lactam antibiotic. This case emphasizes the importance of exercising caution when administering botulinum toxin injections, particularly in patients with comorbid conditions. A thorough review of the patient's medication history, including the use of β-lactam antibiotics, is recommended to minimize the risk of hypersensitivity reactions.

Abbreviations

BTX-A, Botulinum toxin serotype A; CBTX-A, Chinese botulinum toxin serotype A.

Ethics Declarations

This report was approved by Beijing Badachu Plastic Surgery, Fifth Medical Aesthetic Hospital and gave approval to publish the case details. This study adhered to the tenets of the Declaration of Helsinki, and written informed consent was obtained from the patients for the publication and use of clinical photographs.

Acknowledgments

We thank the patient for providing her photographs and her medical records.

Disclosure

The author(s) report no conflicts of interest in this work.

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