A case of eperisone hydrochloride-induced anaphylaxis: A true type I reaction?

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Letter to the Editor

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Dear Editor,

Centrally acting muscle relaxants (CMRs) are often used to alleviate musculoskeletal pain. Among them, eperisone hydrochloride is the most popular in Japan.[1] Although it is a well-tolerated drug,[2] allergic reactions to eperisone have been reported, most of which are anaphylactic or urticarial reactions.[1] Acute generalized exanthematous pustulosis[3] and fixed drug eruption[4] are reported rare manifestations of eperisone-induced drug eruption. Tolperisone hydrochloride, an analog of eperisone hydrochloride, is another CMR often used in European countries. Ribi *et al.* reviewed the adverse effects of tolperisone hydrochloride; almost half of the adverse effects were immediate-type hypersensitivity reactions.[5] To date, reported CMR-related drug eruptions have mainly been immediate-type hypersensitivity reactions. However, it is not clear whether this hypersensitivity is IgE mediated, a so-called "true" type I allergic reaction. Here, we report a case of eperisone-induced anaphylaxis in which skin prick test (SPT) and basophil activation test (BAT) showed negative results. An oral challenge test was the most reliable procedure for diagnosing eperisone-induced immediate-type hypersensitivity.

A 64-year-old woman was referred to our dermatology department to determine potential allergens causing anaphylaxis. She had taken eperisone hydrochloride and loxoprofen sodium, which resulted in urticaria, throat swelling, and loss of consciousness. She was taken to the emergency room, where she responded well to administration of corticosteroids. The patient had a history of low-back pain for which she was prescribed eperisone hydrochloride and loxoprofen sodium. She also had a history of bronchial asthma but not food allergy. SPT was negative for all tested drugs, including eperisone hydrochloride and loxoprofen sodium. Oral challenge test was negative for non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin (up to 500 mg), loxoprofen sodium (up to 60 mg), and paracetamol (up to 400 mg), indicating that the patient did not have aspirin-sensitive urticaria. Oral administration of 0.5–5 mg of eperisone induced slight itchiness on the palms. About 90 min after oral administration of 16 mg of eperisone, the patient developed general pruritus and swelling of the face, tongue, and palms (Fig. 1). Thus, she was diagnosed with eperisone hydrochloride-induced anaphylaxis.

To investigate whether eperisone hydrochloride itself directly induced basophil activation, we performed a BAT.[6] Contrary to our expectations, no increase in CD203c expression was observed on incubation with eperisone hydrochloride (Wako Pure Chemical Industries, Osaka, Japan) (Fig. 2). BAT with tolperisone hydrochloride (Wako Pure Chemical Industries) also induced no increase in CD203c expression (data not shown).

Eperisone is commonly used in combination with NSAIDs. Therefore, clinicians should determine the causative allergen in drug eruption patients taking combinations of eperisone and NSAIDs. In this case, because the oral challenge test for NSAIDs was negative and oral administration of eperisone caused a hypersensitivity reaction, we concluded that eperisone was the cause of anaphylaxis. Though we did not perform challenge tests for the excipients, we suspect that eperisone itself was the causative allergen

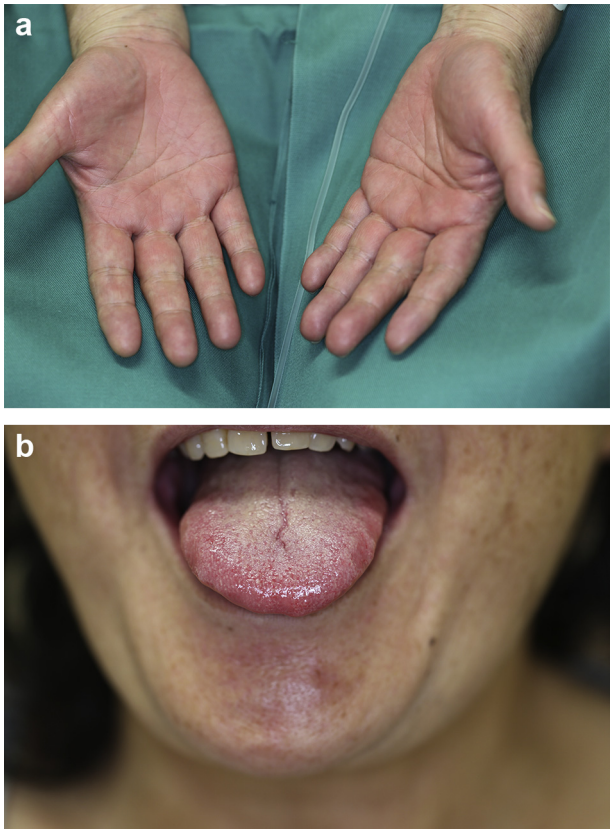

Fig. 1. Eperisone-induced acute hypersensitivity reactions (**a,** palms; **b,** tongue).

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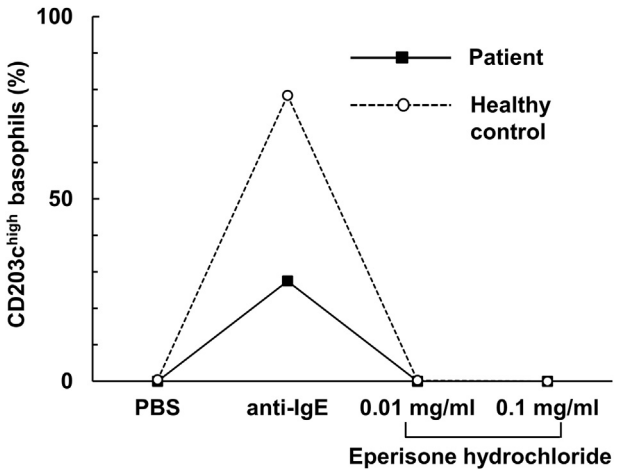

Fig. 2. Basophil activation test (BAT). Peripheral blood samples from the patient and healthy control were collected in EDTA tubes and incubated for 15 min with Ca^{2+}-rich buffers, fluorescent-labeled anti-human CD203c, CD3e, and CRTH2 antibodies, and antigens (PBS, anti-IgE antibody, and eperisone hydrochloride), according to the manufacturer's instructions (Beckman Coulter, Brea, CA, USA). After that, red blood cells were lysed. Samples were washed with PBS, re-suspended in 0.1% PFA in PBS, and analyzed with a FACS Verse flow cytometer (BD Biosciences, San Diego, CA, USA).

because the patient showed acute hypersensitivity to two different commercially available eperisone tablets, Myonal® and Myorelark®, which have different excipients. However, our patient's BAT results with eperisone were negative.

Hur *et al.* performed a BAT with afloqualone, another CMR, and reported increased expression of CD63 with afloqualone stimulation.[7] It is generally accepted that positive BAT results *in vitro* indicate that a hypersensitivity reaction is IgE mediated.[8] A positive SPT *in vivo* also provides evidence that the culprit agent induces an IgE-mediated reaction.[8] In our patient, both SPT and BAT results were negative. In fact, most SPT for eperisone are negative, according to the literature.[1] To the best of our knowledge, there have been no definite reports that eperisone itself induced IgE-mediated allergic reaction.

There are several possible explanations for eperisone-induced acute hypersensitivity reactions. First, because eperisone changes into several metabolites *in vivo*, these metabolites might induce IgE-mediated reactions. Second, because eperisone has vasodilating effects,[9] hypersensitivity reactions and urticarial reactions might have occurred as a result of rapid vasodilation by eperisone in our patient. Lastly, a recent report clarified the pseudo-allergic (IgE-independent) release of histamine from mast cells via specific receptor MRGPRX2.[10] Because muscle relaxant drugs such as tubocurarine and atracurium have been proved as potential agonists for MRGPRX2, eperisone might also stimulate mast cells via MRGPRX2 to induce their degranulation via IgE-independent fashion. In fact, our patient showed dose-dependent side effects with administration of eperisone. Administration of 0.5–5 mg resulted in only slight itchiness on the palms, but 16 mg of eperisone induced systemic reaction; such dose-dependent effect of eperisone may suggest either vasodilation or pseudo-allergic reaction, but not IgE-mediated type I allergic reaction.

In conclusion, we report a case of eperisone-induced anaphylaxis, in which SPT and BAT were negative. Our results indicate that eperisone itself does not directly induce IgE-mediated hypersensitivity reactions. An oral challenge test is necessary to diagnose eperisone-induced acute hypersensitivity. The exact mechanism by which eperisone induces type I allergic reactions should be clearly determined in the future.

Conflict of interest

The authors have no conflict of interest to declare.

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