

MRGPRX2 signaling and skin test results



To the Editor:

In their recent clinical communication, Giavina-Bianchi et al¹ describe a patient with systemic mastocytosis who suffered recurrent anaphylactic episodes after insect stings and treatment with ciprofloxacin. Measurements of serum specific IgE to hymenoptera venoms were negative as were results of skin tests performed with the venoms as well as ciprofloxacin. The authors, along with Weiler² in an accompanying editorial, suggest that these reactions are likely due to activation of the MAS-related G protein-coupled receptor-X2 (MRGPRX2), which has been shown to be activated by a venom constituent as well as quinolone antibiotics. There is a conundrum regarding this proposed mechanism of anaphylaxis; why are the skin test results negative? MRGPRX2 is expressed at high levels in human skin mast cells, and they can be stimulated to release histamine in a dose-dependent fashion *in vitro* by other agonists such as morphine.³ It would thus seem that the stimulation of these receptors on mast cells *in vivo* by skin testing with hymenoptera venoms and ciprofloxacin would also result in histamine release and positive skin test results even in the absence of IgE. Other authors have speculated that this discrepancy between *in vivo* and *in vitro* results may be related to the affinity of MRGPRX2 relative to IgE signaling or the relative dispersal of mast cells in the skin compared with cell culture.⁴ These would seem to be inadequate explanations, given that other MRGPRX2 agonists such as morphine cause positive skin test results even in opiate-tolerant subjects.⁵ The observation that hymenoptera venom and medications such as quinolone antibiotics can cause non-IgE-mediated anaphylaxis through the activation of MRGPRX2 receptors on mast cells is an important and intriguing concept. Perhaps Giavina-Bianchi et al and Weiler can offer additional thoughts on why these agents do not also cause positive skin test results.

John M. Kelso, MD

Division of Allergy, Asthma & Immunology, Scripps Clinic, San Diego, Calif.

Conflicts of interest: The author declares no relevant conflicts of interest.

Received for publication August 13, 2019; accepted for publication September 15, 2019.

Corresponding author: John M. Kelso, MD, Division of Allergy, Asthma & Immunology, Scripps Clinic, 3811 Valley Centre Dr, San Diego, CA 92130. E-mail: kelso.john@scrippshealth.org.

REFERENCES

1. Giavina-Bianchi P, Gonçalves DG, Zanandrea A, Borges de Castro R, Garro LS, Kalil J, et al. Anaphylaxis to quinolones in mastocytosis: hypothesis on the mechanism. *J Allergy Clin Immunol Pract* 2019;7:2089-90.
2. Weiler CR. Mastocytosis, quinolones, MRGPRX2, and anaphylaxis. *J Allergy Clin Immunol Pract* 2019;7:2091-2.
3. Varicchi G, Pecoraro A, Loffredo S, Poto R, Rivellesse F, Genovese A, et al. Heterogeneity of human mast cells with respect to MRGPRX2 receptor expression and function. *Front Cell Neurosci* 2019;13:299.
4. Navines-Ferrer A, Serrano-Candelas E, Lafuente A, Munoz-Cano R, Martin M, Gastaminza G. MRGPRX2-mediated mast cell response to drugs used in perioperative procedures and anaesthesia. *Sci Rep* 2018;8:11628.
5. Nasser SM, Ewan PW. Opiate-sensitivity: clinical characteristics and the role of skin prick testing. *Clin Exp Allergy* 2001;31:1014-20.

<https://doi.org/10.1016/j.jaip.2019.09.038>

Reply



To the Editor:

Recently, we described a patient with indolent systemic mastocytosis who developed anaphylaxis to ciprofloxacin. We recommended ciprofloxacin avoidance in patients with mastocytosis and provided a warning that ciprofloxacin may induce anaphylaxis in these patients by activation of the MAS-related G protein-coupled receptor-X2 (MRGPRX2).^{1,2} Kelso,³ in his letter to the editor, brings up a very interesting and important question, “why were the skin tests to quinolones negative?”

Some drugs, such as the neuromuscular blocking agents, opioids, and quinolones, induce direct mast cell degranulation through the MRGPRX2. If we perform intradermal tests with these drugs using their regular therapeutic concentration, all tested subjects develop positive test results. That is why the standardization of intradermal test for these drugs is complex and difficult. It is challenging to define a proper drug concentration to be used in the intradermal test to detect IgE-mediated mast cell degranulation (good sensitivity), but not to induce direct mast cell degranulation (good specificity).

Morphine induces positive skin test results in normal volunteers when administered intradermally.⁴ The problem, however, is that there is no correlation between skin test results to morphine and the allergic status of the patient.⁵⁻⁷ Skin testing for other opioids, whose mechanism of action is mediated via MRGPRX2, is also not predictive of the allergic status of the opioid-allergic patients.⁶

A similar situation is seen with quinolones, specifically, with ciprofloxacin. Performing intradermal tests in normal volunteers with 1/10, 1/50, and 1/100 dilutions of 2 mg/mL ciprofloxacin, false-positive test results were observed 100%, 31%, and 0% of the time, respectively (P. Giavina-Bianchi, MD, PhD, unpublished data, 2019). Then, if the aim is good specificity, we should use the 1/100 dilution to perform intradermal test with ciprofloxacin. However, there are not enough data with real allergic patients to ciprofloxacin showing that the 1/100 dilution has good sensitivity to diagnose allergic reactions. Other studies suggest the use of lower concentrations in the intradermal tests, but this, according to our experience, is not necessary.⁸ However, higher concentrations may be irritative and induce false-positive test results.

We could speculate that the intradermal test with ciprofloxacin should be done with lower drug concentrations in patients with mastocytosis, because these patients may have increased number of cutaneous mast cells. Our patient has indolent systemic mastocytosis without skin involvement and that could explain why the intradermal tests with proper concentrations of ciprofloxacin and *Hymenoptera* extracts did not show nonspecific mast cell activation.

In conclusion, ciprofloxacin and *Hymenoptera* venom may induce anaphylaxis through IgE-mediated hypersensitivity or MRGPRX2 receptor activation in patients with mastocytosis. More studies are needed to further evaluate the utility of