

Clinical Communications

Sensitization to trometamol in patients with delayed local reactions after administration of the Moderna mRNA-1273 vaccine against SARS-CoV-2

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Clinical Implications

Trometamol could be a sensitizing agent in patients with nonimmediate large local reactions to the Moderna vaccine ("COVID arm"). In this study, delayed-reading intradermal testing was a useful confirmatory tool. Importantly, these patients can safely receive another dose of the vaccine if needed.

The Moderna vaccine is a single-stranded messenger RNA (mRNA) vaccine that encodes the spike protein of the SARS-CoV-2 virus. Each 0.5-mL dose contains 100 µg of this highly purified mRNA encapsulated in lipid nanoparticles, as well as the excipients PEG2000 DMG and trometamol, both of which have been associated with immediate and nonimmediate reactions to other drugs.¹⁻³

The skin reaction that has come to be known as "COVID arm" is considered a mild adverse effect of the vaccine, which consists of erythema, induration, and pruritus at the injection site. It occurs some 8 days after administration of the first dose of the Moderna vaccine and some 2 days after the second dose.³ Remarkably, this reaction has been observed less frequently with the Pfizer vaccine, which does not contain trometamol.^{1,2} Therefore, we decided to assess the role of a possible sensitization to trometamol in patients experiencing this type of reaction to the Moderna SARS-CoV-2 vaccine.

We conducted a prospective pilot study including all health care professionals referred to the allergy department from the vaccination hub at Henares University Hospital, Madrid, Spain, between February and April 2021. We selected those patients presenting with nonimmediate local reactions that could be considered large (reddened and edematous plaques >10 cm in diameter) and occurring over 6 hours after injection and on the injection site of the Moderna vaccine.³⁻⁵ We planned to recruit a rate of 2:1 controls:cases from a pool of healthy hospital staff who had received vaccination with no reactions. The study and informed consents were approved by our hospital's ethics committee.

The data recorded in the clinical history included atopy, previous adverse drug reactions, previous tolerance of vaccines and contrast media, and polymerase chain reaction—confirmed previous infection by SARS-CoV-2.

All patients and controls underwent skin prick testing (SPT) and intradermal testing (IDT) with the Moderna vaccine and excipients (see Table I). Skin testing (ST) was performed and interpreted as per European Academy of Allergy and Clinical

Immunology (EAACI) guidance.⁵ Moreover, all underwent patch testing with a standard contact allergen series (TRUE-TEST) and trometamol 10% aq.

Drug challenge with the Moderna vaccine was performed in an allergy-dedicated area for drug challenges with expert staff, resources to treat severe anaphylaxis, allergist on-site, and rapid access to an intensive therapy unit, following EAACI guidelines for drug provocation testing. Given the characteristics of these reactions, the chosen protocol for these patients was a 1-step administration of a full dose of the vaccine, mimicking real-life administration as per EAACI guidance.⁵

A total of 7 patients met the inclusion criteria, and all of them had reacted to the administration of the first dose of the Moderna vaccine against SARS-CoV-2 (see Figure E1, available in this article's Online Repository at www.jaci-inpractice.org, for a photograph of a reaction).

All the patients were women (median age 52 years, ranging from 46 to 56 years). Four of them had a history of atopy (confirmed hay fever), and all had previously tolerated the influenza vaccine and were up to date with their vaccine schedule without incident. Four of the 7 patients had had SARS-CoV-2 between 8 and 12 months before being vaccinated. The median time to onset of the local reaction was 7 days (ranging from 6 to 9 days) after the first dose of the vaccine. The median duration of the reaction was 96 hours (ranging from 72 to 144 hours). See Table I for further patient characteristics.

The intradermal tests with the Moderna vaccine were positive in all patients (at 20 minutes in 4 patients and 24/48 hours in 3 patients, remaining positive up to 96 hours). Remarkably, the results for trometamol were positive for IDT in all 7 patients, with most occurring at 0.001 and 0.01 mg/mL (see Table I). The tests performed on the 15 control patients yielded negative results. These controls were vaccinated individuals who had experienced no reactions. Four had been vaccinated with the Moderna and 11 with the Pfizer vaccine; they were all women (median age: 58, ranging from 40 to 62), 5 of whom were atopic and 10 nonatopic. The skin tests with PEG were negative in all cases and controls. See Figure E2 (available in this article's Online Repository at www.jaci-inpractice.org) for a photograph of positive ST with trometamol.

Patch testing with the standard contact allergen series and trometamol was negative at 48, 72, and 96 hours in all patients.

Three of the 7 patients had tolerated trometamol-containing iodinated contrast media during the previous 3 years. Five patients had tolerated dexketoprofen/trometamol before and after administration of the vaccine, thus confirming previous exposure and subsequent tolerance, at least when administered orally.

All patients completed their vaccination with the second dose via a drug challenge. All patients developed edema and erythema (4 × 4 cm) on the injection site after a median of 48 hours (ranging from 24 to 72 hours). They were treated with topical corticosteroids and antihistamines. Two patients required prednisone 30 mg for 48 hours, with complete resolution. The median duration of the reaction was 72 hours (ranging from 48 to 96 hours).

Only 3 patients (1, 4, and 6 in Table I) have received a third dose of Moderna yet. All these patients experienced an earlier

TABLE I. Characteristics and skin tests results of the cutaneous reactions reported after Moderna COVID-19 vaccination

Patient	Age	Sex	Time between administration and onset of symptoms	Previous SARS-CoV-2 infection	Skin tests with the Moderna vaccine	Skin tests with polyethylene glycol	Skin tests with trometamol	Patch tests with trometamol 10% aq	Time between drug challenge with Moderna and local reaction
1	51	Female	9th day	No	Positive IDT 1/100 at 20 min	Negative	Positive IDT 0.01 mg/mL at 20 min	Negative	72
2	53	Female	7th day	Yes	Positive IDT 1/100 at 20 min	Negative	Positive IDT 0.01 mg/mL at 20 min	Negative	24
3	54	Female	7th day	Yes	Positive at 1/100 at 20 min	Negative	Positive IDT 0.01 mg/mL at 20 min	Negative	48
4	52	Female	7th day	Yes	Positive at 1/100 at 20 min	Negative	Positive IDT 0.1 mg/mL at 20 min	Negative	24
5	56	Female	6th day	No	Positive at 1/10 and 1/100 at 48 h	Negative	Positive IDT 0.001 mg/mL at 20 min	Negative	48
6	48	Female	7th day	No	Positive at 1/10 and 1/100 at 24 h	Negative	Positive IDT 0.001 mg/mL at 20 min	Negative	48
7	46	Female	7th day	No	Positive at 1/10 and 1/100 at 24 h	Negative	Positive IDT 0.001 mg/mL at 20 min	Negative	48

SPT and IDT with the Moderna vaccine (sequentially, 1/100 - 1/10). SPT with polyethylene glycol (Roxall, Germany, magistral pharmaceutical preparation to reach 0.1%, 1%, and 10%). SPT and IDT with trometamol (Tris 36.34% solution for infusion 20 mL ampoules, Braun, Germany, magistral pharmaceutical preparation to reach 0.001-1 mg/mL). SPT and IDT with Tween 80 (Sigma-Aldrich/Merck, Germany, magistral pharmaceutical preparation to reach 0.004 mg/mL). Trometamol and Tween 80 were tested in 15 control patients. Skin testing with drugs was performed on the volar aspect of the arm, following the recommendations and interpretation criteria of the European Academy of Allergy and Clinical Immunology guidelines.

IDT, Intradermal test; SPT, skin prick testing.

reaction with the third dose (onset within 24 hours). However, they experienced considerably milder local reactions that were controlled within 48 hours with topical steroids. Of note, patients receive a lower dose of the Moderna vaccine for their third dose booster, which could be an unconfirmed factor for better tolerance.

Trometamol is used as an excipient in the pharmaceutical industry and as a pH stabilizer for improving the solubility and stability of various substances (eg, contrast media, vaccines, eye drops, cosmetics).⁶ Although widely used, trometamol has rarely been involved in allergic reactions. In addition, its role in such reactions has not been assessed.

In 2001, on the basis of a positive patch test result with trometamol 1% aq, Bohn et al⁶ confirmed the involvement of the excipient in a type IV hypersensitivity reaction caused by Oculac eye drops in a patient with eczema affecting both eyes.

In 2019, Lukawska et al⁷ reported the case of a patient who experienced anaphylaxis after the administration of gadolinium. The reaction was caused by hypersensitivity to trometamol, which was confirmed by a positive intradermal test result (0.01 mg/mL). The results were negative in controls.

The skin reaction known as “Covid arm” has mainly been observed with the Moderna vaccine and not the Pfizer vaccine.¹⁻³ Therefore, even if there are likely multiple causes for this type of reaction, sensitization to trometamol could be responsible for some cases of “Covid arm.” All our cases and none of our controls were positive for trometamol on ST, supporting this hypothesis.

Subsequent spontaneous oral tolerance by 5 of the study patients of drugs containing trometamol indicates that the reaction could depend on the dose of the excipient administered and differences in bioavailability depending on the route of administration. However, the mechanisms of systemic tolerance in patients with nonimmediate cutaneous reactions are yet to be elucidated.

Previous guidance supports that patients with nonimmediate local reactions to vaccines can receive them even if sensitization is confirmed.⁶ Furthermore, recent experience with COVID vaccines shows how most reactive patients can go ahead with their vaccination in a supervised environment.⁸ Our data confirm that patients with large, delayed reactions and positive skin tests to trometamol can safely receive their second and third doses and that their reactions can usually be controlled with antihistamines and topical steroids, with only some patients needing oral steroids.

All patients experienced an earlier onset reaction on each re-exposure. Reassuringly, the symptoms were progressively milder in all patients.

Interestingly, some patients showed immediate results for IDT, despite the nonimmediate onset of their local reaction. A similar phenomenon is also observed for subcutaneous allergen-specific immunotherapy, where many patients might experience nonimmediate local reactions despite having immediately positive SPT or positive specific IgE to the injected allergen.⁵ There is no clear explanation for this, but the injection depth (IDT is superficial, whereas vaccine injections are deep) might play a role in the appearance of local reactions.⁶

The delayed ST reactions to the vaccine are most likely unrelated to the reactions, because IDT with COVID-19 vaccines has shown positive results in nonallergic patients, explained by an immune response like that of Mantoux testing.⁹ ST with the vaccine could give false negatives given the lower concentration of trometamol, whereas ST with trometamol alone might be more sensitive, but the sample size is too small to draw definitive conclusions.

The results of this pilot study in a subset of health care professionals from our local hospital are limited by the small sample size and the unexplained heterogeneity in the timings for the ST positivity. However, these promising data seem to identify

trometamol as a culprit allergen for these reactions and justify further studies in a larger population.

The positivity of ST with nonirritant concentrations in all patients suggests that hypersensitivity to trometamol could play a role in some patients experiencing nonimmediate large local reactions to the Moderna vaccine. Interestingly, these patients will experience an earlier onset but milder, local reaction on each re-exposure. However, they can safely receive further doses with alleviating measures such as antihistamines and topical steroids in case of a reaction, with only a subset of patients needing oral steroids.

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FIGURE E1. Photograph of a nonimmediate local reaction to the Moderna vaccine in one of our patients.

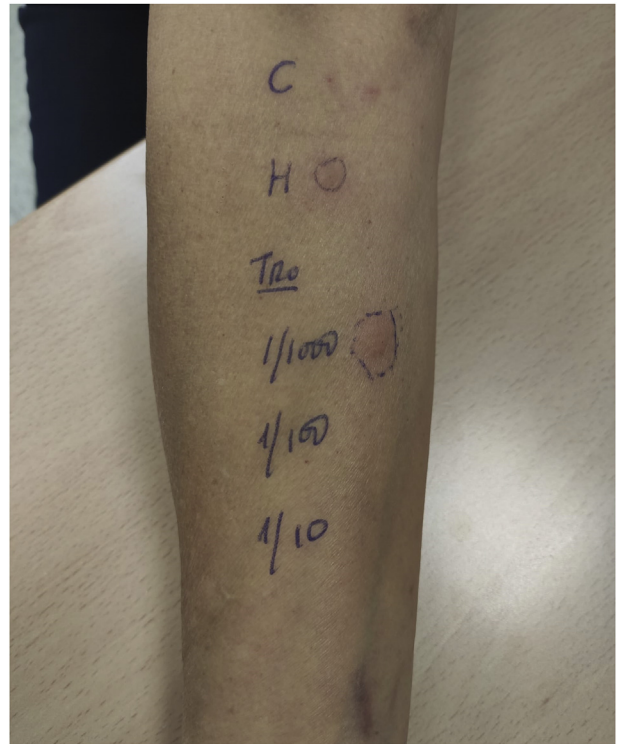


FIGURE E2. Photograph of an immediate positivity in intradermal testing with trometamol at a 1/1000 dilution (concentrations 1/100 and 1/10 not done because the patient was positive at 1/1000).