

Letters

ASSOCIATION OF DERMOGRAPHIC URTICARIA WITH THE USE OF PROGESTERONE IN COTTONSEED OIL

Dermographic urticaria, or urticaria factitia, is a chronic form of physical urticaria, with skin whealing occurring at sites of minor trauma induced by light stroking pressure, rubbing, or scratching.¹ Whealing occurs within seconds to minutes after mechanical stimulation and typically resolves within 30 minutes to 2 hours. Symptomatic dermographism usually persists for months to years. Severe symptomatic dermographism causes significant morbidity that negatively affects the patient quality of life.² Precipitating factors are usually unknown, with some cited causes including viral infections and drugs.³

There is evidence that luteal support with progesterone improves clinical outcomes after in vitro fertilization–embryo transfer cycles. Therefore, current clinical practice consists of intramuscular injection of progesterone in oil or vaginal administration of micronized progesterone preparations.⁴ Use of progesterone in oil remains common practice in many assisted reproductive technology programs. Treatment is initiated by the time of embryo transfer and continued through the first 6 to 12 weeks of pregnancy. Although repetitive intramuscular injections can frequently cause local discomfort and induration, this is not reported to result in dermographic urticaria.

In the present case report, we present a series of 9 female patients who were administered serial intramuscular injections of progesterone in cottonseed oil for the treatment of infertility at a tertiary referral reproductive medicine unit (Table 1). Patients received the standard protocol of 25 to 50 mg of progesterone in cottonseed oil intramuscularly daily, beginning on the day of oocyte retrieval and continuing until pregnancy confirmation ultrasonography (5–6

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Table 1. Patients With Dermographic Urticaria Associated With Progesterone in Cottonseed Oil

Patient	Age, y	Drug	Reaction	Skin test results ^{a,b}	ImmunoCAP cotton seed, kU/L	Challenge
1	34	Progesterone in cottonseed oil	Acute urticaria with severe dermographism	Negative skin prick test result, positive intradermal test result	<0.35	Negative progesterone oral challenge result
2	37	Progesterone in cottonseed oil	Acute urticaria with severe dermographism	Dermographism, skin prick test results could not be interpreted, positive intradermal test results	<0.35	Vaginal cream (90 mg)
3	37	Progesterone in cottonseed oil	Acute urticaria with severe dermographism	Positive skin prick test result, positive intradermal test result	<0.35	Vaginal cream (90 mg)
4	32	Progesterone in cottonseed oil	Acute urticaria with severe dermographism	Dermographism, skin prick test results could not be interpreted, positive intradermal test results	<0.35	Vaginal cream (90 mg)
5	22	Progesterone in cottonseed oil	Acute urticaria with severe dermographism	Positive skin prick test result, positive intradermal test result	<0.35	Vaginal cream (90 mg)
6	35	Progesterone in cottonseed oil	Acute urticaria with severe dermographism	Positive skin prick test result, positive intradermal test result	<0.35	Vaginal cream (90 mg)
7	38	Progesterone in cotton seed oil	Acute urticaria with severe dermographism	Negative skin prick test result, positive intradermal test result	Not performed	Vaginal cream (90 mg)
8	41	Progesterone in cottonseed oil	Acute urticaria with severe dermographism	Positive skin prick test result, positive intradermal test result	<0.35	Vaginal cream (90 mg)
9	34	Progesterone in cottonseed oil	Acute urticaria with severe dermographism	Dermographism, skin prick test results could not be interpreted, positive intradermal test result	<0.35	Vaginal cream (90 mg)

^a Positive skin prick and intradermal test results were defined as wheal responses greater than 4 and 6 mm, respectively, above the negative control.

^b Four control patients had negative intradermal (50 mg/mL) skin test results.

weeks). These patients developed acute urticaria with a large local reaction at the injection site. Severe dermographism occurred a few days to 2 weeks after the initiation of intramuscular progesterone injections and persisted for weeks to months. The dermographism was generalized over the affected cutaneous area. Intramuscular injections were discontinued, and these patients were subsequently treated with a different vehicle of progesterone administration (Crinone 8%, 90 mg vaginally), with no further documented reactions.

The diagnosis of dermographism was confirmed by graded pressure induced by stroking the skin on the back with a tongue blade. Dermographic reactions occurred with minimal pressure provocation.

Skin testing with progesterone powder in cottonseed oil (50 mg/mL) mixed with 10% benzyl alcohol was performed in 9 patients. Histamine (1 mg/mL) and saline were used as the positive and negative controls. Positive skin prick test results to progesterone in cottonseed oil were documented in 4 patients (defined as wheal diameter greater than 4 mm above the negative control), whereas the results of skin prick testing to cottonseed oil alone were negative in all patients. Intradermal skin test results were positive to progesterone in cottonseed oil in all 9 patients, demonstrating greater than 6-mm wheal responses for each patient. Intradermal test results in 4 controls were negative. Specific IgE determinations (Pharmacia CAP System; Pharmacia, Uppsala, Sweden) were completed for cottonseed and were negative (<0.35 kU/L) in 8 patients. An open oral challenge test to progesterone (Prometrium) was performed in a single patient with no adverse reaction, and all others received intravaginal progesterone cream with no adverse events. The acute urticarial reaction generally resolved within weeks, although milder residual symptoms persisted for months. Patients were advised to avoid progesterone in cottonseed oil and use an alternative form of progesterone if necessary. Dermographic urticaria was treated with histamine₁-antihistamines for symptomatic relief.

Symptomatic dermographism is the most common physical urticaria and may be associated with the systemic use of drugs.⁵ Dermographism has been reported in up to 5% of the general population.⁶ Passive transfer studies have suggested an IgE-mediated reaction induced by stroking of the skin. Therefore, many patients appear to have an abnormal circulating IgE that confers a particular form of pressure sensitivity to dermal mast cells.⁷ In this series of patients, we identify a close temporal relationship between the

appearance of symptomatic dermographism with the intramuscular injection of progesterone in cottonseed oil.

We propose that this unusual allergic reaction is related to this combination of progesterone in cottonseed oil, although the exact mechanism remains unclear. This is the first reported series of patients with symptomatic dermographism associated with progesterone in oil, although there has been an isolated case report documenting hypersensitivity to progesterone in oil for patients undergoing fertility treatment.⁴ We recommend alternative forms of progesterone in the treatment of allergic individuals.

In conclusion, progesterone in cottonseed oil may lead to the development of an acute dermographic response. Patients may be treated with topical progesterone without allergic reactions. Specialists who provide care to patients using progesterone in oil products should be aware of these adverse reactions and their management.

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ANALYSIS OF ANAPHYLAXIS CASES AFTER VACCINATION: 10-YEAR REVIEW FROM THE NATIONAL VACCINE INJURY COMPENSATION PROGRAM

The National Vaccine Injury Compensation Program (VICP) was established in 1986 in response to vaccine safety concerns. A unique feature is a table of compensable injuries, the Vaccine

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Injury Table (VIT). Anaphylaxis is a listed adverse event with an interval of 0 to 4 hours for vaccines containing tetanus toxoid (tetanus, diphtheria, and pertussis vaccine and tetanus-diphtheria [Td] vaccine), pertussis (diphtheria, pertussis, and tetanus [DPT] and diphtheria and tetanus toxoids with acellular pertussis [DTaP] vaccines), measles, mumps, and rubella (MMR), inactivated polio virus (IPV), and hepatitis B virus (HBV).¹ In 2009, the VICP charged the Institute of Medicine with the task of completing a comprehensive review of the medical literature regarding adverse events related to vaccines so that the VIT could be updated.² Concurrent with the Institute of Medicine's review, we undertook a systematic analysis of the VICP's anaphylaxis case experiences.

The VICP administrative database was queried for all cases submitted to the VICP alleging "anaphylaxis or anaphylactic shock" for the 10-year period from January 1, 2000, through