

Clinical Communications

Polyethylene glycol may be the major allergen in depot medroxyprogesterone acetate

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Clinical Implications

- The contraceptive depot medroxyprogesterone acetate can cause hypersensitivity reactions. Polyethylene glycol rather than medroxyprogesterone acetate itself appears to be the major allergen in depot medroxyprogesterone acetate.

Depot medroxyprogesterone acetate (DMPA) is a long-acting progestin contraceptive, administered intramuscularly every 12 weeks. Although generally safe, 117 cases of suspected anaphylaxis have been registered with the Medicines and Healthcare Product Regulatory Agency, United Kingdom.

However, only 4 cases, including 1 fatality, have been reported in the literature.¹⁻³ A responsible allergen was not identified.

Apart from the active ingredient medroxyprogesterone acetate (MPA), the depot formulation contains the excipient polyethylene glycol (PEG), molecular weight (MW) 3350, that has been identified as the cause of hypersensitivity reactions to macrogol laxatives and some cases of depot steroid formulations.⁴⁻⁶

Our retrospective study of female patients with a history of anaphylaxis to DMPA confirms for the first time that PEG 3350 is the likely culprit allergen. We propose a practical algorithm for diagnostic workup of immediate hypersensitivity reactions to DMPA.

Clinical notes of 15 female patients (age 19-37 years, median 25), referred with a history of anaphylaxis to DMPA to 3 tertiary UK allergy centers (Guy's London, Cambridge, and Sheffield) between 2007 and 2019, were reviewed (Table I). All patients received standard medical care, and ethical approval was not required.

The severity of the index reaction was graded according to Brown.⁷ Depo-Provera (Pfizer Ltd., Tadworth, Surrey, United Kingdom) containing MPA 150 mg/mL and PEG 3350 29 mg/mL was used for skin prick testing (SPT) in all centers. Intradermal tests (IDT) were carried out with a 1:100 and 1:10 dilutions. A sachet of Compound Macrogol Oral Powder (eg, Galen Limited, Craigavon, United Kingdom) containing PEG 3350 was dissolved in water to give a 100 mg/mL (10%) solution of PEG 3350 for SPT in all centers. This solution was further diluted in 0.9% sodium chloride to obtain final concentrations of 0.01 mg/mL (0.001%), 0.1 mg/mL (0.01%), 1 mg/mL (0.1%), and 10 mg/mL (1%) of PEG 3350 for IDT.

The single-dose intramuscular challenge was undertaken with 15 mg (10% of the full dose) of DMPA followed by a 2-hour observation period.

All patients were referred with either grade 2 (8 of 15; 54%) or grade 3 (7 of 15; 46%) anaphylaxis. Eight of 15 (53%) patients reported hypersensitivity reactions to other medications containing PEG: 3 to phenoxymethylpenicillin (penicillin V, PEG 6000), 3 to Moviprep (PEG 3350), 1 to both alginate (Gaviscon, PEG 20000) and Laxido (PEG 3350), and 1 to indomethacin suppositories (PEG 4000 and 8000).

Acute mast cell tryptase, measured in 6 of 15 patients, was significantly (baseline $\times 1.2 + 2$ ng/mL) raised (median, 57.5; range, 12-114 ng/mL) against a normal baseline (median, 6.75; range, 3.2-10.2 ng/mL).

Twelve of 15 (80%) patients had SPT to undiluted DMPA and 2 of 12 (17%) were positive. Twelve of 15 patients had SPT to 10% PEG 3350 and 5 of 12 (42%) were positive. Nine of 13 patients with negative SPT to either DMPA and/or PEG 3350 100 mg/mL (10%) proceeded to IDT with DMPA 1.5 mg/mL (1:100). Two of 9 (22%) were positive. Only 2 of 7 patients proceeded to IDT to DMPA 15 mg/mL (1:10) with a positive result in both cases. Two patients (patients 14 and 15) underwent serial IDT with PEG 0.01, 0.1, and 1 mg/mL (0.001%, 0.01%, and 0.1%, respectively). Both patients suffered systemic reactions at PEG 0.1% and 1%, respectively. They responded promptly to the treatment with oral antihistamine (cetirizine 20 mg PEG free oral solution), prednisolone 30 mg, nebulized salbutamol 2.5 mg, and ipratropium 250 mcg.

Drug provocation with 15 mg/mL DMPA was performed in 2 skin test negative patients (patients 1 and 10). Both patients developed a mild-to-moderate systemic reaction and responded to the same treatment. Adrenaline was not required.

Two patients (patients 1 and 2) subsequently tolerated oral MPA not containing PEG. One patient (patient 15) underwent patch testing to parabens with a negative result.

All 3 patients who had presented with anaphylaxis to phenoxymethylpenicillin (penicillin V) subsequently tolerated penicillin V oral solution that does not contain PEG.

Three of 15 patients tolerated oral PEG-containing medications after presentation.

For the first time, we provide evidence that immediate hypersensitivity to DMPA is caused by the excipient PEG 3350. Indeed, 60% of our patients reported a history of anaphylaxis to other PEG-containing medications.

The clinical presentation of PEG hypersensitivity is influenced by factors unique to this compound: PEG of MW higher than 1000 is poorly absorbed; hence, the route of administration is important. The parenteral route would appear to require lower doses of PEG than the oral route.

In a case of anaphylaxis to depo methylprednisolone (PEG 3350, 29 mg/mL) where PEG was identified as the allergen, a cumulative dose of 7100 mg of PEG 4000 was required to elicit a reaction during oral challenge with macrogol.⁸

Our patients reported both severe hypersensitivity reactions to other PEG-containing medications, mostly macrogol laxatives, and tolerance to oral medications containing PEG with MW ranging from 400 to 8000. The amount of PEG in medications tolerated is likely to be micrograms only.⁹ This and low systemic absorption of PEG with an MW higher than 1000 would be the likely explanation of tolerance in these cases.

TABLE I. Clinical presentation and outcome of investigations in 15 cases

No.	Year	Grading of anaphylaxis and index reaction (all patients reacted within minutes)	Acute and baseline mast cell tryptase (ng/mL)	Relevant drug history	Hx of atopy	Skin prick			Intradermal test			IM challenge to index drug	Additional drug challenge
						DMPA	10% PEG 3350	Other	1:100 DMPA	1:10 DMPA	PEG		
1	2007	Grade 2. Generalized erythema, shortness of breath	N/A	N/A	Nil	Neg	N/D	N/D	Neg	N/D	N/D	15 mg/mL DMPA: chest tightness and urticaria	Tolerate oral MPA
2	2009	Grade 2. Facial, pharyngeal angioedema. Generalized urticaria	N/A	Anaphylaxis to penicillin V	Nil	Neg	N/D	N/A	Neg	N/D	N/D	Pt unwilling	Tolerate liquid penicillin V and oral MPA
3	2012	Grade 2. Urticaria, wheeze, facial angioedema	N/A	N/A	Nil	Neg	Neg	N/A	Pos	N/D	N/D	N/D	
4	2014	Grade 3. Hypotension, vomiting, diarrhea, urticaria	Acute: 114. Baseline: 10.2	Hx of contact rash to cosmetics	Nil	Neg	Neg	N/A	Neg	Pos	N/D	N/A	
5	2015	Grade 2. Generalized urticaria and angioedema, vomiting		Generalized urticaria and angioedema to Moviprep. Contact urticaria to cosmetic	Nil	Neg	Neg	N/A	Neg	N/D	N/D	Pt unwilling	
6	2015	Grade 3. Urticaria, angioedema, bronchospasm, hypotension	Acute: 53. Baseline: 9.8	Anaphylaxis to Indocid suppository and NSAIDs	Asthma and allergic rhinitis	N/D	Pos	N/A	N/D	N/D	N/A	N/A	
7	2016	Grade 3. Vomiting hypotension, generalized urticaria, facial angioedema		Anaphylaxis to Moviprep	Nil	Not done	Pos	N/A	Not done	Not done	N/A	N/A	
8	2016	Grade 3. Bronchospasm, dizziness, hypotension	Acute: 62. Baseline: 5.6	None	Nil	Neg	Neg	N/A	Equivocal	Pos	N/D	N/A	

9	2017	Grade 2. Facial angioedema, wheeze, generalized urticarial		None	Allergic rhinitis	Neg	N/D	N/D	N/D	N/D	N/D	N/A	
10	2017	Grade 2. Wheeze, vomiting		Anaphylaxis to Gaviscon	Nil	Neg	Neg	Not done	Neg	Not done	Not done	15 mg/mL: rhinitis and chest tightness	
11	2017	Grade 3. Urticaria, bronchospasm, hypotension	Acute: 31 Baseline: 3.2	None	Asthma and allergic rhinitis	Pos	Pos	N/D	N/D	N/D	N/D	N/A	
12	2018	Grade 3. Collapsed, generalized urticaria and angioedema	Acute: 98 Baseline: 7.9	Anaphylaxis to Moviprep. Contact dermatitis to cosmetic, shampoo	Nil	N/D	Pos	N/D	N/D	N/D	N/D	N/A	
13	2019	Grade 2. Generalized urticaria, wheeze, laryngeal swelling, facial angioedema	Acute: 12. Baseline: 8	Anaphylaxis to penicillin V. Contact urticaria to cosmetics	Nil	Pos	Pos	Neg to MPA	N/D	N/D	N/D	N/A	Has tolerated erythromycin
14	2019	Grade 2. Generalized urticaria and wheeze		Anaphylaxis to penicillin V	Asthma and allergic rhinitis	Neg	Neg	N/A	neg	N/D	Pos to 1% PEG 3350	N/A	Tolerate penicillin V. Taking Rigevidon (PEG 6000)
15	2019	Grade 3. Generalized urticaria, wheeze, hypotension			Allergic rhinitis	Neg	Neg	Neg to MPA	Pos	N/D	Pos to 0.1% PEG 3350	N/A	

DMPA, Depot medroxyprogesterone acetate; IM, intramuscular; NSAID, nonsteroidal anti-inflammatory drug; PEG, polyethylene glycol.

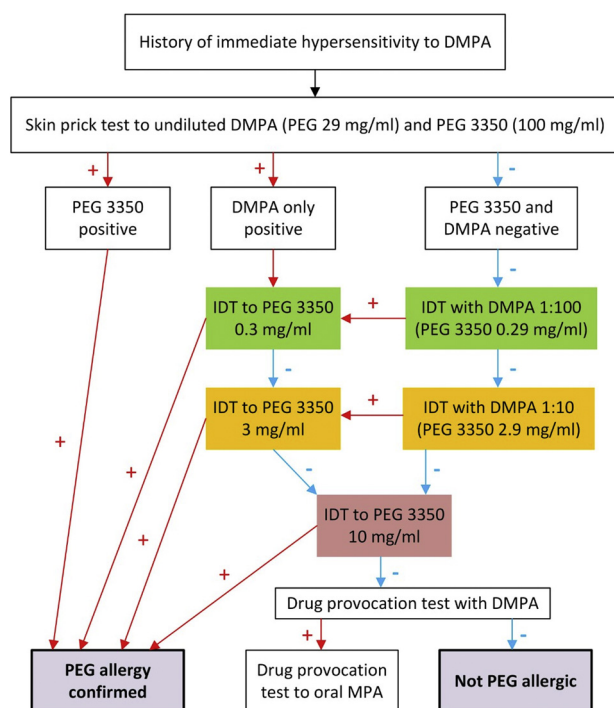


FIGURE 1. Algorithm for the investigation of anaphylaxis to DMPA. Simultaneous IDT testing to confirm PEG 3350 allergy in patients with a positive IDT to DMPA should be avoided. If possible, patients should be tested on a separate occasion to reduce the risk of a systemic reaction. *DMPA*, Depot medroxyprogesterone acetate; *IDT*, intradermal tests; *PEG*, polyethylene glycol.

Confirming a diagnosis of PEG allergy remains challenging. SPT with PEG 3350 10% (100 mg/mL) increases the percentage of positive results in comparison with DMPA (PEG 2.9%; 29 mg/mL). Higher MW PEG formulations may increase sensitivity further but are not commercially available for use in humans.⁴

A further increase in the number of positive results was observed when IDT was performed with PEG 3350 at a concentration of 2.9 mg/mL (DMPA 1:10). However, systemic allergic reactions occurred at or above a concentration of PEG 1 mg/mL, when serial testing was performed or when positive IDT was repeated, thereby increasing the cumulative dose of PEG administered. This confirms the observation of others.⁴

We propose a practical algorithm for the diagnosis of immediate hypersensitivity to DMPA. In patients with a negative skin test to both DMPA and PEG 3350, graded intramuscular DPT with DMPA is recommended (Figure 1).

Oral challenge with macrogol, if negative, is of uncertain diagnostic value.

In summary, we provide evidence that PEG 3350 is likely to be the causative allergen in immediate hypersensitivity to DMPA and propose a protocol for testing to increase diagnostic accuracy and prevent further inadvertent exposure and potentially severe adverse reactions due to PEG as an excipient in other drugs.

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