When leuprolide acetate is essential to care: A review of the literature and framework for assessing drug allergy

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Gonadotropin-releasing hormone agonists are uncommonly associated with hypersensitivity reactions. To date, there have been few reports of these cases by allergists and no clear published protocols on testing. Here, we report the case of a patient who had a potential reaction to leuprolide acetate depot and a framework for assessing for drug hypersensitivity with the available literature in mind. (J Allergy Clin Immunol Global 2024;3:100210.)

Key words: *Adverse drug reactions, drug allergy, leuprolide acetate*

Gonadotropin-releasing hormone (GnRH) agonists are synthetic peptide analogs commonly used to treat a myriad of conditions, including prostate cancer, endometriosis, uterine leiomyomata (fibroids), and precocious puberty. They are also being utilized increasingly for hormone therapy for transgender males, with limited alternatives. GnRH agonists are available in several formulations, including various depot and subcutaneous formulations, all long-acting, and most with shared or similar chemical structures. Although reactions are rare, these agents have been implicated in immediate hypersensitivity reactions. A small number of case reports suggest that they may also provoke delayed or protracted reactions, as well as recurrent anaphylaxis.

Abbreviation used
GnRH: Gonadrotropin-releasing hormone

CASE

A 13-year-old transgender male who was assigned female at birth and had a history of anxiety was receiving 7.5 mg of leuprolide acetate depot (Lupron, AbbVie, North Chicago, Ill) monthly as part of gender-affirming therapy. Minutes after receiving his fifth dose in the primary care office, he reported feeling "unwell," with lightheadedness and dyspnea. He reported diffuse "pins and needles." He was noted to have a hoarse voice, facial swelling, and erythema of his hands. His vital signs demonstrated tachycardia (125 beats per minute), hypotension (74/45 mm Hg), and hypoxia (84%). He was given a single dose of intramuscular epinephrine (0.3 mg) with subsequent resolution of his symptoms. Atryptase level drawn within an hour of the episode yielded a result of 6.6 ug/L. After withdrawal of the therapy, the patient developed significant anxiety and depression with suicidal ideation. His treating physician noted limited other options for puberty blockade in alternative pharmacologic categories and requested an allergy evaluation.

IgE-mediated allergy to GnRH agonists is quite rare.[1,2] The largest study to date, which examined safety in more than 1000 children with central precocious puberty, found adverse reactions in 0.69% of patients, with the most common adverse reaction being sterile abscess.[1] No patients had an immediate drug reaction or anaphylaxis, and only 1 patient had delayed urticaria.

Previous evidence for immediate hypersensitivity reactions to GnRH agonists stems mainly from case reports[3-8] (Table I[9]). There are 7 published cases with conventional features consistent with IgE-mediated allergy. In contrast, a number of the other cases seem less consistent with IgE-mediated allergy based on atypical symptoms, delayed onset of symptoms, and persistence of symptoms over weeks. Although there is a possibility that IgE-mediated reactions present atypically given long-acting formulations, it is also plausible that at least some of these presentations reflect alternative clinical diagnoses. Positive skin testing results in such cases may reflect false positives.

To add to this background evidence, using previously published methods, we reviewed reports included in the US Food and Drug Administration Adverse Event Report System from 2013 to 2022.[9] We found 49,775 distinct adverse event reports in association with any form of leuprolide-containing drug, with 64 of 49,775 reports of anaphylaxis (0.1%), 22 reported hospitalizations, and 0 reported deaths. Of these, 45 of 64 patients (70%) indicated that leuprolide acetate was the only agent given at the time of the reported reaction. A total of 30 reactions were reported to have occurred in women (46.9%), 27 in men (42.2%), and 7 in individuals of unspecified sex. Although the US Food and Drug Administration Adverse Event Report System reports do not constitute confirmed cases, they do provide evidence that patients might report an allergic reaction that will need to be evaluated by an allergist.

When evaluating patients with a potential hypersensitivity reactions to GnRH agonists, it is important to consider the

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The authors have obtained patient consent for the case to be part of the submission and have documented this fact in the medical record as well. The project met the criteria for ethical standards set by the Yale institutional review board.

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TABLE I. Summary of available case reports on reactions to gonadotropin-releasing agents

Age (y), sex	Disease	Atopic history	Agent, dose no., route	Dose (mg)	Reaction (duration)	Reaction onset	Treatment	Testing results	Reference
7, F	CPP	None	LA, third, IM	3.75	Dizziness, diaphoresis, syncope, abdominal pain (<1 d)	3 h	Steroids, AH	+ TA SPT 1:100 + LA ID 1:100	Ökdemir et al[3]
8, F	CPP	None	LA, seventh, IM	7.5	Urticaria, swelling, polyarthralgia (weeks)	2 wk	Steroids, AH	+ LA ID 1:100	Lam et al[4]
			GA, 79th, SC	10.8	Urticaria, polyarthralgia, facial swelling, dysphagia, "recurrent anaphylaxis" (1-2 wk, rash >4 wk), with concurrent illness	5 d	Steroids, AH, Epi	None	
27, F	Endo	N/A	LA, fourth, IM	7.5	Urticaria, respiratory distress (intubated), recurrent similar episodes (~3 wk)	6 h	Epi, AH, steroids	+ LA SPT 1:100, 1:1000	Lettrie et al[7]
33, F	Endo	N/A	LA, second, SC	3.75	Dizziness, confusion, dysarthria, muscle weakness (5 h)	2 h	No therapy	Reportedly + LA, GA (details N/A)	Lüchinger et al[5]
			GA, third, SC	3.6	Blurred vision, weakness (hours)	5-10 min	AH		
36, F	Endo	AR Asthma Contact dermatitis	GA, third-fifth, SC implant GA, sixth, SC	3.6 3.6	LLR LLR → diffuse rash; 48 h later developed facial swelling, dyspnea, throat tightness (2 wk)	2 d 8 h	No treatment AH, Epi, Steroid taper	+ GA SPT (1:100, 000-1:1) – LA SPT – PLGA SPT	Raj et al[9]
66, M	PC	None	LA, first, SC	22.5	Flushing, wheezing, respiratory distress, hypoxia, shock, pulmonary edema (<1 d)	2 min	Intubation, Epi, famotidine, steroids, AH	None	Grant et al[6]
68, M	PC	None	LA, sixth-ninth, SC LA, 10th, SC	3.75 3.75	LLRs (unknown duration) Urticaria, hypoxia, hypotension (<1 d)	N/A 30 min	None Fluids, steroids, AH	DLST + LA (SI = 225%) + PLGA (SI = 217%) – PLA (SI = 175%)	Fujisaki et al[7]
74, M	PC	N/A	LA, first, SC	7.5	"Anaphylaxis," details N/A	5 min	None	None	Taylor et al[7]

Skin testing concentrations reported when available.

AH, Antihistamine; *ARC*, allergic rhinitis; *CPP*, central precocious puberty; *Endo*, endometriosis; *Epi*, epinephrine; *DLST*, drug lymphocyte stimulation test; *GA*, goserelin acetate; *ID*, intradermal; *IM*, intramuscular; *LA*, leuprolide acetate; *LLR*, large local reaction; *N/A*, not available; *PC*, prostate cancer; *PLA*, Polylactic acid; *PLGA*, polylactic and glycolic acid; *SC*, subcutaneous; *SI*, stimulation index; *SPT*, skin prick testing; *TA*, triptorelin acetate.

pharmacologic properties of those agonists, particularly in the common depot formulation. The active drug is housed within biodegradable hydrophobic polymer matrices, which allows for a 2-phase release of leuprolide via initial diffusion and subsequent bioerosion. Dosing intervals are determined by the components in the polymer, which influence drug release from the matrix over time; thus, the excipients in the 1-month and 3-month products differ. Furthermore, excipients also differ between the intramuscular depots and the shorter-acting subcutaneous products. The excipients in the various formulations of leuprolide acetate received by our patient are outlined in Table II. Formulations can sometimes include carboxymethylcellulose, mannitol, or polysorbate 80, which have been reported as potential culprit allergens in some cases of IgE-mediated anaphylaxis.[10]

For our patient, skin testing was performed using subcutaneous leuprolide acetate with a full-strength concentration (5 mg/mL) through skin prick testing, followed by intradermal testing in duplicate with the following dilutions: 1:1000 (0.005 mg/mL) and 1:100 (0.05 mg/mL). The skin test results were negative, with appropriate controls. On the basis of shared decision making with the family, a drug challenge with the preferred agent and dose (ie, 11.25 mg of leuprolide acetate depot) was planned. This higher dose was chosen by the primary prescriber to achieve dosing every 3 months rather than monthly. The medication was reconstituted in the original device and then extracted into a sterile vial. Because peak concentrations for the diffusion phase occur 1 hour after administration, doses of 1.125 mg (10%) first and then 5.1 mg (45%) were administered with 1-hour observation periods, followed by a final dose of 5.1 mg (45% of the total dose) with a 2-hour observation window. Doses were administered in bilateral arms (2 in the right arm, 1 in the left). This was considered a high-risk drug challenge, and it was done in the hospital setting. The patient tolerated the drug challenge without reaction. He subsequently tolerated 2 doses of leuprolide acetate (Lupron) administered intramuscularly (11.25 mg per dose) and 1 dose (22.5 mg) of subcutaneously administered leuprolide acetate (Eligard, Tolmar, Buffalo Grove, Ill).

In summary, given the rare occurrence of immediate hypersensitivity reactions to GnRH agonists, it is important to consider evaluating patients with skin testing and, potentially, drug challenges, particularly in clinical contexts in which these drugs could be considered essential to care. Alternative explanations in our patient's case could include a vasovagal reaction (with or without inaccurately reported vital signs), a panic attack, an illness, or a reaction from direct mast cell activation. Of note, an excipient reaction has been excluded, as the patient subsequently received all excipients in the Lupron formulation from the index reaction (Table II). In this report we have demonstrated how we applied a conventional drug allergy assessment framework to a patient with a potential reaction to a

TABLE II. Excipients in the leuprolide acetate formulations received by our patient

Agent and dose	Administration	Excipients
Leuprolide acetate (Lupron depot, 7.5 mg, 1-mo administration)	Index reaction	D,L-Lactic and glycolic acid copolymer, gelatin, D-mannitol, carboxymethylcellulose sodium, polysorbate 80, glacial acetic acid
Leuprolide acetate (Subcutaneous, 1 mg/0.2-mL vial)	Skin testing	Acetic acid, benzyl alcohol
Leuprolide acetate (Lupron depot, 11.25 mg, 3-mo administration)	Drug challenge, ongoing therapy	D-Mannitol, polylactic acid, carboxymethylcellulose sodium, polysorbate 80, glacial acetic acid
Leuprolide acetate (Eligard, 22.5 mg, 3-mo administration)	Subsequent therapy	Poly (D,L-lactide-co-glycolide) polymer

GnRH agonist (see Fig E1 in the Online Repository at www.jaci-global.org) and reported nonirritating concentrations for skin testing. Although future studies are needed to further characterize reactions to GnRH agonists, evaluate for cross-reactivity between agents, and validate testing protocols, we believe that our case demonstrates a reasonable approach for assessing for drug allergy with the currently available literature in mind.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: S. Leeds is a paid consultant on an independent data monitoring committee for Regeneron, and she also receives funding from Food Allergy Research and Education (FARE). C. A. Stone receives funding from an American Academy of Allergy, Asthma & Immunology Foundation Faculty Development Award. The rest of the authors declare that they have no relevant conflicts of interest.

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