

Successful Prevention of Local and Cutaneous Hypersensitivity Reactions to Seminal Fluid with Intravaginal Cromolyn

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ABSTRACT

Seminal fluid hypersensitivity usually is characterized by postcoital vulvovaginal itching, swelling, redness, with or without systemic signs and symptoms. Efforts to manage this condition have either met with poor patient acceptance or have not been uniformly successful. We describe a 23-year-old atopic woman with documented IgE-mediated local and cutaneous hypersensitivity to SF. Using a controlled, single-blind challenge method, pretreatment with intravaginal 4% cromolyn sodium in a water-based cream completely blocked both local and cutaneous immediate hypersensitivity reactions to SF in this highly sensitive patient. We believe this may represent an alternative and more desirable method of preventive management in such patients.

The first report of seminal fluid (SF) hypersensitivity in 1958 was by Specken.¹ Since that time, there have been 33 cases reported in the literature (English). Seminal fluid hypersensitivity is usually characterized by the postcoital onset of vulvovaginal itching, swelling, redness, burning, or pain with or without progression to systemic signs and symptoms of anaphylaxis. Fixed cutaneous eruptions also have been described.² Most reported cases have been of women (age 16 to 44) with both local and systemic immediate hypersensitivity responses, with local reactions usually preceding the sys-

temic reaction. There are eight reported cases of pure local hypersensitivity reactions;³⁻⁶ pure systemic reactors are unusual but have been reported.⁷⁻¹⁰ The majority of these women had either personal or family histories of atopic disease, i.e., allergic rhinitis, asthma, or atopic dermatitis.

Efforts to manage this frustrating problem have been either poorly accepted by patients or not uniformly successful. Abstinence and the proper use of condoms are effective,⁵ albeit less-than-desirable methods of preventing these reactions. Parenteral desensitization attempts have been reported to be effective⁹ but not uniformly successful¹¹ and require purified antigen fractions^{10,12} (because whole SF contains immunosuppressive factors). A state of tolerance has been achieved^{10,13} in successful cases, however, regular (2 to 3 times per week) intercourse was required to maintain the desensitized state.^{10,13} Antihistamines prior to intercourse have provided moderate but incomplete relief of symptoms in a few cases.^{6,14}

We report the first controlled, single-blind, successful trial of intravaginal cromolyn sodium in the prevention of local and cutaneous hypersensitivity reactions to SF.

CASE PRESENTATION

A 23-year-old woman presented to the Allergy and Immunology Division at Scripps Clinic for evaluation of urticaria following sexual intercourse. Shortly after her marriage, she noted occasional episodes of transient pruritis in her vaginal area immediately after

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coitus. At that time, she was using an oral contraceptive as a means of birth control. After one year of marriage, she began using a diaphragm, but she continued to experience mild vaginal itching after intercourse, again, only lasting for a matter of seconds. There was no discharge accompanying this itching. After two years of marriage, she noted the itching had become more pronounced and lasted for several minutes.

Shortly thereafter, the patient noted an episode of significant itching immediately following intercourse, progressing to marked swelling of the labia and a sensation of marked internal vaginal swelling. She abstained from intercourse for one week and once again experienced itching and marked labial swelling immediately following intercourse. This progressed to urticaria involving the neck, chest, and arms. She immediately went to her gynecologist who prescribed diphenhydramine and a cortisone cream for her vaginal area. Within 4 hours her hives disappeared, and the swelling also decreased gradually. One week later, she engaged in unprotected intercourse, misattributing her previous reaction as being caused by the diaphragm. Again, she had immediate intense itching postejaculation. She quickly self-administered three 25 mg diphenhydramine tablets. Despite this, within 15 minutes she had severe generalized urticaria, which included upper eyelid swelling.

Since that last episode, her husband began wearing condoms during intercourse, and she remained symptom-free using this method.

This patient gave a history of spring hay-fever symptoms dating back to age 6. She also had a 2-year history of hand eczema. She denied a history of adverse reactions to food or drug. There was a strong family history of atopic diseases. Her past medical history was significant for mitral valve prolapse, ovarian cysts, and premenstrual syndrome. She had never been pregnant. Menarche was at age 13. Her periods were regular and occurred every 28 days with a normal amount of flow. They lasted approximately 4 days. Her sexual history revealed that prior to marriage she had only one conjugal partner and had no history of pruritis or hives after intercourse with this partner. There is no history of engaging in fellatio. The only medication she took was mefenamic acid (Ponstel, Parke-Davis, Morris Plains, NJ) as needed for menstrual cramps. At the time of evaluation, her husband was taking no medications. Her physical examination was entirely normal, inasmuch as we were unable to observe this patient during her acute reaction.

MATERIALS AND METHODS

Seminal Fluid Separation Method

Ejaculates from the patient's husband were allowed to liquefy at room temperature for 60 minutes; an

equal volume of 0.05 M phosphate buffered saline (PBS) was added, and the specimen was centrifuged at 4.5C for 30 minutes at 2000 rpm.⁵ The sperm pellet was then washed and centrifuged (37.5C, 900 rpm, 10 min) twice with 3 cc sperm washing medium (Irvine Scientific, Santa Ana, CA). This medium contains sodium chloride, potassium chloride, magnesium sulfate, HEPES (N-2-Hydroxyethylpiperazine-5 N' 2-ethanesulfonic acid), glucose, sodium pyruvate, sodium lactate, phenol red, and human albumin powder. The supernatant seminal fluid was removed by suction pipette. Microscopic examination was performed on a sample of the specimen to ensure adequate removal of sperm.

Skin Testing

Cutaneous skin testing for immediate hypersensitivity to SF was performed using supernatant SF diluted 10-fold to make 1:10, 1:100, and 1:1000 dilutions. Skin testing was performed using Morrow-Brown standardized prick testing needles. Histamine (1 mg/mL) as well as phosphate buffered saline were used as positive and negative controls, respectively.

Intravaginal Challenge

Intravaginal challenge was performed using 2 cc of progressive 10-fold dilutions (starting at 1:1000) of SF; 2 cc PBS was used as control. A 5 cc syringe was used, and the SF dilution was injected into the posterior fornix under direct visualization using a catheter attached to the syringe. Vaginal speculum examination was performed at baseline and every 15 minutes for 1 hour after SF challenge.

Cromolyn Cream

A 4% cromolyn cream was compounded by dissolving powdered cromolyn sodium (Intal, Fisons Corporation) into an inert water-based cream (HEB cream, Barnes-Hind Inc., Sunnyvale, CA).

HEB cream contains purified water, mineral oil, white petrolatum, stearyl alcohol, cetyl alcohol, sodium lauryl sulfate, methylparaben, and propyl paraben as preservatives.

RESULTS

Skin Testing

Dilutional prick skin testing with supernatant seminal fluid and washed sperm was performed; results are shown in Table I. Further control was performed by skin testing the patient's husband with concentrated seminal fluid (1:1); this yielded a negative result (0/0).

TABLE I

Dilutional Prick Skin Testing Results (Wheal/Flare in mm)

Seminal fluid (1:1000)	0/0
Seminal fluid (1:100)	4/13
Seminal fluid (1:10)	7/18
Seminal fluid (1:1)	11/35
Histamine (1 mg/mL)	6/25
Phosphate buffered saline	0/0
Washed sperm	0/0

Intravaginal SF Challenge

Vaginal itching was first reported within 15 minutes of 1:100 challenge; moderate cervicovaginal swelling was also apparent within 30 minutes of this challenge. PBS challenge was negative (Table II).

Pretreatment with 5 cc (one vaginal applicator full) 4% cromolyn cream 30 minutes prior to intravaginal challenge with 2 cc of seminal fluid resulted in complete protection from itching, swelling, and urticaria after 1:100, 1:10, and 1:1 (undiluted) challenges (Table III). Pretreatment with HEB cream (as control) did not prevent the reaction to SF at 1:100 dilution (provoking dose). Using this cromolyn cream pretreatment method at home, the patient has been asymptomatic following unprotected intercourse (6-month follow-up).

DISCUSSION

In this case study, we performed single-blind, controlled, intravaginal SF challenges on a young woman in whom we documented (by cutaneous testing) IgE-mediated hypersensitivity to SF. Pretreatment with a 4% cromolyn cream resulted in complete protection

from signs and symptoms of immediate hypersensitivity after challenge with SF at the provoking dilution (1:100) as well as further concentrated dilutions, including undiluted (1:1) SF. Continued use of this regimen at home has resulted in asymptomatic unprotected coitus for the past several months. Interestingly, on one occasion, the patient reported having mild pruritis on a small area of her labia minora after penile withdrawal; this occurred the only time she neglected to apply a thin layer of the cream to the labia prior to intercourse. The area of pruritis corresponded to the precise location where a large drop of SF contacted the labia on withdrawal.

Systemic reactions to seminal fluid are uniformly IgE-mediated, immediate hypersensitivity responses, with presumed mast cell degranulation and mediator release into the systemic circulation leading to classic anaphylaxis.⁵ Four out of 6 pure local reactors who have undergone cutaneous testing for immediate hypersensitivity to seminal fluid had evidence for IgE antibody.^{5,6} In a report by Bernstein et al.,⁵ of 2 pure local reactors, one subject demonstrated lymphocyte transformation (*in vitro* correlate of delayed hypersensitivity) after stimulation with seminal fluid; however, both subjects were found to have lymphocyte transformation after spermatozoal stimulation. Chang et al.⁶ reported a family of pure local reactors (a mother and three daughters). Two out of three family members had definite evidence for IgE antibodies to SF on cutaneous testing.

The inciting antigen has been characterized as a heat stable, basic glycoprotein found in seminal plasma, not in sperm.⁷ It appears to be prostate derived, as evidenced by analysis of surgical specimens.¹⁵ The antigen has an approximate molecular weight of 20–30 kd and is eluted in fraction IV on a Sephadex G-200 column chromatograph.^{7,16} The antigen appears to be present in all men.⁵

Previous effective management strategies for this condition have included abstinence and condom use. The former is not feasible to recommend to most patients, and the latter is usually not very well accepted among sexual partners of those affected. Prophylactic use of antihistamines has not provided adequate protection in the few cases thus far reported.^{6,8}

Parenteral desensitization has been reported to be an effective mode of therapy in some cases, however, it has not been uniformly successful.^{9,11} Initial attempts using whole seminal plasma may have been unsuccessful due to the presence of immunosuppressive factors in these crude preparations.¹⁷ Bernstein and coworkers have reported a case of successful desensitization using purified antigen fractions obtained by Sephadex G-100 column chromatography.¹⁰ However, regular (2 to 3 times per week) intercourse was required to maintain the tolerant state in this patient, suggesting that im-

TABLE II

Results of Baseline Intravaginal Challenge

Challenge	Dilution	Volume (cc)	Reaction
Seminal fluid	1:1000	2	None
	1:100	2	Moderate cervicovaginal pruritis (15 min) and swelling/erythema (30 min)
Phosphate buffered saline	1:1	2	None

TABLE III

Effect of Cromolyn Pretreatment on Intravaginal Challenge

Challenge	Dilution	Volume (cc)	Reaction	
			4% Cromolyn Cream Pretreatment	HEB Cream Base Pretreatment (Control)
Seminal fluid	1:100	2	None	Moderate cervico-vaginal pruritis (15 min) and swelling/erythema (30 min)
	1:10	2	None	—
	1:1	2	None	—

munomodulation of the hypersensitivity response to SF did not occur. Recently, Ohman¹⁸ reported a successful decline in specific serum IgE to SF with a concomitant rise in specific IgG, 12 months after initiation of immunotherapy using purified antigen fractions. Systemic reactions following topical contact with SF no longer occurred in their subject, however, unprotected intercourse or intravaginal challenge was not attempted.

In an uncontrolled trial, Goldenhersh and Saxon⁴ successfully pretreated a pure local reactor with 3 b.i.d. doses of an 8% cromolyn vaginal cream before a single challenge with 0.6 cc seminal fluid. In this study, the subject was not blinded, only 0.6 cc of SF was used for challenges (normal ejaculate contains 1.0 to 5.0 cc SF), and details of the challenge protocol were not provided. In addition, their 24-hour pretreatment protocol was not designed for practical, spontaneous p.r.n. use.

In conclusion, we have described a patient with documented IgE-mediated, immediate local and cutaneous hypersensitivity to SF, in whom 4% cromolyn cream applied intravaginally 30 minutes before challenge and intercourse successfully prevented both reactions. We believe this may represent an alternative and more desirable method of preventive management in such patients. However, it should be noted that as yet cromolyn has not been demonstrated to be successful therapy in cases of severe anaphylactic reactions. Thus, appropriate caution should be exercised when evaluating patients with such reactions.

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