Basophil Activation Test-Confirmed, Ortho-phthalaldehyde-Induced Anaphylaxis after Cystoscopy

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0505

Key words: Anaphylaxis, Basophil activation test, Cystoscopy, Drug hypersensitivity, OPA (ortho-phthalaldehyde)

Palabras clave: Anafilaxia. Test de Activación de Basófilos. Citoscopia. Hipersensibilidad a medicamentos. OPA (ortoftaldehído).

Anaphylactic reactions to OPA have been reported [**1,2].** A skin test using OPA has been reported to be useful for the diagnosis. However, it could induce a large late-phase cutaneous reaction in some patients [2]. Therefore, basophil activation tests (BAT) would be useful in cases with patients who cannot perform skin testing, or for those patients who have experienced life-threatening grade IV allergic reactions to OPA. We report two cases of OPA-induced anaphylaxis after cystoscopy with positive BAT.

Case 1

A 79-year-old Thai man was diagnosed with bladder cancer and treated with transurethral resection of bladder tumor. His comorbidities included end-stage renal disease with regular hemodialysis, type 2 diabetes, dyslipidemia, and stable coronary heart disease. He had no atopic diseases nor a history of drug allergies. His medications included carvedilol, losartan, manidipine, and doxazocin. Seven flexible cystoscopies were done over 2 years for post-bladder

doi: 10.18176/jiaci.0505

surgery surveillance. Shortly after the eighth cystoscopy, he developed generalized pruritus in the recovery room, followed by lip angioedema and hypotension (61/40 mmHg).

Case 2

A 70-year-old Thai man was diagnosed with urothelial cell carcinoma and treated with transurethral resection of bladder tumor. His comorbidities included stable coronary heart disease, dyslipidemia, and stage-4 chronic kidney disease. He had no atopic diseases nor a history of drug allergies. Six flexible cystoscopies were done every 3 months over 1.5 years for post-bladder surgery surveillance. He developed generalized erythema and pruritus 30 minutes after the seventh cystoscopy, followed by hypotension (66/40 mmHg).

In both cases, anaphylaxis was treated. All symptoms improved without a biphasic reaction. The urologist used chlorhexidine for skin preparation and wore latex-containing gloves with lubricating gel (Xylocaine Jelly® 2%) during the examination. The equipment was disinfected by immersion in 0.55% OPA and thoroughly rinsed and flushed according to the manufacturer's instructions before cystoscopies [3].

After the anaphylactic episodes, skin tests were performed at 4-week intervals in case 1 and 5-week intervals in case 2. All possible culprit agents, including those used during cystoscopy, were prepared for the test, including OPA (5.5 mg/ml) [1], glutaraldehyde, lidocaine, chlorhexidine gluconate, latex, Xylocaine Jelly®, and other drug excipients **(summarized in Table 1).** The skin test was negative in both cases, except positive prick tests to OPA with wheal sizes of 24 and 8 mm at 20 minutes, respectively, and expanding late-phase reactions 24 hours later with average indurations of 35.5 and 15 mm, respectively. Skin irritation was excluded by negative skin prick tests with OPA (5.5 mg/mL) in all four control individuals.

doi: 10.18176/jiaci.0505

BAT was done according to the previous protocol [4]. Briefly, 100 microliters of EDTA-whole blood were mixed with reaction cocktail containing 0.005, 0.01 and 0.025 microgram/mL OPA in the condition with and without IL-3. Anti-CCR3-PE, CD63- FITC, and CD203c-APC monoclonal antibodies were included in the reaction cocktail. OPA concentrations used in BAT were based on a previous cytotoxicity study [5]. Positive controls included basophils activated with anti-IgE antibody, anti-FceRI antibody and fMLP. Negative control included basophils incubated with reaction cocktail without the drug. Blood samples from 4 healthy controls with no known history of allergic reactions were also included. Reactions were incubated for 30 minutes at 37°C incubator with 5% CO_2. Red blood cells were then lysed with BD lysis buffer. Basophil activation was determined by flow cytometry using $CCR3^{+}$ SSC^{low} gating strategy. Basophil activation was determined by CD63+ activation marker. CD203c+ activation marker was also used when the reaction was performed in the absence of IL-3. The percentage of CD63 or CD203c positive cells was obtained and the stimulation index was calculated. SI > 2 was considered as positive in our study. BAT showed positive results on three different concentrations of OPA **(material supplementary figure).** All healthy controls showed no increase in the activation markers at all OPA concentrations.

After discontinuation of OPA and implementation of an alternative process using autoclaving for cystoscopic equipment disinfection, no allergic reactions associated with subsequent cystoscopies in both cases.

Repeated exposure to OPA residues on the scope might produce sensitization in both allergic and non-allergic individuals after being used for 4-5 times. [1,2] Although the warning in the package insert [3] included a contraindication to OPA use in bladder cancer patients, other patient populations may also be at risk for sensitization through repeated cystoscopies, such as

doi: 10.18176/jiaci.0505

patients with prostatic pathology, recurrent calculus, urethral stricture, and also in patients who undergo repeated laryngoscopies or repeated colonoscopies.[1,6]

Despite rinsing a cystoscope with water, OPA cannot be completely washed off and could bind irreversibly to the rubber coating on the endoscopes.[7] Therefore, it should not be used for repeated procedures for whatever reason.

This is the first reported positive BAT in such cases. The BAT results were compatible with skin prick tests in both OPA-allergic and control individuals. Skin prick test in case 1 elicited quite a large wheal with pseudopods formation, and the late phase spread beyond the borders of the reaction. Although it is unclear why the wheal from the OPA skin test increased over time, there were possible explanations. First, the IgE-mediated mechanism itself could explain the immediate and late-phase skin test reactions [8]**.** Second, OPA has delayed irritancy potential which was demonstrated in the animal model [5]**.** This should raise the safety concern in patients with severe comorbidity or a history of a severe reaction. Therefore, BAT might be a safer option in the allergological diagnostic instrumentation to document IHRs, particularly when the diagnosis cannot be established by other means [9]. The previous study also recommended the lower concentrations of OPA (0.55 or 0.055 mg/mL) for skin test which has found to avoid the delayed local reaction. **[2]** The underlying mechanism of OPA-induced anaphylaxis is likely to be IgE-mediated. OPA-specific IgE has been demonstrated by enzyme-linked immunosorbent assay [10]. Passive sensitization of the basophils of a healthy donor by serum from the OPA-allergic patient occurred based on the basophil release test [6]. In conclusion, BAT may help the physician to identify OPA-induced anaphylaxis and might be a safer option than skin testing.

doi: 10.18176/jiaci.0505

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

We would like to thank Dr. Anthony Tan for editing the English language.

Conflicts of interest disclosure

The authors have no conflicts of interest to declare pertaining to this article.

Patient consent

Informed consent and permission for publication were obtained from the patient.

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doi: 10.18176/jiaci.0505

Table 1. **Allergological diagnostic testing results**

Diagnostic tests	**Case 1**	**Case 2**
Skin prick test	Wheal size (mm)	Wheal size (mm)
Positive control (histamine 10 mg/mL)	8 x 6	7 x 5
Negative control (normal saline)	0	0
OPA (5.5 mg/ml) At 15 minutes At 24 hours	 28 x 20 (pseudopods) 46 x 42	 9 x 7 16 x 14
Chlorhexidine (5 mg/ml)	0	0
Lidocaine (20 mg/ml)	0	0
Additives; Carboxymethylcellulose (10 mg/ml), Polyethylene glycol (Macrogol® 4000 1%), Polysorbate, Sodium benzoate 5%, Sodium-metabisulfite, Xylocaine Jelly® 2%	0	0
Intradermal test*		
Chlorhexidine (5 mg/ml)	negative	negative
Lidocaine (2 mg/ml)	negative	negative
Specific IgE to latex †	0.02 kUA/L	0.08 kUA/L
Provocation test		
Glove use test (1 hour) ¶	negative	negative
2% Lidocaine (0.5 ml) **β**	negative	negative

Abbreviations = CMC, Carboxymethyl cellulose; IgE, Immunoglobulin E; kAU/L, kilo allergy unit per liter; mg, milligram; ml, milliliter; mm, millimeter; OPA, Ortho-phthalaldehyde;
*Positive test result is defined by a wheal diameter larger than 3 mm than the negative control
† Solid-phase immunoassay: ImmunoCAP.
¶ Put on the complete latex-powdered glove on one hand and put on vinyl glove on another hand (control) for 1 hour. The positive test result is defined by the development of erythema, pruritus, or blisters on the hand area covered by latex glove, and no reactions on the control side.
β Subcutaneous injection of 2% lidocaine (0.5 ml) at the posterior portion of the arm.

doi: 10.18176/jiaci.0505