

Ortho-phthalaldehyde–Induced Anaphylaxis After Cystoscopy: Confirmation by the Basophil Activation Test

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Anaphylactic reactions to ortho-phthalaldehyde (*o*-phthalaldehyde) have been reported [1,2]. Skin testing with *o*-phthalaldehyde has been shown to be useful for diagnosis, although this has been shown to induce a large late-phase cutaneous reaction in some patients [2]. Therefore, the basophil activation test (BAT) could prove useful in patients who cannot undergo skin testing and who have experienced life-threatening grade IV allergic reactions to *o*-phthalaldehyde. We report positive BAT results in 2 cases of *o*-phthalaldehyde–induced anaphylaxis after cystoscopy.

The first patient was a 79-year-old Thai man with bladder cancer treated using transurethral resection. His comorbidities included end-stage renal disease with regular hemodialysis, type 2 diabetes, dyslipidemia, and stable coronary heart disease. He had no atopic diseases or history of drug allergy. His medications included carvedilol, losartan, manidipine, and doxazocin. Seven flexible cystoscopies were performed over 2 years for postsurgery surveillance. Shortly after the eighth cystoscopy, he developed generalized pruritus in the recovery room, followed by lip angioedema and hypotension (61/40 mmHg).

The second patient was a 70-year-old Thai man with urothelial cell carcinoma treated using transurethral resection. His comorbidities included stable coronary heart disease, dyslipidemia, and stage-4 chronic kidney disease. He had no atopic diseases or history of drug allergies. Six flexible cystoscopies were performed every 3 months over 1.5 years for postsurgery surveillance. Thirty minutes after the seventh cystoscopy, he developed generalized erythema and pruritus followed by hypotension (66/40 mmHg).

Anaphylaxis was treated in both cases. 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% *o*-phthalaldehyde and thoroughly rinsed and flushed according to the manufacturer's instructions before the cystoscopy [3].

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

BAT was performed according to a previous protocol [4]. Briefly, 100 μ L of EDTA-whole blood was mixed with a reaction cocktail containing 0.005, 0.01, and 0.025 μ g/mL *o*-phthalaldehyde with and without IL-3. The monoclonal antibodies CCR3-PE, CD63-FITC, and CD203c-APC were included in the reaction cocktail. The *o*-phthalaldehyde concentrations used in the BAT were based on a previous cytotoxicity study [5]. Positive controls included basophils activated with anti-IgE antibody, anti-Fc ϵ RI antibody, and fMPL. The negative control comprised basophils incubated with the reaction cocktail without the drug. Blood samples from 4 healthy controls with no known history of allergic reactions were also included. The reaction products were incubated for 30 minutes at 37°C with 5% CO₂. Red blood cells were then lysed with lysing buffer (BD Biosciences). Basophil activation was determined using flow cytometry based on a CCR3⁺ SSC^{low} gating strategy and CD63⁺ activation marker. CD203c⁺ activation marker was also used when the reaction was performed in the absence of IL-3. The percentage of CD63⁺ and CD203c⁺ cells was obtained, and the stimulation index was calculated. An index >2 was considered positive. BAT showed positive results for 3 different concentrations of *o*-phthalaldehyde (Supplementary Figure 1). No increase in the activation markers was observed in the healthy controls at any of the *o*-phthalaldehyde concentrations used.

After discontinuation of *o*-phthalaldehyde and implementation of an alternative process using autoclaving for disinfection of cystoscopy equipment, no allergic reactions associated with subsequent cystoscopies were observed in either patient.

Repeated exposure to *o*-phthalaldehyde residues on the scope might produce sensitization in both allergic and nonallergic individuals after 4-5 uses [1,2]. Although the warning in the package insert [3] included a contraindication to *o*-phthalaldehyde in bladder cancer patients, other patient populations may also be at risk of sensitization through repeated cystoscopies, namely, patients with prostate conditions, recurrent calculus, and urethral stricture, as well as patients who undergo repeated laryngoscopies or repeated colonoscopies [1,6].

o-Phthalaldehyde cannot be completely washed off a cystoscope—despite rinsing with water—and may bind

Table. Allergological Diagnostic Testing Results

Diagnostic tests	Patient 1	Patient 2
<i>Skin prick test</i>	Wheal size, mm	Wheal size, mm
Positive control (histamine 10 mg/mL)	8×6	7×5
Negative control (normal saline)	0	0
<i>o</i> -Phthalaldehyde (5.5 mg/mL)		
At 15 min	28×20 (pseudopods)	9×7
At 24 h	46×42	16×14
Chlorhexidine (5 mg/mL)	0	0
Lidocaine (20 mg/mL)	0	0
<i>Additives</i>		
Carboxymethylcellulose (10 mg/mL), polyethylene glycol (macrogol 4000 1%), polysorbate, sodium benzoate 5%, sodium-metabisulfite, Xylocaine Jelly 2%	0	0
<i>Intradermal test^a</i>		
Chlorhexidine (5 mg/mL)	Negative	Negative
Lidocaine (2 mg/mL)	Negative	Negative
Specific IgE to latex ^b	0.02 kU _A /L	0.08 kU _A /L
<i>Provocation test</i>		
Glove use test (1 h) ^c	Negative	Nnegative
2% Lidocaine (0.5 mL) ^d	Negative	Negative

^aA positive test result is defined as a wheal diameter >3 mm larger than the negative control.

^bSolid-phase immunoassay: ImmunoCAP.

^cA complete latex-powdered glove on one hand and a vinyl glove on the other hand (control) for 1 hour. A positive test result is defined as the development of erythema, pruritus, or blisters on the hand covered by the latex glove, and no reactions on the control side.

^dSubcutaneous injection of 2% lidocaine (0.5 mL) on the volar surface of the arm.

irreversibly to the rubber coating on the endoscope [7]. Therefore, it should not be used for repeated procedures under any circumstances.

This is the first reported positive BAT result in such cases. The BAT results were compatible with skin prick tests in both *o*-phthalaldehyde-allergic patients and control individuals. Skin prick testing in patient 1 elicited quite a large wheal with pseudopod formation, and the late phase spread beyond the borders of the reaction. Although it is unclear why the wheal from the *o*-phthalaldehyde skin test increased over time, we can offer 2 likely explanations. First, the IgE-mediated mechanism itself could explain the immediate and late-phase skin test reactions [8]. Second, *o*-phthalaldehyde has delayed irritancy potential, as demonstrated in an animal model [5]. This should raise a safety concern in patients with severe comorbidity or a history of severe reaction. Therefore, BAT might be a safer option in the allergological study of immediate hypersensitivity reactions, particularly when the diagnosis cannot be established by other means [9]. The previous study also recommended lower concentrations of *o*-phthalaldehyde (0.55 or 0.055 mg/mL) for skin testing, since this has been shown to prevent delayed local reactions [2]. The underlying mechanism of *o*-phthalaldehyde-induced anaphylaxis is likely to be IgE-mediated. *o*-phthalaldehyde-specific IgE

has been demonstrated by enzyme-linked immunosorbent assay [10]. Passive sensitization of basophils in a healthy donor by serum from the *o*-phthalaldehyde-allergic patient occurred based on the basophil release test [6]. In conclusion, BAT may help the physician to identify *o*-phthalaldehyde-induced anaphylaxis and might be a safer option than skin testing.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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