

Allergy to ortho-phthalaldehyde in the healthcare setting: advice for clinicians

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This study summarizes and reviews the available health information on ortho-phthalaldehyde (OPA), a recently introduced and widespread disinfectant for heat-sensitive medical equipment, particularly focusing on its possible immunological effects in the healthcare setting. OPA properties derived from laboratory and clinical studies, and *in vivo* and *in vitro* tests for the diagnosis of OPA allergy are described. The available evidence suggests the spreading of OPA as disinfectant in endoscopy units despite the little available scientific evidence on its safety. Indeed, some papers reported on serious adverse reactions to OPA in patients and, to a lesser extent, in exposed workers, and *in vivo* studies suggested that OPA is a dermal and respiratory sensitizer. Finally, until more definite safety data become available only suggestions on possible preventive measures can be provided.

KEY WORDS: anaphylaxis • endoscopy • glutaraldehyde • healthcare workers • high-level disinfection • low-molecular weight • occupational asthma • ortho-phthalaldehyde

Patient-care items that touch mucous membranes or nonintact skin (e.g., endoscopes and respiratory therapy equipment) require high-level disinfection consisting of the elimination of all microorganisms, except a high number of bacterial spores [1]. Owing to its proven effectiveness, for the past 40 years, glutaraldehyde (GA) in 2–4% solution with water has been the primary choice for disinfecting heat-sensitive medical equipment [2]. Nevertheless, owing to its irritative and sensitizing properties [3], its use has been associated with a number of serious health problems in exposed workers, including dermatitis and occupational asthma [4–6]. Furthermore, the increasing frequency of some GA-resistant *Mycobacterium* species [7] has raised the need for its replacement with a safer agent. In this context, in 1999 a new high-level disinfectant, the Cidex® OPA (Advanced Sterilization Products, CA, USA; 0.55% ortho-phthalaldehyde [OPA] solution), received clearance by the US FDA, and was then introduced to the market and promoted as a safer alternative to GA, despite a lack of proper toxicity testing. Some specific characteristics, such as the low volatility and no

need for activation, have also increased the use of OPA as a more practical alternative to GA. Nevertheless, the claims about the safety of OPA may not be sufficiently supported or refuted by the little available scientific evidence [2], and effective preventive measures for OPA exposure have not yet been established [3].

Along with approval for disinfecting medical devices, OPA is also approved for use as an indoor antimicrobial pesticide; as an intermediate for synthesis of pharmaceuticals, medicines and other organic compounds; as a reagent for drinking water analysis and as a diagnostic for urea nitrogen test systems [8,101–103]. Currently, there are no regulations regarding proper use and safe OPA exposure levels, despite the potential exposure of a large number of healthcare workers and patients. In fact, the US National Institute for Occupational Safety and Health (NIOSH) estimated that from 1981 to 1983, 3253 workers had been potentially exposed to OPA in several industries other than healthcare compared with 376,330 for GA in the healthcare field alone [104]. After the introduction of OPA as an alternative to GA, it is reasonable to assume that in the USA

alone, more than 300,000 workers [8], and an unknown number of patients, might be exposed to OPA.

In the last decade, some reports have been published on adverse reactions both in patients and in exposed workers following OPA use as a disinfectant for medical devices, raising the suspicion for its possible adverse health effects. Therefore, the NIOSH promoted an *ad hoc* project, started in 2008 and finished in 2011, aimed at characterizing the potential health hazards associated with occupational exposure to OPA when used as a disinfectant for medical devices in endoscopy units. Dermal and respiratory irritation and sensitization was the focus of the toxicological tests, conducted in experimental animals, because of the absence of published toxicological data on OPA. Through a multidisciplinary approach, the project intended to: develop analytical methods for environmental monitoring of OPA and characterize workplace exposure; develop estimates of exposure for exposure–response studies to identify direct cause–effect relationships; determine the feasibility of an OPA biomarker; and to obtain dose–response data for hazard identification risk assessment, which, along with health assessments, will serve as the basis for establishing exposure limits [105]. Unfortunately, to the best of our knowledge, at present, the report of the study has not been published.

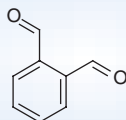
The purpose of this study is to summarize and review the available health information on OPA, with particular attention paid to the possible immunological effects in the healthcare setting, where the agent is widely used as disinfectant for medical devices. For this purpose, the authors took into account all available evidence in the literature (including Medline, Embase, Scopus and ISI Web of Knowledge), using ‘OPA and allergy’ as key words. There were no language or publication restrictions in the literature searches. Nevertheless, only the abstract has been evaluated in papers written in languages different from English, French, Spanish or Italian. Furthermore, bibliographies of published papers for unpublished reports or data sources were searched.

OPA properties

OPA is an aromatic dialdehyde (FIGURE 1) usually produced in the form of a clear, pale-blue liquid (pH 7.5) solution that typically contains 0.55% OPA [106]. Compared with GA, OPA has several potential advantages: it requires no activation, has excellent stability over a wide pH range (pH: 3–9), and has a barely perceptible odor. Material safety data sheets of disinfectant solution containing OPA from different producers are not homogeneous in defining its irritating and sensitizing properties and health effects.

Chemical name: ortho-phthalaldehyde

Formula: $C_8H_6O_2$



Molecular weight: 134.123

CAS RN: 643-79-8

In vitro studies demonstrated that OPA has first-rate microbicidal activity [9]. When tested against a wide range of microorganisms, including GA-resistant mycobacteria and *Bacillus subtilis* spores [10], OPA showed good activity against the mycobacteria tested, including the GA-resistant strains. The property exploited in its use as a biocidal agent results from its high chemical reactivity and the affinity for biological amines, as previously demonstrated also for GA and dialdehydes as a chemical class. By virtue of its ability to react with proteins, OPA may also cause haptenization of native proteins in biological systems and could then possibly lead to aberrant immune responses and to the development of allergic reactions [11]. These hapten reactions form the basis for sensitization resulting from exposure to reactive low molecular-weight chemicals in the workplace [12].

A potential disadvantage is that OPA stains proteins gray, including those of unprotected skin, and thus must be handled with caution and with appropriate personal protective devices (i.e., gloves, eye protection and fluid-resistant gowns) [9].

Sensitizing properties of OPA

Rideout *et al.* performed a relative toxicity review on high-level disinfectants, including OPA and GA [2]. Because of the paucity of available data, the authors adopted a qualitative structure–activity relationship (SAR) analysis to predict relative respiratory sensitization potential.

The Hazassess [13–15,107], a chemical asthma hazard assessment online program for low molecular-weight chemical respiratory sensitizers, was adopted to confirm the findings of the qualitative SAR analysis, by entering the structures of the high-level disinfectant chemicals. The odds ratio of the hazard produced by the program, namely, ‘hazard index’, ranges from the lowest (i.e., 0.00) to the highest (i.e., 1.00) risk of respiratory sensitization potential.

As expected, the SAR analysis correctly identified GA as a typical respiratory sensitizer. OPA is an aromatic dialdehyde and is very similar to GA, contains the same predictors of respiratory sensitization as GA and an aromatic group. In detail, GA received a hazard index of 0.8242 and OPA 0.7251. The latter results suggest that both GA and OPA have the potential to act as respiratory sensitizers. Despite a number of methodological limitation (the method uses modeling based on empirical data from other chemicals, rather than scientific data on the controversial chemical to make predictions), also acknowledged by the authors, this kind of analysis is often used as a first step in the absence of preexisting scientific studies or when other more rigorous studies are not yet available.

Laboratory evidence

A study to describe the mechanism of the OPA-associated immunological reaction was conducted by Hasegawa *et al.* in ovalbumin (OVA)-sensitized mice [16]. Briefly, two groups of mice were injected subcutaneously with 200 μ l of OPA and then challenged with 5% OVA saline solution by means of an ultrasonic inhaler [16].

Figure 1. Ortho-phthalaldehyde.

In sensitized mice, OPA also induced the increase of total cell numbers and the infiltration of neutrophils in bronchoalveolar lavage fluid after allergen challenge, in a dose-dependent manner.

In sensitized mice, OPA induced the upregulation of eotaxin and monocyte chemoattractant protein-1 mRNAs in the lung, and an increase in OVA-specific IgE, without a concomitant increase in the level of OVA-specific IgG, compared with nonsensitized controlled mice. mRNA for cytokines IL-4 and IL-5 mRNA was expressed by allergen (OVA) challenge in both the lungs collected from OPA-administered-nonsensitized mice and OPA-administered-sensitized mice. The two main results of this study are that in sensitized mice OPA accelerates the production of allergen-specific IgE antibody and induces neutrophil infiltration into bronchoalveolar fluid with very low dose concentration. Hence, in accordance with the authors' conclusions, the aforementioned data suggest that OPA acts as an immunological adjuvant.

Similarly, Morinaga *et al.* examined the acute toxicity of OPA in male imprinting control region mice injected with 0.125–0.5% OPA [17]. The study revealed that OPA caused acute inflammation (increase in leukocyte counts and in the proportion of neutrophils) and induced specific IgE and IgG significantly in the sera, suggesting that OPA acts as a hapten.

The irritancy and sensitization potential of OPA was also evaluated by Anderson *et al.* [8]. The EpiDerm Skin Irritation Test was used to evaluate *in vitro* irritancy potential of OPA and GA. OPA was demonstrated to be significantly more cytotoxic than glutaraldehyde ($p < 0.01$) at all concentrations tested. Actually, treatment with 0.4125, 0.55 and 1.1% OPA resulted in an approximately 60% and 90–95% decrease ($p < 0.01$) respectively in cell viability, whereas treatment with GA only resulted in 30% ($p < 0.01$) decrease in cell viability at the highest (1.1%) concentration. To confirm such *in vitro* results, ear swelling was evaluated in mice after dermal exposure to OPA, and it was found to be significantly increased (44% ear swelling, $p < 0.01$) when mice were treated with 0.75% OPA. The local lymph node assay used for the initial evaluation of the sensitization potential showed a concentration-dependent increase in lymphocyte proliferation at OPA concentrations ranging from 0.005 to 0.75%. The mechanisms of OPA sensitization and the type of response (type I or type IV) induced by the chemical was further investigated using phenotypic analysis of B220+ and IgE+B220+ cells in the draining lymph node cells and the measurement of total and specific serum IgE levels. Statistically significant increases in IgE+B220+ cells were identified in the draining lymph node cells of mice treated with 0.1% (percent count) and 0.75% (percent and absolute counts) OPA.

In confirmation and support of the latter result, the authors observed that exposure to OPA produced dose-dependent elevations in total serum IgE levels, commonly used as an indicator of type I hypersensitivity to dermal sensitizers, and a significant elevation in OPA-specific IgE and OPA-specific IgG1 were also found after treatment with 0.75% OPA. In addition, significant increases in IL-4 mRNA and protein expression in the draining lymph node cells were observed in OPA-treated groups. Overall, the comparison of these data to that obtained for GA demonstrates that the sensitizing potential for OPA is comparable with that of GA.

After demonstrating that OPA is a dermal sensitizer in mice [8], the same laboratory performed a study to determine if OPA acts as a respiratory sensitizer following inhalation exposure [11]. Briefly, mice were exposed to OPA vapors by means of a nose exposure system to minimize skin contact, and airway and lymph nodes were examined for cytokine gene expression and alterations in lymphocyte populations. No observable clinical signs of systemic toxicity or respiratory distress throughout the exposure were observed after OPA inhalation. Conversely, a concentration-dependent increase in lymphocyte proliferation, mainly B lymphocytes, was observed in the draining lymph nodes after 3-day-exposure to OPA. Of note, isotype switching to IgE was strongly suggested by the dramatic increase in the population of B lymphocytes expressing IgE after secondary challenge of mice with OPA. Expression of Th2 (IL-4, IL-5 and IL-13) and anti-/proinflammatory (IL-10, TNF- α and IL-1 β) cytokine genes was upregulated in the lymph nodes and the nasal mucosa. Finally, mice exposed to the higher concentrations of OPA produced OPA-specific IgG1 antibodies, thereby suggesting a systemic sensitization.

Recent research was conducted by Adenuga *et al.* aimed at determining whether the toxicogenomic approach can improve the specificity and accuracy of the local lymph node assay in distinguishing and characterizing chemical sensitizers and irritants [18]. For this purpose, female BALB/c mice were topically exposed to two representative low-molecular-weight chemicals for contact sensitizers, respiratory sensitizers (including OPA) and nonsensitizing irritants, and gene expression changes were monitored in auricular lymph nodes. Concerning OPA, the study revealed that induction of certain key genes implicated in Th2 allergic responses was notably higher in response to respiratory sensitizers when compared with contact sensitizers, and that other sets of genes involved in IgE-mediated hypersensitivity responses and responsible for mediating vascular permeability to enhance recruitment of lymphocytes during an allergic reaction were differentially regulated by the respiratory sensitizers but not contact sensitizers.

Clinical evidence

The first documented immunologic reaction caused by OPA dates back to 2004 [19] and describes four patients with bladder cancer who experienced nine episodes of anaphylaxis after cystoscopies. The urologic practice had switched from GA to OPA 2 years before the first reaction. All episodes occurred 15–30 min after exposure, were severe and characterized by urticaria; angioedema, penile itching/edema, laryngeal edema, loss of consciousness, chest tightness and convulsion were also documented or reported by the patients. Local (i.e., penile) itching and edema occurred in seven of the nine reactions, but in only one patient did it precede the first anaphylactic reaction. Authors speculated that because OPA is much less water-soluble than GA, it may be possible that the established protocol for rinsing the disinfectants off the cystoscopes used by the urologists was sufficient to remove sensitizing doses of the water-soluble GA, but not those of the less water-soluble OPA.

Two further cases of allergic reactions (urticaria, angioedema and anaphylaxis) following surveillance cystoscopy associated

with OPA were described by Joshi and Rosenfeld [20]. Anaphylaxis was preceded by pruritus, and angioedema of the genitals occurred immediately during the procedure in both patients. The diagnosis was confirmed by means of prick tests for OPA.

Two further cases of anaphylaxis following cystoscopies with instruments sterilized with OPA were described by Cooper *et al.* [21]. In both cases, the reaction occurred approximately 15 min after the procedure and was characterized by generalized pruritus and shortness of breath. It may be supposed that both patients had already been exposed to OPA since they had undergone previous surveillance cystoscopies (4 to 5). One patient failed to report to the urologist that he had experienced mild pruritus following his previous cystoscopic evaluation.

Suzukawa *et al.* described three cases of OPA anaphylaxis after laryngoscopy in three different patients [22,23]. Reported symptoms were dyspnea, runny nose, sneezing and systemic urticaria. Of note, the authors reported that all three patients underwent subsequent laryngoscopic examinations using an OPA-disinfected, thoroughly rinsed (>15 min) fiberscope, without any further allergic symptom.

A case of anaphylactic shock as a result of OPA immediately following a colonoscopy has been reported by Fusasaki *et al.* [24]. The diagnosis was confirmed by the high level of phthalic anhydride-specific IgE and the positive reaction for prick test to OPA.

We have recently described the case of a 60-year-old man, with a clinical history of larynx carcinoma, who experienced face and neck edema and generalized urticaria after laryngoscopy performed with endoscopic equipment sterilized with Cidex OPA [25]. The diagnosis was confirmed by the positivity of the patch test and of the basophil activation test (BAT) [26] with OPA.

In 2006, Fujita *et al.* described the first case of occupational asthma and contact dermatitis thought to be caused by OPA exposure in a female nurse employed in an endoscopy unit in a Japanese hospital [27]. Symptoms occurred after introduction of OPA solution in the hospital, whereas no respiratory or cutaneous symptoms were reported when handling GA. The diagnosis was made on the basis of the clinical history, and particularly of the stop-resume test (appearance or worsening of symptoms when exposed to OPA and disappearance or improvement when not exposed to the chemical). Nevertheless, no immunologic test (prick tests, patch tests or sIgE detection) was performed, and the worker did not undergo the specific inhalation challenge test, which is considered the reference standard for the diagnosis of occupational respiratory disease [28]. Therefore, in that case, the diagnosis of occupational asthma as a result of OPA should be considered likely, but not definitive.

The same authors [29] carried out a study in an endoscopy unit in Japan, due to increasing OPA use as an alternative to GA, and reported that 17 out of 70 healthcare workers exposed to OPA had experienced skin, respiratory or eye symptoms. Contact dermatitis occurred in four workers, one of whom also developed asthma.

The results of a questionnaire administered in 17 endoscopy disinfection rooms in Japan revealed that among 80 females employed in disinfection work who used only antiseptic solutions

containing OPA, the incidence of disinfection-related complaints were 10% skin, 9% eye and 16% respiratory symptoms [30].

Finally, it is worth noting that, although not published in medical literature, there are hundreds of voluntary reports about health effects caused by OPA, both in healthcare workers and in patients submitted to endoscopic procedures, in the Manufacturer and User Facility Device Experience [108]. Epidemiological data on OPA allergy in patients and healthcare workers are summarized in TABLE 1.

***In vivo* & *in vitro* tests for the diagnosis of OPA allergy**

Sokol prick-tested four patients and five volunteer control subjects with OPA 5.5 mg/ml, and results were interpreted at 20 min and 24 h [19]. All four patients developed both an itchy wheal and flare reaction within 20 min after the OPA test, and a late-phase reaction, which continued to progress for 24 h, showing an average induration of 56.3 mm described as swollen, hot, tense and hard. All controls showed negative reactions to OPA skin testing. In view of the large reactions on skin-prick testing in the four patients, the authors recommended that lower concentrations of OPA should be used in skin testing with OPA (i.e., 0.55 or 0.055 mg/ml). In the two patients with anaphylaxis following cystoscopy, Joshi and Rosenfeld [20] reported positive prick tests for OPA in serum albumin at 1:10,000 dilution.

In the aforementioned papers by Suzukawa *et al.* [22,23], two of the three patients with anaphylactic reactions were *in vivo* tested by means of intracutaneous test with a disinfectant solution containing OPA at 1:1000 and 1:100 dilution, respectively, and interpreted at 15 min. *In vitro* basophil histamine-release tests were performed in a buffer containing 0.03% human serum albumin. Of note, the tests demonstrated that both the disinfectant used in the endoscopy unit (OPA solution) and pure OPA (obtained by a producer) evoked release of histamine from the basophils of the three patients. By contrast, basophils obtained from healthy control donors did not show histamine release in response to OPA, excluding a nonspecific response. Furthermore, the presence of OPA-specific IgE in the sera from all three patients was detected by enzyme-linked immunosorbent assay system.

In the paper by Cooper *et al.* [21], two patients who experienced anaphylactic reactions following cystoscopies were prick-tested with Cidex OPA 1:10 and dilution and with the full strength compounds. A positive reaction was obtained only with the undiluted compound.

The patient described by our group [25] was challenged by patch test with Cidex OPA on the antecubital fossa, which gave a positive result (itching and nonvesicular erythema) 30 min after application [31].

Furthermore, a significant basophil activation after stimulation with Cidex OPA 1:1000 and 1:10,000 was demonstrated by the BAT test (CD63⁺ basophils: 37.2%, stimulation index: 10.3 and CD63⁺ basophils: 10.6%, stimulation index: 2.9, respectively; normal values CD63⁺ basophils: <5%, stimulation index: <2). 2h application of Cidex OPA to the antecubital fossa in two healthy controls only resulted in a golden brown staining of the skin, as described for GA dermal application [32], and the BAT with Cidex OPA performed in 20 nonexposed controls excluded the

Table 1. Epidemiological data on ortho-phthalaldehyde allergy in patients and healthcare workers.

Study (year)	Patients (n)	Type of procedure	Type of reaction	Time of the reaction	Diagnostic tools	Ref.
<i>Patients</i>						
Sokol (2004)	4	Cystoscopy	Anaphylaxis	15–30 min	SPTs	[19]
Joshi and Rosenfeld (2004)	2	Cystoscopy	Anaphylaxis	Immediate	SPTs	[20]
Fusasaki <i>et al.</i> (2007)	1	Colonoscopy	Anaphylaxis	Immediate	SPTs, specific IgE	[24]
Suzukawa <i>et al.</i> (2007)	3	Laryngoscopy	Anaphylaxis	NR	Intracutaneous test, HRT	[23]
Cooper <i>et al.</i> (2008)	2	Cystoscopy	Anaphylaxis	15 min	SPTs	[21]
Pala <i>et al.</i> (2012)	1	Laryngoscopy	Neck edema, generalized urticaria	Immediate	Patch test, BAT	[25]
<i>Healthcare workers</i>						
Fujita <i>et al.</i> (2006)	1	Endoscopy disinfection	Occupational asthma, contact dermatitis	NR	Stop–resume test	[27]
Fujita <i>et al.</i> (2007)	70	Endoscopy disinfection	Skin, respiratory or eye symptoms (21% [†])	NR	Questionnaire	[29]
Miyajima <i>et al.</i> (2010)	80	Endoscopy disinfection	Skin (10%), eye (9%), respiratory (16%)	NR	Questionnaire	[30]

[†]Cumulative figure referring to all reported symptoms.

BAT: Basophil activation test; HRT: Histamine release test; NR: Not reported; SPT: Skin prick test.

possibility of a nonspecific activation (average CD63⁺ basophils was $3 \pm 1.5\%$, the stimulation index 1 ± 1.5).

Measurement of environmental exposure

Several studies have been carried out to evaluate OPA concentration in endoscopy units, although at present the exposure limits for OPA are not available [106], for either the general population or for the occupational setting.

Marena *et al.* compared air levels of GA and OPA, by means of both infrared spectroscopy and of HPLC with UV detection, in several endoscopy units in an Italian hospital [33]. To allow a homogeneous comparison of the measurements, GA and OPA concentrations were detected in identical operating conditions and for identical periods of time. A significantly lower aldehyde value was detected when using OPA compared with that obtained when GTA was used to disinfect endoscopes. Indeed, the mean OPA level was $8.4 \mu\text{g}/\text{m}^3$ (equivalent to 1.53 ppb), equivalent to 0.039% of the mean GA level ($21.2793 \mu\text{g}/\text{m}^3$).

Fujita *et al.* measured OPA concentration in the air of an endoscopic sterilization room by HPLC with UV detection and found OPA concentrations ranging from 0.4 ppb in the endoscopy room to 2.0 ppb near the dust box [27]. A subsequent study by the same group [29] reported OPA concentration in the endoscopy unit ranging from 0.06 to 2.01 ppb, with the highest concentration found while the cover of a bucket for dipping endoscopy instruments was opened.

The study conducted by Miyajima *et al.* also considered the OPA concentration in the different scenarios found in 17 endoscopy disinfection rooms (i.e., manual disinfection rooms in which workers used immersion vats for endoscope disinfection, and automatic disinfection rooms in which automatic washers were used) [30]. As expected, they observed that OPA exposure concentrations

during the disinfection process of endoscopes was significantly higher in the manual group (median: 1.43 ppb; range: not detected [ND]–5.37 ppb) than in the automatic group (median: 0.35 ppb; range: ND–0.69 ppb). Similarly, during charging and discharging of the antiseptic solution, OPA levels were significantly higher in the manual group (median: 2.58 ppb; range: 0.92–10.0 ppb) than in the automatic group (median: 0.46 ppb; range: ND–1.35 ppb). Time-weighted averages of OPA exposure concentration during work shifts were 0.33–1.15 ppb (median: 0.66 ppb) in the manual group and 0.13–1.28 ppb (median: 0.33 ppb) in the automatic group, which suggests that manual workers are exposed to higher levels of OPA.

Tucker developed three sampling and analytical methods for OPA detection (one for OPA in air and two for analysis of surfaces for OPA contamination) [34]. The authors suggest a great utility, in industrial monitoring in occupational areas where OPA is used, of both the method for air detection and of the surface wipe method involving fluorescent detection.

Prevention

According to the currently available literature on OPA, and considering what we have learnt from GA, prevention strategies should be addressed both to exposed workers and to patients. Concerning healthcare workers, at present only one documented case of ‘likely’ occupational asthma [27] and few questionnaire-based surveys [29,30] have been reported. Nevertheless, the awareness that occupational allergic disorders are often under-reported, and/or underdiagnosed [28,35], along with the results of the laboratory studies suggesting that OPA is a potential sensitizer [8,16,17] also by inhalation [11], impose a precautionary attitude. Primary prevention should minimize the exposure or, whenever possible,

substitute the agent suspected (or confirmed) to cause adverse health effects in the exposed workers.

The replacement of a known hazard, like GA, with a chemical with largely unknown toxicity, like OPA, is not perforce the best solution, although this practice is generally considered to be the paramount option for risk reduction in occupational settings. Indeed, the lack of knowledge of serious health effects of a substance should be carefully evaluated and taken as a warning, rather than an indication of safety [36]. Unfortunately, the current absence of exposure limits for OPA [106] and of available data on 'safe' exposure levels, only allows one to suggest that OPA air levels are kept as low as possible and for the use of proper personal protective devices. The sole study that compared the OPA concentrations in two different settings found in several endoscopy units, revealed that workers using immersion vats for endoscope disinfection were exposed to higher levels of OPA than workers using automatic washers [30]. That study suggests that automatic washing procedures should preferably be adopted to reduce the risk of exposure, and manual endoscope disinfection in vats implies the environmental dispersion of dangerous aerosols containing high disinfectant concentration.

Concerning the appropriateness of the personal protective device, Marena *et al.* compared the resistance of various types of gloves to OPA [33]. Tests showed that OPA permeated vinyl gloves more rapidly (26,628 ng/cm²/h) than nitrile gloves (13.9 ng/cm²/h); hence, the latter should preferably be adopted by healthcare workers handling OPA.

Concerning the prevention of adverse events in patients submitted to endoscopic procedures, the available medical literature [19,21–25], although scarce, reports on serious events (i.e., anaphylaxis) in almost all cases described; therefore, particular attention should be paid. The paucity of the literature on the topic should also be considered in the contest of the recent FDA permission received for OPA, and the subsequent recent introduction of OPA in the endoscopy units. The available data allow inference that repeated procedures with endoscopes disinfected with OPA may expose the patients to the risk of serious adverse reactions, with warning symptoms occurring rarely [19] and without any other known risk factor. In some cases [19], the diagnostic tests for OPA were performed only after other possible causal agents (e.g., latex, antibiotics and anesthetics) had been excluded.

A doubt about the reliability of the protocol for rinsing the disinfectants off the cystoscopes has been raised by Sokol, who speculated that the established protocol used for GA is not sufficient for OPA, because of the different water solubility of the two compounds [19]. A recent paper [37] examined this possibility by means of a zone-of-inhibition test, and also a test to extract residues of OPA with acetonitrile from sections of endoscope insertion tube materials after exposure to these disinfectants followed by a series of rinses in water or by aeration overnight. The endoscope material soaked in OPA produced zones of inhibition even after 15 serial rinses with water, and was extracted from the rinsed endoscope material by acetonitrile. The authors concluded that OPA cannot be rinsed away from flexible endoscope material with any practical number of rinses with water, or by drying overnight. By contrast, the report by Suzukawa *et al.* in which

the three patients with a history of anaphylaxis following laryngoscopic examinations using an OPA-disinfected device never again manifested allergic symptoms when the OPA-disinfected endoscopes were thoroughly rinsed (>15 min), suggested that the disinfection procedure should probably be revised and adapted to the new agent chemical properties [22,23].

Patients and healthcare workers with suspected adverse effects after exposure to OPA should first be investigated by skin testing with OPA solution, which has been reported to be a reliable tool in all tested patients; it is easy to perform, not time consuming and cheap. A prudential approach, using increasing OPA concentration (from 1:10,000 to the full-strength compound) is suggested, until more information becomes available.

Expert commentary

The need for GA replacement with a safer agent, owing to the health problems related to its use, has led to the spreading of OPA use, before sufficient scientific evidence about its safety had been available. The current literature on the topic, although scarce, suggests that OPA is a dermal and respiratory sensitizer, with sensitizing potential at least comparable to that of GA, and may cause severe reactions, especially in patients repeatedly submitted to endoscopic procedures performed with endoscopes disinfected with OPA. The rapid onset of the reactions, along with the positivity of skin tests and the detection of specific IgE to OPA, suggest a type I response. Until more definite data become available, the limitation of air OPA levels to be as low as possible, and the use of appropriate personal protective devices, can only be suggested.

Concerning the safety of patients undergoing endoscopic procedures with OPA-disinfected devices, a thorough rinse (>15 min) of the instrument may be suggested, although its efficacy is still unproven. Furthermore, in patients with adverse reactions during these procedures, the possible occurrence of a reaction to OPA, in addition to the other more common causes (e.g., latex, anesthetics and antibiotics), should always be considered and investigated.

Finally, the hundreds of voluntary reports may raise the suspicion that the published papers on a dozen of cases only represent the tip of the iceberg, while undersea the paramount of missed or unreported cases may yet be located.

Large controlled studies are highly recommended to exactly estimate the real prevalence of the allergic reactions to OPA in both healthcare workers and in patients, thus allowing us to confirm or refute the claim about the safety of OPA.

Five-year view

Considering the diffusion of the OPA, and the incoming evidence on its health effects, large studies on this 'new' disinfecting agent will probably be carried out in the near future, and more accurate data will be made available. A valuable source of information will also be the forthcoming report by NIOSH on the potential health hazards associated with occupational exposure to OPA. Finally, the definition of convenient procedures for rinsing OPA-disinfected endoscopic equipment and the standardization of *in vivo* and *in vitro* tests for the diagnosis of OPA allergy are mandatory.

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Key issues

- The use of ortho-phthalaldehyde (OPA) as disinfectant in endoscopy units is widely spreading despite the little available scientific evidence on its safety.
- In the last decade some papers reported serious adverse reactions to OPA in patients and, to a lesser extent, in exposed workers.
- Exposure limits and effective preventive measurements for OPA exposure have not yet been established.
- *In vivo* animal studies suggested that OPA acts as an immunological adjuvant and is a dermal and respiratory sensitizer.
- A type I immunologic response to OPA is suggested by the detection of serum-specific IgE in both sensitized individuals and animal models.
- Skin-prick tests proved effective in demonstrating the sensitization to OPA, but the method needs standardization.
- The basophil histamine release test and basophil activation test have been occasionally used to demonstrate sensitization to OPA.
- Until safety data become available, OPA air levels should be kept as low as possible, and proper personal protective devices should be adopted to prevent work-related allergies.
- In patients with adverse reactions following endoscopic procedures, the use of OPA as a disinfectant should be investigated.
- The rinsing procedure of OPA-disinfected endoscopes need to be revised and adapted to the new agent chemical properties.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

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