

Rapid Communication

A Case of Occupational Bronchial Asthma and Contact Dermatitis Caused by *ortho*-Phthalaldehyde Exposure in a Medical Worker

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Ortho-phthalaldehyde (OPA) has been considered a powerful disinfectant for medical devices because it is more effective against glutaraldehyde (GA)-resistant mycobacteria, less irritating and faster-acting than GA, and does not require an activation step^{1–4}. Since many nurses have developed dermatitis and bronchial asthma as a result of GA exposure^{5, 6}, the use of OPA as an alternative to GA is increasing. Although the lowest published lethal dose (LDLo) of OPA is reported to be 7 mg/kg in the mouse⁷, few safety tests on OPA have been performed.

There have been reports of chemical burn⁸) and anaphylaxis^{9, 10}) in patients which were caused by OPA. However, a company producing it advertises that OPA is much safer than GA for workers because its vapor pressure is lower and solutions of it are thinner than those of GA.

In this report, we describe the first case of occupational bronchial asthma and contact dermatitis thought to be caused by OPA exposure in an endoscopy unit, and we also report the OPA concentrations measured in the air at the patient's workplace.

Case

A 57-yr-old female had been employed as a nurse in an endoscopy unit at our hospital from April 2000. She had handled 2.5% GA solution for disinfection of endoscopes using auto-washers and a bucket for soaking. She exhibited no respiratory or cutaneous symptoms while handling GA.

In March 2003, use of 0.55% OPA solution in place of GA began at our hospital. Subsequently, the patient exhibited slight dyspnea and dry cough in December 2003. On January 6, 2004, she had a checkup at a respiratory outpatient department because her dyspnea had worsened and she was experiencing shortness of breath. Although chest X-ray revealed no abnormal findings, there was wheezing bilaterally in the lung fields. The results of laboratory examinations are shown in Table 1. No eosinophilia or increase in non-specific IgE was noted. All other laboratory findings were within normal limits. The patient had no past history of bronchial asthma. She was clinically diagnosed with bronchial asthma and prescribed β_2 -stimulant tapes (Tulobuterol) and steroid inhalers (Budesonide), which improved her respiratory symptoms. However, episodic attacks of asthma occurred repeatedly once or twice per month during work in the endoscopy unit, as shown in Fig. 1.

In April 2004, serous papules and urticaria were found disseminated on both lower extremities of the patient. These rashes were diagnosed as contact dermatitis by a dermatologist.

The patient was transferred to the emergency room from the endoscopy unit on May 1, 2004. After the change of workplace, she experienced no further episodes of asthma or dermatitis. Her asthma and dermatitis thus appear to have been caused by OPA exposure.

Measurements of Work Environment

We measured the OPA concentrations in the air of the endoscopic sterilization room at the hospital in November 2004. Active air sampling was performed at 1.0 l/min for 30 min using a 2,4-dinitrophenylhydrazine-silica cartridge (LpDNPH S10, Spelco, Bellefonte, PA, USA). The hydrazone derivative of OPA was eluted with acetonitrile and analyzed with a high performance liquid chromatograph (HP1100, Ailent, USA) with a UV detector (UV-VIS, Ailent, USA)¹¹. The results are shown in Fig. 2.

Discussion

There are reports that insufficient washing of endoscopes has had severe effects including chemical burn⁸) and anaphylaxis^{9, 10}). However, cases of occupational respiratory disease and dermatitis caused by OPA exposure have not been previously described in the literature.

While our patient was handling GA, she was asymptomatic. Although measurements of her work environment were not performed during that period, GA concentration in the air may have been higher than that of OPA, as suggested by previous reports^{5, 12, 13}). In addition, the method of sterilization using OPA was the same as that using GA, and only gloves were used for protection.

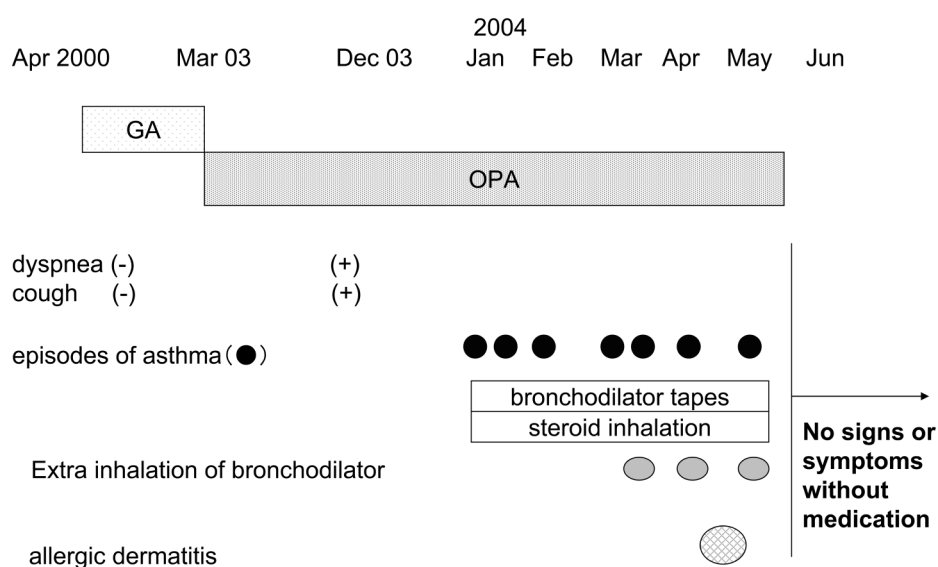
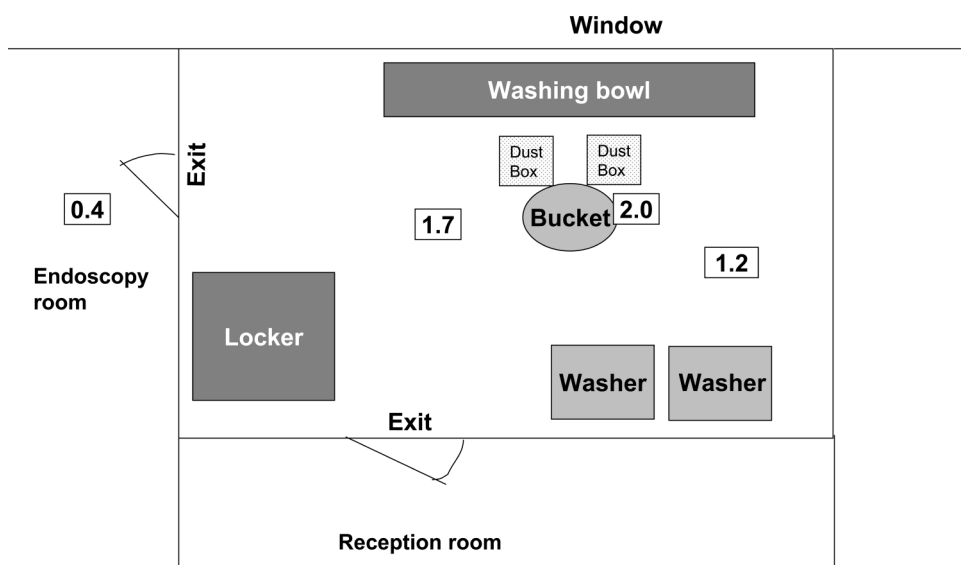
The diagnosis of occupational asthma should include

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Table 1. Results of clinical laboratory examinations at the first episode of asthma

Hematology (reference value)	Biochemistry (reference value)
RBC $404 \times 10^4/\mu\text{L}$ (357–497)	CRP 0.30 mg/mL (0.00–0.30)
Hb 13.2 g/dL (11.4–14.2)	AST 22 IU/L (10–37)
Hct 38.3% (32.3–42.1)	ALT 27 IU/L (10–37)
Platelets $37.1 \times 10^4/\mu\text{L}$ (13–35)	TP 7.8 g/dL (6.0–8.3)
WBC $8,300/\mu\text{L}$ (3,500–9,500)	BUN 15 mg/dL (7–20)
(Seg 52.8%, Lym 33.2%, Mo 7.1%, Eo 5.7%, Baso 1.2%)	Cr 0.5 mg/dL (0.4–0.9)
	Non-specific IgE 88 IU/mL (<250)

**Fig. 1.** Clinical course of the patient.**Fig. 2.** A sketch of the endoscopy unit and OPA concentrations in air. □: Sampling point and concentration of OPA (ppb).

both the diagnosis of asthma and the establishment of work-relatedness¹⁴⁾. Based on the definition of a surveillance case, diagnosis of occupational asthma requires A) diagnosis of asthma, B) onset of asthma after entering the workplace, C) association between symptoms of asthma and work, and D) one or more of the following criteria: 1) workplace exposure to an agent known to give rise to occupational asthma; 2) work-related changes in FEV₁ or peak expiratory flow (PEF) rate; 3) work-related changes in bronchial responsiveness; 4) positive response to specific inhalation challenge tests; and 5) onset of asthma with a clear association with a symptomatic exposure to an irritant agent in the workplace¹⁴⁾.

In this case, although the pulmonary function test was not performed, we diagnosed the patient's respiratory symptoms as bronchial asthma. Chest X-ray revealed no abnormal findings, and laboratory examination yielded no findings of inflammation. Therefore, diagnosis of her respiratory symptoms as those of other diseases such as chronic obstructive pulmonary disease (e. g. emphysema), cardiac dysfunction or bronchitis, which can also cause wheezing, dyspnea and shortness of breath, would not have been reasonable. Moreover, her symptoms improved under treatment with steroid inhalers and β_2 -stimulant tapes. Steroids are used as controller medications for bronchial asthma, while β_2 -stimulants function as supportive treatment¹⁵⁾. We therefore diagnosed her respiratory symptoms as bronchial asthma based on the results of the laboratory examination, check-up findings and the effects of treatment. The patient had no history of bronchial asthma before the use of OPA, and her asthma corresponded to OPA exposure with a latency period of 9 months. Moreover, as shown in Fig. 1, her symptoms nearly disappeared after she was free from OPA exposure. These findings suggest a strong relationship between her symptoms and her workplace environment. Since there has been a report of chemical burn in a patient exposed to OPA⁸⁾, OPA can be considered an irritant. Thus of the criteria¹⁴⁾ noted above, the present case meets A), B), C), and D)–5). We therefore believe that this patient's asthma was occupational asthma caused by OPA exposure. The inhalation challenge test would be useful for confirming whether the patient's asthma were caused by OPA, but we did not perform it since we considered the risks greater than the potential benefits to this patient. It is reported that even if inhalation challenge tests are considered the gold standard, they are not common practice and should not be considered for routine diagnostic tests¹⁶⁾. Moreover, inhalation challenge tests have seldom been performed outside of a few specialized centers in Canada and Europe¹⁷⁾.

According to the ACCP (American College of Chest Physicians)¹⁴⁾, asthma in the workplace is classified as (1) occupational asthma or asthma caused by exposure to specific agents in the workplace, or (2) work-

aggravated asthma or concurrent asthma worsened by workplace exposure. Moreover, two types of occupational asthma are distinguished by whether they appear after a latency period. Immunological occupational asthma is characterized by a latency period prior to the onset of asthma¹⁶⁾. Anaphylaxis caused by OPA is strongly suggested to be due to an immunological mechanism, since skin prick tests for OPA were positive in all patients⁹⁾ and a histamine release test using basophils from a patient was positive¹⁰⁾. OPA may thus cause asthma by an immunological mechanism, although eosinophilia and increase in non-specific IgE were not observed in the present case. Mapp *et al.*¹⁶⁾ mentioned that low molecular weight agents cause occupational asthma that has the clinical and pathologic features of immunologic asthma, but does not consistently induce IgE antibody.

Alternatively, one report states that evidence for an immunological mechanism is still lacking or may not exist for some agents causing occupational asthma with a latency period¹⁴⁾.

Serous papules and urticaria were found disseminated on both lower extremities. We concluded that this eczema was contact dermatitis caused by OPA because of the cutaneous findings, the diagnosis by a dermatologist, and the relationship between the period of onset of this eczema and the use of OPA. It is known that the patch test is very helpful in the diagnosis of allergic contact dermatitis¹⁸⁾, though it was rejected by the patient.

Since GA exposure is a major cause of occupational asthma, according to the HSE in the UK¹⁹⁾, GA exposure is now strictly regulated in Europe. In Japan, the Ministry of Health, Labour and Welfare in February 2005 recommended that GA exposure be kept below 0.05 ppm in sterilization units²⁰⁾. Many hospitals in Japan have subsequently come to use OPA in place of GA¹³⁾ despite the fact that little is known concerning the risks to employees of exposure to OPA^{6, 13)}.

Marena *et al.*¹²⁾ compared air levels of GA and OPA in several endoscopy units in their hospital, and reported that the mean OPA level was 8.4 $\mu\text{g}/\text{m}^3$ (1.53 ppb), with a range of 6.38–11.01 $\mu\text{g}/\text{m}^3$ (1.16–2.00 ppb). These OPA levels were nearly equal to those we measured. Despite the fact that concentration of OPA in the air was quite low, at only a few ppb, bronchial asthma and contact dermatitis occurred in our patient.

This case indicates that OPA itself can be a powerful sensitizer, suggesting that widespread use of OPA as a substitute for GA may result in serious health risks for workers.

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References

- 1) Walsh SE, Maillard JY and Russell AD: Ortho-phthalaldehyde: a possible alternative to glutaraldehyde for high level disinfection. *J Appl Microbiol* 86, 1039–1046 (1999)
- 2) Fraud S, Maillard JY and Russell AD: Comparison of the mycobactericidal activity of ortho-phthalaldehyde, glutaraldehyde and other dialdehydes by a quantitative suspension test. *J Hosp Infect* 48, 214–221 (2001)
- 3) Hession SM: Endoscope disinfection by ortho-phthalaldehyde in a clinical setting: an evaluation of reprocessing time and costs compared with glutaraldehyde. *Gastroenterol Nurs* 26, 110–114 (2003)
- 4) Hamasuna R, Nose K, Sueyoshi T, Nagano M, Hasui Y, Osada Y and Hamasuna R: High-level disinfection of cystoscopic equipment with ortho-phthalaldehyde solution. *J Hosp Infect* 57, 346–348 (2004)
- 5) ACGIH. Glutaraldehyde Documentation of the TLVs and BEIs with other world wide occupational exposure values CD-ROM 2005. Cincinnati: ACGIH, 2005.
- 6) Takigawa T and Endo Y: Effects of glutaraldehyde exposure on human health. *J Occup Health* 48, 75–87 (2006)
- 7) RTECS. Phthalaldehyde. Canadian Center for Occupational Health and Safety, (online), available from <<http://ccinfoweb2.ccohs.ca/rtecs/>>, (accessed 2006-05-18).
- 8) Venticinque SG, Kashyap VS, O'Connell RJ: Chemical burn injury secondary to intraoperative transesophageal echocardiography. *Anesth Analg* 97, 1260–1261 (2003)
- 9) Sokol WN: Nine episodes of anaphylaxis following cystoscopy caused by Cidex OPA (ortho-phthalaldehyde) high-level disinfectant in 4 patients after cytoscopy. *J Allergy Clin Immunol* 114, 392–397 (2004)
- 10) Suzukawa M, Yamaguchi M, Komiya A, Kimura M, Nito T and Yamamoto K: Ortho-phthalaldehyde-induced anaphylaxis after laryngoscopy. *J Allergy Clin Immunol* 117, 1500–1501 (2006)
- 11) Yamamoto Y, Katagiri H, Suzuki T, Aizawa K and Kadowaki T: About examination of the measuring method of Ortho-phthalaldehyde, and measurement of the medical spot. *San Ei Shi* 45, 614 (2003) (in Japanese with English abstract)
- 12) Marena C, Lodola L, Marone Bianco A, Maestri L, Alessio A, Negri S and Zambianchi L: Monitoring air dispersed concentrations of aldehydes during the use of ortho-phthalaldehyde and glutaraldehyde for high disinfection of endoscopes. *G Ital Med Lav Ergon* 25, 131–136 (2003) (in Italian with English abstract)
- 13) Sakano N, Yamasaki Y, Takigawa T, Kojima S, Kanbara S, Kurosawa C, Takemura Y, Tokumori K, Horita M, Nishide T, Kishimoto T, Uchida G, Ishikawa T and Kira S: Work environment questionnaire and environmental study of biocide for endoscopy instruments—Glutaraldehyde in air, working condition, and subjective symptoms—. *Jap J Occup Med Traumatol* 52, 219 (2004) (in Japanese)
- 14) Chan-Yeung M: Assessment of asthma in the workplace. ACCP consensus statement. American College of Chest Physicians. *Chest* 108, 1084–1117 (1995)
- 15) O'Byrne P, ed. Global initiative for asthma. Pocket guide for asthma management and prevention. (online), available from <<http://www.ginasthma.org> 2005>, (accessed 2006-08-07).
- 16) Mapp CE, Boschetto P, Maestrelli P and Fabbri LM: Occupational asthma. *Am J Respir Crit Care Med* 172, 280–305 (2005)
- 17) Ong TH, Tan KL, Lee HS and Eng P: A case report of occupational asthma due to glutaraldehyde exposure. *Ann Acad Med Singapore* 33, 275–278 (2004)
- 18) English JS: Current concepts of irritant contact dermatitis. *Occup Environ Med* 61, 674, 722–726, (2004)
- 19) Health & Safety Executive of UK. Substitution of glutaraldehyde in healthcare endoscope disinfection—WATCH findings on three possible alternatives. *Toxic Substances Bulletin*, 2003.
- 20) Labour Standards Bureau of Japanese Ministry of Health, Labour and Welfare. Preventive measures against health hazard of workers caused by GA exposure in medical facilities. Issue from Labour Standards Bureau 0224007, 2005.