

Occupational Asthma Due to Azodicarbonamide

Cheol-Woo Kim¹, Jae-Hwa Cho¹, Jong-Han Leem², Jeong-Seon Ryu¹, Hong-Lyeol Lee¹, and Yun-Chul Hong²

Departments of ¹Internal Medicine, and ²Occupational & Environmental Medicine, Inha University College of Medicine, Incheon, Korea.

Azodicarbonamide is a low molecular weight foaming agent for plastics and rubbers. Azodicarbonamide can elicit acute and chronic health related problems due to its potential for pulmonary and cutaneous sensitization. Some cases of occupational asthma associated with exposure to azodicarbonamide have been reported, of which only a few cases were confirmed by specific inhalation challenges. Here, the first case of occupational asthma due to azodicarbonamide in Korea, in which the diagnosis was confirmed by specific inhalation challenge, is reported.

Key Words: Occupational asthma, azodicarbonamide

INTRODUCTION

Azodicarbonamide or 1,1' azobisformamide ($\text{H}_2\text{N-OC-N=N-CO-NH}_2$) is a condensation product of hydrazine and urea. It is a low molecular weight amide widely used in industry as a foaming agent. It is manufactured predominantly as a fine, yellow powder of particle sizes in the 2-10 micron range. Mixing with other chemicals may produce modified products for a specific purpose such as high expansion, self-dispersion and adjustment of decomposition temperature. The main usages are in the manufacture of plastics and rubbers for wall coverings, floor coverings, insulation and packaging materials.

Azodicarbonamide has been reported to cause pulmonary and cutaneous sensitization.^{1,2} Despite

its widespread use in industrial processes, it only sporadically causes occupational asthma. To date, over 37 cases of occupational asthma associated with exposure to azodicarbonamide have been reported, of which only 4 cases were confirmed by specific inhalation challenges.³⁻⁷ For uncertain reasons, however, no further study concerning occupational asthma due to azodicarbonamide has been reported after the late 1980's.

We report the first case of occupational asthma due to azodicarbonamide in Korea, in whom the diagnosis was confirmed by specific inhalation challenge.

CASE REPORT

A 56-year-old man presented with cough, dyspnea, and wheezing. Ten years earlier, he had commenced employment at an azodicarbonamide producing factory and his main job included monitoring the quality of finely ground azodicarbonamide powder. Seven years after beginning this work, he began to experience a cough, shortness of breath and wheezing. He was clinically diagnosed as bronchial asthma at another hospital and had been under medical treatment accordingly. However, his symptoms did not improve and became progressively aggravated, especially during the evening after work. He had to stop the work and visited the Inha University Hospital for further evaluation and treatment of asthma. He had no medical history apart from respiratory symptoms, and had smoked half pack of cigarettes a day between the ages of 30 and 50 years.

When initially evaluated, the patient had been treated with fenoterol 5 mg orally 3 times a day,

Received August 4, 2003

Accepted November 4, 2003

This study was supported by Inha University Research Grant. (INHA-30378)

Reprint address: requests to Dr. Cheol-Woo Kim, Department of Internal Medicine, Inha University College of Medicine, 7-206 Shinheung-dong 3ga, Jung-gu, Incheon 400-711, Korea. Tel: 82-32-890-3490, Fax: 82-32-882-6578, E-mail: cwkim1805@inha.ac.kr

and inhaled fenoterol 200 microgram as needed. Hemoglobin, white blood cell count and differential counts were normal and the serum total IgE was 20 U/ml. Allergy skin prick tests with 50 common inhalant allergens were all negative. Chest X-ray film findings were normal.

The patient's forced expiratory volume in one second (FEV₁) was 1.78 L (67.7% pred.) with a forced vital capacity (FVC) of 2.71 L (82.9% pred.) and a normal carbon monoxide diffusing capacity. The provocative concentration of methacholine causing a fall of 20% in FEV₁ (PC₂₀) was 0.85 mg/mL. He was treated with budesonide dry-powder inhaler two puffs (200 µg/puff) inhaled twice daily, theophylline 200 mg orally twice daily, bambuterol 10 mg orally once daily, and salbutamol metered-dose inhaler for as-needed use with a 2-week course of oral prednisolone treatments. After 4-week treatment, his FEV₁ and FVC increased to 2.58 L (98.1% pred.) and 3.24 L (98.9% pred.) respectively and airway hyperresponsiveness was improved (PC₂₀ 4.69 mg/mL).

The patient showed a stable clinical condition and diurnal variability of peak expiratory flow rate (PEF variability < 20%) with treatments, thus specific inhalation challenge tests were planned to assess the possibility of occupational asthma. The challenge tests were performed by the previously reported method with slight modification at 5 weeks after initial treatments.⁵ Because azodicar-

bonamide is not water-soluble and insoluble in all common solvents, inhalation challenges were performed with azodicarbonamide and lactose powder. On day 1, as a control challenge, the patient was asked to move 30 g of lactose powder from one tray to another for 10 minutes in a small isolated room. No significant change in FEV₁ was noted over the next 7 hours. On day 3, challenge with a mixture of 50% lactose powder and 50% azodicarbonamide powder was done by the same method. Five hours after the inhalation, his FEV₁ decreased from 2.54 to 1.97 L (22.4% fall) and the patient complained of cough and chest tightness (Fig. 1). Nonspecific bronchial hyperresponsiveness increased after the inhalation challenge (PC₂₀ at 7 days before challenge - 4.69 mg/mL; PC₂₀ at 2 days after challenge - 0.47 mg/mL).

To investigate the mechanism of azodicarbonamide-induced asthma, skin prick tests were performed with 0.1, 1.0, and 5.0% (w/v) solutions of azodicarbonamide in dimethyl-sulphoxide, and patch tests were performed with azodicarbonamide in petrolatum at concentrations of 0.1, and 1.0% (w/w). The prick tests were negative at all concentrations, but the patch test showed ++ reaction (erythematous papules with edema) at 48 and 96 h to 1.0% concentration. *In vitro* test for antibody measurement was impossible due to the insolubility of azodicarbonamide.

The patient was confirmed to have azodicar-

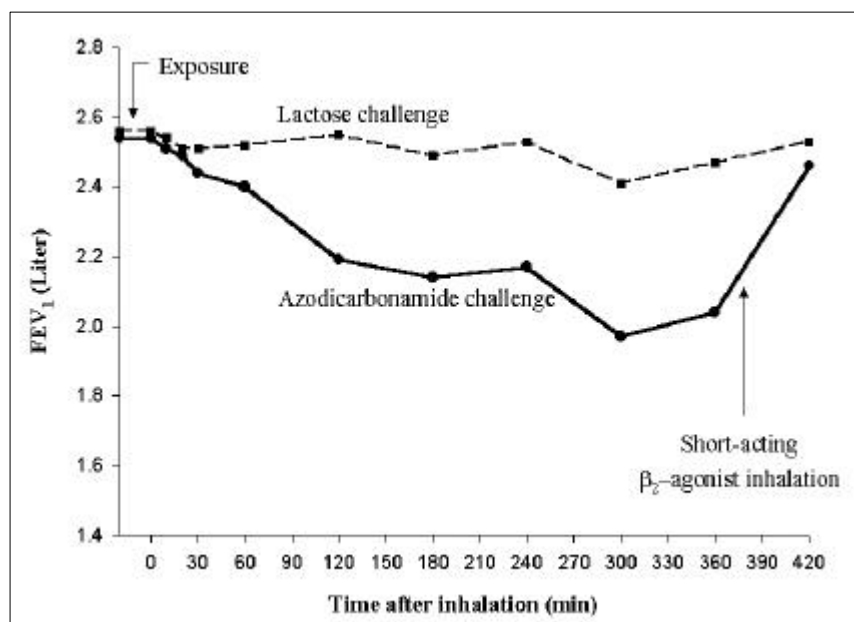


Fig. 1. Specific inhalation challenges by exposing the subject to lactose (closed squares) or to azodicarbonamide (closed circles) powder for 10 min. No significant change in FEV₁ was noted after exposure to lactose powder. Late asthmatic reaction with significant fall in FEV₁ was noted after exposure to a mixture of 50% lactose and 50% azodicarbonamide powder. FEV₁: forced expiratory volume in one second.

bonamide-induced occupational asthma. He was advised to discontinue exposure to azodicarbonamide and to take anti-asthma medication including inhaled corticosteroid.

DISCUSSION

Azodicarbonamide is a chemical foaming agent, which is an additive that decomposes when heated to yield at least one type of gaseous decomposition product. This evolved gas produces micro-cellular materials for plastic and rubber products. It is one of the most widely used blowing agents due to its self-extinguishing, relatively high decomposition temperature, and relatively large gas evolution properties. Animal experiments showed that it has no toxic or side effect after acute or chronic exposure.^{8,9} Although it is considered to be a non-toxic for man, several reports indicated that it has a potential for pulmonary and cutaneous sensitization.^{1,2}

Asthma and asthma-like symptoms after long-term exposure to azodicarbonamide powder have previously been reported. Azodicarbonamide caused substantial (8-21%) falls in FEV₁ over one shift in a grinding factory in the USA and 2 cases of occupational asthma were identified.³ In the United Kingdom, 28 cases were detected on the basis of a questionnaire study in the plastic industry.⁴ Another case was described in the Italian literature.⁵ However, specific inhalation challenges were not carried out to confirm the diagnosis in these reports. Up to now, only 4 cases of occupational asthma due to azodicarbonamide have been confirmed by specific inhalation challenges.^{6,7} In addition, there has been no report of azodicarbonamide-associated occupational asthma during the last decade.

The patient in this study demonstrated typical features of occupational asthma similar to those described elsewhere; a strong relationship between work and asthmatic symptoms, presence of the latency period, worsening of symptoms at the end of the day's work or in the evening, and the characteristic late-phase response to inhalation challenge. The most distinguishing clinical difference between our patient and previously reported cases is the duration of work exposure

before the onset of respiratory symptoms. Most cases generally developed the attacks of asthma within one year of exposure.³⁻⁷ Our patient had only begun to experience asthma symptoms seven years after beginning the work where he was exposed to azodicarbonamide. There are, however, interindividual variations of the latency period from months to years, and various factors such as improved working condition and individual susceptibility may contribute to the long latency period of our patient.

The specific inhalation challenge in this study was performed using azodicarbonamide powder, because it is not water-soluble. We consider that the bronchial reaction to the inhalation challenge is not an irritant but a specific response. Asthmatic reaction was noted after exposure to azodicarbonamide powder, but no significant reaction was noted after lactose powder exposure. The patient developed late-phase reaction and it is unlikely that this late reaction is due to irritation.^{10,11} Worsening of nonspecific bronchial hyperresponsiveness to methacholine after inhalation challenge also suggests that the reaction is specific.^{10,11} In addition, we carried out azodicarbonamide inhalation challenges on 2 control asthmatics with similar nonspecific bronchial hyperresponsiveness (PC₂₀ of 3.91 and 5.13 mg/mL) and no occupational exposure to azodicarbonamide. There was no significant change in FEV₁ at these challenges.

The mechanism of azodicarbonamide induced asthma remains unclear. Immunologic hypersensitivity to azodicarbonamide in the form of allergic contact dermatitis is well recognized.² Valentino et al. described the protective effect of disodium cromoglycate pretreatment and suggested an immunopathological mechanism of azodicarbonamide-induced asthma.⁵ In general, patients sensitized to high-molecular-weight allergens show typical early- and late-phase reaction in inhalation challenge. In contrast, patients sensitized to low-molecular-weight chemicals may show isolated late-phase reactions.¹² The mechanism of airway obstruction in isolated late-phase reactions may be different from that of the late-phase in typical dual reactions. Recent study showed that injection of short peptide fragments of cat allergen that did not cross-link IgE in patients with cat allergy elicited isolated late-phase reactions with no

visible early-phase reactions.¹³ This suggests that the isolated late-phase response is probably driven by T cell reactivity.^{13,14} Prick test to azodicarbonamide was negative, but patch test was positive in our patient without sign of allergic contact dermatitis. Thus we consider that immunologic mechanisms, especially T cell immunity rather than IgE-mediated immunity, may be involved in the development of azodicarbonamide-induced occupational asthma.

In this regard, there have been some interesting studies which demonstrated that azodicarbonamide is a T cell immunosuppressant both *in vitro* and *in vivo*. It inhibits both the proliferative response of CD4+ T cells and their secretion of IL-2, IFN- γ , IL-4 and IL-5, and these inhibitory actions may have a negative effect on the development of azodicarbonamide-induced asthma.¹⁵⁻¹⁷ But it display immunosuppressive effects in a dose-dependent manner, and relatively large amounts are required to exert T cell immunosuppressive action (over several grams/day orally in human).^{15,17} Although our patient had been chronically exposed to azodicarbonamide, the exposure dose was relatively low to exhibit immunosuppressive action because his exposure was by the inhalation route only. Thus we think that T cell immunosuppressive activity of azodicarbonamide may have no direct effect on the development of asthma in this case.

The prognosis of azodicarbonamide-induced occupational asthma has not been clearly determined mainly due to a paucity of case detection. Previous reports described the disappearance of symptoms and bronchial hyperresponsiveness following the complete cessation of exposure or even improved working conditions.^{6,7} Our patient, however, had persistent symptoms of bronchial hyperresponsiveness in spite of complete avoidance of exposure for 6 months. Delayed avoidance from the onset of symptoms may be the most important cause of such an incomplete recovery, because the patient had had prolonged exposure to azodicarbonamide for more than 3 years after the onset of symptoms. In fact, more than half the patients who develop occupational asthma will continue to have symptoms even if they leave the workplace, and the duration of exposure after the onset of symptoms and the severity of the asthma

at the time of diagnosis are important determinants of the prognosis.^{10,11}

In conclusion, we report upon a case of occupational asthma due to azodicarbonamide. Occupational history and details of working conditions should be carefully obtained whilst examining any suspected case, and specific inhalation challenge should be performed.

REFERENCES

1. Whitehead LW, Robins TG, Fine LJ, Hansen DJ. Respiratory symptoms associated with the use of azodicarbonamide foaming agent in a plastics injection molding facility. *Am J Ind Med* 1987;11:83-92.
2. Bonsall JL. Allergic contact dermatitis to azodicarbonamide. *Contact Dermatitis* 1984;10:42.
3. Ferris BG Jr, Peters JM, Burgess WA, Cherry RB. Apparent effect of an azodicarbonamide on the lungs. A preliminary report. *J Occup Med* 1977;19:424-5.
4. Slovak AJ. Occupational asthma caused by a plastics blowing agent, azodicarbonamide. *Thorax* 1981;36:906-9.
5. Valentino M, Comai M. Occupational asthma caused by azodicarbonamide: clinical case. *G Ital Med Lav* 1985;7:97-9. (Italian)
6. Malo JL, Pineau L, Cartier A. Occupational asthma due to azobisformamide. *Clin Allergy* 1985;15:261-4.
7. Normand JC, Grange F, Hernandez C, Ganay A, Davezies P, Bergeret A, et al. Occupational asthma after exposure to azodicarbonamide: report of four cases. *Br J Ind Med* 1989;46:60-2.
8. Mewhinney JA, Ayres PH, Bechtold WE, Dutcher JS, Cheng YS, Bond JA, et al. The fate of inhaled azodicarbonamide in rats. *Fundam Appl Toxicol* 1987;8:372-81.
9. Medinsky MA, Bechtold WE, Birnbaum LS, Bond JA, Burt DG, Cheng YS, et al. Effect of inhaled azodicarbonamide on F344/N rats and B6C3F1 mice with 2-week and 13-week inhalation exposures. *Fundam Appl Toxicol* 1990;15:308-19.
10. Malo JL, Chan-Yeung M. Occupational asthma. *J Allergy Clin Immunol* 2001;108:317-28.
11. Chan-Yeung M, Malo JL. Occupational asthma. *N Engl J Med* 1995;333:107-12.
12. Perrin B, Cartier A, Ghezzi H, Grammer L, Harris K, Chan H, et al. Reassessment of the temporal patterns of bronchial obstruction after exposure to occupational sensitizing agents. *J Allergy Clin Immunol* 1991;87:630-9.
13. Haselden BM, Kay AB, Larche M. Immunoglobulin E-independent major histocompatibility complex-restricted T cell peptide epitope-induced late asthmatic reactions. *J Exp Med* 1999;189:1885-94.
14. Larche M, Haselden BM, Oldfield WL, Shirley K, North J, Meng Q, et al. Mechanisms of T cell peptide epitope-dependent late asthmatic reactions. *Int Arch*

- Allergy Immunol 2001;124:272-5.
15. Tassignon J, Ismaili J, Le Moine A, Van Laethem F, Leo O, Vandewelde M, et al. Azodicarbonamide inhibits T-cell responses *in vitro* and *in vivo*. Nat Med 1999;5: 947-50.
 16. Tassignon J, Vandewelde M, Goldman M. Azodicarbonamide as a new T cell immunosuppressant: synergy with cyclosporin A. Clin Immunol 2001;100:24-30.
 17. Goebel FD, Hemmer R, Schmit JC, Bogner JR, de Clercq E, Witvrouw M, et al. Phase I/II dose escalation and randomized withdrawal study with add-on azodicarbonamide in patients failing on current antiretroviral therapy. AIDS 2001;15:33-45.