[Environmental Health and Preventive Medicine 7, 40–46, May 2002]

Review Article

Diagnosis and Prevention of Diseases Induced by Isocyanate

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Abstract

Isocyanates are among the most frequent causes of occupational asthma in industrialized countries. Early diagnosis of diisocyanate asthma followed by prompt termination of chemical exposure can prevent chronic morbidity due to persistent asthma. Chronic exposure to isocyanates also induces hypersensitivity pneumonitis (HP). The accurate diagnosis of diisocynate asthma requires a systematic approach that combines information obtained from the occupational history, immunologic tests and physiologic studies. The prevention of health problems from toluene diisocyanate (TDI), 4,4'-methylenediphenyl diisocyanate (MDI) and 1,6'-hexamethylene diisocyanate (HDI) is essential for all those handling the chemicals. Regulatory exposure limits should be observed. However, wheezing, coughing or even asthmatic attacks may occur after exposure much below the regulatory exposure limits especially in sensitive individuals. Preventing or minimizing exposure is of prime importance and should be supported by the installation of engineering controls, by education of the workforce, by regular monitoring of the workplace exposure and by medical surveillance. To prevent such asthma it is suggested that workers should be tested airway sensitivity and should avoid working in areas that have dust containing specific-IgE. Such tests must be periodically performed after working. Symptoms induced by isocyanate need earlier discover and early isolation of the associated individuals.

Key words: isocyanates, diisocyanate, review, diagnosis, prevention

Introduction

In many industrialized countries, isocyanates such as toluene diisocyanate (TDI), 4,4'-methylenediphenyl diisocyanate (MDI) and 1,6'-hexamethylene diisocyanate (HDI) are commonly utilized in industry as cross-linking and polymerizing agents in the manufacture of urethane foams, elastmers, polyurethane coating, adhesives and paints (1). TDI, MDI and HDI are the best examples of the diisocyanate group of chemicals, used for urethane products. Developments in the chemical industry have contributed to our daily lives. However the products of the chemical industry elicit many symptoms in workers who participate in their production. Macromolecule chemical compounds made from isocyanates have become extensively used in modern times, and their production will continue to grow (2).

Worldwide, as well as in Japan, isocyanates are major chemicals which often induce occupational allergic diseases. They are the chemicals that induce various allergic symptoms even in small doses. In small scale factories, exposure to isocyanates is a serious problem.

Responses to high levels of exposure to airborne TDI, MDI and HDI, depending on exposure levels or dose, may vary widely from mild irritation to more severe effects, even to bronchospasm. In extremely rare cases, particularly with individuals who have previously become sensitized to isocyanates, the effects may be life-threatening (3, 4). Long lasting respiratory effects may develop following repeated exposure to these isocyanates above the standard levels.

Exposure limits

The American Conference of Governmental Hygienists (ACGIH)' STEL (short term exposure limit) for TDI or MDI is 20 ppb, and the 8-hour time-weighted average TLV (threshold limit value) is 5 ppb (5, 6). This limit prevents acute irritation. However, this level is dangerous for people who have previously been sensitive to other isocyanates (7). Each type of isocyanate (TDI, MDI and HDI, etc.) has a different sensitizing potential (8, 9). It is important to be aware that isocyanates are harmful not only by themselves, but also in mixtures (5).

There is a possibility that these values do not match the working states, because, in general, these criteria are made based on 8 hours work per day, and 40 hours work per week. It was reported that there was an ill health effect of exposure to concentrations below the TLV (10, 11) in animals. No deterioration in lung function, but an increased frequency of respiratory symptoms

Received Mar. 5 2001/Accepted Jan. 16 2002
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Table Current exposure standards (levels) of isocyanate exposure. Limits for major isocyanates used in the workplace. This table shows the criteria for exposure limits by several organizations

Organization	Toluene diisocyanate (TDI)	Methylenediphenyl diisocyanate (MDI)	Hexamethylene diisocyanate (HDI)
ACGIH (1996)	0.005 ppm [0.036 mg/m^3] (TLV-TWA) 0.02 ppm [0.14 mg/m^3] (TLV-STEL)	0.005 ppm [0.051 mg/m^3] (TLV-TWA)	0.005 ppm [0.034 mg/m^3] (TLV-TWA)
JSOH	0.005 ppm (OEL-M) [1992] 0.02 ppm (OEL-C) [1992]	0.05 mg/m^3 (OEL-M) [1993]	0.005 ppm [0.034 mg/m^3] (OEL-M) [1995]
NIOSH (1994)		0.005 ppm [0.05 mg/m^3] (TWA) 0.02 ppm (10 minute ceiling)	0.005 ppm [0.035 mg/m^3] (TWA) 0.02 ppm [0.14 mg/m^3] (10 minute ceiling)
OSHA (1997)	0.02 ppm	0.02 ppm [0.2mg/m^3]	

Abbreviation: ACGIH (American Conference of Governmental Industrial Hygienists), JSOH (Japanese Society for Occupational Health) (65, 66), NIOSH (Occupational Safety and Health), OEL-C (Occupational Exposure Limit-Ceiling), OEL-M (Occupational Exposure Limit-Mean), OSHA (Occupational Safety and Health Administration), TLV (Threshold limit value), STEL (Short Term Exposure Limit), TWA (Time weighted average).

was observed in a follow-up study among non-sensitized workers with a mean exposure to TDI of 3 ppb (21.3 μg/m^3) (12). This previous study also suggested that among workers with a mean exposure of 8 ppb (57 μg/m^3) and with peak exposures of 30 ppb (213 μg/m^3) and above there was an associated loss of ventilatory function among workers not sensitized to TDI (13). In short, if the overall exposure dose is low enough, there is no effect on lung function (14–16). However, even if there is a very low concentration, there may be effects in individuals already sensitized (17). In addition, Nguyen et al. (18) concluded that total cumulative exposure is more important than momentary exposure. From the results of an investigation of secretion of IgE in isocyanate exposed mice, it may be the case that non-IgE-mediated mechanisms are active in short exposure and IgE-mediated mechanisms work in long exposure (19) scenarios. In addition, it was reported that the unit 'ppb' using for exposure limits is not suitable for actual circumstances, because of the chemical characters (5). Differences between individuals may be due to their different sensitivities. Not only real exposure but also real situations of exposure (20) is important.

There are several organizations in addition to ACGIH that submit their own criterion of exposure limits. The table shows the current criteria for isocyanate exposure among workers. The criteria must be re-examined to clarify if they are suitable to present conditions.

Diagnosis

Diagnosis of the symptoms caused isocyanates is based on clinical measurements, works recording, measurement of lung function, and inhalation tests (21). History taking is especially important, to help clarify the relation between the clinical recording and the work recording and between the change in symptoms and work (22). If there is an acute response during and after exposure of dust and gas, or symptoms appear in the workplace, or recover at the weekend or on days off work, the case needs attention. Symptoms such as dry cough, roaring, dyspnea, and strangulation of the chest appear to be frequent. Measuring the Peak Expiratory Flow Rates (PEFR) before and after work and the change within one week over several months can help confirm the relation between work and symptoms. If needed, the inhalation challenge test can be performed under medical supervision. If the origin of the exposure, e.g. a physical form of gas or mixtures, is not clear, an environment provocation test made at the workplace of the patients by means of observation of the appearance of the symptoms and lung function changes may be necessary (23, 24). If causative allergens are clear, they may be used to examine skin reactions and to detect specific-IgE antibodies. In addition, as for other methods of diagnosing asthma, inhalation of histamine or acetylcholine is used for the airway reactivity test (25).

In diagnosis, careful recordings are needed. The lung function test reveals obstructive disorders or normal appearance. Even if isocyanate exposure is fugitive, i.e. when airway flow or an increase in airway reactivity using the methacholine or histamine challenge test are observed after its exposure, the symptoms are diagnosed as isocyanate asthma (7).

Peculiar guideline

Special blood or urine tests are not yet established. However, from *in vivo* and *in vitro* studies using ^{14}C, isocyanate is known to be metabolized and voided extracoporeally (7, 26, 27). In blood and urine, the amount of amine which was produced by isocyanate hydrolysis e.g. toluene diamine (TDA) from TDI, methylene diamine (MDA) from MDI, appears to be related to the quantity absorbed (28). Moreover, there was an investigation that reported the detection of metabolites of diisocyanates in plasma and urine (29). Therefore, it is possible to determine the inhalation dose by measuring isocyanate and amine in blood and urine (30, 31). However, sensitivity to isocyanates and the degree of symptom appearance are according to each individual. Therefore, an accurate inhalation dose is only an assumption.

The inhalation challenge test with the original antigen is important for certain diagnose. In hypersensitivity pneumonitis (HP), at four to six hours after antigen inhalation, fever, cough, chokes, rales, and leukocyte increases are found, FEV_1 decreases, PO_2 decreases and abnormal chest X-ray findings appear. Therefore the challenge test is recognized to be positive (32). Since, the isocyanate inhalation challenge test has grave risks, it should not be performed except in specialist facilities by experienced staff equipped with recovery equipment. This is because there is a possibility that even at low doses, such as 1 ppb, sensitized patients may provoke a severe asthmatic response (33).

The isocyanate antibody test is useful in epidemiology, but results of antibody testing are difficult to interpret, and currently are accepted only as an indication of exposure but not of sensitization. Antibody cannot be detected in all patients with asthma, and despite antibody detection, the patients may be asymptomatic. Various toxicological and immunological mechanisms were suggested for isocyanates related health problems. Individual

differences such as exposure doses and genetic differences were also suggested, but there was no clear conclusion drawn on why various mechanisms act in different patients.

Useful tests as diagnostic criterion

Arterial blood gas, oxymetry and respiratory function test

In general, the characteristics of respiratory function disorder are restrictive ventilation consisting of decreasing vital capacity and lung compliance, lung diffusion disability (decreasing DL_{CO}), and gas exchange disability, i.e. decreasing PaO_2. At an acute stage, peripheral airway disorder can be observed. In addition, hypersensitivity is strengthened in the airway test (33). In isocyanate asthma in Japan, there has been no case report of lung diffusion disorder (34).

Chest X-ray, and Computerized Tomography (CT) (35)

Diagnosis using chest X-ray is useful in HP, but in asthma it shows normal appearance. Chest X-ray of HP patients often shows a diffuse ground-glass pattern. However, the appearance of earlier stages of HP are normal, similar to that of asthma.

X-ray CT is superior to chest X-ray radiographs in density analysis. Even if chest X-ray radiographs show normal appearance, a CT can show a slight increase in the density of the lung window levels. Recently, in the diagnosis of diffuse lung disorder, High-resolution CT (HRCT) was used. HRCT is the best tool to detect the disorder related to secondary pulmonary lobules in peripheral lung zones. In addition to using HRCT, it is useful to investigate bronchoalveolar lavage fluid (BALF) or transbronchial lung biopsy (TBLB).

Pulmonary function test

The lung function test is also useful, but smoking effects should not be neglected (36). The lung functions of smokers is lower than that of non-smokers, and the similar things are also seen in ex-smoker (14, 37). For this reason, patients are asked for their smoking history in detail. There are asthmatic cases that have slight obstructive disorder (38) or their function is normal (34). Furthermore, PEFR in some affected cases is sometimes normal during holidays (39).

Skin test

The skin test including the patch test and scratch test is performed in a simple way and is useful for diagnosis. However, there is anxiety about sensitization using test chemicals themselves. Therefore, the tests need the greatest consideration.

There are many methods of diagnosis, but each way has good points and bad points. Therefore, it is important to diagnose using

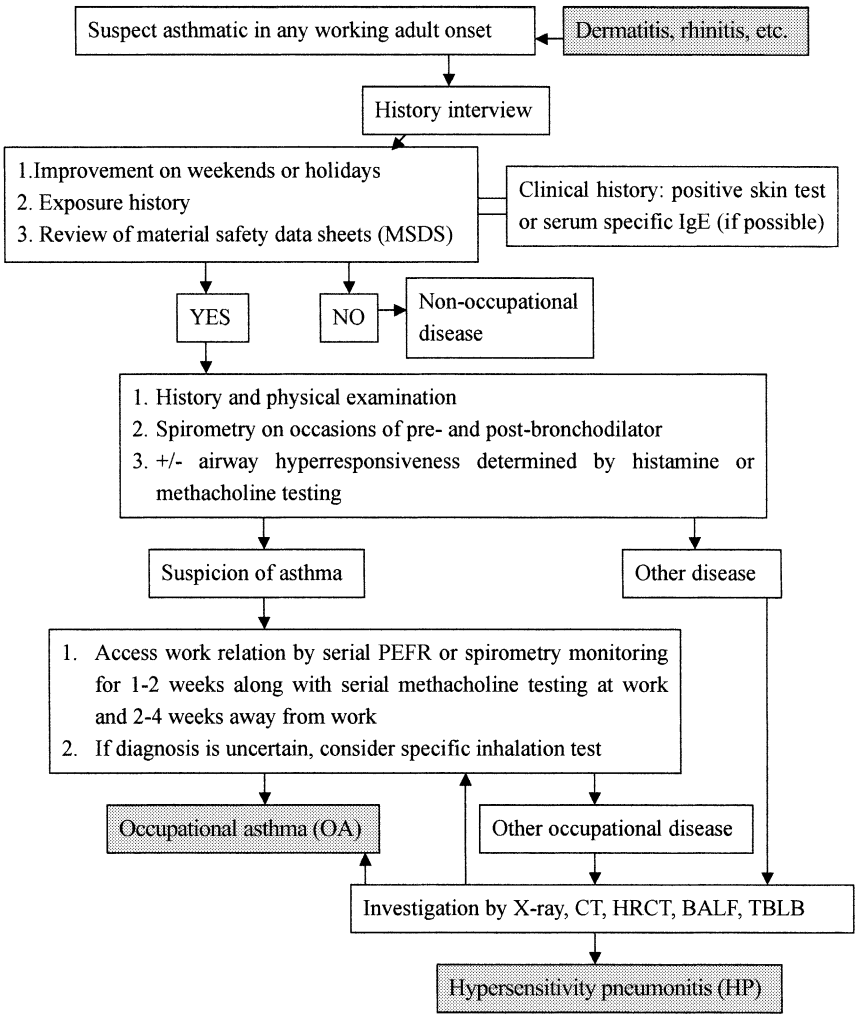

Figure Steps in diagnosis of isocyanate-induced respiratory diseases.
Abbreviation: BALF (Bronchoalveolar Lavage Fluid), CT (Computed Tomography), HRCT (High-resolution CT), PEFR (Peak Expiratory Flow Rates), TBLB (Transbronchial Lung Biopsy)

several methods. In 1998, the Canadian Thoracic Society announced the guidelines for diagnosis of occupational asthma (39). According to a modification of this guideline, the steps in diagnosis of isocyanate-induced diseases are presented in the Figure.

Treatments

There is no specific medicine or antidote. For example, medicine such as bronchodilators for asthma of other origins are used. Recently, in an investigation of a mouse model of isocyanate asthma, vitamin E suppressed the secretion of cytokines that induced inflammation, and symptoms improved (40). It may be possible to use vitamin E for treatment. Since medication is not specific to isocyanate-induced asthma, earlier diagnosis or prevention of sensitization is more important. First aid is also important. Compiling the above-mentioned measures, the first aid is discussed in the following section.

First aid

Vapor inhalation

Segregation from the exposure site is necessary, and if possible, oxygen therapy should be performed. In acute exposure, maintaining the airway or treatment with an appropriate dosage of bronchodilator for roaring is necessary. Attention to pulmonary edema, and progress for 8 to 12 hours are needed. More inhalation of isocyanates is dangerous for patients with sthenia of airway response. With public health institutions or related administrative organizations, judgement regarding whether other workers are in danger is warranted.

Eye contamination

Contaminated eyes should be washed with large volume of physiological saline or warm water (41). The eyes should be flushed immediately with the contents of several sterile eye wash bottles or copious amounts of tap water. Then, contact lenses should be removed, if present and easily removable, and eye irrigation continued for more than fifteen minutes. After first aid treatment, the patients should be seen by a physician or attend the local hospital, since additional treatment may be necessary. A physician may wish to apply a suitable eye cream, oil or medication.

Skin contamination

Contaminated clothing should be removed from and polluted skin washed with a lot of soap and water (41). Cleaning shortly after exposure is important. Organic solvents such as acetone, toluene or chlorinated hydrocarbons should not be used under any circumstances for dissolving isocyanate products, because they may promote absorption of the diisocyanates though the skin and into the body. If cold water is used to wash, TDI and MDI may become more vicious, making decontamination more difficult. Very cold water may cause TDI to crystallize.

Swallowing

There have been few reports of MDI or TDI being swallowed. Oral toxicity appears to be very low, in agreement with animal test results (26, 42). Vomiting should not be induced. The mouth should be washed out with water. The person affected should be made to rest. Medical attention should be given immediately. Advice on treatment varies: for example, one author recommend giving the patient water or milk to drink (43, 44); others recommend giving activated charcoal as an aqueous slurry within the first hour to patients who are awake and have a protected airway. Others recommend that nothing is given orally.

Discussion

In general, if isocyanates exposure continues, allergic symptoms do not recover, sometimes progress and may be lethal (45, 46). For this reason, to improve working related health, it is important to remove the causative materials completely, such as by adjustment and improvement of workplace.

If lung functions improve by removal of causative materials, hypersensitivity reaction is slight with a delayed reaction. With short exposure with a delayed reaction, prognosis of these cases will be good. However, even if patients stop exposure to the causative materials, if they have non-specific bronchial hyperresponsiveness (NSBH), they cannot recover (47). Symptoms do not disappear when structural changes are present in the airway wall of sensitized patients, such as subepithelial fibrogenesis and hypertrophy (48).

In most cases, if causative materials are removed, prognosis is fairly good (49–56). If complete removal is impossible, the second-best measure is to decrease exposure concentrations (14, 20). Improvements in working practices, consideration of workplace layout, renewal of construction and instillation of ventilation must be achieved. For the employee, protection with filter masks may be needed. Wearing a mask has been shown to be useful (57, 58), and development of more protective masks is ongoing. Once a worker is sensitized, the only safe course is to remove them from the exposure. In very few cases, death may occur when sensitized patients continue to be exposed to the diisocyanate (3, 4). Even wearing masks is not sufficient protection especially for sensitized patients. Masks in the workplace are for the protection of healthy workers, from sensitization.

Pharmacological therapy is similar for non-occupational asthma, butis inadequate alone. Basically, a β stimulator, with antiallergic and antiphogistic agents are central in pharmacological therapy. For immediate and dual asthmatic reactions, disodium chromoglycate (DSCG) is useful, especially when used before working (37). A late asthmatic reaction and severe symptoms relate deeply to allergic inflammation, and thus inhalation of steroid is needed (59, 60). Since predonisolone is often used as an asthma drug, it is also useful for isocyanate asthma (45, 60–63). In cases where the avoidance of the causative materials and their therapy are in effective, change of workplace or work itself needs to be considered (60–64).

Conclusions

For prevention of isocyanate-induced disease, it is useful that investigations on whether people are atopic when they are recruited are carried out. It is also useful to instruct people with specific-IgE or airway sensitivity before they work with isocyanates. Such people do well to avoid working with isocyanates. Immunological tests must be performed periodically after recruitment. For this reason, it is necessary that the employer, employee, doctors and occupational health staff mutually communicate and

co-operate. Those with symptoms induced by isocyanate need to be discovered earlier and to be isolated earlier. It is difficult for minor enterprises themselves to consider the countermeasures for diseases from isocyanate exposure. Under certain circumstances using isocyanate, active communications with research organizations such as the International Isocyante Institute (III) are valuable and helpful.

Acknowledegments

The authors are in depted to the III (International Isocyanate Institute) for collecting information. We also thank Dr. K. Tanaka of Kyoto Industrial Health Association for assistance in collecting information.

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