DIISOCYANATES PANEL

Scientific Information Statement (with references)

MDI Antibody Testing

Methylene diphenyl diisocyanate (MDI) is a chemical compound that reacts rapidly with polyols, amines and itself to form a variety of products such as rigid polyurethane foam, elastomers, coatings, and binders in wood and other plant products. Exposure to MDI at levels above exposure limits designed to provide safe workplace environments may cause individuals to experience asthma-like symptoms upon re-exposure to MDI at levels below the exposure limit. Some cases of MDI-induced asthma have been considered to be the result of antibody formation resulting in allergic disease, although the exact mechanism remains unclear. Antibody formation, as well as cell-mediated immune mechanisms, and non-immune mechanisms have been investigated.

Background

Antibody formation is a general defense against organisms and substances that are foreign to the body. The detection of specific antibodies can be used to determine whether the immune system of an individual might have been triggered as a result of contact with a particular foreign material. The presence of antibodies, in itself, is not considered to be a definitive indication of allergic disease, such as asthma. Allergic disease occurs when the immune system reacts to a foreign substance and causes a response that might result in sneezing, itchy eyes, hives, or breathing difficulty. Antibody production is only one of the components of this type of response.

Despite considerable research around the world over the last 20 years, it is not yet possible to reliably correlate serum levels of antibodies with clinical signs of airway diseases such as MDI-related asthma. MDI-related asthma can be more accurately diagnosed using a stepwise approach to determine whether there is a relationship between the individual's asthmatic symptoms and a specific triggering activity in the workplace. This includes a carefully collected work history, respiratory questionnaire, and examination of lung function. Observation to determine whether pulmonary effects occur on exposure to low levels of MDI and abate when exposure is avoided is key to the assessment. Specific provocation challenge with MDI is considered the ‘gold standard’, an effective and highly reliable diagnostic tool, but it is not readily available and is also expensive.

Among reports investigating the mechanism of MDI asthma, several researchers have reported that in vivo MDI can react with carrier proteins to form a complex, which the immune system could recognize as "foreign". This may result in the production of two types of MDI-specific antibodies, IgE and IgG. To detect MDI-specific antibodies, an individual’s serum is mixed with MDI-protein conjugates, prepared in a laboratory, then tested with either a radioallergosorbent (RAST) or enzyme-linked immunosorbent (ELISA) assay. The results for specific IgE or IgG are expressed as a titer of percent bound radioactivity for the RAST assay or optical density for

† Material Safety Data Sheets, available from MDI suppliers, provide additional health and safety information regarding this chemical.
ELISA. A review of the medical literature indicates that there are a variety of methods in use to prepare the MDI-protein conjugate as well as protocols to perform the assay, and that no standard protocol has achieved general consensus. In addition, the criteria for a test to be considered positive have not been standardized and vary among laboratories. Therefore, the results from one laboratory often are not comparable to those from another laboratory. Interpretation of MDI-specific antibody assay results is, thereby, complicated.

Accuracy and Validity of Antibody Testing

Current antibody tests do not reliably identify individuals with or without MDI-related asthma as the presence of antibodies does not necessarily indicate disease. Like most medical tests, antibody assays may yield both false negative and false positive results. More specifically:

1. Some investigators have suggested that people who have worked with MDI and have MDI-specific antibodies in their blood may be more likely to have an asthmatic reaction with subsequent re-exposure to the chemical. However, various studies demonstrated that circulating MDI-specific IgE antibodies can be detected in 0 to 83 percent, and MDI-specific IgG antibodies in 33 to 80 percent, of individuals who showed a positive response in a specific provocation challenge (that is, showed an asthmatic reaction to a challenge test with MDI). On the other hand, MDI-specific antibodies have been found in 9 to 57 percent of exposed non-asthmatic workers.

2. Researchers have tried to add various stringent criteria to produce more accurate results, but still fall short of predicting disease. In order to reduce the number of ‘false positive’ readings, researchers have raised the titer that is required to call a test positive and have recommended confirming questionable results with inhibition tests. When antibody assays are conducted in a manner to minimize false positive results, the presence of MDI-specific IgE antibodies has a slightly higher association with the presence of asthma. However, a person with MDI-induced asthma will not necessarily show a positive test for MDI-specific IgE antibodies. On average, IgE assays have been shown to be capable of confirming the diagnosis in only one out of five individuals known to have diisocyanate-induced asthma. In addition, MDI-specific IgE has been detected in 12% of a control population.

3. MDI-specific IgG is considered to be a more sensitive indicator of occupational asthma than MDI-specific IgE, but a positive test for MDI-specific IgG has been demonstrated in up to 57 percent of non-asthmatic individuals who work with MDI.

4. A factor that may influence the predictive ability of the test is the interval from last exposure. In one study, after thirty days away from exposure, the positive antibody tests decreased from 41 percent to 14 percent. This relationship has not been firmly established. For example, after one year of non-exposure diisocyanate-specific antibodies were detected in 63 percent of individuals showing a positive response in a specific provocation challenge, while only 36% of recently exposed positive responders were positive for diisocyanate-specific antibodies. A decrease of antibody levels does not always correlate to improvement in asthma symptoms.

5. There have been many reports regarding cross-reactivity of the various diisocyanates during antibody testing. This cross-reactivity may be due to the formation of new
antigenic determinants, which could be similar for the different diisocyanate compounds.\textsuperscript{25,30} Although unproven, there may also be cross-reactivity with non-diisocyanate substances; one instance of concurrent bronchial reactivity to another diisocyanate, TDI, and radishes (isothiocyanates) has been reported.\textsuperscript{30}

6. Other reasons suggested for the low and variable association between detection of antibodies and presence of diisocyanate-related asthma include:
   a. a small number of subjects in each study (in some studies only 2 to 4 individuals were tested\textsuperscript{5,6,28})
   b. different and non-validated testing methodologies;
   c. variability in conjugate preparation including the type of protein used;\textsuperscript{12,31} and
d. perhaps most importantly, the possibility of a non-antibody-mediated immune mechanism for some cases of diisocyanate asthma.\textsuperscript{1,2,4,23}

**Summary**

In summary, given the low predictive ability and the various confounding factors presently associated with antibody testing, a positive test for MDI-specific antibodies alone has not proven to be a reliable marker for diagnosing MDI-related asthma. Establishing work related bronchoconstriction with serial lung function monitoring during the work week and after a period away from work is considered to be the most practical method of making the diagnosis. Specific provocation challenge with MDI is considered the ‘gold standard’, highly effective and reliable as a diagnostic tool, but not readily available and also expensive. A body of research suggests that a positive MDI-specific IgE antibody test result may be useful in the diagnosis of MDI-related asthma only if (1) there is a strong pre-test probability of work-related asthma, (2) there is current or recent exposure to MDI, (3) the test is conducted in a manner to minimize false positive results. Research has also shown that MDI-specific antibody assays used independently have demonstrated low predictive ability (confirming the diagnosis in only one out of five individuals) and lack of accuracy (9 to 57 percent positive responses in non-asthmatic individuals). Current test methods have not been standardized or validated. Therefore, the antibody assay does not replace any of the exposure-related physiologic measurements in making the clinical diagnosis of MDI-related asthma. Currently, the detection of MDI-specific antibodies has not demonstrated reliability as an index of adverse health effects or exposure because the current analytical method has a low degree of accuracy, or as recently proposed, diisocyanate-induced asthma is a non-IgE-mediated disease.\textsuperscript{32}

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