

Review of Trimellitic Anhydride (TMA) Induced Respiratory Response

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ABSTRACT

Acid anhydrides such as trimellitic anhydride (TMA) are of interest due to their important industrial uses and to their adverse health effects in exposed populations. Important industrial uses of TMA include the production of epoxy and alkyd resins used to manufacture a variety of coating materials. The adverse health effects are a result of its direct irritant effects on mucosal surfaces in all exposed humans as well as its ability to cause immunologic sensitization in a small proportion of humans. In those individuals who are immunologically sensitized, reexposure to TMA can result in well described immunologic syndromes: asthma-rhinitis, late respiratory systemic syndrome (LRSS), and very rarely pulmonary disease anemia syndrome (PDA). In summary, adverse health effects of TMA are due to its effects as an irritant, an immunologic sensitizer, or a combination of both. (Allergy and Asthma Proc 18:235-237, 1997)

The acid anhydrides are produced in millions of tons annually and have been used in a variety of manufacturing processes for more than five decades. The major uses of these chemicals are in the production of epoxy and alkyd resins.¹ Alkyd resins that form the bases for paints and reinforced plastics commonly employ maleic anhydride (MA) or phthalic anhydride (PA). Epoxy resins are made

from bisphenol A and epichlorhydrin, cured by a reactive chemical like an amine or an acid anhydride such as trimellitic anhydride (TMA); these resins are excellent electrical insulators and highly resistant to most chemicals. A very common use of TMA is in the production of trimellitate esters, which are used as plasticizers for polyvinyl chloride, particularly when temperature stability is required.

The acid anhydrides are of major interest, not only as related to their important industrial uses but because of their adverse health effects in exposed populations. These adverse health effects are a result of their direct irritant effects as well as their ability to cause a spectrum of hypersensitivity reactions with well-defined immunologic mechanisms.² In the United States, it was estimated that approximately 20,000 employed persons are exposed to TMA.³ It is clearly appropriate to classify TMA as a respiratory sensitizer and as an irritant to mucosal surfaces such as those of the ocular and respiratory systems. The adverse human health effects of TMA can be attributed to one or both of those recognized properties: sensitizer and irritant. Therefore, it does not appear necessary to add an additional toxic classification.

When human mucosal surfaces are exposed to TMA, a direct irritant effect can result.² In addition, TMA can react with autologous proteins to form trimellityl (TM)-protein conjugates.¹ These TM-protein conjugates can act as antigens in susceptible individuals who then produce specific antibodies directed against the TM-protein conjugates. With reexposure to TMA, individuals who have produced specific antibodies may experience an immunologically mediated hypersensitivity reaction to TMA.² Patterson and co-investigators have delineated the immunologic aspects related to the reaction of antibody classes with TM-protein conjugates.⁴ The immunologic responses can be classified

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by the Gell and Coombs schema into four types of possible immunologic injury.⁵

Type I or immediate hypersensitivity is mediated by IgE antibody against TM-protein. IgE antibody is bound by high affinity receptors to mast cells and basophils. When antigen, in this case TM-protein, is encountered, it crosslinks IgE molecules bound to cells and effects the release of mediators and cytokines, resulting in clinical symptomatology. Type II or cytotoxic reaction results if TMA has combined with cell surface proteins. Antibody against TM-cell surface protein causes cytotoxic injury that is complement-mediated. Type III or immune complex injury occurs if IgM or IgG against TM-protein complexes with TM-protein. Antigen-antibody complexes are well-recognized causes of immune mediated injury. Finally, Type IV or cell-mediated immunologic injury can occur if TM-proteins are recognized by T cell receptors. This induces a T cell response with expansion of T cell clones that can participate in cell-mediated immunologic injury.

A key concept in these immunologic considerations is the ability of TMA to modify self-proteins. Experimentally, two different modifications have been described. First, the anhydride can act as a hapten, and antibody can recognize the trimellityl hapten as foreign.⁶ Alternatively, TMA can combine with self-proteins to generate new, carrier-dependent antigenic determinants with antibody combining sites being specifically directed against a conformational change in the self-protein.⁷ Irrespective of whether TMA induces a simple haptenic determinant or a new antigenic determinant, the immunologic and clinical sequelae are the same.

Three different immunologically mediated syndromes have been described in individuals exposed to TMA.^{1,2} In each case, there is a latency period that varies from weeks to years, during which time immunologic sensitization occurs. The nature of the hypersensitivity syndrome depends on the antibody isotype and degree of exposure.

Asthma-rhinitis is a syndrome characterized by immediate onset asthma and allergic rhinitis that is mediated by IgE against TM-protein. Like all immunologically mediated syndromes, this one requires a latent period of exposure before onset of symptoms. Once an individual is sensitized, however, the symptoms occur immediately, within minutes to an hour of exposure.

The late respiratory systemic syndrome (LRSS) is a hypersensitivity pneumonitis-like syndrome that is characterized by cough, dyspnea, and mucus production. Systemic symptoms including malaise, chills, myalgias, and arthralgias also occur. These systemic symptoms are due to the inflammatory reaction in the lung that is caused by respiratory sensitization. These systemic symptoms are due to local pulmonary production of inflammatory mediators including cytokines, not to systemic toxicity. That is, TMA does not cause systemic, toxic effects on other organ systems. These systemic symptoms are analogous to those symptoms that accompany hypersensitivity pneumonitis due to a variety of organic antigens such as avian proteins.⁸

These symptoms occur 4 to 12 hours after exposure, whether the antigen is avian protein or TM-protein. The syndrome, which requires a latent period for respiratory sensitization to occur, is associated with elevated specific IgG, IgM, and IgA directed against TM-protein.

The pulmonary disease anemia (PDA) syndrome is characterized by pulmonary infiltrates, dyspnea, hemoptysis, restrictive lung function, and hemolytic anemia. It is associated with high level specific IgG, IgA, and IgM antibody to TM-protein; antibodies to erythrocytes with TM conjugated to their surface have been identified in these individuals.⁹ Subjects with PDA are systemically ill; however, just as in individuals with LRSS, these systemic symptoms are caused by the pulmonary inflammation that is due to respiratory sensitization. These systemic symptoms are not the result of systemic toxicity. Because the cytotoxic mechanism can cause significant tissue damage, erythrocytes circulating in pulmonary vessels can also be exposed to TMA, become haptenized with TMA, and serve as the immunologic target for a hemolytic anemia. This syndrome usually develops only in individuals with exposure to high levels of TMA fumes. After the description of PDA as an immunologic hypersensitivity syndrome approximately 15 years ago, the syndrome has essentially disappeared, primarily due to environmental control of TMA exposure.

The first descriptions of cases of PDA appeared in the 1940s²; however, until the late 1970s, no immunologic studies were performed. At that time several reports of PDA appeared with accompanying immunologic data. In all cases, the subjects with PDA had high level antibody.⁹⁻¹¹ Similarly exposed co-workers with no antibody did not develop PDA. Another acid anhydride, PMDA, has been reported to cause a similar syndrome in a worker with very high antibody levels.¹² An analogous situation exists with hemorrhagic rhinitis due to another acid anhydride, HHPA.¹³ Those individuals with high level antibody are at risk for development of hemorrhagic rhinitis whereas similarly exposed employees without antibody do not develop the disease.

Conclusion

In summary, three different immunologically mediated syndromes have been described due to TMA. It is important to realize that the correlation between clinical syndromes and antibody must be linked to the clinical presentation. For example, IgE against TM-protein should not be the focus in individuals with a hypersensitivity pneumonitis-like syndrome. A 3-year clinical and immunologic survey study of almost 300 employees who had never developed an immunologically mediated respiratory disease due to TMA was conducted at a facility that manufactures TMA.¹⁴ Each employee was assigned an exposure classification from 1 (highest) to 5 (lowest) based on industrial hygiene data and job description. None of these employees developed PDA. There were more than 100 employees in

class 4 and 5; none of them developed an immunologically mediated respiratory disease during the 3-year period of followup. It is apparent from this study that there are TMA exposure levels that are very unlikely to cause immunologically mediated respiratory disease.

TMA is clearly an irritant to human mucosal surfaces. In addition, a small proportion of humans develop immunologic sensitization as a result of inhalational exposure to TMA. In those individuals, reexposure can result in the immunologically mediated syndromes described: asthma-rhinitis, LRSS, and, very rarely, PDA. In summary, the adverse health effects of TMA are due to its known ability to act as an irritant in all humans and as a sensitizer in a small proportion of humans. Thus, classification in addition to irritant and sensitizer does not appear necessary.

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