

Acid anhydrides

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Acid anhydrides are low molecular weight chemicals used industrially as curing agents in the production of epoxy and alkyd resins and in the manufacture of plasticisers such as dioctyl phthalate. These have widespread applications as surface coatings and adhesives and in plastic manufacture. The chemical reactivity of acid anhydrides, which is the basis of their commercial value, is also the major determinant of their biological effects. Acid anhydrides bind covalently to free amino groups, in particular to the amino group of lysine of body proteins to form immunogenic hapten-protein conjugates, able to stimulate a specific immunological response.

Several of the different acid anhydrides used commercially have been reported to cause asthma in those exposed to them in their work. These include phthalic (PA), trimellitic (TMA), tetrachlorophthalic (TCPA), maleic (MA), hexahydrophthalic, himic and pyromellitic di-anhydride.

We have studied cases of asthma caused by acid anhydrides and populations occupationally exposed to them to investigate the nature of the airway response in patients with acid anhydride induced asthma, the IgE response to acid anhydrides, its specificity, its determinants and its relationship to asthma and also outcome after avoidance of the exposure of both the immunological and airway response.

Airway response to inhaled acid anhydrides

Inhalation tests with each of PA, TCPA, TMA, and MA provoke both immediate and late asthmatic responses. Late, but not immediate asthmatic responses provoked by these chemicals are associated with an increase in non-specific responsiveness to inhaled histamine which is detectable 3 hours after the inhalation test, and prior to the development of the late asthmatic response [1]. The magnitude of the increase in non specific airway responsiveness at 3 hours is significantly associated with the maximum fall in FEV1 during the late asthmatic response suggesting the change in airway calibre (the late asthmatic response) depends upon the tissue events (probably inflammatory) which underly the preceding increase in airway responsiveness.

Inhalation testing in four patients with TCPA induced asthma exposed to increasing concentrations until a 20% decrease in FEV1 was reached, showed the magnitude of the late asthmatic response to be determined primarily by the atmospheric concentration of TCPA [2]. The authors estimated that a fall in FEV1 of 15% for one hour would be provoked in a sensitised individual by an atmospheric concentration of 0.99 ug/m^3 , a level difficult for industry to achieve.

Immunological response to inhaled acid anhydrides

Specific IgE antibody to PA was originally demonstrated in one case of asthma by Maccia et al [3] and to TMA in 3 cases of asthma by Zeiss et al [4]. We reported 7 cases of asthma caused by inhalation of TCPA in an epoxy resin powder used to encapsulate electronic components in a protective plastic coat at their place of work. A TCPA-human serum albumin (TCPA-HSA) conjugate provoked immediate skin prick test responses in all 7 and identified specific IgE antibody (by RAST) and IgG and IgG4 (by ELISA) [6] in their sera. Comparison of specific IgE and IgG4 in the sera of these 7 cases with 8 comparably exposed but non asthmatic individuals and 7 unexposed individuals demonstrated that specific IgE was present only in those exposed

and significantly associated with asthma, whereas total specific IgG was associated with exposure equally present in those with and without asthma. In another study of two factory populations exposed to PA respiratory symptoms were more closely associated with specific IgG4 than with specific IgE [9].

We investigated the specificity of IgE for the epitopes formed by conjugation of PA, TMA, TCPA and MA with albumin by comparing the reactivity of sera from cases of asthma caused by each anhydride with RAST and by RAST inhibition [7]. For those sensitised to TCPA and TMA the anhydride-HSA conjugate was a more effective inhibitor of RAST than either the sodium salt of the anhydride or an anhydride-bovine serum albumin conjugate, whereas for those sensitised to PA the free hapten was as effective an inhibitor as the HSA conjugate. HSA conjugates of anhydrides to which the individual was not sensitised, although binding to specific IgE in RAST, were weaker inhibitors of RAST than the sensitising acid anhydride human serum albumin conjugate. These findings provide strong evidence that the anhydride is involved in the IgE antibody combining site.

Determinants of the IgE response

The factory population where our original 7 cases of TCPA induced asthma were employed was studied to determine the distribution of specific IgE and examine potential determinants of the immunological response [9]. Specific IgE antibody binding to TCPA-HSA conjugate was present in 24 of 300 factory floor workers exposed to TCPA. The major factors associated with the presence of specific IgE to TCPA-HSA were intensity of exposure and cigarette smoking. Ten per cent of those working in the coating areas of the factory had specific IgE as opposed to 5.4% of those working in other areas. 12.7% (18 of 42) smokers, as compared with 2.2% (3 of 134) non smokers had specific IgE, a relative risk for smokers of developing specific IgE of 5.8. Atopy (defined as one or more immediate skin prick test responses to common inhalant allergens) did not differ significantly between those with and without specific IgE, but

interacted with cigarette smoking to increase the risk of specific IgE. There was a trend of prevalence of specific IgE from atopic smokers (16.1%) to non atopic non smokers (0). The consistency of these and other similar observations suggests the association of specific IgE and asthma with smoking may be causal. This seems likely to be due to local non-specific damage to the bronchial epithelium caused by inhaled tobacco smoke.

Outcome of immunological and airway response

The 7 patients with TCPA induced asthma have been followed up for 4 years from leaving work and avoiding exposure to TCPA [10]. One of the 7 died one year after leaving work. During the period of follow up, specific IgE to TCPA-HSA conjugate in the 6 living patients fell exponentially with $t_{1/2}$ of one year. Inhalation tests for a maximum duration of 30 minutes with atmospheric concentrations of up to 0.96 mg/m (in comparison to the recommended control limit of 12 mg/m) were associated with a transient rise in specific IgE showing the serum concentration of specific IgE to be a sensitive index of exposure. At the end of the study period showed all 6 continued to have episodic respiratory symptoms and their airway response to inhaled histamine was less than 8 mg/ml in 4 of the 5 tested.

Radiolabelled myeloma IgE antibody has a $t_{1/2}$ in the circulation of 2.5 days in normal subjects and of 5.1 days in a patient with IgE myeloma [11]. The $t_{1/2}$ of one year of specific IgE in our patients indicates continuing antibody secretion. The consistent and parallel declines make it unlikely to be due to continuing TCPA exposure and it may reflect retained hapten or autonomous B cell IgE production.

Airway hyper-responsiveness has now been shown to persist after avoidance of exposure to its cause in a significant proportion of those who develop occupational asthma. This seems particularly to occur where the cause of asthma is a low molecular weight chemical such as isocyanates [12], colophony [13] (possibly abietic acid) and Western Red Cedar [14]

(pilocarpic acid). We now have similar information for one of the acid anhydrides. The reason for continuing asthma and airway hyper-responsiveness is unclear but the problem of persistent airway hyper-responsiveness in asthma caused by an agent inhaled at work is an important one whose solution is likely to be relevant to an understanding of the determinants of airway hyper-responsiveness in asthma in general.

Conclusions

Acid anhydride induced asthma is to date the most informative human model of hapten induced asthma. This is primarily because of the preparation of relevant anhydride-albumin conjugates has allowed study of the immunological response to these chemicals in man and the relationship of the immunological to the airway response. The reason similar progress has not been made with other low molecular weight organic chemical causes of asthma such as isocyanates is unclear but some light may have been shed by a study comparing the immunogenicity of two β -lactams, a clavam, clavulanic acid, which is not immunogenic, and a carbapenem, MM22383, which is immunogenic in experimental animals and a cause of occupational asthma in man. The authors identified 3 characteristics of low molecular weight chemicals relevant to the development of a specific immunological response were identified: (1) reactivity with body proteins (as recognised by Landsteiner) (2) homogeneity with respect to the chemical hapten and (3) stability of the conjugate formed [15]. All three are true of the conjugation of acid anhydrides with body proteins.

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