

## INVITED REVIEW

# Allergic and asthmatic reactions to alcoholic drinks

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### Abstract

*Alcoholic drinks are capable of triggering a wide range of allergic and allergic-like responses, including rhinitis, itching, facial swelling, headache, cough and asthma. Limited epidemiological data suggests that many individuals are affected and that sensitivities occur to a variety of drinks, including wine, beer and spirits. In surveys of asthmatics, over 40% reported the triggering of allergic or allergic-like symptoms following alcoholic drink consumption and 30–35% reported worsening of their asthma. Sensitivity to ethanol itself can play a role in triggering adverse responses, particularly in Asians, which is due mainly to a reduced capacity to metabolize acetaldehyde. In Caucasians, specific non-alcohol components are the main cause of sensitivities to alcoholic drinks. Allergic sensitivities to specific components of beer, spirits and distilled liquors have been described. Wine is clearly the most commonly reported trigger for adverse responses. Sensitivities to wine appear to be due mainly to pharmacological intolerances to specific components, such as biogenic amines and the sulphite additives. Histamine in wine has been associated with the triggering of a wide spectrum of adverse symptoms, including sneezing, rhinitis, itching, flushing, headache and asthma. The sulphite additives in wine have been associated with triggering asthmatic responses. Clinical studies have confirmed sensitivities to the sulphites in wine in limited numbers of individuals, but the extent to which the sulphites contribute to wine sensitivity overall is not clear. The aetiology of wine-induced asthmatic responses may be complex and may involve several co-factors.*

### Introduction

Although many of the adverse health effects associated with alcoholic drink consumption are well documented,<sup>1–3</sup> relatively little is known about allergic and allergic-like responses to these drinks. Sensitivity to alcohol itself (ethanol) has been found to play a role in inducing these types of reactions; however, this appears to be more

common in those of Asian extraction as well as certain populations such as American Indians, Eskimos and Mexicans, and is much rarer among other ethnic groups.<sup>4,5</sup> Alcoholic drinks are, however, extremely complex, consisting of many hundreds of components in addition to ethanol. These components play an important role in determining the flavour and character of these

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drinks<sup>6,7</sup> and some of these components have also been linked with the triggering of adverse responses. For example, sulphite additives and histamine have been implicated in sensitivity to wine, while allergy to grains and yeast have been suggested as a cause of sensitivity to beer. Asthmatics seem to be particularly affected by sensitivities to alcoholic drinks, and in some asthmatics these reactions may be severe and even life-threatening.<sup>8,9</sup> This review discusses our current understanding of adverse responses to alcoholic drinks that fit the broad definition of being allergic or allergic-like in nature.

### **Epidemiological studies addressing sensitivities to alcoholic drinks**

Only three epidemiological studies have addressed alcoholic drink sensitivities specifically.<sup>8,10,11</sup> In the first of these, Ayres & Clark<sup>10</sup> surveyed a cohort of 168 asthmatics, consisting primarily of those attending outpatient chest clinics at four hospitals in the United Kingdom. Those surveyed were asked specifically about the triggering of asthma following consumption of alcoholic drinks. In this study, 32.1% of patients reported wheeze associated with alcoholic drink consumption, with sensitivities to a variety of drinks being reported. Wine and beer were the most commonly reported triggers for asthma, with 30.1% of wine drinkers and 22.6% of beer drinkers reporting sensitivities. Interestingly, an improvement in asthma symptoms following alcoholic drink consumption was also reported in a subgroup of patients. This effect was mainly associated with the consumption of spirits, and was attributed to the ethanol content of these drinks, as ethanol has been shown to have a bronchodilatory effect.<sup>12,13</sup>

A similarly high frequency of alcoholic drink sensitivity was reported in two recent surveys of Australian asthmatics in which both allergic and asthmatic responses to these drinks were addressed.<sup>8,11</sup> In a survey of 150 consecutive hospital-based patients, 48.0% indicated that they had previously experienced an allergic, allergic-like or asthmatic reaction following the consumption of alcoholic drinks.<sup>11</sup> A total of 35.3% of those surveyed indicated that alcoholic drinks worsened their asthma, with 30.7% reporting asthmatic responses to wine. In a survey of 366 asthmatics recruited from a community-based asthma group, 42.6% of respondents

reported sensitivities to alcoholic drinks, indicating a diverse range of symptoms including hayfever, cough, facial swelling, itching, eczema and headache as well as asthma.<sup>8</sup> Asthma was once again the most commonly reported symptom, with 33.1% reporting the triggering of asthma following alcoholic drink consumption. Asthmatic responses to alcoholic drinks were, in the main, rapid in onset (< 1hour) and of mild to moderate severity, although many individuals reported reactions that they considered to be severe or very severe.

Wine was clearly the most commonly reported trigger for asthmatic responses in the survey of community-based asthma patients, with 30.3% reporting sensitivities to this drink.<sup>8</sup> While there were many individuals specifically sensitive to either red or white wines, most individuals reported sensitivities to both, suggesting that a component present in significant levels in both these wine types was important in triggering asthma. More detailed analyses of this cohort indicated an association between sensitivity to sulphite additive-containing foods and sensitivity to wine, implicating the sulphites in wine as playing an important role in wine-induced asthma. Although several investigators have suggested that sulphite additives may be important triggers for wine-induced asthma,<sup>14-16</sup> to our knowledge this is the only epidemiological study that has demonstrated an association between sulphite sensitivity and wine sensitivity. An association between wine-induced asthma and aspirin-intolerant asthma was also demonstrated, suggesting a common underlying mechanism for these sensitivities, or a possible role for salicylates present in wine in wine-induced asthmatic responses.

### **Mechanisms of alcoholic drink sensitivities**

#### *Sensitivities to ethanol*

#### *Ethanol and immune system-mediated effects.*

Although it has been suggested that the immunological recognition of ethanol may be responsible for sensitivities to alcoholic drinks in some individuals, this does not appear to be common. Due to its size, ethanol is unlikely to act directly as an allergen by cross-linking IgE molecules on mast cells, and it has been suggested that this molecule may conjugate with protein, forming a hapten, allowing it to be recognized by antibody.<sup>17</sup> Interestingly, it has also been suggested

that by-products of ethanol metabolism such as acetaldehyde and acetic acid are capable of forming protein adducts which may play a role in alcoholic drink sensitivities in certain individuals.<sup>18-22</sup> The binding of various metabolites of ethanol to proteins and the formation of immunogenic adducts is now implicated as playing an important role in some of the more recognized adverse effects associated with chronic alcohol consumption such as liver disease.<sup>23,24</sup>

Ethanol does, however, appear to play a more direct role in modulating immune function. In particular, ethanol has been shown to have a number of immunosuppressive effects, including downregulation of cytokine production,<sup>25</sup> suppression of lymphocyte activity,<sup>26,27</sup> inhibition of mast cell degranulation,<sup>27</sup> modulation of prostaglandin production<sup>28-30</sup> and upregulation of corticosteroid production.<sup>31</sup> These immunosuppressive effects, together with the smooth muscle relaxant properties of ethanol<sup>32,33</sup> and the putative ability of ethanol to increase the threshold of response to asthma triggers,<sup>34</sup> may all play a role in the reported capacity for ethanol to induce bronchodilation in certain individuals.<sup>10,13</sup> Interestingly, in more recent times, the consumption of alcohol has also been associated with an increase in both total and specific IgE levels, although the mechanism by which this occurs is unclear.<sup>35,36</sup>

*Intolerances to ethanol.* Sensitivities to alcohol resulting from differences in alcohol metabolism associated with racial and ethnic origin have been well described.<sup>4</sup> As many as 50% of individuals of Asian origin appear to be affected.<sup>37,38</sup> In these individuals, symptoms characteristically develop within 30 minutes of alcohol ingestion and include increased facial flushing and skin temperature, peripheral vasodilation, elevated heart rate, nausea, abdominal discomfort and bronchoconstriction.<sup>39</sup>

Acetaldehyde, an intermediate in the metabolism of alcohol, appears to be the primary mediator of alcohol-intolerance reactions,<sup>37,40,41</sup> with the kinetics of acetaldehyde production in affected individuals following the time-course of symptoms,<sup>38</sup> and individuals with the highest levels of serum acetaldehyde experiencing the most intense intolerance symptoms.<sup>37</sup> Acetaldehyde has also been shown to play an important role in the skin responses of Asians to primary alcohols applied topically.<sup>42,43</sup> Importantly, acet-

aldehyde does not seem to induce bronchoconstriction in healthy subjects, and bronchial responsiveness to methacholine seems to correlate with bronchial responsiveness to acetaldehyde in asthmatic subjects, suggesting that non-specific bronchial hyperreactivity is a necessary requirement for acetaldehyde-induced bronchoconstriction in asthmatics intolerant to alcohol.<sup>44</sup>

Individuals intolerant to alcohol appear to have an impairment in the enzyme that converts acetaldehyde to acetic acid.<sup>39</sup> The reduced activity of this enzyme, acetaldehyde dehydrogenase (ALDH), results in these individuals being unable to metabolize acetaldehyde quickly and effectively, and hence levels of this toxic chemical are increased in intolerant individuals. The mechanism by which acetaldehyde mediates asthmatic responses is not fully understood, and may involve a number of different mechanisms.<sup>41</sup> Histamine release, however, clearly plays an important role.<sup>44-46</sup> In support of this, both H<sub>1</sub>- and H<sub>2</sub>-histamine receptor antagonists have been shown to be efficacious in blocking alcohol intolerance symptoms.<sup>45</sup> However, it is not clear whether histamine release occurs as a result of the binding of acetaldehyde to antibody,<sup>18,21</sup> or whether acetaldehyde is able to induce histamine release directly.<sup>38</sup>

Certain medicines can also induce intolerance to alcohol, through the inhibition of ALDH activity.<sup>47</sup> In fact, the inhibition of ALDH by disulfiram (Antabuse) has clinical application in the treatment of alcohol addiction by inducing the spectrum of unpleasant alcohol-intolerance symptoms following alcohol consumption.<sup>48</sup> The intolerance to alcohol induced by disulfiram is so severe that even small amounts of alcohol in other medications, or the topical application of alcohol, may lead to serious adverse responses in individuals taking this medication. Other medications tend to have far smaller, but still significant, effects on alcohol metabolism. Oral hypoglycaemic agents (notably chlorpropamide and tolbutamide) and various antimicrobial medications (e.g. chloramphenicol, furazolidine, griseofulvin and metronidazole) are known to be associated with adverse responses to alcohol.<sup>49</sup>

#### *Sensitivities to spirits, distilled liquors and beer*

There are only a few reports describing the sensitivity of individuals to distilled alcoholic drinks. Sherry and whisky, as well as some other

liquors, have been shown to be capable of inducing adverse responses in certain individuals. These appear to be due to allergic reactions to specific non-alcohol components of these drinks. In the study by Breslin *et al.*,<sup>50</sup> an individual reporting an asthmatic response following the consumption of whisky was challenged with this drink, and inhalation of disodium cromoglycate was found to inhibit this reaction, supporting a type I allergic mechanism. Intriguingly, there have been reports of individuals exhibiting dermatitis associated with the consumption of gold-containing schnapps, resulting from an allergic sensitivity to the gold present in this drink.<sup>51-53</sup> In all these cases rashes resolved when ingestion of the offending drink was discontinued.

There are surprisingly few reports describing allergic or asthmatic responses to beer, despite the fact that this drink is perceived to be a common trigger for asthma in epidemiological studies.<sup>8,10</sup> Nevertheless, sensitivity to particular cereal components of beer, such as barley and malt, have been described and, as is the case with distilled alcoholic drinks, these sensitivities appear in the main to be attributable to IgE-mediated reactions.<sup>54,55</sup> It has been shown that brewer's yeast is a potent allergen, and consequently it has been suggested that there may be a role for yeast allergy in beer sensitivity. However, whether significant levels of yeast allergen are present in beer and other alcoholic drinks or whether individuals react to the low levels present in these drinks is unclear at present.<sup>20,56,57</sup>

#### *Sensitivities to wine*

Wine is clearly the most commonly reported alcoholic drink trigger for allergic and allergic-like sensitivities.<sup>8,10,11</sup> Clinical and epidemiological data suggest that there are likely to be a number of different mechanisms underlying wine sensitivity.<sup>8,16</sup> However, our understanding of the various mechanisms that may be involved, and the relative importance of these, is limited. Immunological mechanisms seem only to play a minor role in sensitivities to wine, with only a few reports describing putative anaphylactic reactions.<sup>9,58,59</sup> In the main, sensitivities to wine appear to be due to pharmacological intolerances to specific components of these drinks.

*Salicylates and sensitivity to wine.* Despite the epidemiological evidence to suggest that there is a link between sensitivities to aspirin (acetylsalicylic acid) and wine,<sup>8</sup> whether individuals sensitive to aspirin also react to other non-acetylated forms of salicylate or react to natural salicylates in foods is controversial.<sup>60</sup> Limited data suggest that some individuals with asthma or urticaria may be sufficiently sensitive to salicylates that they react to the low levels present in certain foods (including wines), and that these individuals may benefit greatly from the avoidance of salicylate-containing foods.<sup>61-64</sup> However, both the actual levels of salicylates in foods and the biological relevance of these levels are disputed.<sup>65-67</sup> To date, there is no direct evidence for a role of salicylates in sensitivities to wine.

*Biogenic amines and sensitivity to wine.* Biogenic amines are found in a variety of foods, including wine.<sup>68,69</sup> Although the chemistry of biogenic amine formation in wine is not fully understood, it is believed malolactic fermentation by lactic acid bacteria are the source of these chemicals.<sup>70</sup> Red wine generally contains much higher levels of biogenic amines than white wine, which is thought to be due to the greater importance of malolactic fermentation in red wine manufacture.<sup>70</sup> The levels of biogenic amines, however, vary greatly from one wine to the next, probably due to differences in wine-making techniques and differences in the characteristics of the grape varieties used to make wine.<sup>70,71</sup>

Biogenic amines have been suggested as possible triggers for a variety of adverse responses to wine,<sup>15,72,73</sup> with a number of different amines having been found to be present in significant levels in these drinks.<sup>71,74</sup> Although possible roles for several of these biogenic amines in sensitivities to wine have been suggested, histamine and tyramine have been implicated most often.<sup>72,73,75</sup> Both tyramine and histamine in red wine have been suggested as playing an important role in triggering headache, particularly migraines.<sup>73,75-77</sup> Tyramine in red wine has been associated specifically with the triggering of headaches in subjects being treated with monoamine oxidase (MAO) inhibitors, and interestingly red wine itself may be able to inhibit MAO.<sup>75</sup>

Histamine is a potent mediator of the allergic response, and following ingestion has been shown to induce a wide range of allergic symptoms in

susceptible individuals, including flushing, sneezing, itch, rhinitis, headache and shortness of breath.<sup>78</sup> Histamine has consequently been suggested as playing an important role in allergic-like and asthmatic sensitivities to wine. The exact role of histamine in these reactions, however, remains unclear. In some studies an important role for histamine has been strongly suggested.<sup>72,79</sup> This is supported by the elimination of allergic symptoms in individuals after pretreatment with antihistamines<sup>72</sup> and following adherence to histamine-free diets.<sup>76,80</sup> In contrast, some studies have suggested that sensitivity to histamine does not play an important role in adverse responses to wine, and that other mechanisms are important.<sup>15,81</sup>

One hypothesis that has been proposed to explain sensitivities to histamine suggests that it is due to the reduced activity of the enzyme diamine oxidase (DAO), which results in a reduced capacity to metabolize histamine. This is supported by increased basal levels of histamine, and increased post-wine challenge levels of histamine in wine intolerant individuals compared with controls.<sup>72</sup> The extent to which intolerance to histamine plays a role in wine-induced asthma, however, remains uncertain. Certain foods that are reported to contain higher levels of histamine than red wine have not been as commonly associated with adverse reactions.<sup>81</sup> Consequently, it has been suggested that there may be other components in wine that play an important role in wine intolerance reactions, and that these components either induce the release of histamine directly, or interfere with histamine metabolism.<sup>81</sup> Interestingly, polyphenolic compounds, which are found in abundance in red wine,<sup>82</sup> have been shown to inhibit the release of histamine.<sup>83,84</sup>

*Sulphite additives and sensitivity to wine.* Sulphite additives play an integral role in the wine-making process. These additives are used to sterilize barrels or tanks before fermentation takes place and are added to the grape must and wine at various stages during production to control the growth of undesired species of yeast and bacteria that cause spoilage. Sulphites are also present in the final bottled wine and by preventing oxidation help to maintain the desirable sensory characteristics of wine during its production, transport and marketing.<sup>85</sup> Importantly, the sulphite additives have been associated with the triggering of

asthmatic responses in certain individuals.<sup>86,87</sup> It is generally estimated that somewhere between 5–10% of asthmatics are sensitive to the ingestion of sulphites.<sup>88,89</sup> However, sensitivity to the sulphites appears to be heightened when individuals are exposed to solutions of sulphite, and this is accentuated even further when these solutions are acidic in nature.<sup>90–92</sup> For these reasons, sulphites have been implicated as major culprits in triggering wine-induced asthmatic responses, although studies addressing this issue have been inconclusive.

The sulphite additives have been clearly shown to play a role in asthmatic responses to wine in certain individuals.<sup>15,16</sup> Interestingly, however, in many individuals who provide strong histories suggesting sensitivity to wine, and more specifically to the sulphites in wine, reactivity to these additives has not been demonstrated when controlled challenges have been conducted.<sup>16</sup> One possible explanation for this is that other factors may play a role in wine sensitivity, and that asthmatics may be more sensitive to wine at times when their asthma is unstable. Similarly, it is possible that cigarette smoke or other airway irritants and triggers may potentiate sensitivities to wine, or that wine consumption may in fact potentiate sensitivity to these exogenous factors. In support of this, there are anecdotal reports of asthma patients with pollen allergy who report sensitivity to red wine during the pollen season, but not at other times of the year when, presumably, their asthma is more stable.<sup>15</sup> In one study, an individual who was able to tolerate low-sulphite wine in a challenge test when asthma symptoms were well controlled was found to be sensitive to this identical wine on a second occasion when baseline asthma symptoms had worsened.<sup>16</sup> In a separate phase of this same study, when three asthma patients were challenged in a clinical setting with the identical brand and vintage of wine to which they had reported a history of asthmatic reactions, no positive responses were observed. The fact that these asthmatics were challenged at a time when their asthma was very stable, and in an environment free of any possible co-factors, may have resulted in an increased tolerance to these self-selected wines.

Despite uncertainty as to the extent to which the sulphite additives are involved in wine-induced asthma, individuals who are clearly sensitive to the sulphites in wine have been shown

to respond rapidly when sulphite-containing wine is consumed.<sup>93</sup> In mild to moderate responders, this fast onset of response is generally accompanied by a relatively quick resolution of symptoms after 15–60 minutes in the absence of therapy. Treatment with  $\beta_2$ -adrenoceptor agonists appears to be efficacious in resolving asthma symptoms and normalizing lung function in those asthmatics with more severe responses. Interestingly, exquisitely sensitive asthmatics challenged with sulphited white wine were found to be able to tolerate wine containing up to 150 p.p.m. of sulphite when challenged in a clinical setting, despite reporting histories suggesting that during natural exposures they were sensitive to wine containing much lower levels of sulphite. Once again, the controlled nature of the challenge environment may have resulted in an increased tolerance to sulphite containing wines in these individuals. In contrast, in studies of red wine-sensitive individuals, wine containing as little as 50–55 mg/l of sulphite has been demonstrated to induce an asthmatic response when consumed in a clinical setting.<sup>15</sup> This raises the question as to whether other components in red wine may potentiate sensitivities to the sulphite additives in these drinks.

### Conclusions

Both epidemiological and clinical studies suggest that alcoholic drinks are important triggers for allergic and allergic-like responses. Despite this, our understanding of these sensitivities is limited. None of the previous surveys addressing this issue can be considered to provide true estimates of the overall prevalence of sensitivities to alcoholic drinks, since they have been conducted solely in asthmatics, and furthermore, in populations of asthmatics that would be expected to be biased towards those with more severe disease. Consequently, there is clearly a need to assess these sensitivities in a randomly selected population to better understand the extent of this problem. Despite this, the fact that so many individuals have reported sensitivities in the surveys conducted, and that many of these individuals have reported sensitivities which are severe, suggests that sensitivity to alcoholic drinks should not be ignored. There is clearly a need for both health professionals and patients to be aware that this is another possible adverse health outcome following the consumption of alcoholic drinks. This is

particularly so for asthmatics, and particularly pertinent for wine sensitivity, which appears to affect many individuals.

The mechanisms underlying sensitivities to alcoholic drinks are not fully understood. While classical allergic responses play a role in some individuals, sensitivities to alcoholic drinks for the most part do not appear to be immune-mediated, but are more frequently pharmacological intolerances to specific chemicals in these drinks. Intolerance certainly plays an important role in sensitivity to ethanol itself, which affects many individuals of Asian extraction, and is due to a reduced capacity to metabolize acetaldehyde. Similarly, although our understanding of wine sensitivities is limited, these responses also appear to be due predominantly to intolerances to specific components in wine. Intolerance to biogenic amines in wine, such as histamine, may play a role in triggering a wide range of adverse symptoms and sensitivity to the sulphite additives also clearly plays an important role in asthmatic responses to wine. However, the aetiology of wine sensitivities appears to be complex, and a number of contributing factors such as unstable asthma and the presence of other irritants or triggers in the environment may all play a role in determining whether an individual will react to wine. Clearly there is a need for more research to be completed if we are to better understand sensitivities to alcoholic drinks.

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