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Sensitivity to tartrazine

Patients who are sensitive to aspirin may also be sensitive to tartrazine, a yellow dye used in medicines and foods.[1] Symptoms of an allergic reaction (urticaria, rhinitis, or asthma) may occur after exposure to many chemicals used to colour, flavour, or preserve food and drugs, but tartrazine (F D & C yellow No 5) is the colour most frequently incriminated. Intolerance to tartrazine was first reported in 1959,[2] and its part in the induction of intractable urticaria has been recognised since 1975.[3] Non-thrombocytopenic purpura is also reported to be due to hypersensitivity to tartrazine—which suggests the possibility that tartrazine may act as a hapten bound to the endothelial cells of small blood vessels.

Tartrazine is a coal-tar derivative with a similar chemical structure to the benzoates, other azo compounds, pyrazole compounds, and the hydroxyaromatic acids, which include salicylates. It shows relatively little protein binding in comparison with non-azo dyes[4] and may require prior metabolism before it can induce an immune response. The azo group can be reduced in the intestine and liver[5]—one of the several routes through which the compound could be conjugated to form a potentially antigenic hapten structure.[6]

Recent studies have shown that clinical hypersensitivity to tartrazine may be associated with a humoral immune response to part of the molecule—namely, its sulphophenyl antigenic determinants.[7] The antibodies were of the immunoglobulin IgD class, which suggests that immunological mechanisms other than those usually concerned in drug and food allergy play a part in hypersensitivity responses to additives. Additional evidence suggests that the clinical symptoms of intolerance to acetylsalicylic acid and tartrazine are probably not mediated by antibodies of the IgE class.[8] The important mechanism behind the observed adverse response to aspirin is thought to be inhibition of prostaglandin-synthesising enzymes[10 11]; and the sensitivity of patients showing abnormal reactions to acetylsalicylic acid extends to other non-steroidal anti-inflammatory drugs and correlates with the ability of the drug concerned to inhibit prostaglandin synthesis.[12] Possibly both the generation and effector function of suppressor cells may be modulated by prostaglandin inhibitors.[13] Though patients have similar pathological reactions to tartrazine and acetylsalicylic acid, however, no effect of tartrazine on inhibition of prostaglandin pathways has been observed,[13a 13b] indicating that different biological pathways are concerned.

In practical terms, depending on the test protocol followed,[14–16] between 10% and 40% of patients sensitive to aspirin respond to tartrazine, with reactions ranging from systemic anaphylaxis and severe asthma to urticaria and mild rhinitis. Medical practitioners need to know which drugs contain this dye so that they do not prescribe them for their aspirin-sensitive patients.

The prevalence of tartrazine sensitivity is not known but figures of 1 in 10 000 have been suggested[17]—remarkably low, given the exposure. Several cases have been reported where the only possible source was a soft drink,[18] and other people may have been adversely affected by tartrazine in foods. The incidence of tartrazine sensitivity appears to be higher in asthmatic or allergic subjects than in the general population.[19] Subjects hypersensitive to one substance tend to be allergic to a variety of substances, which again suggests a difference in the general regulation of immune responses. People sensitive to acetylsalicylic acid who are allergic to foods[20] should avoid tartrazine as a food dye.

The mechanism of the adverse reaction to tartrazine is not known. Existing tests are largely of low predictive value, and new methods to detect such reactions need to be investigated. Further research is needed into basic mechanisms and, if feasible, the epidemiology of the conditions provoked by tartrazine and corresponding agents to provide reliable data on the number of allergic responses associated with them. Only then can the hazard of tartrazine be properly evaluated.

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Sjögren's syndrome

The era of scientific medicine has greatly reduced the number of eponymously named diseases. Once a specific and relatively sensitive test has been found, many syndromes coalesce into one disease. Sarcoidosis is an excellent example of this evolution but with Sjögren's syndrome we still lack a diagnostic test, as shown by the number of alternative names that have been used—such as autoimmune exocrinopathy, primary and secondary sicca syndromes, and keratoconjunctivitis sicca. Autoimmune exocrinopathy[1] emphasises the generalised lesions of the exocrine glands that may occur together with autoantibody markers of "autoimmune" disease. As its name suggests, these findings should encourage clinicians faced with one feature of the sicca syndrome to look for others and to perform a screening test for autoantibodies by immunofluorescence. But few would think of Sjögren's syndrome when faced with presenting systemic manifestations such as pulmonary lesions, renal tubular acidosis, or hyperglobulinaemic purpura. The terms primary and secondary sicca syndrome attempt to differentiate between the serious primary systemic disease with sicca features but without an associated "autoimmune" disease and the minor but frequent occurrence of sicca features in systemic illnesses such as rheumatoid arthritis, systemic sclerosis, primary biliary cirrhosis, and chronic active hepatitis.

Keratoconjunctivitis sicca is the most easily recognised sicca component: patients have sore, itchy eyes with decreased lacrimal secretion as shown by testing with filter paper (Schirmer test). Keratitis may be shown by rose bengal staining. Keratoconjunctivitis sicca is usually most severe in primary sicca syndrome and systemic sclerosis, and mild or moderate in rheumatoid arthritis and other "autoimmune" diseases. Occasionally it may be found in sarcoidosis, lymphoma, or leukaemia. All structures with exocrine glands may be affected, with the production of rhinitis, laryngitis, bronchitis, gastritis, and possibly pancreatitis and vaginitis sicca. The dry mouth unaccompanied by swelling of the salivary glands is difficult to assess, as sialographic appearances are non-specific and measurement of salivary secretions is unsatisfactory.

The results of diagnostic tests in Sjögren's syndrome tend to be positive when the diagnosis is obvious, and equivocal when one most needs them. Labial mucosal biopsy[2 3] is the most useful test, being sensitive, specific, and very easy to do (by an oral surgeon). In the early stage of disease, the histological appearances tend to be indefinite; serological markers of autoimmune disease are often present but tend to be non-specific. The combination of a positive rheumatoid factor test, keratoconjunctivitis, and dry mouth is diagnostic in a patient without inflammatory polyarthritis but unhelpful in one with polyarthritis. Antinuclear antibodies, with normal concentrations of DNA antibodies, are frequently present, as are thyroid autoantibodies. Precipitating antibodies to two nuclear antigens, usually called SS-A and SS-B, seem closely associated with Sjögren's syndrome,[4] and their predictive value has been tested in two recent reports. Forstot *et al*[5] studied patients with keratoconjunctivitis sicca in an ophthalmology clinic, showing that antibodies SS-A and SS-B were found only in those patients with keratoconjunctivitis and xerostomia. SS-B was more closely associated with Sjögren's syndrome than SS-A, and was more usually found in patients with longstanding disease and abnormal labial biopsy specimens; it was thus of little diagnostic value in early cases. Isenberg *et al*[6] looked retrospectively at 15 patients out of 55 patients found to have precipitating antibodies to SS-B in a screening programme. Unsuspected Sjögren's syndrome was confirmed on review in 11 of the 15 patients; the remaining four had no evidence of the disease. These reports suggest that SS-A and SS-B antibodies may have diagnostic value in patients with unexplained parotid swelling, renal tubular acidosis, pseudolymphoma, or pulmonary disease. A careful medical history, ophthalmic examination, and a screen for autoantibodies is likely to be more useful in those with a single component of the sicca syndrome. Labial mucosal biopsy may be useful in all cases.

Of the various sicca components, the eye and vaginal symptoms are best alleviated by replacement lubricants. Hypromellose eye-drops are now generally available, but must be used often enough to prevent drying out of the conjunctival sac. There is no satisfactory treatment for the dry mouth, and the variety of lozenges and mouth washes available on prescription supports this. Frequent sips of water and regular dental checks are important, and one saliva substitute has recently been tested in a controlled trial[7]; more such trials are needed to establish whether chlorambucil is of use in the systemically ill patient.

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