

Treatment of urticaria

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SYNOPSIS

Urticaria and angioedema can be caused by allergic and non-allergic mechanisms. While acute urticaria usually resolves quickly, chronic urticaria can persist for years. Management begins with a classification of the type of urticaria. Extensive investigations are usually unnecessary. Treatment includes avoiding the factors which provoke the reaction. When this is not possible, antihistamines remain the treatment of choice. A non-sedating antihistamine is preferred. More severe cases may require corticosteroids or immunosuppressant drugs.

Index words: anaphylaxis, angioedema, antihistamines.

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Introduction

Urticaria is a common condition affecting approximately 25% of the population at some time. It has many causes. Urticaria is unpredictable and results in a great deal of distress because of the intense pruritis, and the interference it causes to sleep and daily life. The fundamental step in managing a patient with urticaria is to try and classify the nature of the condition. This will determine which, if any, investigations are necessary. Antihistamines remain the mainstay of treatment, but in some cases other strategies are necessary.

In approximately 50% of patients, urticaria and angioedema coexist, while 40% experience urticaria alone and 10% will have isolated angioedema. The hallmark of urticaria is transient (less than 24 hours duration) pruritic wheals. Angioedema is a deep dermal, subcutaneous or submucosal oedema resulting in swelling which generally lasts 24 hours and sometimes longer.

Urticaria/angioedema is generally classified as acute (lasting up to six weeks) and chronic (lasting longer than six weeks). Urticaria may also occur intermittently, where lesions appear for days or weeks with symptom-free intervals lasting weeks or months.

Chronic urticaria is relatively common, occurring in 0.1% of the population, with 20% still having problems 10 years after its onset. Pruritus is invariably distressing, usually at its worst in the evening and during the night. Chronic urticaria causes a major impairment to the individual's quality of life and its impact on the patient should never be underestimated.

Aetiology

The final common pathway in the induction of urticaria/angioedema involves local increase in the permeability of capillaries and small venules triggered by mediators released as a consequence of mast cell

degranulation. This degranulation may result from immunological or non-immunological triggers.

IgE-mediated reactions are the commonest causes of acute urticaria and are generally severe, with a dramatic onset. Other manifestations of anaphylaxis may be evident. Symptoms will occur within minutes to a few hours of exposure to an allergen. Acute reactions are most commonly experienced in childhood. Foods such as nuts, eggs, milk and seafood account for many of these reactions. Reactions to insect stings also fall into this category. Some patients react to a physical stimulus, for example cold or vibration.

Any drug is capable of producing an acute allergic reaction manifested by acute urticaria but antibiotics, particularly penicillin, remain the commonest cause of an acute urticarial drug reaction. Non-steroidal anti-inflammatory drugs including aspirin are other common drugs causing acute urticaria/angioedema. Although the reaction is indistinguishable from an IgE-mediated reaction, the mechanism is considered to be related to inhibition of cyclo-oxygenase. Aspirin and related compounds are also common non-specific provokers of chronic urticaria/angioedema and should be avoided by all patients with the condition. ACE inhibitors are associated with provocation of angioedema and should not be prescribed to patients with urticaria/angioedema.

Infection may play a role in some cases of urticaria as is seen commonly in children with viral infections, during prodromal stages of hepatitis B and with Epstein Barr virus infection. Intercurrent viral infections commonly exacerbate chronic urticaria.

Most urticaria occurring on a daily basis will not have an IgE-mediated mechanism. There is no increased frequency of atopy in chronic urticaria – systemic involvement is minimal although patients will often complain of excessive fatigue.

Diagnosis of chronic urticaria

The evaluation of a patient with prolonged symptoms begins with an attempt to classify the type of chronic urticaria.

Patients should be differentiated into those whose lesions occur spontaneously and those with symptoms caused by physical factors. If a patient suffers primarily from a physical urticaria there is usually no need for further investigation beyond any challenge necessary to confirm the diagnosis. Many patients who have physical urticaria are subjected to costly tests and unnecessary dietary examinations which never influence the management of their long-term condition.

The physical urticarias¹ are characterised by whealing and itching following the appropriate physical stimulus. It is

common to observe patients with more than one type of physical urticaria. Dermographism, literally 'writing on the skin', may occur as an isolated finding. Individuals present with traumatically induced urticaria. This condition is present in approximately 5% of the population.

Cholinergic urticaria is a commonly seen physical urticaria, predominantly found in teenagers and young adults. It probably occurs at some time during the lives of 15% of the population. Characteristically, it appears as very small, intensely itchy wheals, over the neck, arms, thighs and trunk in response to increased body heat. Activation of the cholinergic sympathetic innervation of the sweat glands is a likely mechanism.

Most commonly, the wheals of physical urticaria come on soon after the appropriate stimulus and are usually transitory. Delayed pressure urticaria is the exception to this. In this condition, there is a delay of two or more hours between the stimulus and the appearance of the lesions, which are often painful as well as itchy. They can last more than 24 hours.

Once the physical urticarias are excluded, some of the remaining cases of chronic urticaria may be the result of food/food chemical intolerance. As the mechanisms for this intolerance are not understood, there are no *in vitro* or *in vivo* tests which aid diagnosis. An elimination diet, followed by blinded, placebo-controlled challenges, is the appropriate investigation. Any elimination diet should be monitored carefully and not continued for long periods of time.

In the remaining patients, an underlying cause is usually not found. Recently, it has become clear that 25–50% of patients with chronic urticaria have an autoimmune problem. Certain autoantibodies have been identified and these are responsible for the repeated release of histamine from activated mast cells.

Urticarial vasculitis

This is a differential diagnosis of chronic urticaria. Historically, patients have their lesions for longer than 24 hours and these often fade leaving a bruise or an area of pigmentation. A skin biopsy, preferably of a recent lesion, is necessary to confirm the diagnosis. Once confirmed, patients require investigation to exclude an underlying cause such as hepatitis B and C, systemic lupus erythematosus, paraproteinaemia and inflammatory bowel disease. Urticarial vasculitis is usually non-responsive to antihistamines and often requires corticosteroids to bring the condition under control. A second immunomodulatory agent is frequently required to minimise long-term exposure to steroids.

Management

Treatment begins with an attempt at classifying the nature of the patient's urticaria.

Management of the patient with a physical urticaria begins with an explanation of how the physical factor(s) provoke the reaction. No laboratory investigations are necessary. Avoidance measures can be very effective in limiting the number of episodes. Antihistamines may have a useful role in some cases although they are typically ineffective in patients with delayed pressure urticaria.

Those patients who have suffered an acute, severe episode, usually with other features of an acute allergic reaction, require careful assessment, including skin testing with appropriate allergens. Most cases of urticaria and angioedema of less than six weeks duration will settle with symptomatic measures and rarely require investigation.

In patients with chronic urticaria, an explanation of the condition and its tendency to be a long-lived problem is essential if they are to come to terms with a very distressing situation and learn to manage it. Reassurance that the problem is not a sign of cancer or any other severe disease is important. Extensive laboratory investigation is unnecessary and rarely yields useful results, but appropriate investigation should follow any clues from a careful history and physical examination.

Patients with chronic urticaria and angioedema require counselling about the avoidance of non-specific aggravating factors such as overheating, overexertion, alcohol excess, and the use of aspirin and related compounds. Simple measures such as tepid showers, oatmeal baths and ice packs can give some temporary relief.

Antihistamines

The cornerstone of pharmacological management is the use of H₁ antagonists. All patients with frequent symptoms should use an antihistamine every day in an attempt to achieve complete suppression of wheals. This is more effective than taking a drug 'as needed' when symptoms become severe. For regular use, the newer, non-sedating antihistamines have distinct advantages over the older drugs in their superior safety profile and in particular, their relative lack of sedation. There are few data to suggest that one drug in this class is superior to another, although patients usually express a preference for a particular product. When night-time pruritis is severe and interrupts sleep, a sedative antihistamine may be useful before bedtime, but the patient must be warned about early morning drowsiness. In severe cases, some practitioners advocate a non-sedating antihistamine in the morning and a sedating one at night.

Doxepin

In troublesome cases, doxepin is certainly worth a trial.² Doxepin is a tricyclic antidepressant, which possesses both H₁ and H₂ antagonist properties. Its sedative action may be beneficial when sleep disturbance is troublesome. The mild anxiolytic effects may also be an advantage if the patient has a lot of psychological distress. A dosage of 25–50 mg at night is usually effective.

Cimetidine

In many patients, H₁ antagonists do not adequately control symptoms. Following the discovery that the blood vessels of the skin contain H₂ receptors in addition to H₁ receptors, a number of trials have studied the effect of adding an H₂ antagonist to an H₁ antagonist in the management of chronic urticaria. While the early studies were inconclusive, a number of studies have found a benefit from adding cimetidine.³ This strategy is worth a trial for a few weeks in patients not well controlled with H₁ antagonists alone.

Leukotriene antagonists

The leukotrienes are important products of mast cell activation and degranulation. Inhibition of these mediators may play a useful role in the management of chronic urticaria. With the advent of the leukotriene receptor antagonists, there is the opportunity for exploring this possibility. Results of clinical trials are awaited.

Other drugs

A variety of other drugs have been tried in resistant cases. Small studies have been published regarding the use of calcium antagonists and thyroxine in those with thyroid autoimmunity. Hydroxychloroquine and dapsone have also been used in occasional cases but in general, none of these drugs has been dramatically effective and all have significant potential adverse effects.

Immunomodulatory drugs

In patients identified as having autoimmune urticaria, initial treatment is the same as for any other urticaria, commencing with an adequate trial of antihistamines. However, patients with autoimmune urticaria tend to be more severely affected and less responsive to simple drugs. When the condition is causing marked disruption, other strategies may be considered. Reports of success with plasmapheresis and immunoglobulin infusions have been published, but this treatment should be regarded as experimental. A placebo-controlled trial of cyclosporin has had impressive results.⁴ None of these treatments cures the condition, but they may be preferable to prolonged steroid use.

Corticosteroids

When rapid control of urticaria is needed, a short tapering course of steroids may be used, but in any other situation their role is limited. If prednisolone is to be used, it is advisable to give a moderate starting dose, e.g. 0.5 mg/kg (20–25 mg) for a few days before tapering slowly over a 10 day period.

Invariably, prolonged use of steroids leads to numerous adverse effects and severe rebound in urticaria when withdrawal is attempted.

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Self-test questions

The following statements are either true or false (answers on page 131)

9. H₂ antagonists are ineffective in urticaria as there are no H₂ receptors in the skin.
10. Hepatitis C is a cause of urticarial vasculitis.

Facilitators file

The National Prescribing Service (NPS) has provided funds to divisions of general practice to employ facilitators. These facilitators visit general practitioners to discuss common prescribing problems. During their visits the facilitators are finding some interesting issues. *Australian Prescriber* is planning to publish some of these findings from time to time.

Combination antihypertensives

If a patient's blood pressure cannot be controlled by lifestyle changes drug treatment is needed. Therapeutic guidelines recommend starting treatment with one drug and adjusting the dose.¹ The NPS facilitators have, however, discovered that many patients are being started on fixed dose combination products.

The Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee has also found evidence that combination products are being used as first-line therapy. A review of new prescriptions for a product containing irbesartan

and hydrochlorothiazide found that 17% of patients had not previously been prescribed an angiotensin receptor antagonist, an ACE inhibitor or a diuretic. Approximately 16% of patients who were prescribed a combination containing fosinopril and hydrochlorothiazide had not previously taken an ACE inhibitor, an angiotensin receptor antagonist or a diuretic.

Although some patients will need more than one drug to control their hypertension, it is best practice to start with a single product. Even some cases of severe hypertension can be managed with a single drug. Patients who do need two drugs may need doses which differ from those found in combination products. The fixed doses in these products make it difficult to titrate the dose to achieve optimum control of each patient's blood pressure.

REFERENCE

1. Writing Group for Therapeutic Guidelines: Cardiovascular. Therapeutic Guidelines: Cardiovascular. 3rd ed. Melbourne: Therapeutic Guidelines Ltd.; 1999.