Today's Treatment

Diseases of the Skin

Drug Therapy of Urticaria

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Summary

Most patients with urticaria can be assessed by taking a relatively simple history with few or no investigations and controlled by a suitable antihistamine given at appropriate times until spontaneous resolution occurs without a complete diagnosis ever being made. Those that do not respond in this way require sometimes quite elaborate investigations, the institution of which would be an imposition in a mild case. Even after full investigation and ringing the changes of all available drugs, too many cases persist to the frustration of all concerned.

Introduction

Urticaria, with or without its subcutaneous equivalent angio-oedema, may have many causes, often even in one patient. Its management varies between two extremes. Some clinicians despair of ever making an accurate diagnosis, prescribe anti-histamines, and wait for spontaneous improvement. Others—the over enthusiastic and perhaps uncritical investigators—claim to find a cause in nearly every case and a high cure rate by removing it. Undoubtedly most cases of urticaria do get better with or without an accurate diagnosis or any treatment, but most patients are sufficiently uncomfortable to require some form of treatment, at least at some stages.

In some cases, notably of acute urticaria, a single external cause may be found. This may be a direct histamine-releasing agent—for example, various drugs—or may act by more than one type of allergic mechanism, of which the commonest is mediated by IgE (reagin) and occurs more frequently in individuals with a personal or family history of atopic disorders. Such allergic causes may gain access to the body by ingestion, injection, inhalation, contact, or may even come from within the body—for example, autoimmune disorders and infections. Much time and effort can and should be spent in searching for such allergies but they are seldom found when they are not easily apparent to the patient. Drug allergies should always be considered. Diagnosis has to be made almost entirely on the history with careful avoidance and re-exposure if necessary. Skin tests and laboratory tests are disappointingly unreliable.

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Chronic Urticaria

In chronic urticaria it is seldom that a single external cause can be incriminated. The distinction between acute and chronic urticaria has some value but it is entirely arbitrary and there is much overlap. It seems unlikely that any form of allergy is concerned in most chronic cases, but that there is some pharmacological change within the body whose nature has yet to be discovered. The delicate balance of factors controlling capillary permeability may then be disturbed by various trigger factors which would not in themselves normally be sufficient to provoke wealing.

Often no such factors are found, but among the more important—which may not necessarily be very obvious—are psychological, aspirin, food additives, candida sensitivity, and general medical disorders. Patients with urticaria are seldom grossly disturbed psychiatrically but are often over-sensitive individuals in whom the ups and downs of everyday life may determine exacerbations of their urticaria. Aspirin and related drugs aggravate chronic urticaria in over one-third of all patients, probably not by an allergic mechanism, and should be avoided in all. The ubiquitous yellow dye tartrazine and probably other food additives may have a similar action, whose importance has been suggested only recently. Confirmation of this can best be made by carefully giving test doses. Allergy to candida and food yeasts may also be fairly common, and treatment to remove candida from the mouth, gut, and vagina may then be of value. Urticaria occurs with a wide range of medical disorders, though seldom as the only or presenting symptom. It is often impossible to prove a causal relationship but any other symptoms and signs should be investigated.

Apart from ordinary acute and chronic urticaria, there are several other rather distinctive types of urticaria, each with its own prognosis and management.¹ These include the physical urticarias provoked by pressure, heat, light, and cold; cholinergic urticaria with its small weals associated with sweating; and hereditary angio-oedema.

Diet and Specific Desensitization

Avoidance of incriminated food and drugs is clearly of paramount importance. Strict elimination diets with reintroduction of suspected foods one at a time are seldom helpful. Special diets free of yeasts, of salicylates and related compounds, and of tartrazine may be helpful and may tax the ingenuity of patient and dietitian alike.

Specific desensitization is seldom recommended for urticaria, partly because so many urticarias are not due to allergy. Even when a substance can clearly be incriminated the mechanism may not be due to allergy or may not be due to a Type I, IgE-mediated reaction—the type that can be most expected to be helped by injections. There is no evidence that specific desensitization helps the type III serum-sickness type of illness due to soluble antigen-antibody complexes.

Drug Treatment

ANTIHISTAMINES

Antihistamine drugs are the mainstay in the management of urticaria of all types. Unlike adrenaline and related compounds, which are physiological antagonists, chemically the antihistamines are rather similar to histamine and can combine with and block the histamine receptors on cells, especially mast cells. Histamine is not the only mediator concerned in urticaria: kinins, prostaglandins, and other substances, for which there are no specific antagonists, are also concerned.

There are very many antihistamines, which fall into six pharmacological groups.² In general they all have similar properties. As well as their antihistamine action they have variable other effects, which may be therapeutically useful or undesirable. They include an anticholinergic action, central nervous system depression or sometimes stimulation, suppression of motion sickness, and a local anaesthetic effect.

Though side effects of antihistamines are frequent, variously assessed as occurring in 25-50% of patients, serious side effects are very rare, and these drugs must be considered among the most harmless prescribed. It must be remembered that side effects from placebo drugs given to urticaria patients have sometimes occurred in over half of all cases. Drowsiness and loss of concentration are the most troublesome side effects of antihistamines and may be greatly increased when combined with alcohol or other drugs. Less commonly insomnia or muscle twitching occur.

The anticholinergic action may lead to a dry mouth, trouble with accommodation, urinary difficulties, or impotence. Many of these side effects become less troublesome after the patient has been on the drug for a few days. Blood dyscrasias have occurred, but very rarely. Allergy to antihistamines is relatively common, especially after topical use—which causes an unacceptably high incidence of sensitization and may lead to widespread rashes after subsequent oral doses. As yet the importance of small quantities of tartrazine in urticaria has not been assessed but at least nine commonly used antihistamines contain it and have been known to perpetuate rather than cure chronic urticaria.

Relative contraindications to antihistamine therapy include epilepsy, early pregnancy, liver disease, the administration of other drugs such as antidepressants, and allergy to the drug or related substances. If a patient has to drive a vehicle, caution must clearly be used but many patients on antihistamines do manage to drive safely.

The choice of which antihistamine to use should depend on the ratio of efficacy, side effects, and cost, but there are virtually no comparative trials to give any guidance. The dose contained in a single pill of one drug may not be comparable with that in another and a relative lack of side effects may go with an equal lack of efficacy.

When a patient with urticaria fails to respond to a particular antihistamine or gets too many side effects it is tempting to keep changing to another drug in the hope that greater success will be achieved. Sometimes indeed this does occur, but all too often patients who get a poor response or side effects have the same experience with other drugs.

Adequate attention is sometimes not paid to choosing a drug with a suitable duration of action and administering it at the appropriate times to achieve optimal effect with minimal side effects. For quick action a short-acting drug like chlorpheniramine (Piriton) is to be recommended. Though this is rapidly and well absorbed there is a delay of an hour or two before its maximal effect occurs; there is even a considerable delay after intravenous injection, the time taken for the drug to become attached to the receptors on the cells. In general, antihistamine injections are seldom required, though the drama of an intravenous injection is not devoid of therapeutic efficacy. If a very quick result is essential, adrenaline injections are better.

The action of chlorpheniramine lasts for a few hours, though surprisingly some patients find that a single dose every 24 or even 48 hours may achieve useful results. For the continued suppression of urticaria a long-acting preparation is to be preferred. Promethazine (Phenergan) has its advocates and its rather greater sedative action may be useful in some instances.

Most patients prefer a drug such as long-acting brompheniramine (Dimotane LA). A single 12 mg or double dose at night may provide adequate control over 24 hours and allow most of the sedative side effects to pass off during the night. An extra dose may be required in the morning.

Some patients do not seem to obtain adequate symptomatic relief from any antihistamine. In some of these careful gradual increase above the manufacturer's recommended dosage may prove helpful, but about 20% of cases of urticaria have been described as non-responders.

When treating the physical urticarias, all of which tend to persist over some years, a regular dosage is sometimes required, but often a short-acting drug may be given an hour or two before the urticarial stimulus—for example exercise in cholinergic urticaria.

Combined Action Drugs

Drugs which combine an antihistamine action with some other property may be used in urticaria, but the antihistamine effect is generally the more important. Trimeprazine (Vallergan) combines the antihistamine action of promethazine with an increased central action, which makes it more valuable for treating other types of itching. Cyproheptadine (Periactin) is a useful antihistamine, but there is no evidence that its anti-serotonin properties contribute to its usefulness in urticaria.

Hydroxyzine derivatives (Atarax, Equipose) are mainly prescribed as tranquillizers, but have a very significant antihistamine action as well. In a dose of 25 mg twice daily, often combined with a long-acting antihistamine, they are valuable in chronic urticaria, whether or not emotional problems are apparent, and also in the physical urticarias.

Antihistamine drugs may, if necessary, be continued for months or years with safety. They probably have no influence on the course of the disease, but merely suppress its manifestations while they are being taken. The duration of therapy is therefore as variable as the natural history of urticaria. Nevertheless, just as the side effects of antihistamines may wear off after a few days on regular doses, so may the efficacy seem to decline, though there is no real proof that this occurs. Little work has been done on the body's metabolism of the drug after varying time intervals.

ADRENALINE

Injections of adrenaline (0.5-1 ml 1:1,000 intramuscularly or subcutaneously) are the initial treatment of choice for violent attacks of acute urticaria or angio-oedema, especially when the latter affects the throat or is associated with anaphylactic shock. They are less valuable in the management of chronic urticaria. A few patients find that isoprenaline sulphate (Neo-Epinine) sublingually can be used to abort recurrent acute attacks. Ephedrine 15-30 mg once or twice daily is occasionally used to help control resistant chronic urticaria.

CORTICOSTEROIDS

Corticosteroids are not the treatment of choice for urticaria. Intravenous or intramuscular hydrocortisone may be life-saving in acute anaphylactic reactions (after the administration of adrenaline and an antihistamine). Corticosteroids are also particularly valuable for more severe examples of serum sickness—for example, after penicillin—when a course starting with prednisone 30 mg daily and diminishing over two to four weeks can be given. In the management of other types of acute urticaria, and more especially chronic urticaria, they tend to be disappointing.

OTHER DRUGS

Sedatives, tranquillizers, and antidepressants are valuable in some patients in whom nervous factors play a part. Nevertheless, even in these the nervous factors are not the only cause and a search for other factors and use of antihistamines should still be the first approach.

Many drugs have been used at times but in few have clinical trials proved any useful effect. Of interest is the use of the kininogenase inhibitor aprotinin, which has to be given intravenously and is not devoid of side effects, but is sometimes valuable in patients with severe chronic urticaria. Nevertheless, at present this drug is more useful for the light it throws on the aetiology of the condition than as routine therapy.

Epsilon amino caproic acid and the related tranexamic acid are very valuable in controlling hereditary angio-oedema. This specific biochemical deficiency is rare, accounts for about 2% of all cases of angio-oedema, and should be confirmed by the diag-

nostic deficiency in the inhibitor of the activated first component of complement.

TOPICAL THERAPY

Calamine lotion is often considered as the prototype of all local applications for the skin, though in fact its uses are very limited. Urticaria is one of the few conditions where its cooling, and therefore antipruritic, action make it extremely suitable, and where the lesions are sufficiently transient that its drying effect is not manifest. Topical corticosteroids are valueless, and should not be wasted on urticaria.

References

- Warin, R. P., and Champion, R. H., *Urticaria*. London, Saunders, 1974.
Cannon, P. J., *Practitioner*, 1968, 200, 53.

Any Questions?

We publish below a selection of questions and answers of general interest

Cystitis and Urethritis after Intercourse

Are cystitis and urethritis quite common sequels to intercourse in postmenopausal women?

Yes. A similar problem in younger women has long been known as "honeymoon cystitis." But this designation has tended to obscure the fact that dysuria may often follow sexual intercourse in women of any age. It seems that bacteria at the mouth of the urethra, possibly in Skene's ducts and possibly in the urethral glands, may be carried up into the bladder or into these ducts and glands. Overnight the bacteria flourish and may gain a foothold, so that dysuria may come on within a few hours of intercourse. In older women there is also the further complication of atrophy of the vaginal introitus, which may effect the urethral meatus, and traumatic inflammation here may contribute to dysuria. Such atrophy will usually respond to local oestrogens or to small doses of oestrogen by mouth, while occasionally an operation to enlarge the introitus may be helpful.

Urinary tract infection may be difficult to prove bacteriologically in every attack of dysuria, but diligent search over some time will ultimately find bacteria in most cases. Most infections are cured by the natural defence mechanisms. A decision has to be made in each case on the advisability of fully investigating the urinary tract. In long-standing cases an intravenous pyelogram should be done.

Postcoital urethritis and cystitis can be prevented by the woman voiding urine immediately after intercourse and at the same time taking 500 mg of sulphadimidine. Nitrofurantoin 50 mg might be substituted for the sulphonamide. In this dosage nitrofurantoin has been given nightly for up to five years without ill effect in the prevention of urinary tract infection.¹ It is a good treatment for those with definite episodes of infection, but continuous therapy should not be necessary in older women whose urine is clear of bacteria between acts of sexual intercourse, the frequency diminishing with age. Intercourse in the morning increases in frequency with age and it would be interesting to know if urethritis and cystitis were uncommon in those who follow this practice, but there does not seem to be any evidence about it. It might be

expected that the morning voiding would immediately clear the bladder and urethra of bacteria.

¹ Bailey, R. R., Gower, P. E., Roberts, A. P., and de Wardener, H. E., *Lancet*, 1971, 2, 1112.

Conception Time and Sex of Offspring

Is there any evidence that the time of conception during the menstrual cycle has any influence on the sex of the child?

Most people are sceptical about the time of insemination in relation to ovulation affecting the sex of the baby. Guerrero¹ investigated the matter in 2,009 conception records, using the basal temperature shift as the sign of ovulation. He called the time of the shift day O. Insemination from day -5 to day +2 was considered a possible cause of pregnancy. With natural insemination there was an excess of boys before day -4 and after day +1, and a decreased number of boys for the days around the shift. However, for artificial insemination there was an excess of females for day -3 and before, and for day +1 and after. The frequency of insemination round the thermal shift seemed to make no difference, nor did periods of abstinence from ejaculation.

Before this report it had generally been assumed that insemination in the first 10 days of the cycle produced an excess of boys, but those investigating artificial insemination had found such an excess in the days around the presumed time of ovulation. The general theme appears to be that the younger the ovum the more likely is it to be fertilized by a Y chromosome, and that as it gets older so is it more likely to be fertilized by an X chromosome. For insemination artificially in the two to eight hours after ovulation one author² claims a 100% accurate prediction of the sex of the child—female, and about 75% accurate prediction in the two to 24 hours before ovulation—male, and similarly in the 36 or more hours before ovulation—female. The matter is still controversial and difficult to understand, but this recent distinction between the results obtained by natural and artificial insemination at least suggests one factor in the situation.

¹ Guerrero, R., *International Journal of Fertility*, 1970, 15, 221.

² Kleegman, S. J., in *Proceedings of the 5th World Congress of Fertility and Sterility*, 1966, Excerpta Medica International Congress series, 1967, No. p. 133, 1185.