Pruritic Dermatoses: Overview of Etiology and Therapy

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This review begins with a brief survey of the neurophysiology and neuroanatomy of pruritus, and goes on to describe the etiology of the major allergic and nonallergic pruritic disorders. The etiology of pruritus often suggests the appropriate treatment. For example, urticaria, which is primarily mediated by histamine, is amenable to treatment with H₁ antihistamines. Second-generation, nonsedating antihistamines appear to be more effective than sedating antihistamines, perhaps because of better compliance. Other systemic pharmacologic options may be useful in nonhistamine-mediated disorders, for example, immunomodulators for inflammation-induced pruritus or opiate antagonists for atopic dermatitis. Nonpharmacologic measures, such as proper skin care, and physical modalities, such as phototherapy or acupuncture, may also be helpful. *Am J Med.* 2002;113(9A):25S–33S. © 2002 by Excerpta Medica, Inc.

The skin reacts to physical and inflammatory stimuli in only a limited number of ways. The sensation of itching, or pruritus, is the most common symptom of dermatologic conditions. In 1660, the German physician Samuel Hafenreffer defined itching as an “unpleasant sensation that provokes the desire to scratch,” and although this definition has been modified to correlate with current knowledge, it remains a reasonable one.¹ Pruritus is the subjective sensation of itching. The types and causes are complex and not yet completely understood. Perhaps the unfortunate plight of the itching patient is best described in this brief poem by Julian Verbov²:

I itch, I itch, the whole day through
I also itch at night.
I try so hard to stop myself
I’m looking such a sight.

To itch is not so nice you know,
It really is deplorable
But to scratch is really something
That is often quite enjoyable.

The sensation of itch is the common factor in a multitude of diverse cutaneous disorders. Histamine is the primary mediator of itching in some types of allergic disease, but multiple agents or mediators can provoke itching in both allergic and nonallergic diseases.

This review provides a brief overview of the pathogenesis of itching, describes the major itching skin disorders related to allergic and nonallergic disease, and includes a discussion of nonpharmacologic and pharmacologic therapies.

WHAT CAUSES PRURITUS?

Diffuse itch is believed to be induced by specific, nonmyelinated C-fiber stimulation, whereas itch that is localized both in space and time involves the A- δ fibers.³ A complex plexus of nonmyelinated, dendritic processes are believed to be present at the distal endings of these fibers, which terminate in the lower epidermis and possibly at the dermal–epidermal junction, where the “itch receptors,” not yet morphologically identified, are presumed to be located. These polymodal (responsive to mechanical, thermal, and chemical stimuli) nociceptors are found only in the skin, mucus membranes, and cornea.⁴ No other tissue experiences pruritus. It is now generally accepted that the sensations of itch and pain are transmitted

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NEURAL PATHWAYS

Figure 1. Simplified diagram of the neuroanatomic pathways for pruritus. Dendritic itch receptors in the epidermis and dermoepidermal junction can be activated by (proinflammatory) pruritogenic mediators, which travel through the peripheral sensory nonmyelinated C-fibers to the dorsal root ganglia to the dorsal roots and into the spinal cord. The spinothalamic relay axons cross to the contralateral ventrolateral quadrant rostral to the level at which the sensory neurons enter the spinal cord. The C-fibers reach the thalamus and hypothalamus by means of the reticular formation of the encephalic trunk to the cerebral cortex.

by separate C-fibers. The magnitude of itch can be modulated by changes in stimulus frequency, but the quality of itch does not change into pain at high frequencies.⁵ Both C- and A- δ fibers conduct impulses at varying speeds to the spinal cord by means of the dorsal nerve roots of the spinal nerves. **Figure 1** provides a simplified illustration of the pathway of itch sensations mediated by C-fibers.

Although the peripheral and central mechanisms of itch are not fully understood, both altered peripheral excitation and central disinhibition are involved. Local paroxysmal pruritus is believed to have a central origin. Central inhibition may be partially restored by scratching. This phenomenon is the basis of the “gate-control” theory, which suggests that scratching and vibration cause neural impulses to travel on the larger A-fibers, inhibiting the itch signals in the slower C-fibers.⁶ The A-fiber input “closes the gate” to the C-fiber output.⁷ Endogenous enkephalins are also believed to act at the spinal level to modulate the perception of itch. Scratching may abolish itch by central inhibition rather than by fatigue of the peripheral sensory receptor.

ENDOGENOUS AGENTS THAT CAUSE PRURITUS

Although numerous substances are thought to cause pruritus,⁸ direct evidence exists only for a causal role of histamine in the itching experienced by patients with urticaria or mastocytosis. Other agents that have been investigated in pruritus include serotonin, prostaglandins,

proteases, kinases, cytokines, leukotrienes, neuropeptides, leukotrienes, opioids, and endorphins.

Histamine

Injection of histamine results in the characteristic symptoms of acute urticaria: the “triple response” of Lewis dissipating within 1 hour. Urticaria and pruritus that last >1 hour are unlikely to be caused solely by histamine, and the typical triple response is never noted in other pruritic dermatoses. Histamine generates itch through activation of H₁, but not H₂, itch receptors.⁹ It is also believed to render the zone of surrounding skin abnormally sensitive to other stimuli. Stimuli normally perceived as tactile, pressure, or temperature-change sensations are instead perceived as itch, in a phenomenon known as *alloknesis*.¹⁰

Serotonin and the Prostaglandins

Other chemical mediators of pruritus include serotonin, which is weakly pruritogenic and inconsistently produces a painful itch when injected intradermally,¹¹ and the prostaglandins (PGE₁, PGE₂, endoperoxidases), which are weak pruritogens by themselves, but which can markedly increase the itch response when given with serotonin or with histamine.^{12,13}

Proteinases and Kinins

These substances have also been proposed as mediators of itch. The injection of trypsin or chymotrypsin produces intense itch associated with the triple response of Lewis, an effect that is inhibited by antihistamines, suggesting that histamine is the primary mediator. Administration

of papain or kallikrein causes a painful pricking sensation that is not associated with the triple response and does not respond to antihistamines.¹⁴ However, if proteinases are mediators of pruritus, they probably function by damaging nerve terminals, which results in stimulation of itch fibers, rather than by inducing release of chemical mediators of pruritus.¹⁵

Cytokines

This family of agents, considered to constitute "histamine-releasing factor," have been proposed as mediators of histamine-independent itching. However, except for interleukin (IL)-2, which shows a rapid, mild pruritogenic effect,¹⁶ none has been shown to either induce or prevent pruritus. Interestingly, although the level of tumor necrosis factor (TNF)- α is elevated in many pruritic dermatoses, it does not induce pruritus when injected into the skin.

Leukotrienes

These agents, which are end products of arachidonic acid metabolism, evoke inflammation, but not pruritus, when injected intracutaneously.¹⁷ Although antileukotriene therapy is virtually useless for treating pruritus, there are several reports of some decrease in the itch of Sjögren syndrome with the use of zileuton, a 5-lipoxygenase inhibitor, which suppresses the release of leukotrienes B₄, C₄, D₄, and E₄.¹⁸

NEUROPEPTIDES

Such agents as substance P, vasoactive intestinal polypeptide, and neurotensin A are abundant in the sensory neurons of the skin. Substance P and vasoactive intestinal polypeptide are the most potent histamine-liberating agents in humans.¹¹ Substance P induces the triple response, suggesting that its effects are probably mediated by histamine, which would be consistent with the observation that the pruritic effects of substance P can be blocked by oral antihistamines. However, none of the peptides are directly pruritogenic, and it remains to be determined whether neuropeptides are responsible for clinical pruritus.

Opioids and Endorphins

The role of these agents in the production of itch is unclear. Pruritus is the most common side effect of the intrathecal administration of opioids. Opioids can stimulate κ - and δ -receptors in the central nervous system¹⁹ and induce the release of histamine and other preformed mediators from mast cells.²⁰ Interestingly, the various opioids differ in their capacity to release histamine, which suggests that the mechanism is not immunologic.²¹ In the pruritic dermatoses, opioids and endorphins have not been conclusively implicated in the production of itch. However, opioid antagonists, such as naloxone, naltrexone, ondansetron, and rifampicin, effectively control

Table 1. Allergic and Nonallergic Causes of Pruritus

● Allergic
—Atopic dermatitis
—Urticaria
● Nonallergic
—Endocrine diseases
Hyperthyroidism
Hypothyroidism
Hyperparathyroidism
Hyperphosphatemia
Diabetes mellitus
—Metabolic diseases
Chronic renal failure
Cholestasis
Carcinoid syndrome
—Malignant diseases
Lymphoma
Leukemia
Polycythemia rubra vera
—Autoimmune diseases
Dermatitis herpetiformis
Linear IgA syndrome
—Miscellaneous
Parasites
Pruritus ani and pruritus scroti/vulvi
Neuropsychiatric causes

IgA = immunoglobulin A.

opioid-induced pruritus. Evidence increasingly suggests that endogenous opioids (endorphins) may be involved in transmission of itch.²²

ALLERGIC PRURITUS

Atopic dermatitis (AD) and urticaria are allergic diseases in which pruritus is a predominant symptom. A multitude of nonallergic causes for pruritus also exist (Table 1).

Atopic Dermatitis

AD refers to the chronic, subacute, eczematous skin lesions characterized by an unrelenting itch. AD is generally defined as a chronically relapsing inflammatory skin disease that frequently occurs in patients with a personal or family history of asthma or allergic rhinitis.²³ The disorder, which is increasing in frequency, has an estimated incidence of 10%.²³ In contrast to other dermatologic disorders that are characterized by a primary lesion, e.g., psoriasis (papulosquamous lesions) or dermatitis herpetiformis (DH; vesicular bullous lesions), AD lacks a primary skin lesion. Only the secondary cutaneous findings of excoriation, weeping, and lichenification, as well as pigmentary changes, are apparent. Hanifin and Rajka²⁴ have defined the major and minor criteria for AD. Just as allergic rhinitis is characterized by sneezing and extrinsic asthma is defined by wheezing, AD is characterized by

Table 2. Immune Abnormalities Present in Atopic Dermatitis

- Increased IgE synthesis
- Increased immediate skin-test reactivity to allergens
- Increased basophil histamine release
- Impaired delayed-type hypersensitivity response
- Decreased CD8 suppressor/cytotoxic number and function
- Increased sIL-2 receptor levels
- Increased expression of CD23 on mononuclear cells
- Increased production of IL-4 and IL-5
- Decreased production of IFN- γ

CD = cluster of differentiation; IFN = interferon; IgE = immunoglobulin E; IL = interleukin; sIL = soluble interleukin.

itching.²⁵ Therefore, an AD-like syndrome but without itching should lead one to consider other diagnoses. Because the onset of AD typically occurs at an early age, new-onset pruritic eczematous dermatitis in an elderly adult is more likely to be caused by cutaneous T-cell lymphoma or another disorder.

The itch sensation in AD can be produced by a number of different chemical mediators. Some of them serve as histamine liberators, although it would be naive to think that histamine is the sole or even the primary evoker of the itch in this disease. In addition to an increase in the presence of mediators that provoke itching, it is possible that such patients have a decreased "itch threshold," which may be even more important in the pathophysiology of AD than chemical mediators. The complexity of the perception of itching and the importance of the lowered itch threshold is underscored by the existence of multiple environmental factors that contribute to AD, including exposure to woolen clothing, perspiration, and bacterial toxins; even psychological factors have been implicated.

Immunohistochemical staining of both acute and chronic lesions of AD shows lymphocytic infiltrates consisting of cluster of differentiation (CD)3, CD4, and CD45RO memory T cells. Nearly all T-cell infiltrates in AD lesions express high levels of skin lymphocyte homing receptor, cutaneous lymphocyte-associated antigen. The ability of the memory T cells to target the skin is further enhanced by the presence of vascular cell adhesion molecule-1, which acts as a vascular adhesion ligand for eosinophils. An abundance of major basic protein has been detected in the dermis of patients with AD, representing the "footprints" of eosinophils in this inflammatory battle. Some of the immunoregulatory abnormalities found in AD are listed in **Table 2**. It is clear that Th2 and Th1 cytokines contribute to the pathogenesis of the skin inflammation in AD, but the exact pathogenesis of the itching remains unclear. The skin of patients with AD is inherently pruritic; in no other dermatitis is the relation between physical and emotional components interwoven so tightly.²⁶

Urticaria

Urticaria is a common disorder of the skin characterized by the transient appearance of elevated, erythematous lesions that often have a pale center and that wax and wane, moving from one site to another.^{27,28} Urticaria is typically markedly pruritic. Exceptions are urticarial vasculitis and delayed-pressure urticaria, which are characterized by pain or a burning sensation.²⁷

Histamine is the primary mediator for most types of urticaria. Kaplan et al^{29,30} reported that 93% of patients with chronic urticaria clearly exhibited increased histamine release into skin blisters overlying lesions of urticaria. In 4 of 5 patients with cold urticaria, levels of histamine were significantly elevated in skin blister fluid.

An additional mechanism of chronic urticaria is the production of an immunoglobulin (Ig) G autoantibody directed against the high-affinity α -subunit of the IgE receptor on mast cells and basophils.³¹ This may occur in as many as 30% of patients with chronic idiopathic urticaria. Many of these patients develop a wheal and flare in response to a skin test with autologous serum, suggesting that a serum factor may induce histamine release from cutaneous mast cells. There is also evidence that the histopathologic finding in these patients may resemble those in patients with cutaneous late-phase responses to allergen, with the observation of a polymorphous infiltrate consisting of eosinophils, neutrophils, and mononuclear cells.^{32,33} Although classic antihistamines may show a partial therapeutic effect in these patients, a strong argument can be made for the use of newer nonsedating H₁ antihistamines, which may demonstrate some anti-inflammatory effects, such as inhibition of eosinophil migration and synthesis and release of mast cell mediators, in addition to their H₁-receptor actions.^{34–36}

Urticarial vasculitis is a small-vessel vasculitis in which the morphology of the skin lesions resembles that of ordinary urticaria, whereas the histopathologic features are those of leukocytoclastic vasculitis. A skin biopsy is required to confirm the diagnosis. Clinically, the lesions tend to persist in the same general areas beyond 24 hours and may leave a purpuric stain on the skin.³⁷ Extracutaneous symptoms may occur and are often associated with a decrease in serum complement. Musculoskeletal complaints, such as arthralgias and arthritis, occur in 50% to 75% of patients. Gastrointestinal symptoms, including abdominal pain, nausea, vomiting, and diarrhea, occur in approximately 17% to 30% of patients. Renal or pulmonary involvement may also appear as a late complication.

Unlike the more common types of urticaria, urticarial vasculitis involves more complex mechanisms than histamine release into the skin. This explains why antihistamines, although useful for the control of pruritus in urticarial vasculitis, may not control the disease. Although histamine may play a role in the early phase of urticarial vasculitis, in later stages circulating antigen-antibody

complexes form in the blood and are deposited in the vessel walls. Complement is activated by the classic pathway, and C3a and C5a are generated, both of which are anaphylatoxins that contribute to the clinical lesions of urticaria. These anaphylatoxins are capable of inducing skin mast cells to release histamine but also can set into motion the generation of multiple cytokines and chemokines that function as chemotactic factors, resulting in the influx of neutrophils and eosinophils. The antibody isotype in the immune complexes of urticarial vasculitis is usually IgG or IgM. The antigen may be autologous or exogenous from an infectious agent or a medication.

Cutaneous Mastocytosis

Although there is no evidence that cutaneous mastocytosis is an allergic skin disease, the systemic release of mast cell–derived histamine causes generalized itching, increased vasopermeability, bronchoconstriction, urticaria, and even gastric hypersecretion. Clinical syndromes of mastocytosis range from localized cutaneous involvement to mast cell leukemia, all of which are characterized by the excess production of mast cell mediators, with histamine being the primary culprit.³⁸

Urticaria pigmentosa is perhaps the most common presentation of mastocytosis in both children and adults. The lesions of urticaria pigmentosa are usually erythematous brownish plaques that urticate when stroked or rubbed (Darier sign). Itching may be intense and is sometimes triggered by cutaneous trauma, friction, temperature, alcohol ingestion, and certain drugs (e.g., codeine).

NONALLERGIC PRURITUS

Patients with pruritus unrelated to allergic disease may exhibit a variety of underlying causal medical conditions, among them chronic renal disease, primary biliary cirrhosis, endocrine disorders, and malignant disease.

Chronic Renal Disease

About 50% of patients with chronic renal disease have pruritus, as do an estimated 80% of patients on chronic renal dialysis. Mechanisms include xerosis, hyperparathyroidism, iron deficiency, neuropathy, and possibly cholestasis.³⁹ Rarely are antihistamines effective in suppressing itching in these patients, even though plasma histamine levels are elevated in uremia, and skin mast cells are increased in chronic renal disease.^{40,41} Treatment includes dietary restrictions and phosphate-binding therapy, as well as hydration therapy for xerosis. Although antihistamines may offer some relief, ultraviolet B or psoralen plus ultraviolet A are common treatments.

Primary Biliary Cirrhosis

Itching precedes the appearance of jaundice in 50% of patients with primary biliary cirrhosis, which occurs almost exclusively in women >30 years old. Although pruritus may develop in many disorders associated with bil-

iary obstruction, there is little or no correlation between serum concentrations of bile salts and the actual severity of itching. However, a role of bile salts in the skin cannot be dismissed, because the application of bile salts to skin blister bases in concentrations approaching those found clinically produces intense itching.⁴² Recent studies suggesting that opioid peptides may play a role in the pruritus of cholestasis have generated interest in the potential of opioid antagonists, such as naloxone and naltrexone, as histamine-independent therapies for treating pruritic skin diseases.^{43,44}

Endocrine Disorders

Pruritus is not uncommon in endocrine disorders. Generalized itching may be a presenting symptom of thyrotoxicosis, possibly related, in part, to an increase in blood flow to the skin. Hypothyroidism may also be associated with itching, which is aggravated by the dryness of the skin typical of this condition. Although generalized pruritus is not a feature of diabetes mellitus, localized itching secondary to candidiasis is very common.

Malignant Disease

The possibility of an underlying malignant disease should be considered in the middle-aged or elderly patient who presents with generalized pruritus. An expensive workup is usually not justified, and the evaluation should be guided by a detailed history and physical examination. Lymphoma is the most likely associated neoplasm, with Hodgkin disease the most likely lymphoma. Patients with polycythemia vera report a most unusual water-induced itching that is worse on the lower extremities.⁴⁵ Interestingly, such itching may precede the development of polycythemia by several years. A similar symptom has been reported in association with hypereosinophilic syndrome and myelodysplasia syndrome.⁴⁶

Dermatitis Herpetiformis

DH is an intensely pruritic papular vesicular disorder associated with a gluten-sensitive enteropathy similar to that seen with celiac disease. Pruritus is the primary symptom, although some patients may experience burning. Lesions are distributed symmetrically over the extensor surfaces of the elbows, knees, and buttocks. DH is an autoimmune disorder in which serum IgA and IgG anti-reticulin antibodies are found in many patients. Granular deposits of IgA are seen in the papillary dermis.⁴⁷ These deposits lead to activation of the alternative complement pathway, resulting in an influx of neutrophils and eosinophils, which ultimately contributes to blister formation. Persons with certain human leukocyte antigen (HLA) antigens, including HLA-B8 and HLA-DR3, appear to be predisposed to develop DH. Oral dapsone (diaminodiphenyl sulfone) or sulfapyridine relieves symptoms within a few days.

Linear IgA Dermatitis and Chronic Bullous Disease of Childhood

Linear IgA dermatitis (LAD) and chronic bullous disease of childhood (CBDC) are heterogeneous syndromes in which patients present with annular or grouped papules, vesicles, and bullae. Like DH, the lesions of LAD and CBDC are distributed symmetrically over the extensor surfaces of the elbows, knees, and buttocks. Unlike DH, these diseases are not associated with a gluten-sensitive enteropathy. CBDC is more common in children <5 years, with a slight predominance in girls. Like DH, CBDC and LAD are strongly associated with the presence of the HLA-B8 haplotype, and immunofluorescence of perilesional skin shows a homogeneous band of IgA along the dermal-epidermal junction. In adults with LAD, there is an association with lymphoid and nonlymphoid malignancies. Like DH, LAD responds to dapsone or sulfapyridine but not to a gluten-free diet. CBDC is usually a self-limited disease that tends to remit spontaneously within 2 years but may require treatment with dapsone or prednisone.

TREATMENT OF PRURITUS

The therapeutic objective in pruritus is its cessation. Achievement of this goal can be difficult, and treatments are as diverse as the causes (Table 3).^{48–62} Therapy should focus on the elimination of a definable trigger. Pruritus should always be considered as symptomatic of an underlying problem. However, too often the provocative factor is unidentifiable or not curable. Symptomatic treatment is then the only option.

Histamine-induced pruritus, which is always accompanied by a wheal and flare response, is amenable to treatment with H₁ antihistamines, which effectively inhibit activation of the H₁ receptors. Such agents prevent, to varying degrees, but do not reverse, the responses mediated by histamine alone. The best results are attained when the antihistamine is administered “around-the-clock,” not simply taken as needed. Maximum benefit often requires the administration of doses higher than those recommended. Doenicke et al⁶³ found that currently recommended regimens do not adequately prevent the effects of histamine and suggest that additional doses after 4 hours may be needed to achieve an adequate therapeutic response. Flushing is the first symptom to respond to antihistamine therapy. Flushing syndromes show a better response when both H₁ and H₂ antagonists are administered.

The choice of antihistamine is based on its effectiveness, frequency of administration, and side-effect profile. The dose of the H₁ antagonist should be increased to tolerance, and adding an antihistamine from another group has been shown to be more helpful than increasing the dose of a single agent.⁶⁴

Table 3. Treatment of Pruritic Skin Disorders

- Identify and treat the provocative factors
- Provide patient education on proper skin care
 - Short, cool showers or 20- to 30-minute tepid baths
 - Limit mild soap use to intertriginous areas only
 - Lubricate frequently, especially after bathing
 - Humidify ambient environment (in winter)
- Avoid contact irritants (e.g., wool, hairy pets, cleansers, fiberglass)
- Topical antipruritics may offer short-term relief
 - Camphor/menthol preparations (Sarna lotion*)
 - Crotamiton (Eurax[†])^{48,49}
 - Phenol (0.5%–2.0%)—do not use during pregnancy or in infants
 - Pramoxine HCl (Prax[‡])⁵⁰
 - Capsaicin cream⁵¹—especially for well-localized itches
 - Eutectic anesthetics⁵²—especially for well-localized itches
 - Topical doxepin⁵³—may be suitable for small areas of intact skin
- Systemic treatment
 - Antihistamines—for histamine-induced pruritus (e.g., urticaria)
 - Immunomodulators—for inflammation-induced pruritus
 - Topical: corticosteroids,⁵⁴ macrolides⁵⁵
 - Systemic: corticosteroids, cyclosporine, others
 - Cholestyramine⁵⁶; for renal failure, cholestasis, and polycythemia vera
 - Opiate antagonists: for atopic dermatitis,⁵⁷ cholestasis^{56,58}
 - Oral cromolyn⁵⁹; for systemic mast cell disease⁶⁰
 - Miscellaneous: gabapentin, thalidomide, oral primrose oil
- Physical modalities
 - Ultraviolet phototherapy and PUVA photochemotherapy
 - Thermal stimulation (heating or cooling the skin)
 - Acupuncture
 - TENS⁶¹
 - Plasmapheresis⁶²

PUVA = psoralen plus ultraviolet A therapy; TENS = transcutaneous electrical nerve stimulation.

* Stiefel Laboratories, Inc., Coral Gables, FL.

† Fujisawa Pharmaceuticals Co., Ltd., Osaka, Japan.

‡ Ferndale Laboratories, Inc., Ferndale, MI.

Antihistamine efficacy is assessed in terms of the agent's ability to inhibit the triple response of Lewis⁶⁵ and to bind to H₁ receptors in vitro.⁶⁶ When antihistamines are administered to patients with urticaria, the itching often disappears before the clearance of the wheals and flares, as observed clinically by the author (VSB). Second-generation, nonsedating antihistamines seem to be more effective than sedating antihistamines because they are associated with better compliance.

Comparative Studies with Newer and Older H₁ Antihistamines

H₁-receptor antagonists are widely used to treat allergic skin diseases characterized by pruritus, including urticaria and atopic dermatitis. These agents prevent pruritus

by acting on the H₁ receptors on the small, branching unmyelinated C-fibers in the skin.⁶⁷ Thus, the distribution of the antihistamine into the skin to produce cutaneous H₁ blockade would be important to its antipruritic effect.

Not surprisingly, comparative studies on antihistamine distribution in the skin are rare. In 1 such study, Simons et al⁶⁸ in Canada compared the extent of fexofenadine and diphenhydramine distribution in the skin concomitantly with the H₁-receptor antagonist activity. The results of this double-blind, prospective, randomized parallel-group study, comparing a newer nonsedating antihistamine with a classic sedating antihistamine, showed that fexofenadine given orally penetrated the skin (obtained by punch biopsy), and suppressed whealing, to a significantly greater extent than diphenhydramine given orally.

A review of controlled studies of various oral antihistamines in various types of urticarial disorders by Lee and Maibach⁶⁹ summarized efficacy differences between the newer and older agents. This review found that the newer nonsedating antihistamines were as effective or more effective than the sedating antihistamines.⁶⁹ Controlled, head-to-head comparisons of these agents would be definitive in identifying treatment for specific forms of urticaria. In any event, because the newer antihistamines do not cross the blood-brain barrier, in contrast to the older antihistamines, higher doses may be given if needed without sedation and psychomotor impairment. Accordingly, therapy with a newer nonsedating antihistamine presents a safe and effective alternative to use of an older sedating agent for pruritic skin disorders.

Topical Corticosteroids

Topical corticosteroids provide symptomatic relief of inflammation and/or pruritus associated with acute and chronic corticosteroid-responsive disorders. Zhai et al⁵⁴ reported that the topical application of hydrocortisone 2.5% can significantly benefit histamine-induced pruritus. Systemic corticosteroids are indicated for the treatment of severe or incapacitating allergic disorders that fail to respond to conventional treatment.

Other therapeutic modalities appear in Table 3. Tacrolimus inhibits T-cell activation and has been effective in treating such T-cell diseases as AD,⁷⁰ psoriasis, and alopecia areata. Cholestyramine, opiate antagonists, and gabapentin are effective for certain pruritic conditions but not for histamine-induced pruritus. Aspirin was found more effective than chlorpheniramine for relief of itching in late pregnancy when no rash was present.⁷¹ Phototherapy (ultraviolet B and/or psoralen plus ultraviolet A),⁷² thermal stimulation (cooling or heating), transcutaneous electrical nerve stimulation,⁶¹ acupuncture, and plasmapheresis⁶² have all been used with success in selected cases of pruritus.

CONCLUSION

The sensation of itching, or pruritus, is the most common symptom of dermatologic conditions. The types and causes of pruritus are complex and varied. Although histamine is the primary mediator of itch in some allergic disorders, such as urticaria, there are multiple potential mediators of itch in both allergic and nonallergic disorders. The selection of therapy is facilitated when the etiology of an itching disorder is known. For example, histamine-induced itching generally responds to H₁ antihistamines, whereas tacrolimus may be useful in such T-cell diseases as AD. The challenge is to identify the cause of the symptom and to select the treatment that fits that mechanism.

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