MANAGING PRURITUS- A THERAPEUTIC CHALLENGE

Sarita Goyal1*, Kamal Aggarwal2, M.C Gupta1
1Pharmacology Department, Pt. BD Sharma PGIMS, Rohtak (Haryana)
2Dermatology, Venereology and Leprosy, Skin & VD Department, Pt. BD Sharma PGIMS, Rohtak (Haryana)

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ABSTRACT

Pruritus or itch is defined as an uncomfortable sensation of the skin that provokes the desire to scratch. It can be severe enough to cause interference with work and restful sleep and have a significant impact on quality of life. It has a manifold etiology, is a characteristic feature of many skin diseases and an unusual sign of some systemic diseases such as cholestasis or hyperthyroidism, or simply be caused by dry skin, especially in the cold, winter months. Pruritus may be localized or generalized and can occur as an acute or chronic condition. Therapy is often aimed at eliminating the underlying cause first, followed by the management of the itchy sensation. Treatment options include pharmacological and non-pharmacological measures such as herbal remedies, hydrotherapy, phototherapy, and ultraviolet therapy. This overview provides information regarding the various management and treatment options for pruritus.

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INTRODUCTION:
Pruritus is a major and distressing symptom of numerous and diverse cutaneous and systemic diseases that dramatically affects the quality of life for which the distressed patients seek immediate succour. It can be defined subjectively as “a poorly localized, non-adapting, usually unpleasant sensation that provokes a desire to scratch”. It can affect patients of all age groups as well as both sexes [1]. Chronic pruritus and induced scratching behaviour could have a significant impact on disease course and life quality.

Though a common and important troublesome symptom, pruritus has not received much attention until recently, and the management of pruritic conditions still remains a therapeutic challenge for the treating physicians because of its multifactorial etiology and complex pathophysiology. Herein, we present a comprehensive view of understanding pruritus, including its pathogenesis and management.

ETIOLOGY AND PATHOGENESIS OF PRURITUS:
Pruritus is complex process which can be trigged by exogenous factors (eg. weak mechanical stimuli, thermal and chemical excitation), endogenous factors (eg. systemic drugs) localized, or systemic pruritogenic stimuli (chemically, electrically, mechanically, thermally and / or psychologically).

A variety of pathological processes can lead on to pruritus: inflammation, hypersensitivity, degenerative changes, malignant tumors, and even psychic abnormalities [2]. To understand the pathogenesis of pruritus, it is necessary to know about pruritogens also known as itch mediators. The sensation of itch is transmitted through slow-conducting unmyelinated C-polymodal, type A delta nociceptive neurons with free nerve endings which are located near the dermoeipidermal junction or in the epidermis. These neurons are located more superficially and are more sensitive to pruritogenic substances. Though histamine is one of the primary peripheral mediators of itch, but other chemical substances such as neuropeptide, substance P, neuropeptide, vasoactive intestinal peptide, somatostatin, melanocyte stimulating hormone, serotonin, bradykinin, proteases, endothelin, endogenous opioids such as encephalin and β-endorphin and proteolytic enzymes such as trypsin, chymase and kallikrein etc. have also been implicated as pruritogens. Pruritogens act peripherally, centrally or both, and their receptors are located in various intracutanueous cell types, peripheral and central nerves, as well as sensory neurons [3]. Opioids are known to modulate the sensation of pruritus, both centrally and peripherally. Stimulation of opioid mu receptors increases pruritus, but stimulation of kappa receptors and blockage of mu receptors suppresses pruritus [4].

DIAGNOSIS:
Diagnosing the cause of pruritus can be a very important pointer towards the appropriate drug treatment. A detailed history including information on the onset, extent, severity, type of itch, aggravating and relieving factors, diurnal and seasonal variation, bathing, occupation, hobbies and drug history can be an important step in detecting the cause of itching [5].

When the diagnosis is not certain, laboratory investigations like: complete blood count, complete metabolic panel, hepatitis C antibodies, TSH, and chest x-ray etc. can be contributory in arriving at the diagnosis. Based on the initial results and course of pruritus, further tests such as levels of histamine, mast cell metabolites, serotonin, total IgE etc. can be of help to establish the cause of pruritus [6].

TREATMENT
Thus far, there is no specific anti-pruritic drug because there are a number of possible underlying aetiologies for pruritus. A detailed history and physical examination are thus of prime importance in the treatment of pruritus and allow a more focused treatment plan to be instituted. So, treatment can be either non-pharmacological (by avoiding precipitating factors) or pharmacological. In pharmacological treatment, topical therapies are the mainstay of therapy for mild and localized itch whereas systemic therapies should be reserved for severe and generalized itch.

Non Pharmacological Treatment:
Nonpharmacological measures, generally, are useful in atopic dermatitis and xerosis. To prevent itching, skin lubricants should be applied frequently during the day and immediately after bathing. Non specific measures include avoidance of excessive bathing, frequent use of soap, topical irritants like synthetic or wool clothing, dry environments, frequent use of vasodilators like caffeine, alcohol, overexposure to hot water and to heat [7]. Besides these, other options which may be considered in patients where traditional approaches have been unsuccessful are:

Vibration: Though primarily used in pain management, transcutaneous electrical nerve stimulation (TENS) has also provided symptomatic relief in patients with generalized pruritus through inhibition of central perception of itch [8].

Reflex Therapy, Acupuncture, and Hydrotherapy: might be benefit cases of localised pruritus [9]. Phototherapy: particularly UVB and PUVA are well suited to the treatment of generalised pruritus and have shown remarkable efficacy in alleviating the itch associated with renal or cholestatic pruritus [10].

Pharmacological Treatment:
- Topical
- Systemic
Table-1:TOPICAL TREATMENT

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Drug Treatment</th>
<th>Mechanism of action</th>
<th>Pruritic disorder with reported benefit</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Topical Antihistamines: Doxepin (tricyclic antidepressant) [11].</td>
<td>Blocks H1 and H2 receptors on histamine sensitive sensory fibres</td>
<td>Atopic dermatitis(AD), lichen chronicus, dermatitis nummular dermatitis.</td>
<td>Side effects mostly seen with “Caine” anesthetics include paresthesias, allergic contact dermatitis (because of metabolites of aminoester formulations)</td>
</tr>
<tr>
<td>2.</td>
<td>Corticosteroids [12]</td>
<td>Activates glucocorticoid receptors that inhibit proinflammatory cytokine release.</td>
<td>AD, lichen chronicus, psoriasis, allergic contact dermatitis (ACD)</td>
<td>telangiectasias, skin atrophy, hypothalamus-pituitary axis suppression</td>
</tr>
<tr>
<td>3.</td>
<td>Immunomodulators: Tacrolimus and pimecrolimus[13]</td>
<td>Regulate T-cell activation and inhibit release of various inflammatory cytokines</td>
<td>AD, lichen sclerosus, anogenital pruritus and prurigo nodularis</td>
<td>Transient burning and stinging sensations</td>
</tr>
<tr>
<td>4.</td>
<td>Local Anesthetics: Lidocaine 5%, pramoxine 1% and the eutectic mixture of lidocaine 2.5% and prilocaine 2.5%[14]</td>
<td>Blocks voltage gated Na+ channels</td>
<td>Neuropathic pruritus, Pruritus ani, postburn pruritus, prurigo nodularis (PN) uremic pruritus (UP), psoriasis, AD, contact dermatitis, psoriasis, idiopathic pruritus</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Menthol [15]</td>
<td>Activates TRPM8 on sensory fibers triggering a cooling sensation</td>
<td>Lichen amyloidosis, mustered gas induced pruritus</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Capsaicin[16]</td>
<td>Activates TRPV1 on sensory fibers, depleting substance P over time and prevents neural transmission</td>
<td>AD, aquagenic pruritus, prurigo nodularis, UP, brachioradial pruritus, pruritus ani,</td>
<td>Transient burning sensation and local erythema with initial application</td>
</tr>
<tr>
<td>7.</td>
<td>Topical Salicylic Acid[ 17]</td>
<td>cyclooxygenase inhibitor</td>
<td>lichen simplex chronicus</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>Vitamin D analogues: Calcipotriol [19]</td>
<td>Inhibits tumor necrosis factor-expression, keratinocyte proliferation and differentiation</td>
<td>Psoriasis, PN, polymorphous light eruption</td>
<td>little systemic absorption and does not alter systemic calcium or phosphorous metabolism significantly even when applied to approximately one-third of the body</td>
</tr>
</tbody>
</table>
Antihistamines, particularly diphenhydramine, act by blocking histamine, and are the most widely prescribed medications for this condition. They may be given at bedtime when pruritus is usually at its worst. They take approximately 15–30 minutes to exert their effect and can be short-or long-acting. Newer antihistamines, like cetirizine, loratadine and desloratadine, differ from traditional antihistamines as they are primarily nonsedating as they do not traverse the blood-brain barrier [20].

Mirtazapine, a selective neuroepinephrine re-uptake inhibitor (SNRI), is mostly used in patients with advanced cancer, leukemia, lymphoma, chronic kidney disease, cholestasis and atopic dermatitis as an itch relieving medication. Mirtazapine also has a sedative effect due to its H1-antihistamine properties whereas other newer SNRIs such as venlafaxine and duloxetine have not exhibited significant antipruritic effects [21].

In some clinical trials, selective serotonin re-uptake inhibitors (SSRIs) such as fluvoxamine and paroxetine have shown antipruritic efficacy and have reduced pruritus in 68% of patients with chronic pruritus, particularly patients with atopic dermatitis, systemic lymphoma and solid carcinoma [22]. Sertraline, has been shown to alleviate pruritus due to chronic liver disease [23]. Naltrexone and nalmefine, μ-opioid receptor antagonists have demonstrated reduction of pruritus in patients with atopic dermatitis, cholestasis, end-stage renal disease and burns [12,24] but their initial adverse effects and cost limits their use.

Butorphanol, a κ opioid receptor agonist, has been effective in chronic intractable pruritus associated with systemic diseases or inflammatory skin diseases when administered intranasally at concentrations of 1 mg once a day whereas nalfurafine has been associated with amelioration of chronic kidney disease associated-pruritus [25].

Cholestyramine is a nonabsorbable, basic polystyrene which acts as an anion exchange resin binding and sequestrating bile salts in the gut lumen and thus partially interrupting the enterohepatic circulation and thereby lowering bile acid levels and other pruriogenic factors in plasma and tissues. It is a first-line therapy in cholestasis-related pruritus and a good choice in puritus related to polycythemia rubra vera and uremia. Side-effects commonly encountered are constipation, fat malabsorption, and an unpleasant taste [26].

Gabapentin and pregabalin are structural analogs of the neurotransmitter γ-aminobutyric acid (GABA). The exact mechanisms of their antipruritic effects are not known but may be related to the hindrance of nociceptive sensations to the brain and thus pruritus. They are useful in neuropathic pruritus related to nerve entrapment disorders such as natalgia paresthetica, brachioradial pruritus, post herpetic neuralgia, keloids and burn scars. Side effects include sedation, neurotoxicity and/or coma in patients with reduced renal function and withdrawal symptoms with pregabalin [27].

Aprepitant is an oral antiemetic drug that antagonizes the effect of substance P on neurokinin type 1 receptor. It is effective against pruritus associated with Sézary syndrome but its high cost limits its use [28].

Other Drugs

Rifampicin, Ursodeoxycholic acid and S-adenosyl-L-methionine have also been reported to alleviate pruritus in women with cholestasis of pregnancy [29]. Thalidomide and erythropoietin decrease pruritus in uremic patients [30].

### Nutritional Therapy

Nutritional therapy, though not been sufficiently researched as a monotherapy for pruritus, may be helpful in combination with other anti-itch treatments. Vitamins D, E and linolenic acid have shown some efficacy in the treatment of psoriasis and atopic eczema [31].

**CONCLUSION:** Pruritus is not a diagnosis but a symptom that is associated with multiple etiologies. Pruritus can sometimes be disabling, and it can be extremely difficult to treat it effectively. Stepwise multi-disciplinary assessment is required to search the
underlying systemic, neural and psychophysiological disorders. Topical therapies are the mainstay of therapy for mild and localized itch while systemic therapies should be reserved for severe and generalized itch. Therapeutic ladders can be used to find the appropriate and effective treatment for each individual. In conclusion, pruritus is a symptom which should never be underestimated or ignored.

POSSIBLE FUTURE THERAPIES

Current drug treatment options for the management of pruritus is inadequate because of lack of understanding of the immune and neural pathophysiology which is involved for pruritus. For better treatment with fewer side effects it is necessary to discover, new pathways and receptors and novel antipruritic therapies that may prove helpful in the treatment of pruritus. A specific separate pathway for histamine-induced itch was found more than a decade ago but with discovery of H3 and H4 histamine receptors and their involvement in pruritus and inflammation again rekindled interest in histamine [32]. In one experimental study H4 receptor agonists have been shown to induce pruritus in mice that was independent of mast cells or other haematopoietic cells this suggests that the H4 receptor mediated itch results from a direct action on peripheral nerves [33]. Functional Toll-like receptor 7 (TLR7) was found to be expressed in C-fibre sensory neurons in mice and effectiveness of antagonising TRL7 to inhibit itch at the cutaneous level is still awaited [34].

Gastrin-releasing peptide receptor (GRPR) is a G protein-coupled receptor for gastrin-releasing peptide (GRP). It is widely distributed in the gastrointestinal tract and central nervous system. Mice, pretreated with a GRPR antagonist showed no scratching [35]. Lysophosphatidic acid (LPA) act as a pruritogen in the sera of patients with cholestatic liver disease. LPA is a phospholipid derivative synthesized by the enzyme autotaxin, and acts as a signalling molecule. LPA may be potential future target in the treatment of cholestatic pruritus [36].

Elevated levels of acetylcholine has been found in the skin of AD patients. Botulinum toxin inhibits the release of acetylcholine from synaptic nerve terminals. The subcutaneous injection of botulinum toxin in localised pruritus, cholestatic pruritus [36].

References:


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