

## ***Pruritus, skin allergic reactions – a review of the medicinal substances topically used***

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### **Summary**

Inflammation and allergic skin conditions are common and have various causes. These include insect bites, contact with plants, allergic and non-allergic urticaria and other skin diseases. The publication aims to review current scientific reports on medicinal substances, medical devices and cosmetic products used topically in itchy skin inflammation. The molecular mechanisms of action of frequently used products will be explained. Preparations containing a combination of diphenhydramine and lidocaine effectively soothe the troublesome symptoms of inflammatory and allergic skin changes. The validity of combining diphenhydramine with lidocaine was analyzed. Dimethindene and glucocorticoids also were considered. Medical devices and cosmetics which alleviate the symptoms of bites and allergies are also described. Based on the mechanisms of action of diphenhydramine with lidocaine, it can be concluded that preparations containing both substances effectively alleviate symptoms of inflammatory and allergic skin changes. Understanding the mechanisms of action will facilitate the selection of appropriate treatment. (*Farm Współ* 2023; 16: 239-246) doi: 10.53139/FW.20231629

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### **Introduction**

Inflammatory and allergic lesions localized on the skin can have many causes. These include, for example, mosquito bites (especially *Culex pipiens* and *Aedes albopictus* commonly found in Europe), or stings from hymenopterous insects (bees, wasps, bumblebees, hornets) [1]. Characteristic symptoms of insect stings include the appearance of swelling at the site of the sting, customarily called a wheal, and redness. Late symptoms, i.e. itching and even burning, can occur within 24-36 hours and last for several days. These complaints are mainly related to an allergic reaction in response to the introduction of the saliva of a female mosquito or the venom of hymenopterous insects into the human body. The histamine present in the secretions binds to histamine H1 receptors located on sensitive nerve endings of the skin, resulting in itching. IgE-mediated saliva components contribute to mast cell

activation. This results in the release of inflammatory mediators, including histamine, tryptase, cytokines, and leukotrienes, responsible for the symptoms of a local allergic reaction [2]. In hypersensitive individuals, the reaction can generalize, leading to life-threatening anaphylactic shock.

The most bothersome symptom associated with allergic reactions is skin itching. The mechanism of its formation varies depending on inducing factor. Cells of the immune system, under the influence of certain stimuli, release histamine, which, by attaching to the histamine receptor, activates the 2 isoforms H1R and H4R. This results in an influx of Ca<sup>2+</sup> ions into nerve cells, which stimulates intracellular signaling pathways such as BRAF/ERK1/2 or STAT3. The pruritic signal is then transported from the afferent fibers of the epidermis or dermis to the spinal cord. The mediators released from these fibers, i.e. substance P, calcitonin gene-related

peptide (CGRP), glutamate or brain natriuretic peptide (BNP), stimulate the corresponding receptors on spinal neurons in the outer lamina I and II in the dorsal horn. The signal then reaches the thalamus, and eventually via direct excitatory connections from the thalamus, including the anterior cingulate cortex (ACC), insular cortex (Insula) to primary and secondary somatosensory cortices (SI, SII). The effect of this cascade is a strong itching and scratching sensation [3]. Figure 1 shows a schematic representation of the mechanism of pruritus formation at the molecular level.

Contact with plants often causes inflammatory and allergic reactions of the skin, e.g. common nettle (*Urtica* spp.) and other ornamental plants. Contact allergens (e.g. nickel) and environmental pollutants can also cause inflammatory and allergic skin conditions. Exposure to gents leads to the development of urticaria, characterized by the presence of intensely itchy blisters surrounded by redness. The resulting swelling is caused by dilation and increased permeability of blood vessels in the dermis. Urticaria occurs at least once in a lifetime in up to 20% of the population. We distinguish between

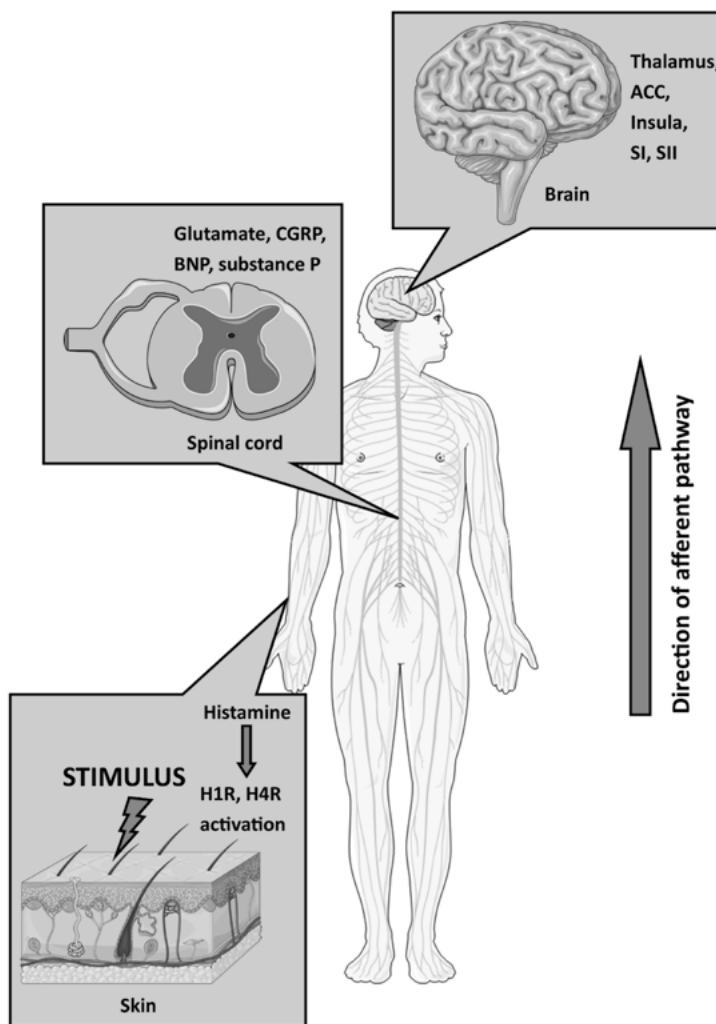


Figure 1. Molecular mechanism of pruritus. Histamine H1 receptor (H1R), histamine H4 receptor (H4R), calcitonin gene-related peptide, (CGRP), brain natriuretic peptide (BNP), anterior cingulate cortex (ACC), insular cortex (Insula), primary and secondary somatosensory cortices (SI, SII). Own elaboration based on [5]

acute urticaria (lasting less than six weeks) and chronic urticaria (with symptoms lasting more than six weeks). The most common causes of urticaria include:

- medications (especially penicillin, sulfonamides, non-steroidal anti-inflammatory drugs, thiazide diuretics, angiotensin-converting enzyme inhibitors, oral contraceptives, codeine, and contrast agents – symptoms appear from 1 hour to 15 days after taking the drug),
- foods (nuts, dairy, fish, seafood, chocolate, some fruits and vegetables),
- inhalant allergens (dust mites, pollen, mold spores, or dander),
- latex, cosmetics, and chemicals that cause contact urticaria,
- insect bites,
- infections and systemic diseases,
- physical agents (heat, cold, pressure, sunlight).

Urticaria can also have an allergic basis, associated with mast cell degranulation and histamine action, which is caused, for example, by inhalant allergens or certain foods. Non-immune response also occurs and is induced by physical factors, among others. In idiopathic urticaria, the cause cannot be identified, making it difficult to eliminate the etiologic agent and thus prolonging the treatment period. They account for a significant proportion of chronic urticaria [4-7].

Inflammatory conditions often accompany both allergic reactions and skin diseases with associated pruritus. These include atopic dermatitis, psoriasis, contact eczema or photodermatoses [8]. Therefore, topical anti-inflammatory drugs play an essential role in treating these conditions.

The purpose of the publication is to review substances used topically in conditions manifested by pruritic, inflammatory, and allergic skin conditions. The latest literature data were analyzed, the results of clinical trials and the safety, as well as contraindications of substances applied to the skin were taken into account.

### **Anti-allergic anti-inflammatory products**

Treatment of allergic and inflammatory skin lesions usually involves topical agents. Based on the mechanism of action, we can distinguish substances with anti-allergic, antipruritic, redness-reducing and anti-edematous effects. These primarily include antihistamines and glucocorticosteroids. Additional substances in the preparations such as local anesthetics,

minimize the sensation of bothersome symptoms. For this reason, therapeutic substances from the above-mentioned drug groups have been subjected to scrutiny [9-12].

### **Diphenhydramine with lidocaine**

A preparation containing a combination of diphenhydramine and lidocaine (Allefin) is available on the Polish pharmaceutical market. It is indicated for the symptomatic treatment of contact allergic and inflammatory skin lesions accompanied by pruritus, resulting from external factors, such as bites (e.g., insects, arachnids), contact with certain plants (e.g., nettle, ivy) or burns by jellyfish [11].

The combination of active substances provides an antihistamine and local anesthetic effect, which brings immediate relief in case of a local cutaneous allergic reaction. Due to their different mechanisms of action, the substances will be discussed separately.

### **Difenhydramine**

Diphenhydramine belongs to the first-generation antihistamines, which means that when used orally, it penetrates the CNS. The mechanism of action is based on blocking the connection of histamine to the corresponding receptors. Blocking H1 receptors inhibits smooth muscle contraction, vasodilation and increased blood vessel permeability. The last two effects are significant for the onset of cutaneous allergic reactions since vasodilation leads to redness and, by irritating nerve endings, feelings of itching and pain. On the other hand, increased permeability of vascular walls leads to oedema and various changes on the surface of the skin. Diphenhydramine is quickly absorbed through the skin inhibiting allergic reactions when applied topically. It maintains a concentration higher than in a serum, and undergoes extensive distribution to tissues. [11,13,14].

### **Lidocaine**

A drug classified as an amide derivative with local anesthetic activity. The mechanism of action of lidocaine is to stabilize cell membranes by inhibiting the flow of sodium ions. This results in the inability of the cell to depolarize under the influence of a specific incoming stimulus. In addition, it reduces excessive capillary permeability, reducing redness, swelling, and exudate.

When administered to intact skin, it is only slightly absorbed. Lidocaine in gel form is successfully used as an anesthetic for surgical and nursing procedures.

Local anesthesia after topical administration of lidocaine in gel form occurs after about 2-3 minutes. It is used primarily for symptomatic treatment due to its short-lasting effect (about 30-40 minutes). Applying lidocaine before topical capsaicin effectively relieves the burning sensation and attenuates thermal hyperalgesia, which is excessive sensitivity to thermal stimuli during treatment [15]. Due to the lack of adequate studies, lidocaine is not recommended for use by pregnant women and during lactation. Caution should be exercised in patients with heart disease and cardiovascular disorders. When administered to the skin, lidocaine can also cause allergic reactions in the form of erythema. [11,16-19].

Topical application of diphenhydramine with lidocaine also relieves symptoms of pruritus in the anal area, providing relief [20]. Thus, the combination of these substances in the treatment of cutaneous allergic reactions has the benefit of directly inhibiting the allergic reaction, and immediately anesthetizing the affected area. The use of a preparation containing both substances for cutaneous allergic reactions is justified and desirable from the patient's point of view.

### **Dimethindene**

Dimethindene, like diphenhydramine, belongs to the first-generation antihistamines. Its mechanism of action also involves antagonism to H1 receptors. In preparations applied to the skin, it is found as a maleate. After application, the therapeutic effect occurs after a few minutes, reaching a maximum after 1-4 hours. Nearly 10% is absorbed into the bloodstream after administration on the skin. When applied to a large area of skin, it may cause irritation after exposure to sunlight. Unlike formulations containing diphenhydramine with lidocaine, dimethindene formulations show a slower onset of action and a weaker anesthetic effect. Dimethindene is not indicated for use on extensive skin areas, in children under the age of two, and pregnant and lactating women [21-24].

### **Glucocorticosteroids**

Glucocorticosteroids (GCS) are synthetic analogs of adrenal cortical hormones. They show high efficacy in the treatment of many inflammatory skin diseases. As lipophilic hormones, they penetrate the cell membrane and interact with a specific receptor (GKR) in the cytoplasm. The hormone-receptor complex travels to the cell nucleus and binds to a specific DNA

sequence, known as a response element to GKS, leading to stimulation or inhibition of the expression of specific genes. The result of these transformations is the anti-inflammatory, vasoconstrictor, and immunosuppressive effects of glucocorticosteroids [12].

According to the strength of action in the European classification, GSKs are divided into four groups, while the American classification considers seven groups. The European division is presented in table I and considers only the type of active substance and its therapeutic concentration.

A 0.5% hydrocortisone acetate ointment and a 1% cream are available without a prescription in Poland. Hydrocortisone acetate is one of the weakest and safest glucocorticosteroids, but it is not without adverse effects, characteristic for this group of drugs [26,27].

A study conducted on healthy volunteers examined how hydrocortisone creams containing 1% and 2.5% hydrocortisone affect the sensation of heat and cold, as well as pruritus, induced by subcutaneous injection of a solution of 100 µg of histamine in 1 ml of saline. The forearm of each volunteer was divided into four squares. To establish baseline levels in each square, sensations of cold, heat, cold-related pain, and heat-related pain were measured. The study used the Thermal Sensory Analyzer (TSA), a computerized device with electrodes capable of sending stimuli read by human nerve endings as heat and cold. Volunteers pressed a mouse button when they felt a temperature change (warm or cold) and again when they felt pain. After the second click, the electrode was switched off, and the next stimulus was sent after a short pause. Once baseline levels were established, the following were administered to the designated fields in a double-blind, randomized order: placebo cream, 1% and 2.5% hydrocortisone cream. No substances were applied to one field, which was the control trial. After 30 minutes, the response to heat and cold was tested again, and then histamine was injected under the skin of each field. For 10 minutes after histamine injection, volunteers determined the level of pruritus every minute using a visual analog scale (VAS). The scale had a length of 10 cm – a score of 0 meant no pruritus and a score of 10 meant the most severe pruritus the patient had ever experienced. In both trials, statistically significant differences were achieved only for the placebo cream containing 2.5% hydrocortisone [28].

Despite promising mechanism of action and high efficacy, glucocorticosteroids should not be used too often due to the risk of severe adverse effects. A large

Table I. European classification of topical glucocorticosteroids in terms of potency [25]

Group	Active pharmaceutical ingredient	Concentration [%]
IV – very potent	clobetasol propionate	0.05
	halcinonide	0.1
III – potent	hydrocortisone 17-butyrate	0.1
	diflucortolone valerate	0.1
	betamethasone dipropionate	0.05
	fluocinolone acetonide	0.1
	betamethasone valerate	0.1
II – moderately potent	betamethasone dipropionate	0.05
	triamcinolone acetonide	0.02
	betamethasone valerate	0.025
	betamethasone benzoate	0.025
	flumetasone pivalate	0.02
	clobetasol butyrate	0.05
	fluocinolone acetonide	0.05
I – less potent	hydrocortisone	0.5-1.0
	hydrocortisone acetate	1.0
	dexamethazone	0.01-0.1
	methylprednisolone	0.25
	fluocinolone acetonide	0.0025
	prednisolone	0.5
	alclometasone dipropionate	0.05

study on European population, showed a positive correlation between the use of topical corticosteroids and the incidence of type 2 diabetes [26].

A severe and well-documented adverse effect of glucocorticosteroids is skin atrophy. Their negative effects can be observed in all layers of the skin. They cause severe hypoplasia, loss of elasticity, epiphora, telangiectasia, increased fragility of blood vessels, and a tendency to bruise and disrupt skin barrier function [29]. However, GCSs are very effective and safe when used as directed by a physician.

### Medical devices and cosmetic products

Medical devices and cosmetics are also used in inflammatory and allergic skin lesions. Although they are devoid of medicinal effects, they can be successfully used supportively to alleviate the symptoms of these conditions.

#### Medical devices with ectoine

Ectoin is a natural substance produced by bacteria living in extreme environmental conditions – extremophiles. It has anti-inflammatory, moisturizing, and protective effects on the epidermis. It also stabilizes and protects cell membranes. It is used in ophthalmology, ENT, dermatology and in allergology. It alleviates symptoms of allergies, including skin problems cha-

racteristic of atopic dermatitis. It is an active ingredient in skin care formulations and sunscreens as additional UV protection. Studies have shown its effectiveness and safety in patients with allergic rhinitis. Ectoin can be an alternative to allergy therapy, especially for people with limited drug treatment options. The advantages of this substance are its natural origin, the possibility of applying it to the whole body, and its high efficacy and safety [30,31].

#### Medical devices and cosmetics used after insect bites

There are medical products on the market for topical application to the skin to reduce irritation or symptoms associated with insect bites, such as itching, burning, and redness. Cosmetics may also contain additional substances such as Baikal Thyroid extract, marshmallow extract, and aloe vera (discussed in the section below). It should be remembered that cosmetics do not have a curative effect, although they can be used supportively in treating skin lesions. When applied to the skin, many of them can cause skin tightening [32].

#### Medical devices with Aloe vera

Aloe vera and tree aloe are widely used in dermatology and cosmetology. Aloe pulp contains substances with anti-inflammatory, antibacterial, protective, regenerative, and moisturizing effects (polysaccharides). It

penetrates the skin very quickly, facilitating nutrient transport deep into the skin.

It is used as a soothing substance for burns, skin irritation and inflammation, helps treat acne and diseases such as eczema and psoriasis, and mitigates the effects of insect bites. Many cosmetic products on the market contain aloe vera in various concentrations. It can appear as an additional substance, and the main component of a given preparation. However, it should be remembered that aloe vera should be used with caution, as it can cause allergic reactions, due to its very high amount of active substances [33,34].

**Medical devices with lipids and dexpanthenol**

Some skin care products on the market contain lipids, which moisturize dry skin and allow the regeneration of the stratum corneum. Dexpanthenol – a popular ingredient in medical products promotes wound healing, inhibits inflammation and has a soothing effect. This type of products can be successfully used in skin allergies with itching, atopic dermatitis, and eczema. There are no contraindications for use by pregnant women or in infant skin care [35-37].

**Medical devices with allantoin**

Allantoin is a chemical compound belonging to the group of ureides, derivatives of urea. It occurs naturally in plants such as rhododendron, nostrum, and viper’s bugloss. However, nowadays synthetically produced allantoin is used. It forms complexes with panthenol, biotin or other organic compounds, which have many of applications, including cosmetics, medicines, or medical devices with moisturizing, regenerating or anti-irritant effects. When applied to the skin, it enhances the repair processes of the epidermis, softens it, promotes wound healing and reduces the inflammatory reaction. In addition, when applied topically, it stimulates the production of neutrophils, shrinks vessels and reduces redness and inflammation.

Allantoin is a safe substance, which has been confirmed by numerous studies, does not cause adverse reactions, does not give incompatibility with other ingredients of cosmetics and pharmaceuticals. These properties have caused it to be widely used in preparations to help treat skin diseases and problems such as psoriasis, acne, allergies, atopic dermatitis, ulcers and sunburn [38,39].

Table II. Medicinal substances and their combinations used in inflammatory and allergic skin conditions

	Topical use		
	Diphenhydramine with lidocaine	Dimetindene	Glucocorticoids
Type of action	Anti-histaminic, anesthetic	Anti-histaminic	Anti-inflammatory, immunosuppressive
Indications	Inflammatory and allergic lesions with pruritus induced by insect bites or plants exposure	Pruritus associated with dermatoses insect bites, sunburn, urticaria	Insect bites and stings, atopic dermatitis psoriasis, contact dermatitis, urticaria, photodermatosis
Adverse effects	Skin and subcutaneous tissue disorders (frequency unknown)	Mild and transient skin reactions in the place of application, skin and subcutaneous tissue disorders (frequency unknown)	Skin thinning and atrophy, stria, steroid acne, facial erythema, perioral dermatitis, folliculitis, increased risk of bacterial, fungal, viral and parasitic infections impaired wound healing, contact allergy to glucocorticoids, intensified relapse after withdrawal
Contraindications	Pregnancy, lactation, children under 2 years old, blistering dermatoses, paralysis, heart failure	Second or third degree burn, children under 2 years old, pregnancy and Lactation, application on extensive skin areas	Active infection in application area, superinfected inflammatory dermatoses treatment, long-term treatment of extensive skin areas with mGKS, preceding contact allergy or systemic allergic reaction to glucocorticoids
Drug availability	OTC drug	OTC drug	Prescription drug, OTC drug (hydrocortisonum)

Table II summarizes the medicinal substances with additional information. Indications, side effects, contraindications or availability category of the drug are included.

## Summary

Effective inflammatory and allergic skin treatment is based on broad-spectrum therapeutic substances. Many medicinal products, medical devices, and cosmetics are available on the market to relieve symptoms of inflammatory and allergic skin conditions. The mechanisms of action of diphenhydramine and lidocaine indicate that their combination is legitimate. Lidocaine produces a rapid local anesthetic effect so the patient feels immediate relief. Diphenhydramine inhibits the symptoms of an allergic reaction.

Despite the proven therapeutic effect of glucocorticosteroids, it is essential to remember the risk of dangerous adverse effects with frequent and prolonged application to the affected skin surface. The medical devices and cosmetics presented in the review support

the treatment of skin diseases, irritations, and allergic lesions. The review facilitates the selection of the appropriate preparation for the patient based on the potency, efficacy and safety of the discussed topical therapeutic agents.

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None

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