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Topical Delivery of Haptens: Methods of Modulation of the Cutaneous Permeability to Increase the Diagnosis of Allergic Contact Dermatitis

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1. Introduction

To be effective an active drug or principle must cross the stratum corneum barrier; this process can be influenced to obtain better functional and therapeutical effects. In spite of the wide variety of the methods studied in order to improve the transdermal transfer to obtain systemic effects, the applicability is limited in this field. Attention to the epidermal barrier and penetration of active principles has been reported mostly in studies concerning dermocosmetics. Studies regarding methods of penetration are gaining experimental and clinical interest. Cutaneous bioavailability of most commercially available dermatological formulations is low. Increase of intradermal delivery can relate to chemical, biochemical, or physical manipulations. Chemical enhancers have been adopted to: (a) increase the diffusibility of the substance across the barrier, (b) increase product solubility in the vehicle, (c) improve the partition coefficient. Moreover, methods of interference with the biosynthesis of some lipids allow the modification of the structure of the barrier to increase the penetration. Recent development of these methods are here reported and underline the importance and role of vehicles and other factors that determine effects of partition and diffusion, crucial to absorption of high molecular weight haptens in allergic contact dermatitis.

The skin represents an important barrier of the penetration of exogenous substances into the body and, on the other hand, a potential avenue for the transport of functional active principles into the skin and/or the body. Several studies have shown the modalities through which these molecules cross the horny layer, which represents the most important limiting factor of the process of diffusion and penetration, and have discussed how to increase the penetration of pharmacologically active substances [1-3]. The stratum corneum has a very peculiar structure: the corneocytes (the *bricks*: about 85% of the mass of horny mass) and intercellular lipids (15%) are arranged in approximately 15-20 layers. It consists of about 70 % proteins, 15 % lipids, and only 15 % water. In the corneocytes contain keratin, filagrin, and demolition products [4]. The corneocyte lacks lipids, but is rich in proteins. The lipids are inside extracellular spaces, in a bilayer organization surrounding corneocytes. The very low permeability of the horny layer to hydrosoluble substances is because of this

extracellular lipid matrix. Cutaneous penetration of hydrophilic substances is limited because of the convoluted and tortuous intercellular space and hydrophobicity of three lipidic constituents: ceramides, cholesterol, and free fatty acids that are present in the molar ratio: 1: 1: 1 (weight ratio: ceramides 50%, cholesterol 35-40%, free fatty acids 10-15%) [5]. This ratio is critical: because the diminution of the concentration of one of these types of lipids alters the molar ratio functional to the normality of the barrier and modifies its integrity [6]. The variations of this lamellar structure and/or its lipid composition are the structural and biochemical basis of permeability variations along with the thickness of the horny layer. The extracellular matrix forms also the so-called the 'horny layer reservoir' (some substances are partially retained in the corneous layer and are slowly released) [7-8]. Various processes carried out serially or in parallel, are involved in cutaneous penetration of substances and these may cross the stratum corneum via an intercellular or a transcellular route. Moreover, entrance through pilosebaceous units and eccrine glands is possible. Many efforts to obtain therapeutic effects in tissues far from the skin have been made. We may have: topical administration, with a pharmacological effect limited to skin, with some unavoidable systemic absorption; loco-regional delivery, when the therapeutic effect is obtained in tissues more or less deeply beneath the skin (muscles, articulations, vessels, etc.) with limited systemic absorption; and transdermic delivery that aims to obtain, through application of preparations on the skin, pharmacologically active levels for the treatment of systemic diseases through skin vascular network or for the diagnosis of a suspected contact dermatitis.

1.1 Stratum corneum barrier and intradermal delivery

The penetration through the stratum corneum involves partition phenomena of applied molecules between lipophilic and hydrophilic compartments. For many substances the penetration takes place through an intercellular way, more than transcellular, diffusing around the keratinocytes.

Intercellular movement. The lipid lamellae (each one including 2 or 3 bilayers and made mainly of ceramides, cholesterol, and free fatty acids) are the intercellular structure of the horny layer, with the main role in barrier function. Most solute substances, non-polar or polar, penetrate across intercellular lipid avenues. The permeability of very polar solutes is constant and similar to the transport of ions (e.g. potassium ions). Lipophilic solute permeability increases according to specific lipophilic properties.

Transcellular movement. Stratum corneum intracellular components are essentially devoid of lipids and lack a functional lipid matrix around keratin and keratohyalin. This results in an almost impenetrability of corneocytes [9]. Degradation of the corneodesmosomes causes formation of a continuous lacunar dominio ("aqueous pore") allowing intercellular penetration; the lacunae formed are scattered and not continuous, and form as a result of occlusion, ionophoresis, and ultrasound waves. These may become larger and connect forming a net ("pore-way"). Various methods can induce this type of permeability increase : physical and chemical methods [10].

Transport through follicular and gland structures. Movement through hair follicles, pilosebaceous units, and eccrine glands is limited. The orifices of the pilosebaceous units represent about 10 percent of all skin delivery in areas where their density is high (face

and scalp) and only 0.1 percent in areas where their density is low. This is a possible selective way for some drugs. Follicular penetration may be influenced by sebaceous secretion, which favors the absorption of substances soluble in lipids. The penetration through the pilosebaceous units is dependent upon the property of the substance and type of preparation.

2. Role of the vehicle and excipients and interaction with the active principles

A vehicle is defined by the type of preparation (cream, ointment, gel) and the excipients (water, paraffin, propilen glycol); the terms "vehicle" and "excipient" refer to different entities.

Vehicle and excipients deeply influence the velocity and magnitude of absorption and consequently the bioavailability and efficacy. The excipients of the vehicle modulate the effects of partition and diffusion in the stratum corneum.

A lipid preparation that promotes occlusion may enhance the penetration of the drug, but ointments and lipid preparations are not always more powerful than creams. Creams, gels and solutions may be formulated so as to obtain an effect equivalent to that of ointments. Topical corticosteroids of different classes of potency may show the same activity when formulated in different vehicles. A gel preparation of kellin, obtaining better penetration, has demonstrated important results in the treatment of vitiligo. Also transfollicular penetration is influenced by vehicle and excipients; better results are given by lipophilic and alcoholic vehicles. Relevant factors include dimension and charge of the molecules of the solute.

3. Pharmacokinetic parameters - Vehicle/ corneous layer partition

For the purpose of the study of the mechanisms of transport and the functions of the skin barrier, it can be considered as a membrane or a cluster of membranes (mathematical principles can be applied) [11]. On the whole, transport through the horny layer is mainly a molecular passive diffusion. The physico-chemical and structural properties of the substance determine the capacity of diffusion and penetration through the membrane: important determinants are solubility and diffusibility.

The diffusibility and the ability of a solute to penetrate through the barrier is influenced by several factors including the tortuosity of the intercellular route. This passive process of absorption follows Fick's law of diffusion: the velocity of absorption - flow - is proportional to the difference of concentration of the substance in relation to that within the barrier. It can finally be noted that the permeability coefficient relates flow and concentration, resulting from partition coefficient, diffusion coefficient, and length of diffusion route [12-16].

4. Conditions that modify the barrier function

During hydration the greater part of the water is associated with intracellular keratin; the natural factor of hydration or natural moisturizing factor (NMF) absorbs a noticeable amount of water (10% of the weight of the corneocyte). Corneocytes swell and the barrier properties of the stratum corneum are deeply altered. In the intercellular space the small

amount of water linked to polar groups by hydration does not alter the organization of lipids and does not reduce of permeability [17]. The effect of the hydration however has a discontinuous effect; the increase in permeability may be by ten times for some substances and very limited for others [18]. Occlusion partially hinders the loss of humidity of the skin, increasing the content of water of the horny layer. However the NMF level in the horny layer is almost zero. It seems therefore that there is a homeostatic mechanism that prevents hyperhydration of the skin [9]. Occlusion may increase the absorption by several times, especially for hydrophilic compounds. However, in some conditions it may promote the formation of a reservoir effect. The acidity of the cutaneous surface, controlling homeostasis and enzymatic activities, influences permeability [19]; the metabolic activity of the skin (enzymatic oxidoreductive processes) may modify the substances applied, influencing permeability and effects.

Absorption is also influenced by other skin properties that vary at different cutaneous anatomical sites. For instance, the absorption diminishes greatly as one moves from the palpebral skin to the plantar surfaces [20].

Age influences skin absorption. Various biological activities are lower in the skin of the aged individual. Great variation is also noted for the premature infant and neonate, who have greater cutaneous permeability [21]. There are no experimental data confirming the validity of friction on transcutaneous absorption [6]. Alterations of the barrier induce modifications of TEWL [9]. In addition, the horny layer may be defined as a biosensor; alterations of external humidity regulate proteolysis of filaggrin, synthesis of lipids, DNA, and proteins within keratinocytes, which can lead also to inflammatory phenomena [22].

The cutaneous bioavailability of most commercial dermatological formulations IS about 1-5% of applied dose [23].

The active substances of topical formulations are generally absorbed in small quantities; only a reduced fraction passes from the vehicle into the stratum corneum. The greater part remains on the surface of the skin, subject to loss in several ways such as by sweating, chemical degradation, and removal. Future standards would therefore aim to make formulations not merely high in concentration, but pharmaceutically optimized to have an elevated (50-100%) bioavailability. On the other hand, one must consider the marked variations of the different cutaneous areas and skin conditions that make uncertain the therapeutic equivalence when compared with other ways of administration in clinical conditions [24].

5. Methods of modulation of cutaneous permeability

When a substance is applied on the skin with a simple vehicle the therapeutic result can be unsatisfactory because of the insufficient concentration obtained in the application area [25]. In the last few years strategies have been developed in order to increase the efficacy of the vehicle [26]. They may be of chemical, biochemical or physical order.

5.1 Chemical enhancers

In order to increase the penetration the vehicle may be integrated with enhancers that by interacting with intercellular lipids improve the diffusion coefficient of the substance in the

stratum corneum. Chemical enhancers may: a) increase the diffusibility of the substance inside the barrier, b) increase the solubility in the vehicle or both, or c) improve the partition coefficient.

These substances may frequently have a not specific action. Enhancers of this type, that are not widely used, are Azone, Dermac SR-38, and oleic acid [27]. In some cases, however, these have an irritating effect and must be carefully evaluated in the various preparations [28].

Excipients like ethanol, propylene-glycol, and dimethylsulfoxide (DMSO) may increase the diffusion by altering the organization of lipids of the horny layer [29]. The interference with the biosynthesis of some lipids may alter the structure of the barrier and increase the penetration. Methods have also been studied that interfere with secretion and organization of lipids (e.g., brefeldine, monetine, and cloroquine). In addition, enhancers that alter the supramolecular organization of the bistratified lamellae (synthetic analogs of fats, inducing abnormalities of the organization of the membranes; complex precursors that can not be metabolized, etc.) have been studied. These methods produce an alteration of the critical molar ratio among ceramides, cholesterol, and fatty acids; if there is decrease or excess of one of these 3 key lipids, the lamellar organization cannot be maintained. There may be separation of the phases with more permeable interstitial spaces and formation of a new way of penetration [30].

The efficacy of the enhancers may be increased by inhibition of the metabolic reaction of repair once the alteration of the barrier has been obtained. This would involve inhibiting metabolic sequences that can rebuild and maintain the barrier function. Inhibitors of enzymes with relevant functions (e.g., lovastatin) or specific inhibitors of enzymes synthesizing ceramides or fatty acids induces alteration of the molar ratio of the three critical lipids and leads to discontinuity in the lamellar layer system [31]. Other enhancements may be obtained by modifying the polarity [32].

The number of drugs for which transdermic methods for systemic use has been possible is very small and restricted to lipophilic and low molecular weight substances (e.g. nicotinic acid, nitroglycerin, clonidine, steroid hormones, and scopolamine) [33].

5.2 Carrier vesicular systems

Liposome formulations can be very effective. However, they probably increase penetration only through the transappendigeal avenue [34]. Niosomes and transferosomes, formed by modified liposomes (phosphatidilcoline, sodium cholate, ethanol), are systems based on the ability of vesicles to cross the unaltered horny layer because of the osmotic gradient between external and internal layers of the barrier. These are "flexible" vesicles able to transport their contents through the intercellular tortuous route of the corneous layer.

5.3 Scratch-patch test

Although closed patch tests are the mainstay for the evaluation of allergic contact dermatitis, occasionally, even when appropriate concentrations of allergens are used and contact allergy is strongly suspected, positive reactions are not always obtained. As in the cases that will be described patch test with high molecular weight substances as heparin,

or low molecular weight as acyclovir may give doubtful results in sensitized patients, possibly due to poor penetration of this substances through the epidermis. Scratch-patch testing, by compromising epidermal barrier function, enables enhanced penetration of substances into the skin [35-37]. The method is performed by causing mechanical injury to the epidermis with a sterile skin prick lancet in order to compromise the stratum corneum, which represents the most important barrier limiting hapten penetration. The test reactions are usually read after D2 and D3, when possible, also after D4 and D7. The method of grading a positive scratch-patch test is identical to that used for conventional patch testing with no differences. It can be used for many drugs: low molecular weight molecules (e.g. β -blockers, antiviral drugs etc.) and also high molecular weight molecules (e.g. heparin etc.):

5.3.1 β -blockers

Contact allergy to topical β -blockers is a well-recognized side-effect of glaucoma treatment [38-41]. Sensitization may be singly to agents such as timolol, befunolol, levobunolol, or, more rarely, to multiple β -blockers in a single patient.

A closed patch test, usually used in clinical practice for the diagnosis of allergic contact dermatitis, is often sufficient to show β -blockers contact allergy. However, there may be difficulties in obtaining positive patch tests to β -blockers, as showed in earlier reports [42-43]. Poor penetration through intact skin on the back, where patch testing is normally applied, may be a factor.

5.3.2 Antiviral drugs

Topical antiviral drugs are frequently used, but although repeated applications can lead to contact reactions [44-45], adverse cutaneous reactions are not commonly observed. Allergic contact dermatitis caused by acyclovir is rare, with only 20 studies reported [46-48]. Because of the doubtful reactions with antiviral, especially acyclovir, and in view of the suggestive clinical history, we recommend the scratch-patch test followed by repeated open application test (ROAT).

5.3.3 Heparin

Heparin is a sulfated glycosaminoglycan with anticoagulant properties. It is usually injected intravenously or subcutaneously but is also available for topical application. Cutaneous allergic reactions due to subcutaneously injected heparin have been reported [49-50].

We report a case of patch-test-negative allergic contact dermatitis, diagnosed by scratch patch testing, from a gel containing heparin. Allergic reaction to subcutaneously injected heparins is not a rare occurrence [51-52] but there are only a few reports of contact dermatitis from topical heparin [53].

In cases of suspected contact allergy, when conventional closed patch test shows negative or doubtful results, scratch-patch testing should be considered. We recommend, after performing scratch-patch test, to execute a ROAT to be sure the drug can be applied safely.

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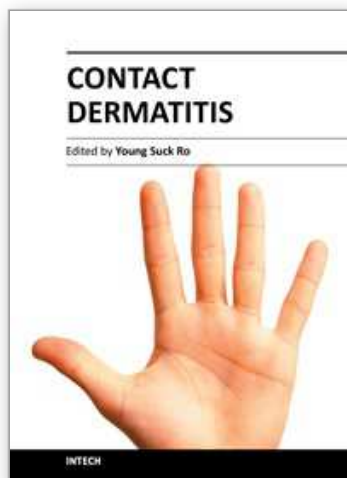
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Contact Dermatitis

Edited by Dr. Young Suck Ro

ISBN 978-953-307-577-8

Hard cover, 180 pages

Publisher InTech

Published online 16, December, 2011

Published in print edition December, 2011

This book centralizes on the subject of contact dermatitis. It aims to provide the dermatologist with a sound base of clinical wisdom and key scientific findings to make an accurate diagnosis and management plan. **SPECIAL FEATURES:** - Describes numerous possible allergens that cause contact dermatitis. - Provides details of research in the basic sciences to help our readers understand more about contact dermatitis. - Provides a comprehensive description of recently developed methods that have evolved for the diagnosis of contact dermatitis. - Provides a concise, clinically focused, user-friendly format, which can rapidly improve your knowledge of the disease. The past decade has seen significant changes in contact dermatitis. Our understanding of the pathophysiology, our diagnostic approaches, and management of the disease has evolved. In this volume, some of the world's most highly regarded experts discuss areas that have seen significant improvement, as well as areas for future development.

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