SKIN CARE INSTANT REPORTS

LEXICON

Volume XXI VEVY EUROPE Nr 2 November 2006

EDITORIAL

Keep up with the change

Evolution of the Market

Over recent years the markets of industrialized countries have undergone rapid and deep rooted changes.
People we might call "progressive" consumers have shifted the center of gravity of their demands towards innovative products that can provide them with an increasingly better quality of life and help optimize their available time and resources.
The credit goes to ever more available technology and to its capillary diffusion which aims at increasing the use of technology.

Acknowledgment of change

Even the sector regarding fine chemistry applied to man has inevitably become aware of, and involved in these changes. This has led to increasingly more specialized products that are guaranteed to be harmless, are of proven efficacy, easy to use, and include competent and definitive documentation and technical support. In other words, nowadays, manufacturers of dermo-pharmaceutical and cosmetic ingredients are being requested to carry out some of the work that was formerly the absolute prerogative of the formulator, who is more and more under pressure by the changing consumer market and its continuous demand for new and differentiated products. The market for skin products is broad, and there is undoubtedly room for all who may want to venture into it, but not everyone is able to fully comply with the very specific and complex demands of this consumer market. Simply supplying the ingredients is no longer the answer to the formulator's needs. The product has to be wrapped in a specialized service package, which is currently required by all quality systems. This ranges from the broadest toxicological guarantees, to qualified formulation support, to complete and exhaustive technical documentation and customer-tailored applicative solutions, which are all services which makeshift producers are unable to provide.

Know your products

When dealing with users, thorough knowledge of your own products and the application trials that have been carried out on them play a fundamental role. The solutions to multifarious problems can only be found through the direct knowledge of the specific disciplines and regulations involved in the study of dermal application related problems. This is an interdisciplinary task which goes far beyond dermo-cosmetic techniques, and calls for competence in the chemical, biochemical and pharmacological sectors. The current position in the sector with regards to Regulations and Standards also requires a great deal of agility to find one's way out of the forest of compulsory and voluntary regulations and specifications that users must or want to follow. Needless to say, those who try to latch onto the success of already existing products by taking advantage of the heightened interest and by attempting to copy them with clumsy imitations, perhaps unsubstantiated documentation and support, are unable to fulfil the requirements of the demanding, modern formulator. Even less credit should be given to the myriad of often alarming and unfounded information which is mainly available on the web, and whose reliability should always be verified.

A serene approach

Modern day formulators should establish a serene relationship with their preferential suppliers of ingredients, including actives and excipients. The formulator needs reliability, consistency of chemical and physical characteristics, good support before and after supply, and intrinsic product quality, so that he need not take up again an already developed and concluded job, especially in a field in which no risk whatsoever is acceptable as far as the desirable benefits are concerned.
Although there may be a cost attached to this, it will be largely paid back by a lesser work load and by the quality of the final result.
The conventional supply process (*product supply*) is therefore enriched by a qualified service (*problem solving*), that is indispensable for creating and consolidating a constructive and satisfactory producer/user relationship.

International information on dermo-pharmaceutics cosmetics and toiletries

Publisher: VEVY EUROPE, via Semeria 16A, 16131 Genova, Italy. **Managing Editor**: Giorgio Rialdi. **Deputy Editor**: Raffaele Rialdi. **Editorial and Advisory Boards**: Skin Applied Sciences Associates (SASA);

Mailing: registered for delivery by post, free of charge to branch specialists. **Circulation**: 12'900 copies. **Document Type**: Trade/Scholarly Publication. Printed in Italy. Publication legally protected by the Literary, Artistic and Scientific bureau of the Italian Presidential Council of Ministers.

Associato all'Unione Stampa Periodica Italiana

Printed by Morino Grafica Scrl — Genova, Italy
Autor. Tribunale di Genova 31/84, del 18/6/84. Iscrizione al Registro Operatori di Comunicazione (ROC) al n. 6411 del 10.12.01. Spedizione in abb. Postale

Editoriale
Al passo con il cambiamento

L'evoluzione del mercato

In questi ultimi anni i mercati dei paesi industrializzati stanno vivendo rapidi e profondi cambiamenti. Quello che possiamo definire consumatore evoluto ha spostato il baricentro delle proprie esigenze verso prodotti innovativi, in grado di offrire una qualità di vita sempre più elevata e di permettere l'ottimizzazione del tempo e delle risorse a disposizione. Il merito va attribuito ad una maggiore diffusione delle tecnologie ed alla più capillare divulgazione finalizzata al loro impiego.

Recepire il cambiamento

Anche il settore della chimica fine applicata all'uomo è inevitabilmente partecipe di questi cambiamenti: prodotti sempre più specializzati, garanzie assolute di innocuità, comprovata efficacia, semplicità d'impiego, supporto documentale e tecnico competente e risolutivo. In altri termini, oggi si chiede al produttore dell'ingrediente dermofarmaceutico e cosmetico di compiere parte di quel lavoro che una volta era appannaggio esclusivo del formulatore, sempre più pressato dall'incessante evoluzione del mercato dei consumatori, con continue richieste di prodotti nuovi e differenziati. Il mercato dei prodotti per la pelle è vasto ed offre certamente spazio a chiunque vi si voglia cimentare ma non tutti sono in grado di soddisfare a pieno le richieste molto definite e complesse che ne provengono. La semplice fornitura dell'ingrediente non rappresenta più la risposta a ciò che il formulatore richiede. Il prodotto deve ormai essere necessariamente avvolto da un involucro di servizi specializzati, requisiti peraltro reclamati a gran voce da ormai tutti i sistemi di qualità: dalle più ampie garanzie sul piano tossicologico al supporto formulativo qualificato, a un corredo documentale tecnico completo ed esaustivo, alla personalizzazione delle soluzioni applicative; servizi, questi, che i produttori improvvisati non possono essere in grado di offrire compiutamente.

Conoscere i propri prodotti

La conoscenza approfondita del proprio prodotto e gli studi applicativi condotti con esso giocano un ruolo fondamentale nel rapporto con l'utilizzatore. Le soluzioni ai più svariati quesiti si raggiungono solo con la diretta competenza nelle molte discipline che intervengono nello studio delle problematiche legate alle applicazioni cutanee. È un lavoro interdisciplinare che va ben oltre la tecnica dermocosmetica e che necessita di competenza in campo chimico, biochimico e farmacologico. Anche l'attuale posizione del settore in campo normativo richiede molta agilità nel districarsi nella selva di norme obbligatorie e volontarie alle quali gli utilizzatori debbono o vogliono sottostare. Va da se che chi si accoda al successo di prodotti già esistenti sul mercato sfruttandone la scia di interesse e replicandoli con maldestre imitazioni, magari accompagnate da documentazione e supporto inconsistenti, non può essere in grado di offrire ciò che l'esigente formulatore moderno si attende. Tanto meno va dato credito gratuito alla miriade di informazioni spesso allarmistiche ed infondate, reperibili principalmente sulla rete, la cui attendibilità è sempre tutta da verificare.

Un approccio sereno

Il formulatore moderno ha necessità di trovare un rapporto sereno con i suoi fornitori preferenziali di ingredienti, siano essi eccipienti o principi attivi. Egli necessita di affidabilità, di costanza nelle caratteristiche chimico-fisiche, di un agile supporto pre- e post-fornitura e di una qualità intrinseca del prodotto, tale da non obbligarlo a rimettere mano al lavoro già sviluppato e concluso, soprattutto in un campo in cui eventuali rischi a favore di auspicati benefici non possono essere accettati. Talvolta tutto ciò ha un costo, ampiamente ripagato però da minori carichi di lavoro e dalla qualità del risultato finale. Il tradizionale processo di fornitura (*product supply*) si arricchisce quindi di un servizio qualificato (*problem solving*), indispensabile per creare e consolidare un rapporto produttore-utilizzatore sempre più costruttivo e di soddisfazione.

Vincenzo Rialdi
CEO of Vevy Europe S.p.A.
Deputy Editor of Relata Technica (International Journal on Dermopharmacological Research, Dermopharmaceutical Technology and Related Cosmetic Subjects) www.relata.info
IRCA Principal Auditor, Pharma GMP Auditor

THE EFFECTS OF EICOSANOIDS ON CUTANEOUS MICROCIRCULATION

Arachidonic acid metabolites

Arachidonic acid metabolites, collectively called eicosanoids are currently considered the best mediators of phlogistic processes. It is therefore no wonder that there is great interest in investigating how they alter cutaneous microcirculation in the presence of inflammation of the cutis.

It is well known that cutaneous vessels may react to stimuli by increasing flow and permeability. Flow is increased both through capillary recruitment and through higher hydrostatic pressure, while changes in permeability involve the post-capillary venules. Direct vasodilation is then increased by axon reflections which require functional integrity of the cutaneous nerve fibres. It is indeed possible to distinguish the two components by blocking nerve conduction with local anesthesia. Histamines are likely involved in this, since reflex vasodilation is inhibited by antihistamines.

Measuring the hyperemic area

A premise concerning the techniques that are used to assess blood flow rate and vessel permeability may be useful.

Standard techniques for measuring the hyperemic area are not able to distinguish direct vascular effects from reflex amplification, and thus cannot estimate the real flow rate. The Laser Flowmeter, which is based on the Doppler principle, represents a simple, versatile and non-invasive means that allows for continuous, repeated recordings, even though it provides a relative measurement whose relationship with the absolute flow is unknown. However, quantitative measurement of the cutaneous blood flow rate can only be obtained by measuring the disappearance of 133 Xenon after it has been diffused into both the cutis and into the subcutaneous layer. When calculating the flow rate within these two tissues we must keep in mind that the kinetics of the 133 Xenon from these two compartments differs. The Valsalva maneuver, which induces generalized stimulation of the sympathetic system on the cutaneous vessels through a reflection mediated by baroceptors, is useful in order to study the action of these fibres on the cutaneous vessels. By infiltrating a cutaneous area with the mediator being examined, and then measuring the flow rate during the Valsalva maneuver, it is easy to identify how sympathetic activity is altered in vivo in the human cutis.

Microvessel permeability

The edema area is often used as an index to determine the effects of microvessel permeability. It must, however, be pointed out that the edema is actually the result of several phenomena: e.g. flow variations, vessel permeability, the ability of exudates to spread throughout the interstitial matrix, etc. Exudation is measured in a cutaneous area that is exposed to the mediator of two different molecules, i.e., albumin and pertechnetate, a tiny hydrophilic ion, in order to individually assess the effects of a mediator on the micro flow rate and on the permeability of the vessel wall. Their diffusion in the area depends on the vascular surface area and on the limits that are placed on this diffusion. The ratio between the two tracers in the exudate is solely determined by the different extraction velocities. This is due to the fact that the capillary recruitment which occurs because of hyperemia does not modify the ratio since both tracers are equally influenced by the modification of the vascular surface area . Therefore, any change in this ratio is caused by a modification of the limits that are placed on the diffusion of the tracers, i.e., by vessel permeability and/or by their possible diffusion within the interstitium.

Eicosanoid LTD4

Let us now consider the effect that various eicosanoids have on cutaneous microcirculation, starting with sulfide-leukotrienes. Laser-Doppler measurements have shown that in man, LTD-4 increases cutaneous hematic flow in a dose-dependent way, while having the opposite effect on other animal species. It has been hypothesized that vasodilation is actually not determined by LTD4 but rather by the release of a second mediator which might be the lissive produced by the endothelium. Conversely, histamine and prostanoids likely do not play an important role in the vasodilation that is induced by the above mentioned sulfide-leukotrienes. However, in-vitro studies indicate that prostacycline vasodilation caused by LTD4 is not the result of decreased orthosympathetic action since it has been proven that vasoconstriction induced by the Valsalva maneuver is maintained after LTD4 infiltration of the cutis.

LTD4 also produces a dose-dependent edema in the human cutis, and it has been found to cause a loss of macromolecules through the vessel wall, regardless of capillary recruitment. Like the effects of histamine, this effect also varies significantly among various animal species. It is absent in the cutis of rabbits and pigs, while it can be found in the cutis of guinea-pigs, as well as in hamster cheeks. What is yet to be explained is why the vascular effects of LTD4 disappear after one hour, whereas edema persists for 4 hours, and erythema for 6 hours.

With regards to both the flow effect and the ability to cause edema, it can be said that on a molar basis, LTD4 has the same effect as histamine. On the contrary, the edemigenous power of LTC4 would appear to be 1000 times greater, which undoubtedly contributes to limiting the effect of the sulfide-leukotrienes and the development of tachyphylaxis .

Eicosanoide LTB4

LTB4, another lipo-oxygenase product, has no immediate effect. It only has a delayed erythematous reaction and slightly increased protein exudation which causes mild edema. Since neutrophilic perivessel infiltrations and mononuclear cells are present, they are likely the cause of vascular modifications. These modifications are boosted by PGE2, and this is an example of the interaction which may occur among various eicosanoids. The effect of 12-HETE (12-S - hydroxy-5,8,10.14 –eicosatetraenoic acid) is similar to that of LTB4, in that it induces an erythematous reaction 6-24 hours after being applied to the cutis. Vascular response seems to be secondary to cell infiltration in this case, as well.

Prostaglandin E1 and E2

When injected into the human cutis, prostaglandin E1 and E2 (PGE1 and PGE2) both cause erythema which lasts several hours and they both highten the effect of histamine. Injecting PGE1 reduces the amount of histamine in the cutis, therefore it was hypothesized that it acts by causing this autacoid to be released

from the mastocytes. However, this hypothesis was ruled out when it was found that preliminary treatment with anti-histamines does not reduce the erythema induced by PGE1.

Conversely, PGE2 inhibits histamine release, and cyclo-oxygenase inhibitors potentiate the response to the allergens in the sensitized cutis. Vasodilation caused by this prostaglandin may be partially due to inhibited release of noradrenalin, which is perhaps caused by the reduced availability of Ca++ ions. There can be no doubt that this vasodilating effect suggests that PGE2 plays an important role as a mediator of phlogistic reactions of the cutis. Furthermore, it has indeed been observed that cyclo-oxygenase inhibitors simultaneously reduce both the erythematous reaction caused by UVB-ray exposure and the PGE2 levels in the exposed cutis.

Clinical data indicating that PGE1 infusion improves cutaneous microcirculation suggest that it may be used in vasospastic skin diseases. This treatment has had a substantial, though unfortunately brief effect on patients suffering from spasms of the peripheral arteries and ischemic pain.

PGE1 and PGE2 both have a mild edemigenous effect on the human cutis, however, they cause strong potentiation of the edemigenous effect of bradykinin and LTB4. One of the characteristics that distinguish PGE1 from other inflammatory reaction mediators is the absence of tachyphylaxis, thus leading to the belief that PGE1 plays an important role in long term inflammatory reactions.
PGE2 represents the main product of the cyclo-oxygenase pathway in mastocytes, and causes long lasting, dose-dependent erythema in the human cutis which is associated with mild edema. Some of its vasodilating activity is attributed to the inhibited tone of the orthosympathetic fibres of the cutaneous vessels, but this component is rather weak, and furthermore, PGD2 is less influential than PGE2.

PGF2a acts as a vasoconstrictor and antagonizes some of the effects of prostaglandin E and D. Studies suggest that it stimulates neurotransmission in the vascular tissue by a postsynaptic effect. This physiologic antagonism is only one example of the complex interactions among various eicosanoids and generally speaking, among various inflammatory reaction mediators. The picture is further complicated by positive and negative feed-back between the final products and the enzymes that catalyze their synthesis.

Endo-peroxide H2 (PGH2)
Among other prostanoids, endo-peroxide H2 (PGH2) triggers a cutaneous response that is similar to the PGE2 response, but this may be because the effect is actually caused by the prostaglandins that form their own degradation products. Indeed, injecting a similar synthetic, non-degradable product leads to very slight vasodilation, most likely due to the axon reflex caused by needle trauma.

Prostacyclin PG12
Prostacyclin PG12 increases microcirculation flow and seems to improve the condition of patients suffering from Raynaud's disease by reducing the frequency and duration of attacks.

It is not easy to draw conclusions from this complex picture regarding the role that eicosanoids play in triggering the changes that occur in the microcirculation system when the cutis is inflammed. The vasodilating and edemigenous effects of PGE1 and PGE2 are undoubtedly important, however the ability of these prostaglandins to potentiate the effect of other mediators, together with their long lasting action and the absence of tachyphylaxis are even more important. This is likely why they are among the autacoids which are most often responsible for phlogistic vascular alterations. PGD2 is less effective, but since it is the main product of the cyclo-oxygenase pathway in human mastocytes, it has been linked to allergic reactions of the cutis. With regards to PGF2a and endoperoxides, they seem to have an antagonistic effect on prostaglandin E and D induced vasodilation, whereas PG12 is a powerful vasodilator. Sulfide-leukotrienes increase the flow rate and cause edema, however their effects are short-lasting and lead to tachyphylaxis. Therefore, although the vessel modifications they cause are similar to the ones caused by acute phlogistic reactions, they will likely not be a determining factor in long term inflammatory alterations. It is believed that the effects of other products of the lipo-oxygenase pathway, such as LTB4 and 12-HETE, which both induce delayed edema and erythema, are actually the result of chemotaxis.

Conclusions
Although these experimental data suggest that eicosanoids are involved in cutaneous inflammation, currently available evidence is still somewhat controversial. This may be pointed out by two examples: firstly by the fact that when cutis inflammation is caused by UVB exposure, the mediator level does not seem to be correlated to the degree of erythema, and secondly, by the observation that cyclo-oxygenase inhibitors boost the allergic reactions of the cutis.