ESSENTIAL RELATIONSHIP AMONG DERMATOLOGY AND PHARMACEUTICAL COMPANIES TO STUDY IMMUNOALLERGIC CUTANEOUS DRUG ADVERSE REACTIONS

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INTRODUCTION

An adverse drug reaction is a harmful or unwanted or unexpected effect directly related to the use of a drug. A drug could be prescribed for diagnosis, prevention or therapeutical purposes. All adverse drug reactions should be reported. Specially those which are life threatening, force to hospitalization, or are unexpected and not previously described in the literature or in the SmPC.
The link between dermatologists and/or allergologists looking for substances responsible of possible cutaneous adverse reactions induced by drugs, and the pharmaceutical companies responsible of production and marketing of these drugs, consists mainly in two aspects:

- shared responsibility in the reporting to the local Health Authorities of all adverse events notified, ensuring the mandatory requirements about notification of adverse events specifically regulated (in Spain, Circular Letter 15/2002)
- collaboration to identify the active ingredients and vehicles responsible of the event.

OBJECTIVE

To show the benefit of a good collaboration among the clinicians and the pharmaceutical industry to demonstrate causality of an immunoallergic cutaneous adverse drug reaction, and accomplish a full correct compliance of the legal requirements about adverse drug reporting.

MATERIAL AND METHODS

The study was carried out in the Immunoallergic Section at the Department of Dermatology (Hospital del Mar, IMAS). Patients suffering for a possible cutaneous adverse drug reaction were included in 2003-04. Each patient gave the respective inform consent and followed the protocol specified in the Figure 1. Upon our request the Medical Departments of Bayer, Recordati, Farma Lepori and Sanofi-Aventis provided us with the forms to report the cutaneous adverse event. These companies as well as, Viñas and Vectem, provided also the active substances and vehicles necessary to perform the study. For the Remicade (infliximab) case, we were specifically asked to report the adverse drug reaction to Centocor, when the case was published at the European Society for Contact Dermatitis meeting (Copenhagen 2003) Even we had a very good response from the major part of the companies asked, this was not always the same in the past. Chart I picks up the active ingredients and the vehicles studied looking for the responsible for the cutaneous adverse reaction. Each test included a control group.

Patients with cutaneous adverse drug reaction referred to our Inmunoallergic Section at the Dermatology Department (Hospital del Mar, Barcelona) 2003/2004

Informed consent — Eczema, Photosensitivity, Urticaria or Rash

Positive cutaneous provocation test with the entire product — Patch, Photopatch, Prick or Intradermal Test

Letter to the Medical Department from the Pharmaceutical company reporting theadverse event asking if active drug and excipients could be supplied to be tested.

Answer drug surveillance form — Centocor, Shering-Plough ; Remicade ®
Viñas ; Capsidol ®
Sanofi-Aventis ; Myolastan ®
Farma-Lepori ; Tantum gel ®
Bayer ; Aspitopic ®
Recordati ; Dalgen spray ®
Vectem ; Mahiou cream ®
(Good Response)

Cutaneous test with active drug and vehicles at recommended concentrations.

Study results report to the Pharmaceutical Company

Chart I. Active principles and exicipients provided by the Pharmaceutical Companies for identify the responsible of the cutaneous adverse reaction.

Product	Active drug	Excipient
Remicade ® Centocor Schering-Plough	Infliximab (I)	Distilled water
Capsidol ® Viñas	Capsaicine / bencyl alcohol 0,075%	Amphisol 10% pet. Isopropyl myristate 10% pet. Estearic acid 10% pet. Propylene glycol 5% pet. Glyceril Monomyristate 10% pet. Cetyl alcohol 10% pet. Benzyl alcohol 2% pet. p-hydroxibenzoate-methylsod 5% pet. p-hydroxibenzoate-propyl 5% vas.
Myolastan ® Sanofi-Aventis	Tetrazepam 0,1%, 0,5%, 1%, 10%, 20%	No provided
Tantum gel ® Farma-Lepori	Benzidamide 0,1%, 1% y 10% pet.	Cetyl alcohol 30% pet. White petrolatum FU Span 60 (Sorbitom TE), 1%,10%,50% pet. Tween 60 (Sorbiton SE) Blicole propilenico FU (Propyilenglicol) 5% ac.
Aspitopic ® Bayer	Etofenamate 0,1%, 1%, 2%, 5% pet.	Triethanolamine 5% pet. Carbopol 0,1%, 1%, 10% y 20% pet.
DalgenSpray ® Recordati	Fepradinol 0,01%, 0,1%, 1%, 5%, 10% pet.	Benzyl alcohol 5% pet. Propilenglicol 5% ac. Fragance,as is. Ethyl alcohol 80% ac. and pet.
Mahiou ® Vectem	Fenoftaleine Vitamin F	Fragance, as is.

RESULTS

The Chart II and the figures 2, 3, 4, 5, show the results of the study by means of cutaneous provocation tests with the complete products, the active principles and the contributed vehicles.

Chard II. Allergen identified as responsible of the cutaneous adverse reaction.

Product	Adeverse event administración	Entire product Positive cutaneous test	Active drug	Positive excipient	Sensitizer
Remicade ® Infliximab	Urticaria I.V.	Positive *Prick Test*	Infliximab *"Prick test ; Positive"*	Negative	Infliximab
Capsidol ® Capsaicine	Eczema *Tópic*	Positive *Patch test*	Capsaicine Patch test and ROAT test *0,075%: Positive*	Negative	Capsaicine
Myolastan ® Tetrazepam	Airborne *Tópic*	Positive *Patch test*	Tetrazepam Patch test 0,5%, 1%, 5%, 10%, *20% pet: Positive*	Negative	Tetrazepam
Tantum gel ® Benzidamide	Photosensibility *Tópic*	Positive *Patch and Photopatch test*	Benzidamide *Photopatch test 10% pet.: Positive*	Tween 60 as is SPAN 60, 50%/10% Photopàtch test	Benzidamide Tween 60 SPAN 60
Aspitopic ® Etofenamato	Contact dermatitis *Tópic*	Positive Patch Test	Etofenamate *Patch test 0,1%, 1%, 2%, 5% pet. : Positive*	Carbopol *Patch test 10% pet*	Etofenamate Carbopol
DalgenSpray ® Fepradinol	Contact dermatitis Topic	Positive *Patch and Photopatch test*	Fepradinol *Match and Photopatch testl 1%, 5% y 10% vas : Positiva*	Negative	Fepradinol
Mahiou ® Fenoftaleine	Contact dermatitis Topic	Positive *Patch test*	Fenoftaleine et Vitamin F *Match test : Negative*	Fragance as is	Perfume

Figure 2. The positivity was observed just with the photopatch test with benzidamide (10% in pet.), Tween 60 and SPAN 60 (50% and 10% in pet.) However, a positive response was obtained with both patch and photopatch test with Tantum gel like whole product.

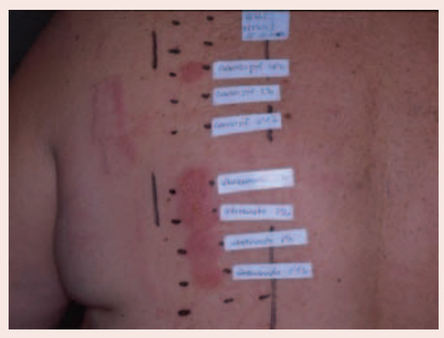

Figure 3.A positive patch test was observed with etofenamate to concentrations superior to 0,1% in pet. as with a component of the Aspitopic vehicles as the carbopol (10% in pet).

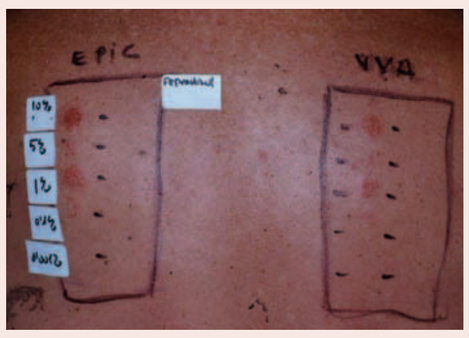

Figure 4. Positivity was observed to patch test and after UVA irradiation with fepradinol (1%, 5% and 10% in pet.) Just as happened when studying the Dalgen whole spray.

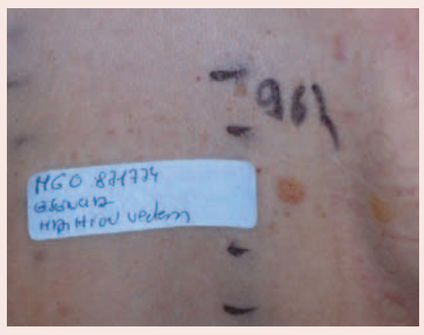

Figure 5. Positivity was observed to the fragrance contained in the cream Mahiou of Vectem. Therefore, the eczema induced in this patient was not for the active drug but for the fragrance included in.

CONCLUSIONS

The collaboration of the pharmaceutical industry to identify the responsible of certain adverse drug reactions shows to be extremely useful. It allows to work with the components that directly have been used in the formulation. Many of these components are difficult to be obtained in the series of marketed patch test. It is necessary to study the active principle and the vehicles to get a complete diagnostic that would allow the patient to avoid the allergen or allergens in other formulations. This excellent collaboration with the pharmaceutical companies has taken us to drive a more active and accurate drug surveillance reporting. Closer relationship between dermatologists and allergologists dedicated to the study of the cutaneous drug adverse events, and the pharma companies shows to be effective and good for best patient care.

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