DOCTOR OF MEDICINE

Photoallergic contact dermatitis in Europe

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Award date:
2012

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2. An occupational outbreak of photoallergy to carprofen

This Chapter describes an outbreak of PACD to the veterinary NSAID carprofen. In doing so, it emphasises the pivotal role of PPT in investigating suspected PACD, and suggests its possible future role in human photosafety testing.

2.1. Introduction

2.1.1 Background

It was the outbreak to TCSA among factory workers in England in the 1960s that first brought PACD as a cause of morbidity to the attention of many dermatologists. The potential for photoallergens to cause outbreaks among well-defined groups of workers was further emphasised by the cases of PACD to quindoxin and olaquindox in farm workers in the 1970s. Therefore, when two employees from the same Dundee factory presented to the Photobiology Unit in 2003 with a photo-exposed site dermatitis, PACD to some agent was carefully considered among the list of differential diagnoses.

2.1.2 Carprofen

Among the pharmaceutical products processed at the factory was the veterinary NSAID carprofen. Its molecular structure is given in Figure 2.1. Carprofen was initially released onto the marketplace for humans under the trade name Imadyl® in 1983.[1] Its main indication was for treating arthritis, and it was marketed as having a preferentially greater inhibitory effect on the enzyme cyclo-oxygenase (Cox) -2 than Cox-1. During the time it was used in humans, phototoxic and photoallergic reactions were reported from Europe and Singapore.[2-5] About ten years after its introduction, it was withdrawn from use as a human medicine in Europe and other

countries for commercial reasons. The precise reasons for this are not entirely clear, but this move may have been precipitated by a concern about adverse effects on the liver.

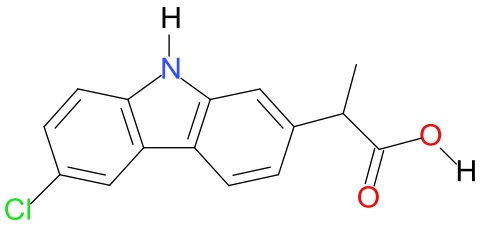

Figure 2.1. The molecular structure of carprofen (6-chloro-alpha-methyl-9H-carbazole-2-acetic acid).

Carprofen was re-launched in 1993 under the trade name Rimadyl® in the U.S.A. as an anti-arthritic for dogs. As in humans, it seems in dogs to be more selective for inhibiting Cox-2 activity rather than Cox-1.[6] As well as being effective for arthritis in dogs, it is used for acute pain relief in cats, cattle and horses.

2.1.3 The Patients

Patient 1: A 42 year old female was referred with itchy, erythematous facial skin. This consistently appeared several hours after she had been at work, where she was involved in the labelling and packaging of carprofen. The problem cleared when she was away from work (on holiday and sick leave due to a limb fracture), but emerged within 72 hours of re-starting work. By the time of presentation, she had left her job at the factory due to her skin problem.

Patient 2: A 47 year old female was referred acutely with a dermatitis which was especially severe on photo-exposed sites (Figure 2.2). Such was the widespread nature of her dermatitis at presentation and its poor response to oral and topical

steroids that she was admitted and nursed in a photo-protected cubicle. She worked in the factory as a secretary, and initially it appeared that she did not apparently come into direct contact with carprofen. However, when it became clear that her dermatitis flared towards the end of each working week, further questioning revealed that she did handle quality control papers, which were possibly contaminated with carprofen, from laboratory personnel.

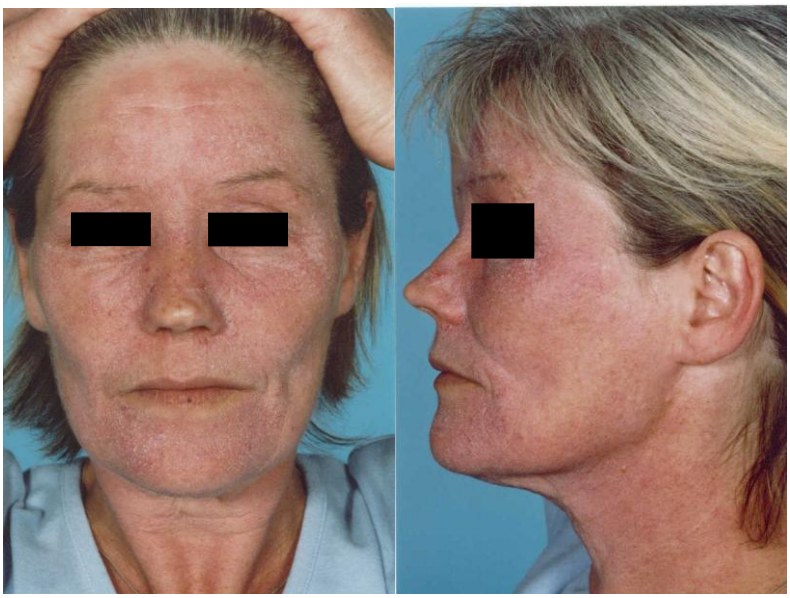

Figure 2.2. Photo-exposed site dermatitis in patient 2.

2.1.4 Objective

The objective of this study was to determine the role of carprofen in both local pharmaceutical factory employees presenting with a photo-exposed site dermatitis by means of PPT.

2.2 Methods

2.2.1 PPT to carprofen

PPT was performed according to the European consensus methodology.[7] At the time of investigation, the cause of the patient's dermatitis was not known and so PPT was performed to the following agents:

1) A series of 11 established and candidate organic sunscreen absorbers plus one commercial sunscreen product ("as is") [8]
2) Piroxicam 0.5% gel (Feldene® gel) "as is"
3) Diclofenac diethylammonium salt gel 1.16% (Voltarol Emulgel®) "as is"
4) Carprofen 2% and 5% in petrolatum and in sterile water

For PPT, approximately 20µl of each agent in petrolatum was applied to an 8mm diameter metal chamber (Finn Chamber®, Epitest Ltd Oy, Tuusula, Finland) mounted on hypoallergenic adhesive tape (Scanpor® tape, Actavis Norway AS, Norgesplaster, Vennesla, Norway). For the carprofen dilutions made up in water, these were applied to a 7mm diameter filter paper disc (20 µL via a pipette) placed in an 8mm diameter metal chamber. The agent photopatches were made up as duplicate sets and then applied to the non-paravertebral skin of the back of subjects. After 24 hours both sets of photopatches were removed and one set was covered with a UV-opaque material whilst the other was irradiated with 5 Jcm^{-2} UVA (vertical bank of 10 Waldmann F15W/T8 tubes; peak emission at 352nm; 99.2% UVA and 0.8% UVB). For irradiation, the subject was placed 20cm from the source sitting with their back in a vertical position, parallel to the middle of the source.

Readings of both sets were made pre-irradiation, immediately post-irradiation and 24 and 48 hours post-irradiation. Readings were also recorded at 72 hours post-

irradiation in patient 1. All reactions seen were graded using the ICDRG visual scoring system.

2.2.2 Rationale for strength of carprofen used

Due to difficulties in obtaining pure carprofen, PPT was initially conducted with powdered carprofen tablets. As above, the carprofen used for PPT was prepared at concentrations of 2% and 5% in both petrolatum and in sterile water suspension. These concentrations and vehicles were selected on the basis of published reports describing PPT with carprofen. Merot and colleagues used 5%, 10% and 20% made up in petrolatum.[5] Another group described using 5% carprofen in petrolatum to photopatch test three patients with "photodermatitis" after oral ingestion of carprofen.[2] That none of these three patients nor 20 controls tested with the same carprofen reacted raised the possibility that this concentration might be too low. However, it also suggested that a 5% or lower carprofen concentration should be safe and unlikely to lead to false positive reactions.

A 1987 German publication that described PPT with carprofen in 86 patients as part of an NSAID series did not report the test concentration used,[4] nor did a case report of a patient with positive carprofen photopatch test reactions.[3] A standard text recommending patch test concentrations for many chemicals suggested a concentration of 10% carprofen in petrolatum.[9] It was decided to test with lower concentrations because of lack of previous experience in the Photobiology Unit in testing with this substance and concerns that a 10% concentration might result in severe reactions and would be more likely to lead to false positive responses.

2.2.3 Control subjects

In addition to the two patients under investigation, three healthy volunteer subjects from within our unit were photopatch tested only to the carprofen concentrations

and vehicles above. The methodology used and timepoints that readings were performed at were the same as for the two patients. The three control subjects had not knowingly been exposed to carprofen previously. The main reason for performing testing in the subjects was to establish if phototoxicity could produce positive results, given the fact that clinicians in the Photobiology Unit were not familiar with carprofen as a PPT agent.

2.3 Results

2.3.1 Initial PPT

In the two patients under investigation, PPT to the series of 11 established and candidate organic sunscreen absorbers plus one commercial sunscreen product ("as is"), piroxicam 0.5% gel (Feldene® gel) and diclofenac diethylammonium salt gel 1.16% (Voltarol Emulgel®) was negative.

No positive reactions to either dilution of carprofen in either vehicle were observed when the patches were removed after 24 hours, or immediately post-irradiation, in either patient. The results of PPT to carprofen in both patients, recorded at 24, 48 and 72 hours post-irradiation are given in Table 2.1.

Patient	24 hours post-irradiation								48 hours post-irradiation								72 hours post-irradiation							
	2% carprofen in pet.		2% carprofen in water		5% carprofen in pet.		5% carprofen in water		2% carprofen in pet.		2% carprofen in water		5% carprofen in pet.		5% carprofen in water		2% carprofen in pet.		2% carprofen in water		5% carprofen in pet.		5% carprofen in water	
	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I
1	-	++	-	++	-	++	-	++	-	+++	-	+++	-	+++	-	+++	-	+++	-	+++	-	+++	-	+++
2	++	+++	++	+++	++	+++	++	+++	++	+++	++	+++	++	+++	++	+++	NR	NR	NR	NR	NR	NR	NR	NR

Table 2.1. The results of PPT to carprofen in patients 1 & 2.

The ICDRG grading of results at 24, 48 and 72 hours post-irradiation is given.

(pet. = petrolatum C = Covered I = Irradiated NR = No Reading performed)

It can be seen from Table 2.1 that patient 1 developed no reactions to carprofen in the covered set, but "++" grade reactions in the irradiated set at 24 hours post-irradiation, which had increased in strength to "+++" grade reactions by 48 and 72 hours post-irradiation. The reactions seen at 72 hours post-irradiation are given in Figure 2.2. The "crescendo" nature of these reactions was consistent with an evolving photoallergic response.

Patient 2 developed "+++" grade reactions to carprofen in the irradiated set at 24 and 48 hours post-irradiation. The reactions seen at 24 hours post-irradiation are given in Figure 2.3. She also developed "++" grade ACD reactions to carprofen in the covered set at the 24 and 48 hour post-irradiation timepoints. The positive reactions observed in the irradiated set were so much stronger than the covered set reactions that the results were interpreted as indicating true PACD in addition to ACD, rather than photoaugmentation of an ACD response. The histology of a skin biopsy taken from a positive reaction to carprofen in the irradiated set in patient 2 showed an exceptionally florid acute dermatitis reaction. The histology from a skin biopsy taken from a positive reaction to carprofen in the covered set demonstrated a much less severe acute dermatitis. The patient's original facial dermatitis was clear at the start of PPT but flared during testing (strengthening the suspicion that the reactions being reproduced on the PPT sites were clinically relevant).

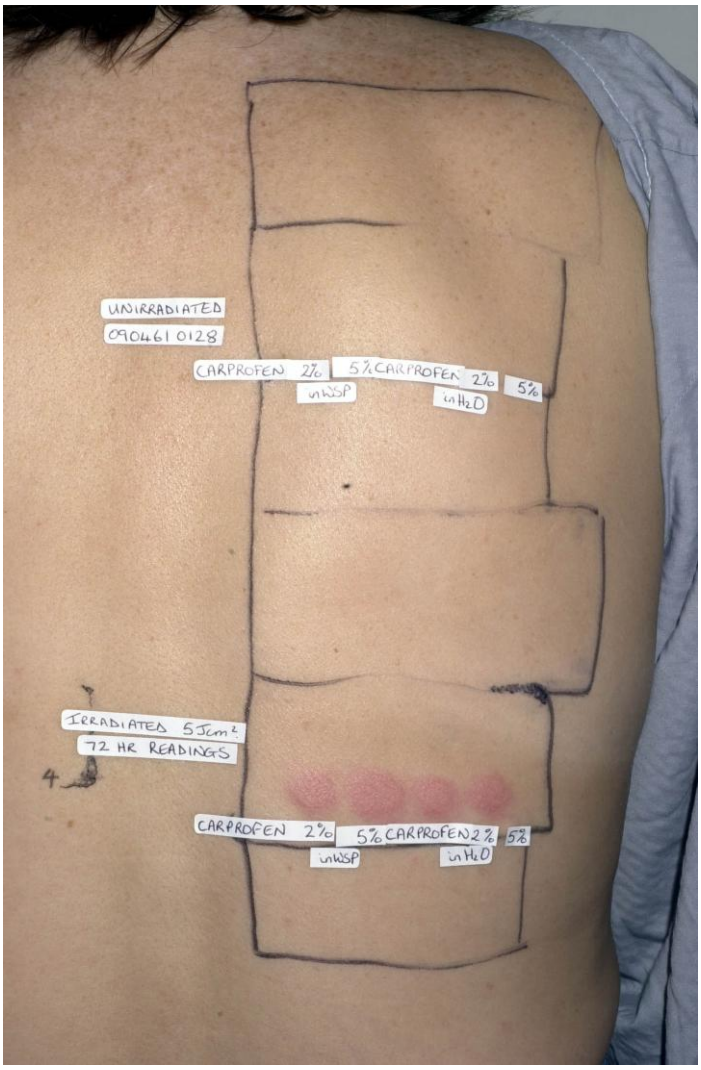

Figure 2.3. Carprofen PPT readings at 72 hours post-irradiation in patient 1.

The ICDRG grade "+++" PACD reactions to 2% & 5% carprofen in petrolatum (white soft paraffin [WSP]) and in water can be seen in the irradiated (lower) set. The covered (upper) set is negative.

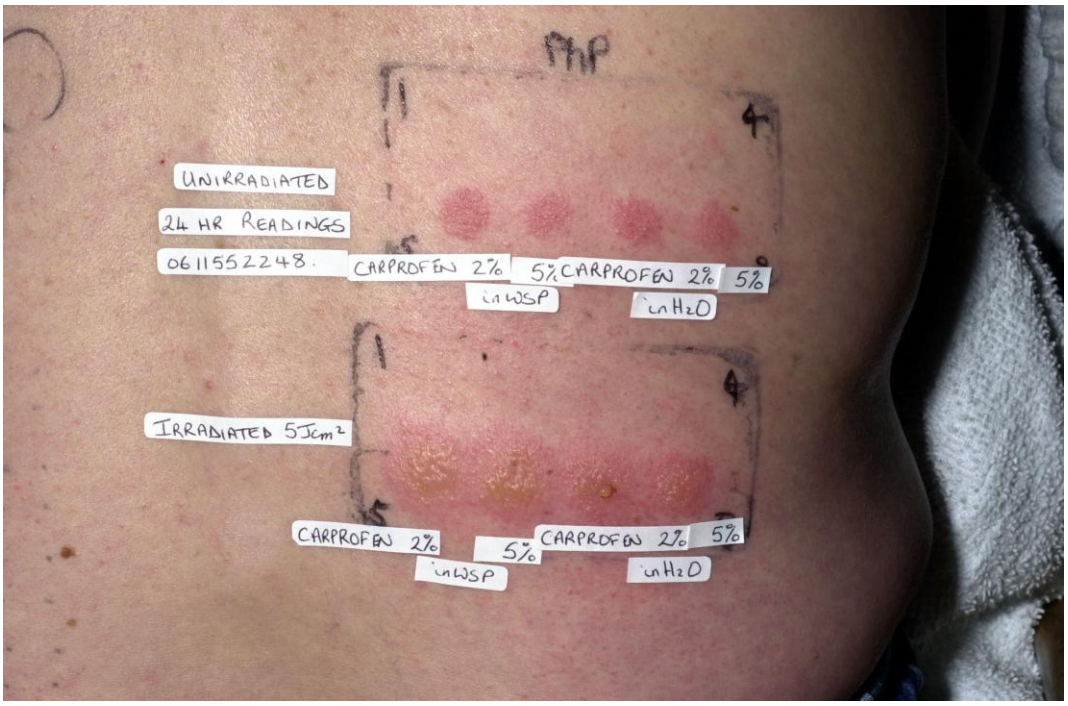

Figure 2.4. Carprofen PPT readings at 24 hours post-irradiation in patient 2.

The ICDRG grade "+++" PACD reactions to 2% & 5% carprofen in petrolatum (WSP) and in water can be seen in the irradiated (lower) set. The covered (upper) set shows less severe ICDRG "++" grade ACD reactions.

2.3.2 Additional PPT

Following the diagnosis of PACD in both patients by performing PPT to carprofen at concentrations of 2% and 5% in petrolatum and water, using 5 Jcm^{-2} UVA for irradiation, further PPT to carprofen was performed. This testing was carried out to determine whether small amounts of visible light and/or fluorescent office lighting could interact with very small amounts of carprofen (all conditions which were present in the factory) to cause PACD. In patient 1, a positive reaction was seen when performing PPT with a 1% concentration of carprofen prepared in water which was subsequently irradiated with visible light (monochromator blue light 47000 $mJcm^{-2}$; 430nm±30nm) instead of UVA.

In patient 2, a positive reaction was seen when performing PPT with a 0.05% concentration of carprofen in petrolatum which was subsequently irradiated with both UVA (PUVA lamp 5 Jcm^{-2}, emission spectrum centered around 365nm) (grade "+++" at 24 hours post-irradiation) and visible light (PUVA lamp covered with transparent film filtering out UVB and UVA, 30 minutes exposure) (grade "++" at 24 hours post-irradiation). These additional tests confirmed that the conditions found in the factory environment could conceivably have led to the PACD reactions seen in patients 1 and 2.

2.3.3 Follow-up of patients 1 & 2

The positive PPT reactions on the skin of the back were slow to settle in both patients. Both reported that the photopatch test sites became red and slightly oedematous again after exposure to sunlight on holiday several months later, following which, chemical leucoderma developed at the sites. The chemical leucoderma persisted for several more months, as given in Figure 2.4.

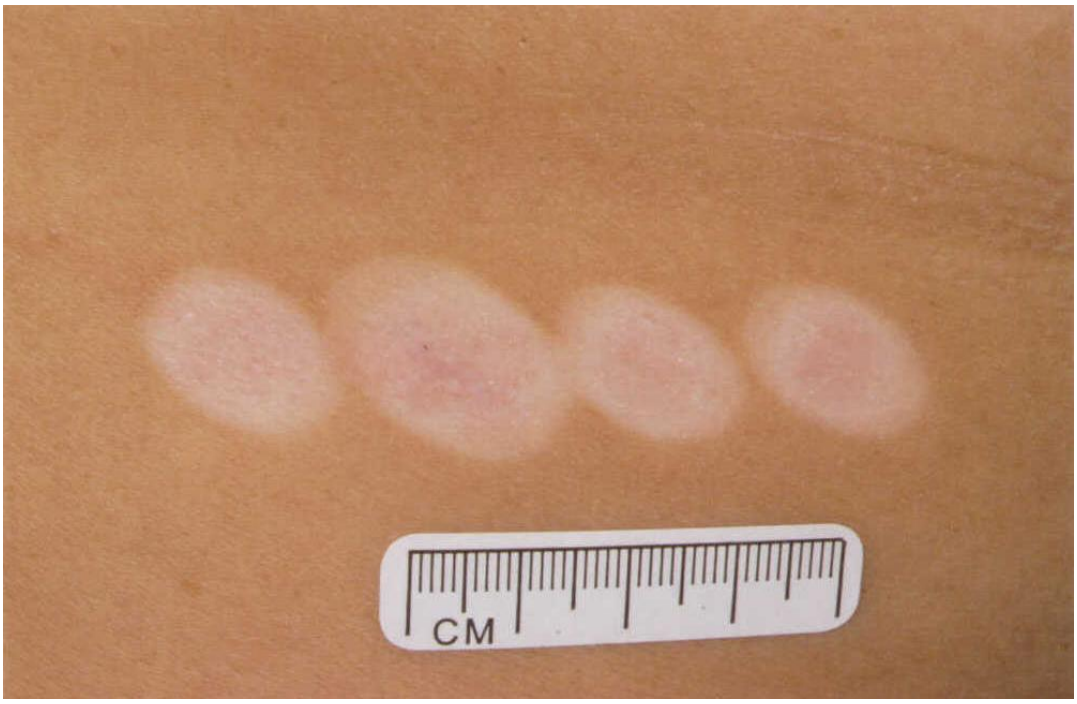

Figure 2.5. Chemical leucoderma in patient 1.

This persisted for 5 months after positive photopatch test reactions on the skin of the back. The central erythema suggests there may possibly be an on-going photoallergic reaction, perhaps due to a “depot” effect of the carprofen or one of its metabolites.

2.3.4 Healthy volunteer controls

In the three healthy volunteer control subjects, PPT to 2% and 5% carprofen in petrolatum and in water was negative at the same timepoints as those recorded in the two patients. The initial intention had been to perform PPT in 20 control subjects. However, a decision was made to discontinue testing in any further control subjects after the development in one of the three controls of a marked delayed (first noticeable 10 days after testing) dermatitis at the irradiated set. This active sensitization is given in Figure 2.5. The delayed time course of this reaction strongly suggested an active photoallergy sensitisation event, i.e. exposure of this individual to a low concentration of carprofen at a small test site plus a low dose of UVA had caused them to develop photoallergy to carprofen.

2.3.5 Visit to the factory

Following the positive PPT results to carprofen, a factory visit was made by personnel from the Photobiology Unit and the potential for extensive dust exposure for some workers was noted. After this time, the Scottish Health and Safety Executive instructed the company operating the factory to arrange Occupational Health Service involvement. As a result, eight further employees were investigated at the Photobiology Unit, of which three were also found to have developed PACD to carprofen. Following these findings, the working conditions in the factory were improved, particularly those relating to dust handling procedures.

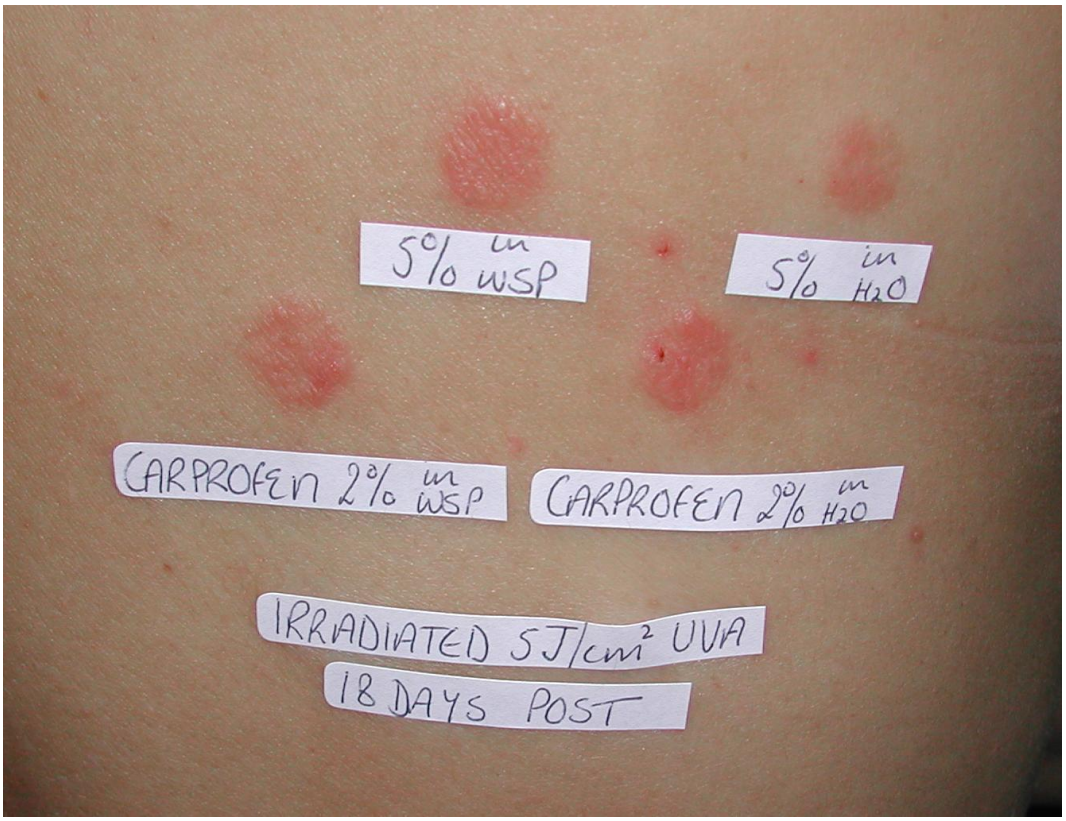

Figure 2.6. Carprofen PPT readings at 18 days post-irradiation in volunteer.

The positive reactions produced by an active sensitization event to 2% & 5% carprofen in petrolatum (WSP) and water (irradiated set) can be seen. The covered set did not show any positive reactions.

2.4 Discussion

The investigation of carprofen in an occupational setting has shown it to be a potent photoallergen. It has the ability to elicit severe PACD reactions in the skin even when present in small quantities, as highlighted by the case of patient 2, who only handled pieces of paper that had been written on by workers handling finished tablets. Further PPT in both cases confirmed that, in addition to UVA, even small amounts of visible light could trigger the response. Its potency was further underlined by the active sensitisation in one of three naïve healthy volunteer subjects.

The investigation findings also indicate there appears to be inter-individual variability in the ability to be sensitised to carprofen, as not all volunteers or factory workers reacted in the same way. The reaction seen at the test sites upon subsequent exposure to sunlight on holiday does lead to the possibility of there being some "depot" effect of carprofen, or a metabolite thereof, in the skin. The later development of chemical leucoderma implies that this second reaction was severe enough to involve other structures within the skin such as melanocytes. A case of leukomelanoderma has been reported previously following topical PACD to ketoprofen, another arylpropionic acid derivative.[10]

There have been two other reports in the literature of PACD to carprofen in pharmaceutical workers in recent years.[11,12] Additionally, the investigation of the two patients and three volunteer controls in the Photobiology Unit stimulated subsequent *in vitro* work, which has shown that the combination of UVA plus carprofen is able to produce potentially carcinogenic DNA photoproducts.[13] Therefore continuing to minimise exposure of the skin to this agent among workers in the pharmaceutical industry will be of significant importance.

Carprofen is one of the arylpropionic acid derivatives, which include the other NSAIDs ketoprofen, naproxen and ibuprofen. Among the NSAIDs, this group are the most commonly reported cause of PACD and ACD, with ketoprofen being a particularly commonly reported cause of PACD.[14,15] As discussed in Chapter 1, cross-reactions between the benzophenone-like moiety-containing arylpropionic acid derivatives ketoprofen and tiaprofenic acid have been reported.[16] However, there have been no reported cross-reactions between the arylpropionic acid derivatives and piroxicam or diclofenac, which was also the case in both these patients investigated in the Photobiology Unit.

The result of testing in both patients further underlines the importance of PPT as an investigation in cases with a photo-exposed site dermatitis. It would not have been possible to diagnose PACD through other means and both cases would likely otherwise have been diagnosed as having "dermatitis of unknown aetiology." For other clinicians investigating cases of possible PACD to carprofen, the methodology described above could be used as guidance. Using a concentration of 1% carprofen, made up in both petrolatum and in water would seem a logical starting test concentration, with this being increased to 2% and 5% in the absence of positive reactions if clinical suspicion remained high. The ongoing widespread use of carprofen by pet owners suggests that there may be cases of PACD which have not yet presented to dermatologists or been accurately diagnosed. However, carprofen is not the only molecule capable of causing photoallergy and the investigation of these cases raises the possibility that there may be many more as yet unrecognised photoallergens present in the everyday human environment.

The findings also serve to highlight how relevant PPT performed in humans is for detecting photoallergens. It would seem the logical choice for pre-market

photosafety testing of pharmaceutical and cosmetic agents. In the case of carprofen, its potency was inferred by the active sensitisation of healthy volunteer controls. However, a more useful method would be to perform repeat human PPT, with a fixed intervening time period allowing sensitisation to occur and then be elicited in susceptible individuals. As outlined in Chapter 1, human testing may become the standard method employed when a European ban on cosmetic products which have been tested in animals, planned for 2013, comes into force.

The following Chapter illustrates the investigation of another suspected photoallergen, chlorproethazine. Like carprofen, chlorproethazine is not a common cause of PACD and the methodology described could also be used as a template for future clinicians suspicious of PACD to this agent. Also like carprofen, the story of its investigation provides further support for the adoption of human PPT in photosafety testing.

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