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Photoallergic contact dermatitis in Europe

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Photoallergic contact dermatitis in Europe

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9. Conclusions and Future Directions

The properties of several photoallergens of clinical relevance in Europe have been elucidated in the preceding Chapters. Likewise, the process of PPT and its role in investigating these agents has also been examined. This Chapter draws some final conclusions and recommendations arising from the information presented within each of the preceding Chapters, as well as suggesting possible areas for future study.

Chapter 1. Introduction

- Several photoallergens of historical interest and clinical relevance were reviewed. Despite the emergence of newer culprit agents with time, many of these older agents have continued to be included in local PPT series in recent years. The reticence of clinicians in relevant societies to remove such agents has inevitably slowed down the necessary process of updating test series according to changes in prevalent photoallergens. In future, there should be less reluctance to remove agents that have been in declining usage and those which have been prohibited by regulatory authorities.
- The mechanisms of PACD were reviewed, and notably, much of the earlier work was conducted using the potent photoallergen TCSA as the investigative agent. It is apparent that the precise events occurring at a molecular level during PACD are still not defined. However, PACD has a relatively low incidence in the population compared with other skin conditions and is usually a self-limiting event, with avoidance of the culprit agent leading to resolution of the clinical problem. For these reasons, it seems unlikely that a large amount

of sustained laboratory work will be conducted in this area in the future. If such research is undertaken, the findings of the EMCPTS in Chapter 6 suggest that perhaps ketoprofen may be an agent of current relevance with high potency which could replace TCSA in ongoing investigative work.

- The concept of agents administered via systemic routes leading to PACD has persisted through intermittent case reporting in the literature. In some instances, this has also led to confusion about the relationship and role of PPT as an investigation. Work disseminated from the Photobiology Unit in Dundee has attempted to more clearly define this relationship. It seems likely that extensive study in this area may be difficult given the sporadic nature of such cases. However, conducting prospective PPT studies using agents normally administered systemically in larger numbers of possible cases would provide useful data regarding the role of PPT. The value of doing so would be augmented if concomitant monochromator phototesting and histological evaluation of positive reactions was performed, followed by repeat monochromator studies off the agent. This would help to determine the relative roles of phototoxicity and photoallergy in such cases.

Chapter 2. An occupational outbreak of photoallergy to carprofen

- The investigation of the NSAID carprofen highlighted that cases of photoallergy can occur to agents not normally used in humans. The emergence of reports of PACD from other centres means that in future, clinicians should be vigilant about investigating possible cases of carprofen photoallergy in pet owners and pharmaceutical factory workers. Although carprofen was excluded from either European PPT series' after the 2012 Amsterdam workshop

meeting, the concentrations and vehicles detailed in this Chapter could be used to guide clinicians investigating other possible cases of photoallergy to carprofen. Of greater overall importance, the findings of the Chapter demonstrate that clinicians should continue to be alert to the possibility of any “new” photoallergens arising in the environment and investigate these by means of PPT agents “as is” if appropriate.

- The investigation of carprofen by means of human PPT also demonstrated the clinical relevance of this methodology in detecting a potent photoallergen. As discussed, a ban on animal testing in Europe in the near future will require the issue of performing photosafety testing in humans to be re-examined. It would seem preferable to incorporate this method rather than the non-validated animal models in use, which have variable sensitivity and specificity for predicting PACD in humans. In particular, human volunteer PPT with re-challenge would seem the best option when screening for potent photosensitisers prior to their release onto the marketplace. Although such a system may sensitise a small number of volunteer subjects, it could avoid mass exposure of the public to such agents.

Chapter 3. Chlorproethazine: a second photoallergen on the marketplace

- The investigation of CPE provided further evidence in favour of using human PPT as a screening tool in photosafety testing in future. Like carprofen, the concentrations and vehicles used for PPT could be used by clinicians as a template for investigating rare, sporadic cases of possible photoallergy to CPE in individuals.

- The investigation findings support the decision by French regulatory authorities to withdraw CPE from the marketplace. As such, it has now joined other agents which are only of historical interest and relevance and, like carprofen, it was also excluded from either European PPT series' after the 2012 Amsterdam workshop meeting.
- It was the question of including CPE in the EMCPPPTS series that led to its initial investigation in the Photobiology Unit, but this was not deemed appropriate because it was found to have the ability to cause both photoallergy and phototoxicity. The PPT methodology used suggests that some agents possessing this property may require lower doses of UVA for irradiation, a concept that clinicians should be aware of.

Chapter 4. A pilot irritancy study of organic ultraviolet absorbers

- The pilot irritancy study was the first study in the open literature to address the problem of determining the optimum concentration of 19 organic UV absorbers for PPT. It seems likely that for most agents, a concentration of 10% allows increased sensitivity, yet is safe, which was further supported by the low number of IRs seen in the EMCPPPTS. To determine more accurately the "real life" optimum PPT concentrations, future similar but larger studies including subjects with problems commonly seen in the clinic e.g. a photodermatosis or history of reacting to sunscreens, could be performed. A similar study using topical NSAID concentrations would also be of value, particularly given the number of weak but unknown relevance etofenamate reactions seen in the EMCPPPTS.

- The agent methylene *bis*-benzotriazolyl tetramethylbutylphenol led to a significant number of reactions, but not in a dose-dependent manner. The subsequent finding that it was the agent most frequently leading to ACD in the EMCPPPTS is also of interest. Future patch and/or photopatch test studies including this agent and the added surfactant decyl glucoside will need to be conducted to determine the role of each.

Chapter 5. A survey of the availability of sunscreen absorbers in the UK

- The UK sunscreen survey provided a surrogate measure of possible exposure patterns to organic UV absorbers, allowing more meaningful interpretation of the EMCPPPTS. In the future, further sunscreen surveys could be episodically performed for similar reasons, and their usefulness could be increased by extending them to multiple sites. However, from a regulatory viewpoint, the preferable situation would be the construction of a Europe-wide database containing usage quantities and sales figures of agents from information provided by sunscreen manufacturers. This could also be undertaken for topical NSAIDs. Such databases would enable regulatory authorities to make more informed decisions about an agent's likely photoallergenic potential when faced with reports of PACD and ACD in the open literature.
- A similar study, examining cosmetic products which are not marketed as sunscreens e.g. moisturising creams and shampoos, could be performed. This would help in determining possible exposure patterns to other organic UV absorbers less frequently used in sunscreens, such as benzophenone-4 and benzophenone-10.

Chapter 6. The EMCPPPTS

- The EMCPPPTS was the first prospective PPT study which incorporated the nine “newer” organic UV absorbers listed in Annex VII. These were shown to lead to PACD and ACD relatively infrequently, which is very important information for sunscreen manufacturers and users, as well as clinicians conducting PPT.
- The EMCPPPTS results revealed that the topical NSAID ketoprofen led to a much higher number of PACD reactions than other agents, suggesting it may be a particularly potent photoallergen. This lends support to the attempts of some within France to have ketoprofen withdrawn from the marketplace not only there, but also from Europe as a whole. The other topical NSAIDs ibuprofen, diclofenac and piroxicam led to far fewer PACD reactions and would seem preferable alternatives for use in Europe in the future.
- The association found between the three agents ketoprofen, benzophenone-3 and octocrylene highlighted that cross-reactions can occur when conducting PPT. The mechanisms of cross-reactivity are not well understood and future collaborative studies between clinicians and chemists are needed. In the case of octocrylene, possible cross-reactivity to ketoprofen has not only clinical relevance for sunscreen users, but also financial implications for sunscreen manufacturers.
- The topical NSAID etofenamate was found to be the agent leading to PACD in the second highest amount of subjects, although many of these reactions were assigned as having unknown relevance. Future studies would be helpful in more clearly determining the photoallergic and phototoxic potential of this agent.

- The issue of determining the true photoallergenic potential of any agent studied using PPT will rely on exposure patterns, a theme emphasised throughout Chapters 5 and 6. However, the methodology used in the EMCPTS offers scope to provide further information on this potential via an alternative future study, in which subjects who did not react to an agent could be invited to return for further PPT to that agent to determine how many had become sensitised. This would be particularly interesting for ketoprofen, given the suspicions regarding its possible high photoallergenic potential.
- The literature reveals that there has been a gradual but progressive move towards standardising the methodology of PPT, a process aided and supported by conducting the EMCPTS. However, for some steps of the process, there remains a lack of good scientific evidence as to the best option to use. Firstly, further studies into the duration of photopatch application would be justified by the findings of the EMCPTS. Secondly, when the wavelengths used for irradiation are considered, the evidence in Chapter 1 illustrates that for most agents of current relevance the action spectrum for photoallergy has not yet been clearly defined. Future work could endeavour to determine the action spectra of more clinically relevant agents, by means of performing PPT using monochromatic sources in previously sensitised subjects.

Chapter 7. Conducting the EMCPTS

- The issues around conducting the EMCPTS were explored and the difficulties entailed for a single coordinator were affirmed. In particular, the current systems in place for obtaining approval to conduct clinical research from the various regulatory bodies in the UK seem to be overly complex and often

redundant. It seems probable that such systems are likely to continue to deter many clinicians in the UK from attempting to conduct research. Future measures should aim to simplify and streamline such processes.

- It seems likely that for future multi-centre PPT studies to be repeated from the UK, more than one primary coordinator may be required. This would allow approval with UK regulation to be obtained, as well as travel to other European sites to facilitate their regulatory compliance and subject recruitment.

Chapter 8. A new European Baseline photopatch test series

- The process of deciding upon a new European Baseline photopatch test series using a workshop methodology was outlined. A new European photopatch test series composed of 20 agents of current clinical relevance was presented, as was an “additional” commercially available series composed of 15 agents. Although these series should allow clinicians to deliver real benefits to patients, they will require ongoing scrutiny and continual updating in the future.