The Use of Diphenylcyclopropenone in the Treatment of Recalcitrant Warts

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Abstract

Background: The treatment of recalcitrant palmoplantar and periungual warts using topical immunotherapy with diphenylcyclopropenone (DPC) was reviewed retrospectively over a seven-year period.

Methods: Two hundred eleven patients were sensitized during this time. The patients consisted of 90 males and 121 females and were between 5 and 78 years old. Twenty-three patients were lost to followup. Of the remaining, 4 were undergoing treatment at the time of evaluation, 1 patient failed sensitization, and 1 patient became pregnant. Four discontinued because of side effects, 3 because of financial reasons, and 18 patients discontinued treatment prior to completing the minimum required applications (defined as 6), producing a dropout rate of 12% (25/211). Three patients had additional treatment during the course of DPC and were not included in the study. The remaining 154 patients were classified as nonresponders or responders.

Results: The responders consisted of 135 individuals (87.7%) that had complete clearance of warts. Reported adverse effects were local and included with pruritus (15.6%), with blistering (7.1%), and with eczematous reactions (14.2%). The majority of the patients tolerated the treatment very well. One patient developed local impetigo. Patients had an average of 5 treatments over a 6-month period.

Conclusions: Topical immunotherapy using DPC is an effective treatment option for recalcitrant warts. It should be considered as first-line treatment for warts based on its high response rate, absence of scarring, and painless application.

Antécédents: Une étude rétrospective de 7 ans a été effectuée sur le traitement immunosuppresseur topique Diphénylcyclopropénone des verrues palmo-plantaires et périunguéaleuses récalcitrantes.

Objectif et méthodes: Deux-cent onze patients, 90 hommes et 121 femmes âgés de 5 à 78 ans, ont été sensibilisés. On n'a pas pu assurer le suivi de 23 patients. Parmi les patients restants, 4 suivaient un traitement au moment de l'évaluation, 1 patient n'a pas réagi à la sensibilisation et 1 patiente est tombée enceinte. Quatre patients ont arrêté à cause des effets secondaires, 3 patients pour des raisons financiéres et 18 patients ont arrêté le traitement avant d'avoir complété les applications minimales requises (soit six applications), pour un taux d'abandon de 12% (25/211). Trois patients ont reçu d'autres traitements en plus de Diphénylcyclopropénone et n'ont pas été inclus dans l'étude. Les 154 patients qui restent ont été classés comme sujets répondants et sujets non répondants.

Résultats: Le groupe des répondants compte les 135 personnes (87,7%) complétement guéries des verrues. Les effets indésirables rapportés étaient localisés et comprenaient le prurit (15,6%), des ampoules (7,1%) et des réactions eczémateuses (14,2%). La majorité des patients on très bien toléré le traitement. Un seul patient a développé un impétigo localisé. En moyenne, les patients ont reçu 5 traitements pendant une période de 6 mois.

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Conclusion: Le traitement immunosuppresseur topique au Diphénylcyclopropénone est efficace contre les verrues récalcitrantes. Il doit être envisagé comme un traitement de première ligne contre les verrues, vu le taux élevé de réussite, l'absence de cicatrices et l'application indolore.

The treatment of warts is a common clinical problem for both the primary care physician and the dermatologist. There are many different treatment modalities for warts, including physical destruction (cryotherapy, surgical removal, carbon dioxide laser), chemical destruction (salicylic acid, glutaraldehyde, podophyllin, cantharidin, bleomycin), and immunomodulation (interferons, retinoids, contact immunotherapy). In addition, there is always the option of watchful waiting and spontaneous resolution. Despite the wide variety of therapeutic options, no one treatment modality is consistently effective in every case. In 1973 Lewis[1] was the first to report the use of dinitrochlorobenzene as a contact allergen to treat resistant warts. Other immunomodulators available include squaric acid dibutlyester and imiquimod. Our study examines the use of the contact immunotherapy agent diphenylcyclopropenone (DPC) in the treatment of recalcitrant palmoplantar warts.

Methods

The use of DPC at the University of Alberta Dermatology Clinic involved sensitizing patients with 2% DPC powder mixed in petrolatum ointment. When not in use, the DPC mixture was stored in the refrigerator in lightproof containers to prevent photodegradation. As a routine, the DPC was replaced every 3 months. To sensitize the patient, DPC was applied to the left medial arm skin within a 1 cm Finn Chamber® (Epitest Ltd. Oy, Tuusula, Finland). Patients were instructed to wash the area after 6 hours. A medium strength topical steroid was given to be used as needed.

The sensitization site was checked in three weeks and if the reaction (erythema/eczema) was <1cm, then the patient was resensitized with 2% DPC. A normal expected test site reaction was 1–1.5 cm. Larger reactions or a vesicular reaction indicated increased sensitivity to the therapy and DPC treatment began at 0.5%. If the erythema was >1 cm, then treatment began with a extremely thin layer of 1% DPC applied directly to the wart with occlusion. The area was covered with paper tape, plus Band-Aids and conforming tape (Medipore™, 3M, St. Paul, MN) tape were placed overtop to prevent autoeczematization. Again the patient was instructed to wash the area with soap and water after 6 hours. The patient returned to the clinic for treatment every three weeks. The sequence of cream strength was 1%, 2%, up to 4%. The concentration was increased or decreased to maintain a good clinical response with minimal side effects. A prescription for a nonsedating antihistamine was given if needed to control pruritus.

Hyperkeratotic plantar lesions were pretreated by paring and 3–5 seconds of liquid nitrogen spray cryotherapy. This was thought to aid in the penetration of DPC by producing a minimal amount of edema. If there was no clinical improvement in the warts after 3 treatments at 4%, the DPC was discontinued. Cure was defined as no clinical evidence of warts one month after stopping therapy. All treatments were carried out in a dermatology clinic under the direct supervision of a dermatologist. Compliance was considered satisfactory if patients generally kept their appointments.

Results

A retrospective review was performed from November 1992 to September 1999, during which time 211 patients were sensitized. Patients were included in the study if they had tried previous treatment modalities without satisfactory results. In addition, it was required that patients have at least 6 treatments of DPC. Patients were excluded from DPC treatment if they were pregnant. In this study facial and perianal warts were not treated.

Of the 211 patients sensitized, 23 patients were lost to followup. At the time of evaluation, 4 were still undergoing treatment and 1 withdrew because she became pregnant. Three dropped out for financial reasons and 4 discontinued treatment because of side effects, including pruritus, eczema, and a vesicular reaction. Eighteen patients did not fulfill the requirement of 6 minimum treatments. These patients were unavailable for comment on reasons of discontinuation. Calculated dropout rate was therefore 12% (25/211). Three patients had additional treatment modalities during the course of DPC and 1 patient failed sensitization. This patient was a 41-year-old male of good general health. He had 20–30 warts on the dorsum of both hands. Sensitization was attempted 3 times.

There were 154 patients 68 male and 86 female that were included for analysis from the original 211. These patients were classified as either responders or nonresponders. The 135 responders ranged in age from 5 to 67 years (mean 24.6 years). Their warts included 38 palmer, 70 plantar, and 27 palmoplantar. One patient was immunosuppressed. This patient was a 17-year-old female renal transplant patient on cylclosporin and prednisone. She had 15–25 periungual warts that resolved with 6 treatments over 7 months. The 19 nonresponders were 15–78 years old (mean 36.1 years) and had 5 palmer, 11 plantar, and 3 palmoplantar warts. Patients had an average of 5 treatments (range: 1–35) over 6 months (range: 1–47). The cure rate for this study was 135/154 (87.7%).

TABLE I

Comparison of studies using diphenycyclopropenone

Author	*Number of patients*	*Wart type*	*Number of treatments*	*% of DPC*	*% Cure*	*% S/E*
Wiesner–Menzel[22]	8	Plantar	8–12	1.0–3.0	75	12.5
Lane[19]	10	Palmoplantar	?	0.1–1.0	50	20
Naylor[21]	45	Palmoplantar, genital	?	0.01–1.0	62	49
Orecchia[18]	44	Palmo plantar, face	3–10	0.2–2.0	45	25
Rampen[20]	111	Palmoplantar	8	0.001–3.0	60	4.3
Buckley[23]	48	Palmoplantar	1–22	0.01–6.0	88	56
Present study	154	Palmoplantar	1–35	1.0–4.0	88	37

The side effects of DPC treatment were all local to the site of application and included pruritus (15.6%), 1–2-cm eczematous reaction (14.2%), and blistering (7.1%). One patient developed local impetigo. No patients developed distal reactions.

Conclusion

The mechanism involved in contact immunotherapy is believed to be induction of a type IV hypersensitivity reaction. The contact agent hatpen is believed to be bound to protein of viral or human origin.[2,3] The Langerhan cells function as the site of antigen formation and are responsible for presentation to regional lymph node.[4] This develops into a successful Th 1 immune response mediated by cytokines, including TNF-β, IFN-γ, IL-12, as well as keratinocyte-derived IL-1α, and IL-1β and TNF-α.[5] The nature of the immune response induced by chemical allergens is essentially no different from that which characterizes protective immunity.[5] It is hypothesized that by allowing this reaction to occur at the site of cutaneous infection with human papillomavirus (HPV), the immune system is directed to and destroys the virus-infected cells thereby producing indirect antiviral activity. Whether this antiwart activity produces any long-term immunity to HPV by this therapy remains unknown.

For immunotherapy to be effective in the clinical setting the compound used must be readily available, able to sensitize at least 95% of the normal population, chemically stable, and economical. It must also be free of significant adverse effects and not found in the human environment to a large extent.

A comparison of the agents currently available shows that they are all readily available, potent sensitizers, and economical. Dinitrochlorobenzene (DNCB) is mutagenic in the Ames test,[6–8] while squaric acid dibutylester (SADBE)[6] and diphenylcyclopropenone (DPC)[9] are nonmutagenic. DNCB is a stable compound, whereas SADBE and DPC require refrigeration and storage in the dark, respectively, to prevent degradation.[9,10]

Before comparing the cure rates of the available agents, it is necessary to consider the natural history of warts. In a two-year period, two-thirds of baseline warts will resolve spontaneously without any therapeutic interventions. New lesions may continue to develop during this time.[11] The cure rates of DNCB vary from 69% to 91%,[12–14] while those of SADBE vary from 60% to 86%.[15–17] DPC has cure rates ranging from 45% to 88%.[18–23] The cure rates using immunotherapy reflect clearance of all warts. The studies using DPC varied in terms of the type of warts treated, number of treatments, and the percent of DPC used (Table I). Studies by Lane[19] and Naylo[21] allowed for self-application of DPC at home vs. clinic treatment.

Topical immunotherapy is effective in the treatment of recalcitrant warts. DPC is particularly suited for plantar, palmer, periungual, and digital warts. Immunotherapy with DPC is not painful and is less destructive than most other treatments for warts. Other benefits from immunotherapy include the fact that several lesions can be treated simultaneously, and treatment is not expensive for the patient or time-consuming for the physician. For these reasons, DPC should be considered as first-line treatment for initial presentation of warts.

DPC should be used in a controlled clinical setting based on the potential for side effects. Patients may inadvertently spread DPC from the application site to normal skin if the area is not well occluded. For this reason DPC application was not allowed at home.

Thus far, this is the largest followup series of wart patients treated with DPC. Our cure rate of 87.7% demonstrates that DPC is an excellent option for recalcitrant warts and should be considered during initial treatment options. The number of patients who experienced side effects was minimal. Pruritus was well controlled with a nonsedating antihistamine, while eczematous reactions responded to topical steroid treatment. The majority of the patients tolerated the treatment very well. Treatment should be limited to the clinical setting and patients need to be motivated to attend sequential applications to ensure resolution.

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