Diphencyprone in the Management of Refractory Palmoplantar and Periungual Warts: An Open Study

**Abstract**

**Background:** Induction of delayed-type hypersensitivity has recently been introduced for resistant viral warts. The method is not painful and less destructive than most other modalities. **Objective:** We assessed the efficacy of topical diphencyprone (diphenylcyclopropenone) treatment for recalcitrant warts. **Methods:** From September 1988 to June 1995, 134 patients with periungual and/or palmoplantar warts were entered into the study. Eight weekly applications were delivered. **Results:** The scheduled treatment course and follow-up were completed by 111 patients. There were 49 complete and 18 partial remissions. The rate of positive responders (60%) compares with the results published by other authors. **Conclusion:** Diphencyprone is an effective treatment for resistant warts, especially in palmoplantar and periungual locations.

Contact immunotherapy for resistant warts has been used since 1973 when Lewis [1] reported promising results with dinitrochlorobenzene. Later, Wiesner-Menzel and Happle [2] introduced diphenylcyclopropenone (diphencyprone) for this purpose. Encouraging cure rates have been published [3–5]. We studied the effect of diphencyprone in 134 patients with refractory palmoplantar and periungual warts.

**Patients and Methods**

From September 1988 to June 1995, 134 patients with resistant warts participated in an open study of topical diphencyprone at the Department of Dermatology of the Sint Anna Hospital in Oss, The Netherlands. The patients comprised 53 males and 81 females, and were between 15 and 71 years of age. All but 8 patients had been treated previously with curettage, cryotherapy, electrosurgery and/or keratolytics, without satisfactory result. The majority of patients had had their warts for over 1 year.

Patients were sensitized on the right upper arm with a 1% or 3% diphencyprone solution. If after 2 weeks no sensitization had occurred, diphencyprone was reapplied to the test site. When sensitization had occurred, a diphencyprone solution of 0.1–3% was applied to the warts. Depending on the severity of the inflammatory reaction, a stronger or weaker solution was used at subsequent visits. The sequence of concentrations used was 0.001, 0.003, 0.01, 0.03, 0.1, 0.3, and 3%.

Treatments were carried out once a week for 8 weeks. Irrespective of the response, applications were then discontinued. Patients were followed after 2 and 4 months. Responses were defined as complete remission, partial remission (at least 50% overall regression) and no response (less than 50% regression, stable disease or progression).

Only patients over 15 years of age were included. Informed consent was obtained. For those 15–18 years of age, also the parents gave consent.
Table 1. Treatment results (percentage in parentheses)

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<tr>
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<th>At end of treatment schedule</th>
<th>After 4 months of follow-up</th>
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<tbody>
<tr>
<td>No response</td>
<td>47 (42)</td>
<td>44 (39)</td>
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<tr>
<td>Partial remission</td>
<td>55 (50)</td>
<td>18 (16)</td>
</tr>
<tr>
<td>Complete remission</td>
<td>9 (8)</td>
<td>49 (44)</td>
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</table>

One-hundred-thirty-four patients were selected for the study. Of these, 11 were excluded for various reasons: unable to sensitize (2), spontaneous resolution of warts before first treatment (3), protocol violation (4) and misdiagnosis (2). Eleven patients did not complete the entire treatment series of 8 weekly applications for the following reasons: severe allergic reactions (5), disappointment in treatment results (5) or unknown reason (1). Thus 112 cases remained for evaluation. The follow-up at 2 and 4 months was nearly complete (111/112; 99%).

Results

At the end of the treatment period, only 9 patients of the 8-week schedule showed a complete remission. In 3 of them, treatment was discontinued before the end of the treatment scheme, after 2, 5 and 6 applications, respectively, because of complete involution of the warts. Partial remissions were encountered in 55 patients.

During the follow-up period, the number of complete remissions increased to 49. Partial remissions were seen in 18 cases. Sixteen patients with incomplete remission of their warts after 2-month follow-up experienced complete remission after 4 months of follow-up.

The overall response rate (partial and complete remissions combined) at the end of the investigation was 60% (67/111). Table 1 shows an overview of our findings.

Side effects were not a problem in the majority of patients. Adverse effects included unusually severe reactions at the sensitization site or at the treatment site, or spreading of contact eczema to other parts of the body.

We also studied risk markers for the outcome of diphencyprone treatment. No statistically significant differences were observed when comparing subsets of patients according to gender, persistence of warts before entering the study, site and number of warts or severity of eczematous reactions at the sensitization and treatment sites. Only age of the patient had an effect on the remission rate. In those younger than 25 years, there were 44/59 remissions (75%) versus 23/52 (44%) in those 25 years or older (p = 0.001, \( \chi^2 \) test).

Discussion

Preliminary results of the treatment of 53 of these patients have been reported previously [6]. The present extended series confirms our earlier findings. The herein reported results compare with other studies so far [2–5]. Diphencyprone appears to be an excellent modality to treat refractory warts. The method is not painful and less destructive than most other wart treatments. Diphencyprone is chemically stable when stored in dark bottles, has no serious side effects, is not mutagenic in the Ames test and is economical. Treatment, however, is time consuming.

The exact mode of action of diphencyprone treatment is unknown. Contact immunotherapy may work by the induction of a delayed-type hypersensitivity reaction. The immunological mechanism is probably a nonspecific cell-mediated immune response, triggering virus-infected cell lysis and death.

Thus far, this is the largest follow-up series of wart patients treated with diphencyprone. Worthy of note is the observation, not mentioned in earlier reports, that many patients who exhibit partial involution of their warts at the end of the 8-week schedule notice further regression during the months thereafter. This may have important implications with regard to the treatment period and the frequency of applications. From our experience we have now modified the treatment course for our patients. Weekly applications for 10 weeks are scheduled. If the warts disappear entirely within 10 weeks, treatment is discontinued. In case of no regression at all, treatment is also ceased. If partial regression is noticed, treatments are continued at fortnightly intervals for another 8 weeks. This treatment regimen is slightly more elaborate than the one used in this study but promises to be more yielding.

Naylor et al. [3] used daily treatments carried out by the patients themselves. Like Orechcia et al. [4], we did not allow patients to apply diphencyprone at home. We regard weekly applications as sufficient. Any delayed-type hypersensitivity reaction will have its zenith within 24–72 h and will last for at least 1 week.

Diphencyprone is an experimental drug. It is not commercially available. Patients must be properly informed and consent must be obtained. So far, no untoward long-term effects have been reported. Diphencyprone seems to be a safe and appropriate addition to our armament against recalcitrant viral warts.
References


N E R V A L ' s  D I A R Y

Le voyageur enthousiaste observe ...

Island of Kos – The place of Hippocrates, venue of the 35th Congress of the International Society for the History of Medicine (ISHM), September 2–8, 1996

μη βλέπτειν – nil nocere

The oldest and central dogma of our profession is said to have originated here – an appropriate setting for this meeting which celebrates the 75th anniversary of the ISHM’s foundation. Originally planned for 1914, the foundation had to await the end of the First World War in Europe to be established. Today it comprises the representatives of 64 countries, altogether some 700 odd members; attendees of 49 countries made it to Kos.

Kos – an island in the sun, an amiable and amicable place, harboring the so-called plane tree of Hippocrates, the Asklepieion and many more witnesses of the ancient world. All lovingly preserved by the Greeks. But due to the nature and the history of the ISHM, a meeting not without innate problems, seen at least by a clinician who is accustomed to the American type of razor-sharp guidelines for congress programs and their setting into practice, the up-to-the-minute schedules, the one-language uniformity and efficiency.

National heritages must be preserved and recently I have engaged myself in stimulating readership of the Annales and the Huitanta. International congresses must have but one language otherwise communication is impeded, and exchange across (speech) borders is what international congresses are all about. The same principles apply to an international journal, e.g. the ISHM’s newly launched (and beautiful) Vessalina. Painful as it may be, some historical ballast will have to be dropped. The ISHM will have to learn this lesson or remain in the shadow of its competitors. And otherwise? I have not been on a beach in the South of Europe for quite a time because of my complexion (phototype I). I am stunned to see how little our message of sensible sun protection has come through. Thousands of square meters of European skin grilling in the sun, 12 h per day, a surprising percentage topless. Alas, dermatoheliosis with all its manifestations of elastosis, keratoses, lentigines, spotty hypomelanosis, later cancers and melanomas can be foreseen. We will remain busy in the profession for some time to come.

At the end of the meeting, a ceremonial declamation of the Hippocratic oath was performed by actors in ancient costumes in the Asklepieion. Many of the physicians present raised their hands and joined in, myself included. Therewith, I repeated my pledge after 36 years, in a sacred site, an unforgettable moment. It was September 7, for a Viennese dermatologist a hallowed date, Ferdinand Hebra’s 180th birthday.

Island of Patmos – Place of one of the great visionaries of mankind, Sunday, September 8, 1996

To conclude my trip to the Aegean Sea, I visited the monastery of St. John the Divine. Compare it to what? Incomparable. But the memories of Bodhgaya, the place where Buddha was enlightened, flash through my mind. An equally unforgettable day.

και εἶδα ὄλον ὄγυγον
ἰσχυρὸν να κατεβάσω ἀπὸ τὸν οὐρανόν ... Apocalypye Χ:1

à bientôt,

K.H., Vienna

à bientôt,