

Treatment of Warts With Contact Allergens

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Contact immunotherapy is an increasingly used, effective means of treating cutaneous viral warts. Dinitrochlorobenzene, diphencyprone, and squaric acid dibutylester are the most frequently used modalities, showing slight variances in adverse effect profiles and efficacy. All of these agents serve as safe treatment modalities when administered according to the guidelines recommended herein. We review the value of contact immunotherapy in the treatment of cutaneous viral warts.

Cutaneous viral warts, caused by human papillomaviruses (HPV), are a very common dermatologic problem. HPV can infect any epithelial surface, resulting in a warty papule or plaque.¹ The many different types of HPV favor distinct anatomical sites. HPV types 2, 4, 27, and 29 generally cause common warts and show preference for the dorsal surfaces of hands and the soles of feet.^{1,2} Flat warts usually present on the distal limbs and face and are caused by HPV types 3, 10, 28, and 49.¹ Spontaneous resolution of cutaneous warts often occurs, likely via the body's natural immunity; some series estimate that up to two thirds of warts are spontaneously cleared within 2 years.³ However, because this process is variable, untreated warts may persist for years, contributing to a pool of HPV infection in the population.² For instance, in patients with congenital or acquired impairment of cell-mediated immunity, viral warts can be especially recalcitrant to treatment.⁴ Warts can also be painful and carry a social stigma if visible, which can contribute to significant distress for the patient.^{2,5} Because of these issues, although treatment of cutaneous viral warts may not always be necessary, it is generally undertaken.

Treatment Options

Treatment of warts can be a challenging undertaking. A wide variety of treatment modalities is available, but there is no 1 universal treatment. Expense, adverse effect profile, and rate of response to treatment should dictate which modality is used. First-line treatment options, safe for nondermatologists and dermatologists alike, can include chemical destruction, usually with salicylic acid and/or lactic acid topical paints, or physical destruction with liquid nitrogen cryotherapy.¹ Treatment options for recalcitrant warts include the use of contact immunotherapy,

which should generally be undertaken by a dermatologist, preferably one experienced in contact immunotherapy.

Contact immunotherapy is classically performed with contact sensitizers such as dinitrochlorobenzene (DNCB), diphenylcyclopropenone (also known as diphencyprone [DPC]), or squaric acid dibutylester (SADBE). It is postulated that these agents act through activation of the host adaptive immune system with a resultant antiviral state-inducing clearance of the wart. Furthermore, the presence of an immune response at both the site of treatment and at untreated wart sites provides some evidence of a systemic reaction in addition to the local immune reaction.

Proposed Mechanism

Infections with HPV can be notoriously difficult to treat because the virus infects basal cells of the epithelium and is able to lie dormant.⁶ HPV are nonlytic viruses; therefore, there is only a small release of virus from infected cells and no release of cytokines upon lysis to activate an immune response.² Also, some HPV types are able to downregulate class I major histocompatibility complex expression,⁷ which interferes with appropriate cell-mediated immunity and facilitates HPV immune evasion. For an immune response to be elicited toward HPV-infected cells, the innate and/or adaptive immune systems must be activated. Epidermal Langerhans cells, which present antigens to lymphocytes in regional lymph nodes, are a key to the activation of the adaptive immune system. Unfortunately, Langerhans cells are not activated in response to HPV infection for unknown reasons.⁶ Thus, contact immunotherapy focuses on aiding in eliciting an effective immune response.

Activation of the adaptive, or acquired, immune system is thought to be the mechanism responsible for the effects of contact immunotherapy via the contact sensitizers DNCB, DPC, and SADBE. These treatments induce a type IV, or delayed-type, hypersensitivity reaction.^{8–11} By applying agents that may enact delayed-type, hypersensitivity reactions to the site of cutaneous warts, it is hypothesized that the immune system then specifically attacks and destroys HPV-infected cells.⁹ These agents can serve as a hapten, which is believed to bind to a carrier antigen of either viral or human origin associated with the cutaneous wart.^{9,11–13} Epidermal Langerhans cells and dermal dendritic cells serve as antigen-presenting cells, processing the hapten-carrier complex

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and presenting them to naive T helper (T_H) cells in regional lymph nodes.^{8,9,14} These naive T_H cells, recognizing foreign antigen, differentiate into the T_H1 phenotype and expand clonally.¹⁴ As a result, a robust T_H1 cell response on reexposure to the contact sensitizer occurs. Such T_H1 responses are mediated by a variety of cytokines, most prominently interferon gamma, interleukin (IL) 2, IL-12, and tumor necrosis factors.^{9,14} These cytokines recruit and activate macrophages, natural killer cells, and other inflammatory cells, destroying keratinocytes at the wart site.^{13,14} Clinically, this process is manifested by an eczematous reaction at the site of re-exposure. In addition, haptens can incite innate immunity via activation of the inflammasome, toll-like receptors, natural killer cells, and natural killer T cells.

Another hypothesized mechanism of action of DNCB, DPC, and SADBE is the induction of a nonspecific, systemic antiviral reaction by activation of antiviral cytokines (eg, IL-2, interferon gamma).^{13,15} Also, it is often reported that treatment with a contact sensitizer can produce resolution of warts at sites other than where it is applied.^{10,16,17} Although unproven to this point, this would suggest that contact immunotherapy can induce the acquisition of HPV-direct immunity, which would prevent future cutaneous wart infection.¹⁰

Efficacy

The efficacy of contact immunotherapy treatment modalities is reported as randomized controlled trials (RCT), case series, and case reports (Table 1).^{8–10,15–28}

Dinitrochlorobenzene

Traditionally felt to be the most efficacious of the contact sensitizers, DNCB has a reported cure rate of 66% to 95%.^{18–24} The only RCTs for the treatment of warts with contact sensitizers are for DNCB. Unfortunately, they are of small sample sizes and have some methodological limitations.

In one of these RCTs, Rosando-Cancino et al²¹ studied the efficacy of DNCB versus placebo on recalcitrant warts in 40 children. Complete clearance was obtained in 16 (80%) of the 20 patients who underwent DNCB treatment as compared with clearance of warts in only 7 (35%) of the 20 placebo patients. The main limitation is that patient follow-up was not clearly reported.

In another RCT, Wilson²² compared the efficacy of DNCB treatment versus cryotherapy versus placebo in adults with hand warts only. Sixty patients were enrolled, with 20 assigned to each of the 3 arms. Patient follow-up was extended to 4 months after the final treatment. Sixteen (80%) DNCB patients, 10 (50%) cryotherapy patients, and 8 (40%) placebo patients showed complete clearance of hand warts.

Case series for the treatment of warts with DNCB represents the bulk of the literature on the use of this treatment. These series typically report higher cure rates than RCTs do. Lee et al²³ reported a case series with 59 patients with verrucae planae and verrucae vulgaris in the assessment of the efficacy of DNCB treatment. Forty-six (78%) patients showed complete clearance. Buckner and

Price²⁴ reported treatment of 51 patients with recalcitrant verrucae vulgares with DNCB. Of the 35 patients who completed the treatment, 23 (66%) patients had complete clearance, whereas 10 (29%) had partial clearance of warts.

Young¹⁸ reported the successful treatment of 95 (95%) of 100 patients with recalcitrant warts with DNCB therapy. Lewis¹⁹ studied 85 patients, of whom 77 completed the prescribed course of treatment. Seventy (91%) of the patients who completed the regimen showed complete clearance of warts. Sanders et al²⁰ reported an 82% cure rate for 69 of 84 patients whose warts showed complete clearance with DNCB treatment. Both Lewis¹⁹ and Sanders et al²⁰ used 40% salicylic acid to reduce hyperkeratosis of warts before DNCB therapy.

Novel combined DNCB and imiquimod treatments were reported in 4 patients by Goihman-Yahr.¹⁶ Two of the patients received DNCB treatment first with little response but showed complete clearance of warts after imiquimod applications. The other 2 patients did not respond to the initial imiquimod treatment but showed complete clearance after DNCB was subsequently tried.

Diphencyprone

Treatment with DPC has reported cure rates of 44% to 88%, slightly less robust than those reported for DNCB.^{9,10,25,29} There is 1 nonrandomized trial but no RCTs; all other evidence for its efficacy comes from case series.

A nonrandomized trial of poor methodology comparing DPC with cryosurgery was undertaken. Diphencyprone treatments were administered every 1 to 3 weeks with dosages varying among patients. The patients in the cryotherapy group were treated with 2 to 3 freeze-thaw cycles every 2 or 3 weeks. Forty-five (63%) of 72 patients showed complete clearance of warts after DPC treatment, whereas 38 (51%) of 75 patients were cured after cryotherapy. Regarding sustained clearance of cured warts at 12 months of follow-up, DPC patients (93%) showed a statistically significant difference as compared with cryotherapy patients (76%) ($P < 0.05$). This supports the acquisition of HPV-directed immunity with DPC therapy.¹⁰ Lack of blinding was a limitation to this study, although it was strengthened by the 12 months of follow-up.

Diphencyprone treatment of recalcitrant warts was studied by Upitit and Krol⁹ in a case series of 211 patients. Of the 154 patients who completed the treatment, 135 (88%) patients showed complete clearance of treated warts. Similar results were shown in another series by Buckley et al,²⁹ in which 60 patients were treated with DPC for recalcitrant warts. Forty-two (88%) of the 48 patients who completed treatment showed clearance of treated warts. In addition, Rampen et al²⁵ reported a case series with 134 patients with warts in the assessment of DPC's efficacy. After 4 months of follow-up, of the 111 patients who completed the treatment course, 49 (44%) patients showed complete clearance and 18 (16%) patients showed partial remission of warts.

The combination of DPC with a keratolytic has been reported by Armour and Orchard,²⁶ who conducted a case series with

TABLE 1. Immunotherapy Cure Rates

Author	Agent	Study Type	Cohort	Completed Treatment	Cure Rate	Follow-Up	Wart-Free at Follow-Up
Young ¹⁸	DNCB	Case series	100	100	95%	—	—
Lewis ¹⁹	DNCB	Case series	85	77	91%	Mean, 8 wk (range, 2–17 wk)	—
Sanders and Smith ²⁰	DNCB	Case series	84	84	82%	Unclear	100%
Rosando-Cancino et al ²¹	DNCB	RCT	40	40	80%	Unclear	—
Wilson ²²	DNCB	RCT	60	60	80%	4 mo	—
Lee et al ²³	DNCB	Case series	59	59	78%	—	—
Buckner and Price ²⁴	DNCB	Case series	51	35	66%	Mean, 19wk (range, 2–39wk)	100%
Goihman-Yahr ¹⁶	DNCB + imiquimod	Case series	4	4	100%	1–3 y in 3 patients	100%
Upitis and Krol ⁹	DPC	Case series	211	154	88%	—	—
Buckley et al ²⁵	DPC	Case series	60	48	88%	1 mo to 8 y in 25 patients	100%
Choi et al ¹⁰	DPC	Nonrandomized trial	147	147	63%	12 mo	93%
Rampen and Steijlen ²⁵	DPC	Case series	134	111	44%	4 mo	44%
Armour and Orchard ²⁶	DPC + salicylic acid	Case series	50	48	92%	—	—
Micali et al ¹⁷	SADBE	Case series	568	443	86%	24 mo	99.7%
Lee and Mallory ⁸	SADBE	Case Series	29	29	69%	Mean, 15.2 mo (3–30 mo range) in 17 cured patients	76%
Iijima and Otsuka ²⁷	SADBE	Case series	20	20	60%	—	—
Silverberg et al ¹⁵	SADBE	Case series	61	59	58%	1 mo to 2 y in 34 cured patients	100%
Silverberg and Silverberg ²⁸	SADBE + TCA	Case series	16	16	100%	—	—
Silverberg and Silverberg ²⁸	SADBE + TCA + cantharidin	Case series	43	43	84%	—	—
Silverberg and Silverberg ²⁸	SADBE + cantharidin	Case series	10	10	80%	—	—

50 patients with palmoplantar warts treated with a DPC and salicylic acid ointment. After being sensitized to DPC, the patients were given a 0.1% DPC and 15% salicylic acid combination to be self-applied every night to warts. Forty-four (92%) of the remaining 48 patients who completed the treatment showed complete clearance.

Squaric Acid Dibutylester

The cure rate of SADBE immunotherapy has been reported to be 58% to 86%, roughly comparable with that seen with DPC treatment. The main limitation in interpreting the cure rate is that there have been no RCTs for the treatment of warts with SADBE. A large number of treated patients have been reported in the literature; however, the bulk is from 1 center.^{8,15,17,27,28}

Micali et al¹⁷ performed a retrospective study with 568 patients (404 adults and 164 children) with recalcitrant warts, reporting efficacy of SADBE treatment at 86% of lesions treated. To reduce hyperkeratosis of warts, 70% salicylic acid in petroleum jelly was applied for 2 to 3 consecutive days before application of SADBE serial

dilutions. Of the 443 patients who completed the study, 86% (382 patients) showed clinical resolution. Follow-up to 24 months from treatment cessation was performed in those who showed complete clearance of warts, with 99.7% of patients remaining wart-free.

Iijima et al²⁷ reported a case series with 20 patients with recalcitrant warts in the assessment of the efficacy of SADBE treatment. Twelve of the 20 patients (60%) showed complete clearance after an average of 6 applications (range, 2–12). Another case series by Lee and Mallory⁸ reported clearance of warts in 20 (69%) of 29 patients. Also, Silverberg et al¹⁵ reported a retrospective series of 61 children with nonfacial warts treated with SADBE. Of the 59 patients who completed the study, complete clearance of warts occurred in 34 patients (58%) and partial clearance in 11 (18%).

The combination of SADBE with destructive agents, including trichloroacetic acid (TCA) and cantharidin, has been reported in a retrospective study in children with nonfacial warts. After sensitization with SADBE, 5 patients underwent only subsequent

SADBE applications. Sixteen patients had TCA applied to warts 1 to 2 minutes before the subsequent SADBE applications, and 10 patients had cantharidin applied to warts 1 to 2 minutes after the subsequent SADBE applications. Forty-three patients had TCA applied before and cantharidin applied after the subsequent SADBE applications. Three (60%) of 5 patients treated with SADBE alone showed complete clearance, whereas 1 patient (20%) showed partial clearance. All 16 patients (100%) treated with TCA before the application of SADBE showed complete clearance. Eight of 10 patients (80%) had complete clearance when treated with cantharidin after the SADBE treatment, whereas the other 2 patients (20%) had partial clearance. Of the 43 patients treated with combined TCA, SADBE, and cantharidin, 36 patients (84%) had complete clearance and 6 patients (14%) had partial response.²⁸

Comparison of Efficacy

Overall, data comparing the efficacy of contact immunotherapy and other treatment modalities are limited by the fact that only 2 RCTs exist, both of which report the efficacy of DNCB. When the 80 patients representing DNCB versus placebo data from these 2 studies are pooled, DNCB treatment is shown to be superior to placebo, yielding a relative risk (RR) of 2.12 and 95% confidence interval (CI) of 1.38 to 3.26.³⁰ Unfortunately, the quality of these data is limited by small sample sizes, lack of blinding, and inadequate reporting of follow-up.

Compared with similar analyses of salicylic acid treatment versus placebo, cryotherapy versus placebo, and aggressive cryotherapy versus gentle cryotherapy, DNCB appears to be superior to placebo over these other treatment modalities. Pooling of 333 patients for 5 studies reveals salicylic acid treatment to be superior to placebo (RR, 1.60; CI, 1.15–2.24).³⁰ Two studies, composed of 72 patients, compared cryotherapy with placebo, showing no statistically significant difference in efficacy (RR, 0.89; CI, 0.27–2.92).³⁰ However, pooling of 361 patients from 4 trials found aggressive cryotherapy to be superior to gentle cryotherapy with an RR of 2.06 and a CI of 1.20 to 3.52.³⁰

The comparison of the efficacy of the large body of case-report literature is not possible because of the differential methodologies and outcome measures of each report. However, some trends can be seen in the data. In the interpretation of these cure rates, it is useful to be cognizant that many trials of wart treatment with contact allergens include patients who have previously failed other first-line treatments. Thus, there is a possible bias to select for warts recalcitrant to treatment, and clearance rates for the general population may actually be higher. Although the reported case series have many limitations including nonrandomized nature, lack of blinding, and lack of intention to treat principles, they can offer a useful framework for clinicians to devise treatment protocols and design future trials.

Safety

Contact immunotherapy is a safe and well-tolerated treatment. Universally, the patient will experience an eczematous reaction:

erythema, pruritus, flaking, and mild vesiculation at the site of treatment. The concentration of the contact sensitizer is typically titrated until this reaction is evident clinically.

Dinitrochlorobenzene

Transient hypopigmentation or hyperpigmentation can develop at DNCB application sites.^{11,23,24} Facial skin reacts more violently to DNCB than does nonfacial skin, rendering DNCB treatment unfavorable for application to the face.¹⁹ Generalized autosensitization has also been reported with DNCB treatment.^{19,23,31} Rarely, cross-reactions with chloramphenicol and reexposure to DNCB as an algicide in older air conditioners can occur.^{12,23,24,32} There has been 1 report on the development of erythema multiforme in association with DNCB as a treatment of alopecia areata. This patient used an inappropriate, excessive amount of the agent against medical advice, applying 2% DNCB in acetone daily for 4 days to the entire scalp.³³ Another concerning characteristic of DNCB is that it may be carcinogenic because it has been shown to be mutagenic on the Ames test.^{12,13,23,32}

Diphencyprone

From an 8-year observation, Buckley et al²⁹ reported that 56% of patients experience adverse reactions to DPC treatment, with blistering and eczematous or pompholyx-like reactions being the most common complaints. Pruritis and transient pigmentary changes at the application site and regional lymphadenopathy are also reported as adverse effects of DPC treatment.^{9,29,34} Rarely, widespread eczematoid reactions due to autoeczematization and widespread urticaria have been reported.¹³ Eight reports on erythema multiforme-like reactions have also been reported in association with DPC use.^{35–39} All such cases occurred in the setting of properly controlled sensitization and/or challenge with DPC.

Squaric Acid Dibutylester

Autoeczematization,¹⁷ severe contact dermatitis at the treatment site,^{8,27} and hypopigmentation⁸ are more severe, infrequently reported adverse effects. Spontaneous sensitization to SADBE is exceptionally rare and is postulated to occur because of cross-reaction of analogs to SADBE in the environment.²⁷ There are no reports on erythema multiforme-like reactions due to SADBE treatment.

Recommendations

For contact immunotherapy to be efficacious, the patient must be sensitized before rechallenge. Sensitization site assessment evaluates cutaneous response to immunotherapy, representative of the integrity of cell-mediated immunity. The contactant can be painted directly onto the wart and its adjacent skin or onto skin of the back, inner arm, or thigh. An area of at least 2 cm² should be painted to ensure the highest rate of success. After 3 weeks, the patient may be treated with rechallenge, and treatments should be repeated every 2 to 3 weeks. Treatment doses are typically lower than the sensitization dose and are titrated to ensure that an adequate inflammatory

response occurs. Although some discomfort may result, an adequate local inflammatory response should be observed with each treatment to ensure an adequate immune response. Controlled studies are lacking in the assessment of the sensitization rates of DNCB, DPC, and SADBE in the general population. However, studies assessing clearance rates of warts with topical immunotherapy often report initial sensitization rates in the studies' patients. A review of pertinent studies by Buckley et al²⁹ showed sensitization rates greater than 90% for each of these 3 topical immunotherapy agents.

Dinitrochlorobenzene

Sensitization may be accomplished with a high concentration of DNCB, usually 2%, 5%, or 10% compounded in acetone. After 2 to 3 weeks, the patient can be treated with lower concentrations titrated to clinical response.

Diphenylprone

On the basis of these studies, it is recommended to use adequate concentrations for both sensitization and subsequent challenges. Generally, sensitization doses range from 1% to 2% DPC compounded in acetone, with treatment doses being lower.

Squaric Acid Dibutylester

Sensitization to SADBE is performed with 1%, 2%, or 3% solution compounded in acetone. After 2 weeks, the patient can be treated with doses ranging from 0.01% to 5% SADBE, titrated to clinical response, every 1 to 2 weeks.

CONCLUSIONS

Although data are limited, the available data support the clinical experience of the authors that contactants are superior to other methods of wart treatment. On the basis of previous data and our clinical experience, we recommend that salicylic acid and cryotherapy should be first-line treatments for the nondermatologist. Other treatments should be held in reserve for recalcitrant cases and under the direction of a dermatologist. Thus, we recommend contact allergen therapy as an effective treatment option for recalcitrant warts.

The adverse effect profiles of DNCB, DPC, and SADBE are mostly similar. However, DPC is more often reported as being associated with erythema multiforme as compared with DNCB and SADBE. Although this reaction is rare, the clinician should be cognizant of its potential. In general, the limited course of treatment and the rarity of reported systemic toxicities make these agents safe to use. The use of immunotherapy of any type is not advocated in women who are pregnant or are planning on becoming pregnant. Concern over vigorous reaction and postinflammatory hyperpigmentation should limit the use of contact sensitizers on the face for the treatment of severe, recalcitrant warts. This should be performed only under the guidance of a clinician experienced in the use of the agent.

All treatment modalities have been postulated to result in long-term immunity to HPV; thus, immunotherapy could provide beneficial prevention of wart recurrence.

In addition, several studies indicate the efficacy of combining immunotherapy agents with salicylic acid, imiquimod, TCA, cantharidin, or both, showing 80% to 100% cure rates.^{16,17,26,28} It has also been reported that quadrivalent HPV vaccine administration can cause regression of common warts, hypothetically from antigenic epitope cross-reactivity between the vaccine's HPV types and HPV types responsible for common warts,⁴⁰ suggesting an immune-based mechanism. Therefore, combining treatments; adding a keratolytic, irritant, or destructive agent; or administering concurrent quadrivalent HPV vaccine could serve as more superior treatment regimens in the future.

Finally, the best measure of efficacy of immunotherapy alone or in combination with another irritant would be RCTs. Certainly, more trials assessing the efficacy of these treatments versus placebo or other modalities are needed.

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