

USE OF CANTHARIDIN FOR VERRUCA

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HISTORY

Cantharidin has been used for more than 2,000 years in both folk and traditional medicine. It was used in China for many medicinal purposes including furuncles, ulcers, and tuberculosis, topically, and for abdominal masses, rabies, and as an anticancer agent, orally. In Europe, it appeared in *Materia Medica*, a medical monograph written in 50 to 100 AD. Hippocrates prescribed cantharidin as a treatment for dropsy (1).

Cantharidin has a long infamous reputation for being an aphrodisiac and is known as Spanish fly. This reputation is based on the observation of pelvic congestion in women and priapism in men after cantharidin ingestion. It is not a true aphrodisiac, and fatal poisonings can occur (2). Cantharidin has also been used as a homicidal agent in South Africa.

Topical cantharidin has been used as a blistering agent for warts and molluscum since the 1950s (3,4). It satisfied all the safety requirements of the Food, Drug, and Cosmetic Act of 1938. However, in 1962, the FDA initiated an amendment to this act, which required manufacturers to submit efficacy data for their products. No manufacturer submitted efficacy data to the FDA, and cantharidin was removed from the market in 1962 (2). In 1997, an amendment, known as the FDA Modernization Act of 1997, was signed into law. This new law provides that certain substances may be compounded by a physician or a pharmacist on a customized basis for individual patients. These substances are neither the subject of a current United States Pharmacopoeia (USP) or National Formulary (NF) monograph nor a component of an FDA-approved drug. The FDA developed and published a list of these substances, known as the "Bulk Substance List." Cantharidin is on this list of bulk substances that may be used in pharmacy compounding (5). Thus, a physician may administer drug products compounded with cantharidin. Because of cantharidin's toxicity, the FDA has proposed that cantharidin should be limited to "topical use in the professional office setting only."

MECHANISM OF ACTION

Cantharidin is a vesicant produced by beetles belonging to the order of Coleoptera and the family of Meloidae. Cantharidin used medically is collected from species of the genera *Mylabris* and *Lytta*, especially *Lytta vesicatoria*, better known as "Spanish Fly." The male blister beetle produces the substance, giving the chemical to the female during mating. Afterwards the female beetle will cover its eggs with the chemical as a defense against predators (6).

Cantharidin acts as a blistering agent or acantholytic. The lipid layers of epidermal cell membranes absorb it. Once applied, cantharidin causes release of neutral serine proteases that cause degeneration of the desmosomal plaque, leading to detachment of tonofilaments from desmosomes (7). This leads to intraepidermal blistering and nonspecific lysis of the skin. The blister causes the tissues containing the virus to separate from the surrounding skin. Since acantholysis is intraepidermal, healing occurs without scarring. This is valuable, especially for plantar warts, since other well-known wart destruction methods, such as cryotherapy or electrical cautery, can produce scarring. There have been no cases of systemic intoxication or scarring reported with the proper use of cantharidin by a physician.

TREATMENT

There are many treatment options for verruca. Since there is no cure for the virus, treatment has been directed at destruction of the skin in which the virus lives (Figure 1). Cryotherapy can be effective for warts but less effective than cantharidin-podophylotoxin-salicylic acid for plantar warts (8). This treatment can be painful, but does not typically require local anesthesia. Cryotherapy may require repeat treatments and can cause discoloration of the skin. Other treatments include electrosurgery, excision, laser treatment, 5-fluorouracil, and bleomycin injections. Immunotherapy where a chemical is applied to the warts to produce an allergic reaction or injections of interferon has been attempted as well.

Cantharidin has been used successfully for more than 60 years. In Epstein's classic article, 56% of digital and 33%



Figure 1. Pre-treatment of plantar verruca.

of periungual warts were cleared after a single application of cantharidin (9). The others generally required one or two additional treatments with a long-term cure rate of about 70%.

Cantharidin was first described in the podiatric literature in 1962 as a treatment for intractable plantar lesions (10). More recently, a retrospective study was reported of 144 patients with simple or mosaic plantar warts that were treated with a topical compound of cantharidin, podophyllotoxin, and salicylic acid. Complete eradication of the plantar warts was noted in 138 of the 144 patients (95.8%). Of these patients, 125 (86.8%) required a single application of the solution, and 13 (9.0%) needed two or more applications (11).

The use of cantharidin is most commonly used as a compounded product combined with podophyllotoxin and salicylic acid. The concentrations may slightly vary, but this mixture has been most effective in the author's experience. The product may be compounded by a compounding pharmacist or is commercially available through a number of manufacturers. Various instructions for its use are reported in the literature.

Basically, the physician applies the compound to the lesion or lesions after debridement (Figures 2, 3). The length of time that the compound is left in place is reported differently. Some authors advocate washing the area of application after two hours. Other recommendations range from leaving the area dry and covered from four hours to a few days. I recommend leaving the area of application clean and dry for one day for digital and dorsal verruca and

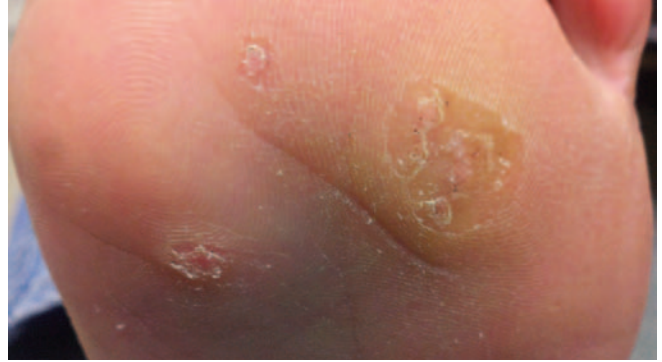


Figure 2. After debridement and before application of cantharidin of plantar verruca.

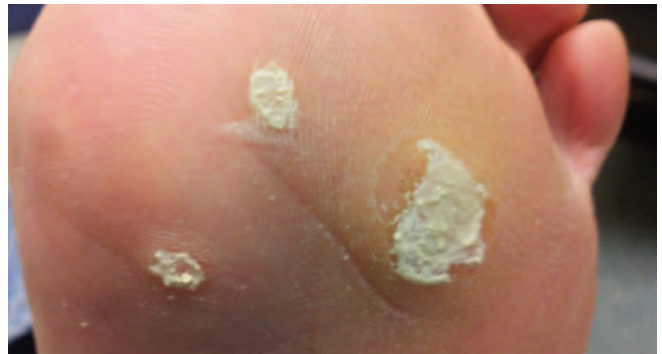


Figure 3. After application of cantharidin.

leaving the area of application clean and dry for two days for plantar warts. The longer the agent is in contact, especially under occlusion, the greater the intensity of the blistering (Figure 4).

Topical cantharidin treatment causes formation of blisters within 24 to 48 hours. Healing is complete 4 to 7 days after application. Patients will typically feel a tingling or burning sensation within a few hours of application. The pain and tenderness associated with the blister usually occurs after about 24 hours and last two to four days. Approximately 50% of patients will experience this discomfort and it is more common with adults than with children in this author's experience. Occasionally, pain medication is required during this time, or the patient may need to be seen earlier than typically scheduled to drain the sterile abscess of the blister. This simple drainage will provide significant relief.

Follow-up visits are recommended at two weeks after application. The healing is complete, the area is usually free of blisters, and the hyperkeratosis at the application site is more easily debrided (Figure 5). If the skin beneath the area is free of obvious verruca, no further treatment is required. If evidence of verruca is noted, reapplication of the cantharidin is carried out (Figure 6).



Figure 4. Bulla formation one week after application of cantharidin.

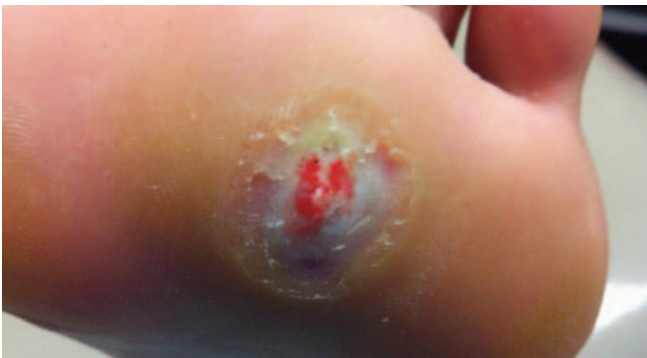


Figure 6. After debridement two weeks after initial application of cantharidin.

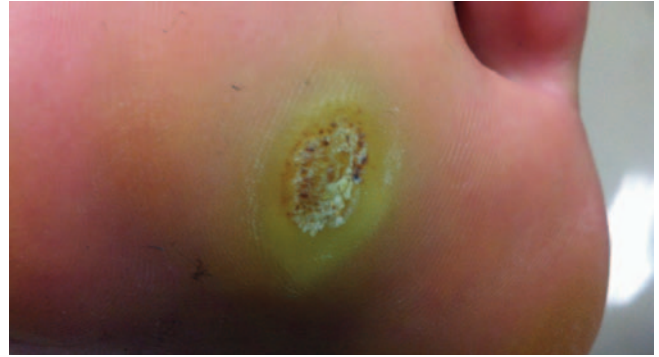


Figure 5. Appearance before debridement two weeks after initial application of cantharidin.



Figure 7. Hypertrophic scar after plastic surgical excision of verruca.

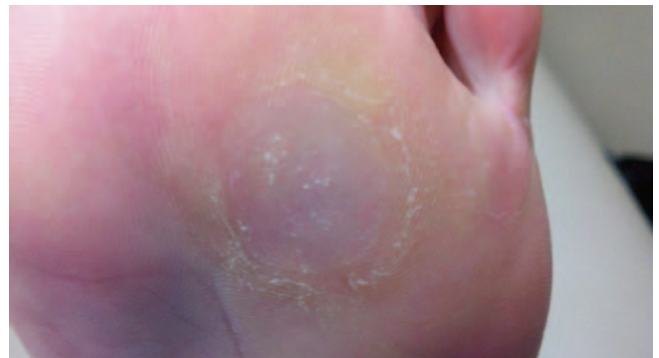


Figure 8. Resolved plantar verruca after two applications of cantharidin.

CONCLUSION

Cantharidin can be used safely and effectively for plantar warts. Plantar verruca have been very difficult to treat in the past and often were painful to treat or left potentially painful or disfiguring scars (Figure 7). Cantharidin has distinct advantages over other destructive methods. A local anesthetic injection is not required for application and the application is painless. This is especially useful in the treatment of warts on children and squeamish adults. Another advantage is that there is no risk of scarring since cantharidin does not go beyond the epidermal cells, the site of the viral infection (Figure 8).

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