Cantharidin Revisited

A Blistering Defense of an Ancient Medicine

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Cantharidin, a vesicant produced by beetles in the order Coleoptera, has a long history in both folk and traditional medicine. In dermatology, topical cantharidin has long been used to treat warts and molluscum. In 1962, cantharidin lost Food and Drug Administration (FDA) approval owing to the failure of its manufacturers to submit data attesting to cantharidin’s efficacy. However, it is expected that the FDA will soon include cantharidin on its “Bulk Substances List,” which would permit physicians or pharmacists to compound cantharidin to be used in the office for individual patients. A comprehensive discussion of the origins, folk uses, current FDA status, current dermatologic uses, and effects of cantharidin poisoning has been compiled herein. No cases of systemic intoxication or scarring have been reported with the proper use of cantharidin by a physician. Cantharidin is a safe and valuable medication and should be readded to the dermatologic therapeutic armamentarium.

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Historically, cantharidin has been used as an aphrodisiac, an abortifacient, and a veterinary medicine diuretic. In dermatology, topical cantharidin has been used as a vesicant for the treatment of warts and molluscum since the 1950s. Despite its removal from the market in 1962, some dermatologists continue to use cantharidin in the United States in either proprietary or nonproprietary formulations, as there is currently no other topical medication that has an equivalent therapeutic effect. However, the availability of cantharidin is limited, and physicians or hospitals may forgo its use because FDA approval is lacking. In this review, the folk and current dermatologic uses of cantharidin, the legal issues involved in the use of cantharidin, and cantharidin poisoning will be discussed.

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BLISTER BEETLES
AND SPANISH FLY

Cantharidin is a vesicant produced by beetles belonging to the order Coleoptera and the family of Meloidae.1 There are currently more than 1500 species of cantharidin-producing beetles.2 Commonly known as blister beetles or Spanish fly, they are variable in color, measure up to 2.5 cm in length,3 and do not bite or sting.1 Epicauta vittata and Epicauta pennsylvania can be found in alfalfa fields, along fence rails, or in flower beds in the South and southwestern parts of the United States.3 Cantharidin is found in all body fluids of blister beetles.4 The male beetle synthesizes cantharidin for use as a defense mechanism, and the female acquires cantharidin as a copulatory gift from her mate.5 Blister beetle dermatosis is a seasonal vesiculobullous skin disorder that occurs several hours after contact with the beetle.6 If contact with a beetle is noted, blowing off the beetle, rather than brushing it off, will minimize cantharidin exposure.3
HISTORICAL AND FOLK USES OF CANTHARIDIN

Mylabris, the dried body of the Chinese blister beetle, has been used medicinally for more than 2000 years in China and is still used as a folk medicine today in Asia. Today in North America, cantharidin continues to be made from blister beetle extracts by a process that is a well-kept trade secret. In Asia, topical cantharidin was used historically for furuncles and piles, ulcers, venomous worms, and tuberculous scrofuloderma. It was used orally for abdominal masses and rabies, as well as an abortifacient and anticaner agent. In Europe, it appeared in Materia Medica, a medical monograph written by Pedanios Dioskorides in 50 to 100 AD. Hippocrates prescribed cantharidin as a treatment for dropsy. In South Africa, the Tswanas grind cantharidin-producing beetles into a powder and use it in a medicine called seletsa as an aphrodisiac, as an abortifacient, and for “purifying the blood.” Seleta fatalities are relatively common.

Cantharidin has a long, infamous reputation for being an aphrodisiac and is known as Spanish fly in the vernacular. This reputation is based on the observation of pelvic congestion in women and priapism in men after cantharidin ingestion. In 1772, the Marquis de Sade is said to have poisoned prostitutes with candies containing Spanish fly to increase sexual pleasure.

Although cantharidin is not a true aphrodisiac, poisonings following surreptitious placement still occur. In England, a man gave coconut ice laced with cantharidin to 2 women, hoping to facilitate a sexual interaction. Both women died of the poisoning. In 1996, 4 young adults presented to the emergency department at Temple University, Philadelphia, Pa, after ingesting a liquid consisting of water and powdered drink mix (Kool-Aid) contaminated with cantharidin, self-administered as a trial run, intended ultimately for one of their girlfriends. All 4 survived. One fatality resulted after a man tried to use cantharidin as fishing bait:

A keen fisherman obtained some pure cantharidin from an illicit source with the object of attracting fish. He mixed the substance with water in a bottle, and, having no stopper for this, he used his thumb to occlude the opening. Immediately following this, the patient handled his fishing-hooks, and in the process accidentally pricked the thumb. This caused him to suck the thumb. In this way, it appears, the cantharidin was transferred to the patient’s mouth.

Cantharidin may be easily (and illegally) purchased from health food stores or erotic Web sites as Spanish fly. But caveat emptor—there has been at least 1 report of poisoning due to strychnine contamination in Spanish fly aphrodisiac pills.

CANTHARIDIN AND THE FDA

Cantharidin in a collodion vehicle has been used by dermatologists as a treatment for molluscum contagiosum and warts since the 1950s. It satisfied all the safety requirements of the Food, Drug, and Cosmetic Act of 1938. However, in 1962, the FDA initiated an amendment to the Food, Drug, and Cosmetic Act, called the Drug Efficacy Study Implementation, which required manufacturers to submit efficacy data for their products. No efficacy data were submitted to the FDA, and cantharidin was removed from the market in 1962. However, the status of cantharidin may be changing in the near future. In 1997, President Clinton signed into law an amendment to the Food, Drug, and Cosmetic Act, adding section 503A, which provides that certain drug products may be compounded by a physician or a pharmacist on a customized basis for individual patients. Among other criteria, section 503A would permit the compounding of drug products that appear on a “Bulk Substances List,” which is to be issued and maintained by the FDA. Although the list has not been finalized, cantharidin was 1 of 30 substances nominated for inclusion on the list. The FDA is on the verge of including cantharidin on its final “Bulk Substances List,” along with other substances that are familiar to dermatologists, such as ferric subsulfate, iodoperfluoroquinolone, secobarbital, and thymol iodide. Diphenylcyclopropamine, squaric acid dibutyl ester, and others are still under consideration. In 1998, the FDA established an interim policy stating that, in general, it would not take regulatory action against drug products compounded with one of the substances nominated for inclusion on the list, as long as there did not appear to be a significant safety risk. Thus, a physician or pharmacist may administer drug products compounded with cantharidin, unless the FDA issues a notice that cantharidin appears to present a significant safety risk. Because of cantharidin’s toxicity, the FDA has proposed that cantharidin should be limited to “topical use in the professional office setting only.”

Proprietary formulations of cantharidin are not uncommonly used in the United States, because it is often impracticable for a physician or pharmacist to compound the drug on each occasion that it is needed in the office. Also, proprietary formulations may offer a greater degree of consistency of product or predictability of performance than a drug that is compounded. We are not aware of any enforcement actions by the FDA against the use of such proprietary formulations.

MECHANISM OF ACTION

Cantharidin is absorbed by the lipid layers of epidermal cell membranes. Application of cantharidin to the epidermis results in the activation or release of neutral serine proteases that cause degeneration of the desmosmal plaque, leading to detachment of tonofilaments from desmosomes. This process leads to acantholysis and intraepidermal blistering, and nonspecific lysis of skin. Lesions heal without scarring, as acantholysis is intraepidermal.

DERMATOLOGICAL USES OF CANTHARIDIN

Cantharidin in a flexible collodion medium has long been considered a viable option for the treatment of warts and molluscum. Proprietary formulations consisting of 0.7% cantharidin in a film-forming vehicle containing acetone, ether, and alcohol can be purchased from several companies (eg, Dormer Laboratories, Rexdale, Ontario; Omniderm, Hudson, Quebec; PharmaScience, Montreal, Quebec; College Pharmacy, Colorado Springs, Colo;
Topical cantharidin treatment causes formation of blisters within 24 to 48 hours. Healing is complete 4 to 7 days after application. The degree of blistering is controlled by instructing the patient to wash the treated site with soap and water after a specified length of time, usually in the range of 2 to 6 hours. Blistering may be intensified by lengthening the contact time or by occlusion with nonporous tape to increase percutaneous absorption. Fair-skinned individuals tend to blister more easily, and contact time should be adjusted accordingly.27 We treat molluscum initially with a 2-hour contact time, without occlusion. Retreatment may be done as early as 1 week. Warts are treated more intensively. Warts are pared, followed by cantharidin application to the wart and a 1-mm rim of normal skin, and occluded with nonporous tape. Cantharidin is washed off in 4 hours. If necessary, paring and retreatment are done in 1 to 2 weeks, with contact time increased if needed. In our experience, pain and excessive blistering are exceedingly rare when these guidelines are followed.

Cantharidin should be applied only in the office by a physician26 or under the direct supervision of a physician. Although 1 report advocates home use of cantharidin for warts, we believe that home use should be strictly avoided,28 because severe blistering can result from improper use,24 and because ingestion, especially by children, can be fatal. Treatment of mucous membranes is contraindicated owing to increased propensity for blistering.17 Also, placement of cantharidin near the eyes and eyelids should be avoided to prevent scleral erosion.29

When cantharidin is used appropriately, complications are exceedingly rare. Mild to moderate pain, temporary erythema, a transient burning sensation, and pruritis may occur.28 There is no scarring with proper use.16,24 Adverse effects include a ring of small satellite warts surrounding the original wart. Ring warts occurred in 1 of 100 patients in one study,28 and in 3 of 61 patients in another.17 The same or different therapy, such as cryosurgery, can be used to remove the larger warts.17 Ring warts can arise after any type of destructive therapy for warts, and this complication deserves mention in the informed consent process. Postinflammatory hypopigmentation or hyperpigmentation can take weeks to months to resolve. Informed consent should also include mention of this temporary but potentially distressing effect.16,31

The treatment of plantar warts may have a higher rate of significant complications. Two patients with plantar warts were treated with cantharidin and 40% salicylic acid plaster, under occlusion for 24 hours. Lymphangitis developed 30 hours later.32 An adult whose plantar warts were treated with 0.7% cantharidin solution developed lymphangitis and refractory lymphedema.33 Cellulitis developed in 4 patients whose plantar warts were initially treated with a mixture of 1% cantharidin, salicylic acid, and podophyllin that was left on for 24 hours, and then the warts were debrided with silver nitrate.28

In a retrospective study of 300 children with molluscum contagiosum treated with cantharidin, 90% of the patients experienced resolution of symptoms and an additional 8% noted some improvement.30 The authors used 52.5 mg of cantharidin crystals mixed in 7.5-mL flexible collodion. Treated areas were rinsed 4 to 6 hours after application. No cases of systemic toxic reactions were noted.30 In 1971, 1 manufacturer of 0.7% cantharidin wart-remover solution reported 1 500,000 mL of product sold over the prior 10-year period, with no reports of systemic intoxication.54

CANTHARIDIN POISONING

Poisoning usually results after aphrodisiac ingestion.11 Beetle ingestion by children has also caused poisoning.35,36 The clinical signs of cantharidin poisoning are nonspecific. Gas chromatography/mass spectrometry can be used to confirm cantharidin poisoning.37,38 The fatal dose of cantharidin is estimated to range from 10 to 65 mg,39 with the median lethal dose being approximately 1 mg/kg,40; however, individuals have survived after consuming oral doses as high as 175 mg.12Fatalities usually result from renal failure, and severe morbidity can result from injury to the gastrointestinal tract.11

With cantharidin ingestion, a burning sensation of the lips, mouth, and pharynx occurs within minutes.12,39 Blisters form shortly thereafter, leading to dysphagia, abdominal cramping, hematemesis, and vomiting. Total loss of normal mucosa of the gastrointestinal tract may occur.12,13,41 Damage is dose dependent and is directly related to the amount of fatty food within the gastrointestinal tract at the time of ingestion, as fats and lipids promote absorption.35 Lumbar pain, dysuria, proteinuria, hematuria, and renal failure can result.9,11,12,41,42 Coagulopathy,11 seizures, and a Guillain-Barré–like flaccid paralysis have been reported.43,44

To the best of our knowledge, there have been no reports of cantharidin intoxication caused by the reasonable application of cantharidin solution by a physician. One unusual report from South Africa describes a case in which topical cantharidin was applied to an area of abdominal skin approximately 18 × 8 cm as a treatment for pleurisy (cantharidin was thought to act medicinally as a counterirritant).45 Dysuria and hematuria occurred, but the patient recovered fully within 1 week.

TREATMENT OF CANTHARIDIN POISONING

The treatment of cantharidin intoxication is largely supportive. There is no known antidote.3 For topical exposures, the affected area should be cleaned with acetone, ether, fatty soap, or alcohol, which helps to dissolve and dilute the cantharidin. The skin should then be cleaned thoroughly with soap and water. A topical steroid may be applied to intact skin if it is symptomatic.3 For oral ingestions, several support measures may be taken. If possible, the patient should swallow generous quantities of water but should avoid fatty foods (such as milk) because they increase cantharidin absorption.35 Vomiting should not be induced, as oropharyngeal and esophageal damage is increased with reexposure. Gas-
tric lavage is recommended in patients who present early and do not have severe esophageal involvement. Activated charcoal may also be administered, although there is no evidence that cantharidin binds to this material. Hospitalization may be necessary for supportive care and pain management.11

INVESTIGATIVE USES OF CANTHARIDIN

Cantharidin has been demonstrated to act as a vasoconstrictor and positive inotrope in guinea pig and human cardiac tissue in vitro. These effects are mediated in part by cantharidin’s action as a protein phosphatase inhibitor.46,49 Although cantharidin is too toxic to administer systemically, it is possible that safer derivatives will be developed in the future, offering new therapeutic options for the treatment of human cardiac failure.

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