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.

Arch Dermatol. 2001;137:1357-1360

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.

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.3 Blister beetle dermatosis is a seasonal vesiculobullous skin disorder that occurs several hours after contact with the beetle.4 If contact with a beetle is noted, blowing off the beetle, rather than brushing it off, will minimize cantharidin exposure.3

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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. 6 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.6,7 It was used orally for abscesses, infections, tumors, and warts since the 1950s.16,17 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, 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.20 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 one 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, iodoform, and thymol iodide. Diphenylcyclopropa-none, 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.21 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 desmosomal plaque, leading to detachment of tonofilaments from desmosomes. This process leads to acantholysis and intra-epidermal blistering, and non-specific lysis of skin.22 Lesions heal without scarring, as acantholysis is intra-epidermal.

DERMATOLOGICAL USES OF CANTHARIDIN

Cantharidin in a flexible collodion medium has long been considered a viable option for the treatment of warts and molluscum.16,17,19-24 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;
The same or different therapy, such as cryosurgery, can be fatal. Treatment of mucous membranes is contraindicated owing to increased propensity for blistering. Also, placement of cantharidin near the eyes and eyelids should be avoided to prevent scleral erosion.

When cantharidin is used appropriately, complications are exceedingly rare. Mild to moderate pain, temporary erythema, a transient burning sensation, and pruritus may occur. There is no scarring with proper use. Adverse effects include a ring of small satellite warts surrounding the original wart. Ring warts occurred in 1 of 100 patients in one study and in 3 of 61 patients in another. The same or different therapy, such as cryosurgery, can be used to remove the larger warts. 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.

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. An adult whose plantar warts were treated with 0.7% cantharidin solution developed lymphangitis and refractory lymphedema. 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.

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. 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. In 1971, 1 manufacturer of 0.7% cantharidin wart-remover solution reported 1,300,000 mL of product sold over the prior 10-year period, with no reports of systemic intoxication.

CANTHARIDIN POISONING

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

With cantharidin ingestion, a burning sensation of the lips, mouth, and pharynx occurs within minutes. Blisters form shortly thereafter, leading to dysphagia, abdominal cramping, hematemesis, and vomiting. Total loss of normal mucosa of the gastrointestinal tract may occur. 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. Lumbar pain, dysuria, proteinuria, hematuria, and renal failure can result. Coagulopathy, seizures, and a Guillain-Barré-like flaccid paralysis have been reported.

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). 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. For topical exposures, the affected area should be cleansed with acetone, ether, fatty soap, or alcohol, which helps to dissolve and dilute the cantharidin. The skin should then be cleansed thoroughly with soap and water. A topical steroid may be applied to intact skin if it is symptomatic.

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. Vomiting should not be induced, as oropharyngeal and esophageal damage is increased with reexposure. Gas-
Intervening charcoal 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.

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. 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.

Accepted for publication April 6, 2001.

We thank Seth J. Orlow, MD, PhD, for his thoughtful review of the manuscript.

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