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**Review**

**Cantharidin: a comprehensive review of the clinical literature**

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**Abstract**

*Background:* Cantharidin is a topical vesicant that causes intraepidermal acantholysis with clinical application that includes the removal of warts, molluscum contagiosum (MC), calluses, and acquired perforating dermatoses.

*Objective:* To provide a comprehensive literature review of the efficacy and safety of cantharidin in the management of various cutaneous conditions.

*Methods:* A PubMed search was conducted using the term “cantharidin” combined with “warts”, “plantar warts”, “verruca vulgaris”, “periungal”, “subungual”, “topical treatment”, “topical therapy for warts”, “molluscum contagiosum”, “perforating collagenosis,” and “acantholysis.”

*Results:* A total of 749 articles were identified and 37 articles met inclusion criteria for this review. The majority of studies show that cantharidin is an effective and safe treatment for removal of warts and MC. Several studies also show potential novel applications of cantharidin in acquired perforating dermatosis, acute herpes zoster, and leishmaniasis. Adverse effects are generally mild but common and should be monitored, particularly in the pediatric population.

*Limitations:* There is a paucity of high-powered clinical studies involving the use of cantharidin.

*Conclusion:* Topical cantharidin is a safe and effective treatment for warts, molluscum contagiosum, and callus removal, with promising uses in perforating dermatoses and leishmaniasis.

**Keywords: cantharidin; verruca vulgaris; molluscum contagiosum; periungal warts; perforating collagenosis; vesicant; acantholysis**

# Introduction

The first recorded uses of cantharidin date back to the Han Dynasty in China and in Europe during 50-100 AD [1, 2]. Medical applications have varied and include its use as an oral aphrodisiac agent and for the topical treatment of warts. Recent medical practice has been controversial since the drug's loss of U.S. Food and Drug Administration (FDA) approval in 1962. Despite the controversy, the role of cantharidin remains a preferred in-office treatment of molluscum contagiosum (MC) and verruca vulgaris.

The male blister beetle in the Coleoptera order and of the Meloidae family produces cantharidin in an oral fluid that is stored in its alimentary canal [3]. In 1952, Stork et al were able to produce cantharidin synthetically for medicinal use [1]. From 1952 to 1962, topical cantharidin was used mainly for the treatment of cutaneous warts [4, 5]. In 1962, marketers of cantharidin failed to produce mandatory efficacy data, resulting in FDA revision of approval of cantharidin.

In 1998, cantharidin was approved under an amendment to the FDA bylaws termed the "Bulk Substances List." This regulation restricts cantharidin to in-office use and to be applied only by a physician. Formulations available for sale today are: 1) Cantharone 0.7% in collodion base (Dormer Laboratories, Ontario, Canada); 2) Canthacur PS (1% cantharidin, 30% salicylic acid, 5% podophyllin) (Paladin Labs, Quebec, Canada); 3) Canthracur 0.7% in collodion base (Paladin Labs, Quebec, Canada); and 4) Cantharidin crystals with collodion base sold separately (Delasco, Council Bluffs, Iowa) [3, 6]. The limited availability of cantharidin has prevented its widespread use.

The labelled indications for topical cantharidin are: verruca vulgaris (including plantar, peri/subungual warts) and MC. Off-label indications include callus removal, cutaneous leishmaniasis, herpes zoster, and acquired perforating dermatosis [7-10]. In addition, it has been used as an inflammatory model and in cancer treatment [11, 12].

Mechanistically, cantharidin is absorbed by lipids in the keratinocyte, in which it activates neutral serine proteases that lead to progressive degeneration of desmosomal dense plaques [13, 14]. A selective acantholysis occurs intraepidermally and heals over time without formation of a scar. A blister will form in 24-48 hours and resolves within 4-7 days [3-6, 15]. Factors that can alter this time frame are the volume or concentration of cantharidin used, contact time (four to twenty-four hours), occlusion, or sensitivity to cantharidin.

Application of cantharidin is painless, which is particularly important for pediatric patients, reducing the psychological trauma caused by injections (local anesthesia) and electrosurgery. Side effects of cantharidin include erythema, pain, ring warts, and post-inflammatory hyperpigmentation. More severe but less common side effects are lymphangitis, secondary bacterial cellulitis, scarring, and varicelliform vesicular dermatitis [5, 16-18].

## Materials and Methods

A search of literature on PubMed was conducted using the terms "cantharidin" and in combination with "warts", "plantar warts", "verruca vulgaris", "periungual", "subungual", "topical treatment", "therapy for warts", "molluscum contagiosum", and "acantholysis". Inclusion criteria were: 1) article is a case study, review of literature, case report or commentary; and 2) cantharidin was used or discussed in article. Important exclusion criteria were non-English articles or those that did not discuss cantharidin as a therapy. Each article was tabulated as follows: study design, number of patients, treatment protocol, list of adverse events, and results.

## Results

A PubMed search for "cantharidin" alone yielded 749 articles. Combining "cantharidin" with various search terms yielded fewer, but more focused articles, which included: "wart" or "verruca vulgaris" (28 articles), "molluscum contagiosum" (33), "plantar warts" (5), "periungual" or "subungual warts" (2), "topical" (50), and "acantholysis" (22). From these 140 articles, only 37 pertained to the following topics: molluscum contagiosum (13), warts (22) (verruca vulgaris (10), plantar warts (8), peri/subungual (2)), side effects (5), novel uses (5), and historical information/mechanism of action (10).

Table 1 summarizes studies of MC. Table 2 summarizes studies of verruca vulgaris. Table 3 summarizes studies of novel uses.

**Table 1. Clinical studies of cantharidin in molluscum contagiosum**

| Reference | Year | Treatment | N | Design | Protocol | Adverse Effects |
|-----------|------|-----------|---|--------|----------|-----------------|
|-----------|------|-----------|---|--------|----------|-----------------|

|                      |      |   |     |    |   |  |
|----------------------|------|---|-----|----|---|--|
| Cathcart et al[18]   | 2009 | cantharidin 0.7%  | 54  | RC | Applied to non-facial lesions for 2-4hrs                        | Pain, pruritus, secondary infection, brisk immune response, and temporary hypopigmentation |
| Hanna et al[21]      | 2006 | cantharidin 0.7%, salicylic acid 16.7%, lactic acid 16.7%, imiquimod 5% | 124 | CT | 10 mollusca chosen for 1 of 4 treatments, applied 3x/weekly.    | Blisters, pruritus, bacterial super-infection, scars                                       |
| Ross and Orchard[37] | 2004 | cantharidin 0.7% Imiquimod 5%   | 16  | CS | Cantharidin applied once; imiquimod applied nightly for 5 weeks | Erythema, burning, pain, post-inflammatory pigment alteration, scarring, and blistering    |
| Silverberg et al[22] | 2000 | cantharidin 52.5mg/7.5mL colloid  | 300 | RC | Applied to non-facial lesions for 4-6 hours; repeat treatment   | Blisters, burning, pain, erythema, pruritus  |
| Funt[35]             | 1961 | cantharidin 0.9%  | 12  | OL | One application followed by wash 4 hours later                  | Pain, blister  |

Abbreviations: PIPA - post-inflammatory pigmentation abnormality; CT - controlled trial, OL - open label, CS – case series, CR – case report, RC-retrospective cohort

**Table 2. Clinical studies of cantharidin in verruca vulgaris (periungual, palpebral, flat, and plantar warts).**

| Reference                           | Year | Disease                        | Treatment  | N   | Design | Protocol   | Adverse effects  |
|-------------------------------------|------|--------------------------------|--|-----|--------|--|--|
| Kacar et al[24]                     | 2011 | Plantar warts                  | salicylic acid 30%, podophyllin 5%, cantharidin 1% mixture | 26  | OL     | Applied 2x/week for up to 5 treatments   | Blistering, bulla, hemorrhagic bulla, pain, PIPA, lymphangitis and lymphedema            |
| Durmazlar et al[33]                 | 2009 | Recalcitrant facial flat warts | cantharidin 0.7% solution                                  | 15  | OL     | Applied and wash off in 4-6 hours; repeat every 3 weeks                                  | Ring warts, PIPA, toxic (ingestion), erythema, blistering, secondary bacterial infection |
| Becerro de Bengoa Vallejo et al[31] | 2008 | Plantar warts                  | salicylic acid 30%, podophyllin 5%, cantharidin 1% mixture | 144 | RC     | Debridement before application with occlusive dressing for 48hrs; repeat every 2-3 weeks | Burning, pain, blistering  |
| Lichon & Khachemoune [26]           | 2007 | Plantar warts                  | cantharidin 0.7% solution                                  | 1   | CR     | Applied with occlusive dressing for  | Blistering, pain, scarring, recurrence   |

|                   |      |                            |  |     |    |  |   |
|-------------------|------|----------------------------|--|-----|----|--|---|
|                   |      |                            |  |     |    | 24hrs; repeat every 1-3 weeks  |   |
| Coskey [38]       | 1984 | Plantar warts              | salicylic acid 30%, podophyllin 5%, cantharidin 1% mixture | 120 | OL | Debridement before application for 24 hours; debridement 1 week post-treatment | Bulla, pain, cellulitis                             |
| Rosenberg [39]    | 1977 | Verruca vulgaris           | cantharidin 0.7%   | 100 | OL | Applied daily until clinical improvement                                       | Well-tolerated                                      |
| Bock[40]          | 1965 | Palpebral warts            | cantharidin 0.7% solution                                  | 27  | OL | Applied to lesions every 8-10 days for 2-3 treatments                          | Blistering, pain, pruritus (most common response)   |
| Panzer[28]        | 1961 | Verruca vulgaris           | cantharidin 0.7% solution; salicylic acid 40% plaster      | 46  | OL | Applied; debrided two days later   | Erythema, burning, pain, ring warts, and blistering |
| Epstein et al[27] | 1960 | Digital & periungual warts | cantharidin 0.7% solution                                  | 40  | OL | Applied once weekly with occlusive dressing for up to 3 treatments             | Blistering, pain, ring wart, erythema               |

Abbreviations: PIPA - post-inflammatory pigmentation abnormality; RC- retrospective cohort; CR- Case Report; OL - open label

**Table 3. Studies of cantharidin in novel uses**

| Reference        | Year | Disease                         | Treatments  | N  | Design | Protocol   | Adverse Effects                     |
|------------------|------|---------------------------------|---|----|--------|--|-------------------------------------|
| Wong et al[10]   | 2012 | Acquired perforating dermatosis | cantharidin 1%, podophyllin 5% and salicylic acid 30% | 1  | CR     | Applied once with occlusive dressing then washed off in 8 hours                                      | Pruritus, PIPA, and mild pain       |
| Akdemir et al[8] | 2011 | Callus removal                  | cantharidin 1%, podophyllin 5% and salicylic acid 30% | 30 | OL     | Debride, then one treatment with occlusive dressing for 5 days; repeat every 5 days until resolution | Erythema, burning, pain, blistering |
| Schencking and   | 2011 | Post-herpetic                   | cantharidin patch                                     | 1  | CR     | Applied patch  | Blistering, pain                    |

|                 |      |               |                           |     |              |   |                  |
|-----------------|------|---------------|---------------------------|-----|--------------|---|------------------|
| Kraft[7]        |      | neuralgia     |                           |     |              | 3x/week for 2 weeks with IV vitamin C   |                  |
| Ghaffarifar [9] | 2010 | Leishmaniasis | cantharidin 0.1% ointment | N/A | Animal study | Mice tails were infected with <i>L. major</i> and cutaneous lesions were treated. | Blistering, pain |

Abbreviations: PIPA - post-inflammatory pigmentation abnormality; CR- Case Report; OL - open label

## Molluscum Contagiosum

Molluscum is a common viral infection that spreads primarily by direct contact inoculation. Spontaneous resolution of the virus usually occurs within 6 months. However, reasons for treatment include cosmetic reasons, decreased transmission of the virus to self or others, and prevention of scarring/suprainfection [6]. There are multiple established treatment modalities including: curettage, cantharidin, cryotherapy, imiquimod, and cidofovir (in immunosuppressed patients).

The blister caused by cantharidin leads to expulsion of the molluscum upon wound healing. The painless and effective nature of cantharidin has produced positive satisfaction with its use ranging from 60-90% in parents and 92% in dermatologists [6]. The main disadvantage is the overall increase in the number of office visits required for complete clearance, which ranges from one to three visits, compared to one visit for curettage or incision and drainage [19-22]. For example, Hanna et al report subjective clearance rates of 36.7% (visit 1), 43% (visit 2), and 20% (visit 3). However, these findings were debated as possibly skewed owing to the ability of MC to spontaneously resolve and the subjective measure used for MC clearance [20].

The incidence of adverse effects associated with cantharidin for MC are: blistering (92%), erythema (37%), pain (14%), burning (10%), and pruritus (6%) [22]. Despite these adverse effects, 95% of parents polled stated they would choose cantharidin for MC treatment [22].

## Warts

The use of cantharidin for warts began in the early 1950s [1]. Since that time, cantharidin has been used to manage flat, palpebral, plantar, periungual, and subungual warts in an office setting. Although the mechanism by which the wart is removed has not been fully elucidated, it is hypothesized to work through physical extrusion, similar to that of cantharidin for MC, or disruption of vascular supply [8, 23]. In warts on volar skin, our practice has found cantharidin useful in un-roofing the wart, allowing for full delineation of its base prior to mechanical removal via shave, curettage, or electrodesiccation (Figure 1).

Protocols vary in contact time (from 4-8hrs), use of pre-application debridement, occlusion, interval between treatments, and number of lesions treated per visit [4, 24-26]. Considerations are the number of treatments required, type of wart being treated, and adverse events, which include blistering, pain, post treatment ring warts, and post inflammatory pigment alteration (PIPA) [6, 18, 21, 22, 27-29].

Efficacy of wart therapy using cantharidin is roughly 80% [30]. de Bengoa Vallejo et al report resolution with one treatment of plantar warts in 125/144 patients, of periungual warts in 4/12 patients, and of digital warts in 32/61 patients [27]. A prior study by Epstein and Kligman illustrated that 1 treatment was required for resolution in 22/55 patients with verruca vulgaris, 4/14 palmar warts, 5/27 plantar warts, and 4/12 periungual warts. When compared to cryotherapy, cantharidin required fewer treatments to achieve resolution (4.14 vs. 2.71) [24]. The rate of recurrence with cantharidin treatment was low, with no recurrences at six months in 144 patients with flat warts and only 1 recurrence at 1 year for digital/periungual warts [27, 31]

## Novel therapies

### *Acquired perforating dermatosis*

Acquired perforating dermatosis (APD) is a collection of disorders that relate to problems with elimination of collagen, elastic tissue, or necrotic connective tissue [10]. The disorders present as a collection of hyperpigmented papules exhibiting a central

keratotic plug. Perforating collagenosis, a type of APD, is usually seen in patients with end stage renal disease on hemodialysis [10]. First line therapies for APD include topical retinoids and UVB phototherapy, although efficacy reports are inconsistent [32].

A recent case study of one patient by Wong et al illustrates that cantharidin may be effective in the management of APD. The proposed mechanism of action is cantharidin-induced acantholysis, allowing for extrusion of the central keratotic plug from the hair follicle [12]. Treatment with cantharidin did not cause scarring and was an effective method of treatment in a patient who had failed multiple other therapies. Further studies are needed to elucidate the efficacy of cantharidin for use in APD.

### *Leishmaniasis*

A recent study by Ghaffarifar illustrates that topical cantharidin may be a useful alternative to antibiotics. In the study, mice tails were infected with *L. major* resulting in cutaneous lesions. Afterward, the lesions were treated with topical cantharidin 0.1% that led to resolution of the cutaneous leishmaniasis. The paper suggests that resolution of the cutaneous lesions is mediated by non-scarring intraepidermal acantholysis [9]. This mechanism is similar to those proposed in the treatment of APD, MC, and warts.

### *Callus Removal*

A recent study has proposed the use of a cantharidin-containing preparation (1% cantharidin, 30% salicylic acid and 5% podophyllin) as an adjunct to paring [8]. The investigators proposed that the cantharidin induces acantholysis within the hyperkeratotic lesion, resulting in its non-scarring removal. Over a 3-year period, calluses in the study were debrided followed by cantharidin placement at the periphery occluded with an antibiotic dressing. Only one treatment was required to achieve resolution of the callus in 57/72 patients (79.2%), two treatments in 9/72 patients (12.5%), three treatments in 5/72 patients (6.9%), and four treatments in 1/72 patients (1.4%) [8]. At one year of follow-up, only one recurrence was reported [10].

### *Post-herpetic Neuralgia*

To manage post-herpetic neuralgia, cantharidin patches were applied in one patient to areas below the affected dermatome-three times daily for two weeks with concomitant use of intravenous vitamin C [7]. Within two weeks, the patient reported a subjective pain score fifty percent less than originally recorded. In addition, the number and degree of skin lesions were reduced after the cantharidin patches were introduced [7]. Limitations of this report include the confounder of intravenous vitamin C and failure to indicate whether or not there were active vesicles. In addition, the report failed state the dose and reasons for not placing the patch directly on the affected dermatome.

## **Application of Cantharidin**

Two components determine the application of cantharidin: 1) the tool used for application, and 2) the decision to occlude after treatment. Three different tools can be used to apply cantharidin directly to a lesion, including an unbroken wooden end of cotton swab, a broken wooden end of cotton swab, or a toothpick.

We feel occlusion after application of cantharidin is beneficial because it prevents the material from being prematurely rubbed away. For the purpose of occlusion, prescribing information recommends the use of non-porous tape and that the medication be washed off the skin after 4-24 hours. However, prescribing information does not provide evidence for which time frame is the best. One must wait for the liquid to dry before application of the occlusive tape so that spread of the liquid outside of treatment boundaries does not occur. Occlusion is recommended in the prescribing information for the product. The authors, on the basis of anecdotal experience, recommend 8 hours for non-volar surfaces or any pediatric application and 24 hours for adult volar surfaces.

## **Adverse effects associated with topical use**

Adverse effects associated with cantharidin are significant and are reported in various studies to occur in 6-46% of patients [6, 18, 21, 22, 28, 33]. Three studies for MC report rates of adverse effects of 18.6%, 37%, and 46% [6, 18, 21, 22]. Some of the most common adverse effects are blistering, pain, erythema, bleeding, and PIPA [6, 18, 21, 22]. In addition, cantharidin has been reported to cause ring warts around area of treatment [27-29]. A study evaluating the use of cantharidin for warts resulted in 7/122 patients' developing ring warts [28].

The most often cited reasons for dissatisfaction relate to the adverse effects, lack of hard scientific data about cantharidin, and lack of agreed-upon treatment protocols [19].

Physicians have proposed measures to reduce the associated side effects with cantharidin, particularly in the pediatric population [6, 19, 20]. These include using a cotton tip applicator to minimize skin contact, using occlusive dressings, using less potent formulations (0.7% vs. 1% cantharidin), and using pain relievers [6, 19, 34]. In addition, some clinicians suggest reducing the contact time to reduce pain and possible overly vigorous response [29, 34, 35].

The degree of adverse effects associated with topical cantharidin is mostly mild. However, severe events – specifically, a case of varicelliform vesicular dermatitis [16] and three cases of lymphangitis [17, 36] – have been reported. In one report, two patients developed lymphangitis on their legs and forearms thirty hours after topical application and after a contact duration of 24 hours [36]. The patients responded well to broad-spectrum antibiotics and warm compresses [36]. In the third case, a young woman developed lymphangitis and permanent lymphedema in her right leg/foot after cantharidin was used for management of plantar verrucae. A few hours after placement of the 0.7% cantharidin on several verrucae, the patient developed swelling, pain, and ulceration at the application sites. Active inflammation resolved over the next week, but lower leg swelling continued over the next 9 months. Inflammation was believed to have caused damage to the lymph microvessels by cantharidin's acantholytic properties [17]. Twenty-six months after application, serial radiographic studies confirmed lymphatic vessel obliteration despite appropriate lymphedema management.

## Conclusion

Cantharidin has been used for dermatologic diseases for over 50 years with the primarily indications of removal of warts and MC. Cantharidin acts a skin vesicant that causes intraepidermal acantholysis, allowing for the successful removal of cutaneous lesions. Potential novel applications of cantharidin include application in acquired perforating dermatosis, acute herpes zoster, and leishmaniasis. Adverse effects are mild, but common, and proper measures should be taken to increase tolerability, particularly in the pediatric population.

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