

**A. INGREDIENT NAME:**

**CANTHARIDIN**

**B. Chemical Name:**

2,3 Dimethyl-7-Oxabicyclo [2.2.1.1 Heptane-2,3 Dicarboxylic Anhydride

**C. Common Name:**

Canthacur, Cantharone, Verr-Canth. Canthacur-PS; Cantharone Plus, Verrusol

**D. Chemical grade or description of the strength, quality, and purity of the ingredient:**

Result: The IR Spectrum exhibits the at  $\text{WN} > 1800$ , which is typical of Anhydrides and it conforms with the data reported in literature [Stork, G. van Tamelen, E. et. al, J Am Chem Soc. 75, 388 (1953)]

**E. Information about how the ingredient is supplied:**

Colorless glistening or orthorhombic plates, scales

**F. Information about recognition of the substance in foreign pharmacopeias:**

Span.

**G. Bibliography of available safety and efficacy data including peer reviewed medical literature:**

Rosenberg, E. W., Amonette, R. A., and Gardner, J. H. Cantharidin treatment of warts at home (letter). *Arch Dermatol*, 1977; 113(8):1134.

Harwell, W. B., Buchanan, Jr., R. N., and Hamilton, J. R. Foot Care. *J. Tennessee Med Assoc.*, 1978;71:830.

Rosenberg, E. W., Amonette, R. A., and Gardner, J. H. Foot Care. *Arch. Dematol.*; 1977;113:1134.

1998-3454B1-02-18-BDL05

**H. Information about dosage forms used:**

Liquid

Apply directly to the lesion and cover the growth completely.

**I. Information about strength:**

0.7%

**J. Information about route of administration:**

Topically

**K. Stability data:**

Melts at about 216-218°. Sublimes at about 110° with some fumes.

Stable

**L. Formulations:**

**M. Miscellaneous Information:**



No. Records Request  
\* 1 14 cantharidin

Record 1 of 3 - IPA 1970-3/98

TI: Warts and their remedies

AU: Lau-J; Grant-D

SO: On-Contin-Pract (OCP-On-Continuing-Practice); 1986; 13(Oct); 29-34

PY: 1986

AB: A review of the different categories of standard wart treatment is presented. Nonprescription therapy including salicylic acid, and collodions and an evaluation of some wart remedies are discussed. Schedule drugs such as cantharidin, podophyllum resin (podophyllin) are described. It was concluded that the pharmacist has a valuable role to play by offering information and advice on the proper use of the many nonprescription medications available to treat warts.

AN: 24-07153

Record 2 of 3 - IPA 1970-3/98

TI: Psoriasis: a defect in the regulation of epidermal proteases, as shown by serial biopsies after cantharidin application

AU: Dubertret-L; Bertaux-B; Fosse-M; Touraine-R

SO: Br-J-Dermatol (British-Journal-of-Dermatology); 1984; 110(Apr); 405-410

PY: 1984

AB: The effect of cantharidin (I) solutions on normal and psoriatic skin was studied in order to elucidate the possible role of epidermal serine proteases in the genesis of psoriatic lesions. In the skin of normal subjects, I induced epidermal damage was followed by the transient appearance of proteolytic activity in the upper epidermis accompanied by temporary hyperacanthosis and perivascular inflammatory cells in the superficial dermis. In the uninvolved skin of 5 psoriasis patients this proteolysis persisted longer, for more than 7 days. Thereafter, in 3 of the patients, the proteolysis abated, and this was followed by the disappearance of the hyperacanthosis and the dermal infiltrate; in the other 2 psoriatics the proteolysis and hyperacanthosis increased. It was suggested that the abnormal persistence of proteolytic activity in the upper epidermis after I application distinguishes the normal from the psoriatic skin injury response and might initiate the psoriatic lesion.

AN: 22-03599

Record 3

TI: Warts and what to do about them

AU: Rasmussen-JE

SO: Drug-Therapy (Drug-Therapy); 1981; 11(Nov); 65-67, 71-72, 74

PY: 1981

AB: Factors influencing the therapy of warts are discussed, and recommendations on the use of cryotherapy with liquid nitrogen, caustics or irritants, cantharidin, and other drugs, are given. The treatment is based on the number, size, location of the warts, as well as the patient's lifestyle and physical condition.

AN: 20-02288



## CANTHARIDIN

### Human Toxicities:

As little as 10 milligrams has been reported to cause death but the usual “minimum lethal dose” quoted is between 32 and 65 milligrams.

Exposure to 175 milligrams caused second and third degree burns of the mouth, seizures, kidney damage and hypotension, but the patient survived.

Ingestion of 105 to 140 milligrams produced ulceration and inflammation of the oral mucosa; the patient developed hematuria and T wave abnormalities, but recovered (adult ingested 1.5 to 2 ml of wart remover containing 0.7% cantharidin). Arrhythmias have been reported to occur.

It is extremely toxic ( 1 mg/kg ) orally and by inhalation and is corrosive to eyes, skin and mucous membranes.

Systemic toxicity can develop after dermal (topical) or oral exposure.

Could be a potential carcinogen (limited evidence) from dermal mouse carcinogenicity studies (squamous cell carcinomas, papillomas). Internal tumors (lymphomas, reticulum cell tumors) may be of significance.

Cantharidin is irritating to the mouth and throat, and can cause keratitis, iritis and edema of the eyelids. Hypotension, tachycardia, arrhythmias, ataxia, syncope and delirium have been noted.

### Cantharidin (cont.)

Symptoms of acute poisoning from ingestion include burning of the mouth, nausea, dysphagia, hematemesis, hematuria, dysuria, erosion and hemorrhage of the upper GI tract, renal dysfunction and failure due to acute tubular necrosis and destruction of the glomeruli. Less common effects are cardiac abnormalities, priapism and seizures.

Low grade disseminated intravascular coagulation has been reported in patients with acute cantharidin poisoning.

Fatty changes, parenchymatous degeneration, and a severe effect on hepatic organ structure may be seen.

TOPICAL application of cantharidin produced acute lymphangitis and persistent lymphedema in one case. Although edema and subpleural hemorrhages may be seen, the lungs are usually not seriously damaged. Respiration is greatly stimulated, then greatly depressed.

Mild to severe skin reactions may occur. Acantholysis has been reported as in pemphigus (skin blistering diseases).

It has been recommended that “owing to the high toxicity of Cantharidin, it is recommended that preparations containing it should not be used medicinally.”

Public Safety: Toxic and/or corrosive. Upon decomposition emits corrosive, toxic and irritating fumes. In contact with metals, it may evolve hydrogen gas.

## **Cantharidin** (cont.)

### **Uses:**

Cantharidin has been used:

-as a homicidal agent in South Africa.

Herbalist uses: for treatment of dropsy, pleurisy, pericarditis, kidney infections, kidney stones, stranguria (painful micturation), certain venereal diseases and amenorrhea, and as a putative aphrodisiac.

Modern uses: a counter irritant and vesicant in a 0.7% concentration in collodion (Verr-Canth, Pallsades Co.; Cantharone).



## REFERENCES

1. Mack P, Ha XF, Cheng LY. Efficacy of intra-arterial norcantharidin in suppressing tumour 14C-labelled glucose oxidative metabolism in rat Morris hepatoma. *HPB Surgery* 1996; 10(2):65-72.
2. Pahan K, Sheikh FG, Namboodiri AM, et al. Inhibitors of protein phosphatase 1 and 2A differentially regulate the expression of inducible nitric-oxide synthase in rat astrocytes and macrophages. *J Biol Chem* 1998; 273(20):12219-26.
3. Knapp J, Boknik P, Huke S, et al. The mechanism of action of cantharidin in smooth muscle. *Br J Pharmacol* 1998; 123(5):911-9.
4. Barr AC, Wigle WL, Flory W, et al. Cantharidin poisoning of emu chicks by ingestion of *Pyrota insulata*. *J Vet Diagn Invest* 1998; 10(1):77-9.
5. Wise R, Jones S, Das I, et al. Pharmacokinetics and inflammatory fluid penetration of clinafloxin. *Antimicrob Agents Chemother* 1998; 42(2):428-30.
6. Stazzone AM, Borgs P, Witte CL, et al. Lymphangitis and refractory lymphedema after treatment with topical cantharidin [letter]. *Arch Dermatol* 1998; 134(1):104-6.
7. Huang X, Honkanen RE. Molecular cloning, expression, and characterization of a novel human serine/threonine protein phosphatase, PP7, that is homologous to *Drosophila* retinal degeneration C gene product (rdgC). *J Biol Chem* 1998; 273(3):1462-8.
8. Hernandez ML, Martinez MJ, Lopez de Heredia M, et al. Protein phosphatase 1 and 2A inhibitors activate acyl-CoA: cholesterol acyltransferase and cholesterol ester formation in isolated rat hepatocytes. *Biochim Biophys Acta* 1997; 1349(3):233-41.
9. Helman RG, Edwards WC. Clinical features of blister beetle poisoning in uquids: 70 cases (1983-1996). *J Am Vet Med Assoc* 1997; 211(8):1018-21.
10. Blaukat A, Muller-Esterl W. Inhibition of B2 receptor internalization delays its dephosphorylation/Immunopharmacology 1997; 36(2-3):115-9.
11. Deshpande MV, O'Donnell R, Gooday GW. Regulation of chitin synthase activity in the dimorphic fungus *Benjaminiella poitrasii* by external osmotic pressure. *FEMS Microbiol Lett* 1997; 152(2):327-32.
12. Ford SL, Abayasekara DR, Persaud SJ, et al. Role of phosphoprotein phosphatases in the corpus luteum: I. Identification and characterisation of serine/threonine phosphoprotein phosphatases in isolated rat luteal cells. *J Endocrinol* 1996; 150(2):205-11.
13. Szoor B, Feher Z, Bako E, et al. Isolation and characterization of the catalytic subunit of protein phosphatase 2A from *Neurospora crassa*. *Comp Biochem Physiol B Biochem Mol Biol* 1995; 112(3):515-22.
14. da Cruz e Silva EF, da Cruz e Silva OA, Zaia CT, et al. Inhibition of protein phosphatase 1 stimulates secretion of Alzheimer amyloid precursor protein. *Mol Med* 1995; 1(5):535-41.
15. Eldridge R, Casida JE. Cantharidin effects on protein phosphatases and the phosphorylation state of phosphoproteins in mice. *Toxicol Appl Pharmacol* 1995; 130(1):95-100.

16. Wise R, Andrews JM, Da Ros L, et al. A study to determine the pharmacokinetics and inflammatory fluid penetration of two doses of a solid formulation of the hexetil prodrug of a trinem, sanfetrinem (GV 104326). *Antimicrob Agents Chemother* 1997; 41(8):1761-4.
17. Tsauer W, Lin JG, Lin PY, et al. The effects of cantharidin analogues on xanthine oxidase. *Anticancer Res* 1997; 17(3C):2095-8.
18. Klimowicz A, Nowak A, Bielecka-Grzela S. Plasma and skin blister fluid concentrations of metronidazole and its hydroxy metabolite after oral administration. *Pol J Pharmacol* 1996; 48(1):47-52.
19. Knapp J, Boknik P, Linck B, et al. The effect of the protein phosphatases inhibitor cantharidin on beta-adrenoceptor-mediated vasorelaxation. *Br J Pharmacol* 1997; 120(3):421-8.
20. Shirasu K, Nakajima H, Rajasekhar VK, et al. Salicylic acid potentiates an agonist-dependent gain control that amplifies pathogen signals in the activation of defense mechanisms. *Plant Cell* 1997; 9(2):261-40.
21. Perez F. Effects of cantharidin and a phorbol ester on bud formation in *Hydra vulgaris*. *Int J Dev Biol* 1996; Suppl 1:273S.
22. Zeretzke S, Berking S. Analysis of a *Hydra* mutant which produces extra heads along its body axis. *Int J Dev Biol* 1996; Suppl 1:271S.
23. Laidley CW, Cohen E, Casida JE. Protein phosphatase in neuroblastoma cells: [<sup>3</sup>H] cantharidin binding site in relation to cytotoxicity. *J Pharmacol Exp Ther* 1997; 280(3):1152-8.
24. Baskin TI, Wilson JE. Inhibitors of protein kinases and phosphatases alter root morphology and disorganize cortical microtubules. *Plant Physiol* 1997; 113(2):493-502.
25. Zimmerman N, Boknik P, Gams E, et al. Mechanisms of the contractile effects of 2,3-butanedione-monoxime in the mammalian heart. *Naunyn Schmiedebergs Arch Pharmacol* 1996; 354(4):431-6.
26. Linck B, Boknik P, Knapp J, et al. Effects of cantharidin on force of contraction and phosphatase activity in nonfailing and failing human hearts. *Br J Pharmacol* 1996; 119(3):545-50.
27. Ladilov YV, Siegmund B, Balsler C, et al. Simulated ischemia increases the susceptibility of rat cardiomyocytes to hypercontracture. *Circ Res* 1997; 80(1):69-70.
28. Zimmerli W, Sasano S, Wittke B. Pharmacokinetics of cefetamet in plasma and skin blister fluid. *Antimicrob Agents Chemother* 1996; 40(1):102-4.
29. Murphy LI, Jones PM. Phospho-serine/threonine phosphatases in rat islets of Langerhans: identification and effect on insulin secretion. *Mol Cell Endocrinol* 1996; 117(2):195-202.
30. Godart H, Ellory JC. KCl cotransport activation in human erythrocytes by high hydrostatic pressure. *J Physiol (Lond)* 1996; 491 (Part 2):423-34.
31. Abayasekara DR, Ford SL, Persaud SJ, et al. Role of phosphoprotein phosphatases in the corpus luteum: II control of progesterone secretion by isolated rat luteal cells. *J Endocrinol* 1996; 150(2):213-21.
32. Penrith ML, Naude TW. Mortality in chickens associated with blister beetle consumption. *J S Afr Vet Assoc* 1996; 67(2):97-9.

33. Mahajna M, Quistad GB, Casida JE. Retro-Diels-Alder reaction: possible involvement in the metabolic activation of 7-oxabicyclo[2.2.1]hepta-2(3),5(6)-diene-2,3-dicarboxylates and a phosphonate analog. *Chem Res Toxicol* 1996; 9(1):241-6.
34. Morana SJ, Wolf CM, Li J, et al. The involvement of protein phosphatases in the activation of ICE/CED-3 protease, intracellular acidification, DNA digestion, and apoptosis. *J Biol Chem* 1996; 271(30):18263-71.
35. Comolli J, Taylor W, Rehman J, et al. Inhibitors of serine/threonine phosphoprotein phosphatases alter circadian properties in *Gonyaulax polyedra*. *Plant Physiol* 1996; 111(1):285-91.
36. Herzig S, Meier A, Pfeiffer M, et al. Stimulation of protein phosphatases as a mechanism of the muscarinic-receptor-mediated inhibition of cardiac L-type Ca<sup>2+</sup> channels. *Pflugers Arch* 1995; 429(4):531-8.
37. Ford SL, Persaud SJ, Jones OM, et al. Phosphorylation phosphatase activities in rat luteal cells. *Biochem Soc Trans* 1995; 23(1):20S.
38. Mallari RQ, Saif M, Elbualy MS, et al. Ingestion of a blister beetle (Mecoidae family). *Pediatrics* 1996; 98(3 Pt 1):458-9.
39. Karras DJ, Farrell SE, Harrigan RA, et al. Poisoning from "Spanish Fly" (cantharidin). *Am J Emerg Med* 1996; 14(5):478-83.
40. Eisner T, Smedley SR, Young DK, et al. Chemical basis of courtship in a beetle (*Neopyrochroa flabellata*): Cantharidin as "nuptial gift". *Proc Natl Acad Sci USA* 1996; 93(13):6499-503.
41. Eisner T, Smedley SR, Young DK, et al. Chemical basis of courtship in a beetle (*Neopyrochroa flabellata*): cantharidin as precopulatory "enticing" agent. *Proc Natl Acad Sci USA* 1996; 93(13):6494-8.
42. Heda GD, Kehoe KJ, Mahdi F, et al. Phosphatase 2A participates in interferon-gamma's induced upregulation of C1 inhibitor mRNA expression. *Blood* 1996; 87(7):2831-8.
43. Child J, Mortiboy D, Andrews JM, et al. Open-label crossover study to determine pharmacokinetics and penetration of two dose regimens of levofloxacin into inflammatory fluid. *Antimicrob Agents Chemother* 1995; 39(12):2749-51.
44. Miller DM, Brodell RT. Human papillomavirus infection: treatment options for warts [see comments]. *Am Fam Physician* 1996; 53(1):135-43, 148-50.
45. Dong Z, Yang X, Xie K, et al. Activation of inducible nitric oxide synthase gene in murine macrophages requires protein phosphatases 1 and 2A activities. *J Leukoc Biol* 1995; 58(6):725-32.
46. Erdodi F, Toth B, Hirano K, et al. Endothal thioanhydride inhibits protein phosphatases-1 and -2A in vivo. *Am J Physiol* 1995; 269(5 Pt 1):C1176-84.
47. Marcovigi P, Leoni S, Calbi G, et al. [Acute poisoning caused by cantharidin ingestion for aphrodisiac purposes. A clinical case.] *Minerva Anestesiol* 1995; 61(3):105-7.
48. Liu XH, Blazsek I, Comissio M, et al. Effects of norcantharidin, a protein phosphatase type 2A inhibitor, on the growth of normal and malignant haemopoietic cells. *Eur J Cancer* 1995; 31A(6):953-63.

49. Neumann J, Herzig S, Boknik P, et al. On the cardiac contractile, biochemical and electrophysiological effects of cantharidin a phosphatase inhibitor. *J Pharmacol Exp Ther* 1995; 274(1):530-9.
  50. Brimfield AA. Possible protein phosphatase inhibition by bis(hydroxyethyl)sulfide, a hydrolysis product of mustard gas. *Toxicol Lett* 1995; 78(1):43-8.
  51. Awong IE, Dandurand KR, Keeys CA, et al. Drug-associated Guillain-Barre syndrome: literature review. *Ann Pharmacother* 1996; 30(Feb):173-80.
  52. O'Neill P, Nye K, Douce G, et al. Pharmacokinetics and inflammatory fluid penetration of cefpodoxime proxetil in volunteers. *Antimicrob Agents Chemother* 1990; 34(Feb):232-4.
  53. Wang GS. Medical uses of mylabris in ancient China and recent studies. *J Ethnopharmacol* 1989; 26(Sep):147-62.
  54. Lau J, Grant D. Warts and their remedies. *On Contin Pract* 1986; 13(Oct):29-34.
  55. Dubertret L, Bertaux B, fosse M, et al. Psoriasis: a defect in the regulation of epidermal proteases, as shown by serial biopsies after cantharidin application. *Br J Dermatol* 1984; 110(Apr):405-10.
  56. Ryan DM, Hodges B, Spencer GR, et al. Simultaneous comparison of three methods for assessing ceftazidime penetration into extravascular fluid. *Antimicrob Agents Chemother* 1982; 22(Dec):995-8.
  57. Rasmussen JE. Warts and what to do about them. *Drug Therapy* 1981; 11(Nov):65-67, 71-72, 74.
  58. Ewart WB, Rabkin SW, Mitenko PA. Poisoning by cantharides. *Can Med Assoc J* 1978; 118(May 20):1199.
  59. Rietschel RL, Akers WA. Effects of harvesting techniques on hydration dynamics: gravimetric studies of stratum corneum. *J Soc Cosmet Chem* 1978; 29 (Dec):777-82.
  60. Simon C, Maleryzk V, Ahlendorf W. Sisomicin: in vitro activity and pharmacokinetics. *Int J Clin Pharmacol Biopharm* 1978; 16(Apr):145-9.
  61. Salama RB, Hammouda Y, Gassim I. Isolation of cantharidin from *Cyaneolytta sapphirina*. *J Pharm Pharmacol* 1974; 26(Apr):268-9.
  62. Guenther H, Ramstad E, Floss HG. On the biosynthesis of cantharidin. *J Pharm Sci* 1969; 58(Oct):1274.
- Sadik F. OTC products for corns, calluses, warts. *J Am Pharm Assoc* 1970; NS10(Jan):8-12.