Podophyllin office therapy against condyloma should be abandoned

Geo von Krogh, Eric Longstaff

Podophyllin, a crude plant extract with low efficacy, high toxicity, and a serious mutagenicity profile does not comply with the WHO guidelines for plant derived treatments and should be removed from clinical treatment protocols. Home treatment with pharmaceutical products based on podophyllotoxin—the purified, standardised active antiwart ingredient of podophyllin—represents safe and effective first line therapy for patients with anogenital warts.

(Sex Transm Inf 2001;77:409–412)

Keywords: podophyllin; podophyllotoxin; condyloma therapy

Introduction
Patients with condylomata acuminata present to many different disciplines, and recent guidelines focus on shared management between specialists and primary care physicians.1,4 This article focuses on the advantages of purified podophyllotoxin preparations over crude podophyllin extract for safe, fast, and cost effective home treatment for condyloma eradication.

Podophyllin
The herbal extract known as podophyllin is a crude, non-standardised, and impure resin preparation obtained from the rhizomes of the Podophyllum plant species P. peltatum, or P. emodi. The antiviral ingredients are antimitotically acting lignans,1 of which podophyllotoxin is the most potent.2 Kaplan demonstrated that topical 25% P. peltatum resin extract could accomplish regression of condylomas. However, long term efficacy rates originally claimed have not been confirmed, recurrence rates being 33–55%.8 Other drawbacks include short shelf life, risk of severe local and systemic toxicity, and mutagenic properties.

Quality Control Problems
Extraction procedures, entailing rhizome treatment with ethanol/precipitation in acidified water, do not allow for quantitative determination of constituents, which vary between batches. Toxic ingredients often cause unpredictable and severe local toxicity including painful burns and ulcerations. Podophyllin is unstable during clinic storage, with frequent crystallisation and formation of inactive microsomes of lignans.6

High Toxicity
Podophyllin must be applied by a trained care giver at weekly intervals. The resin must be washed off 4–6 hours after application; use of a protective inert ointment for the surrounding skin is recommended.

There is a risk of systemic intoxication, as ingredients at high concentrations may be absorbed and distributed to vital organs including the gastrointestinal mucosa, the kidneys, the bone marrow, and the CNS. Of greatest concern are the number of case reports revealing that following podophyllin painting of large condylomas, after subdermal injection into plantar warts, or following accidental ingestion, podophyllin may cause fatal or near fatal intoxication6–17 due to CNS influence, coma, respiratory depression, etc, and cardiovascular crisis. There is no known antidote. Irreversible peripheral neuropathy is a sequel in survivors. Warnings against use of volumes exceeding 0.4–0.9 ml have been issued.12

Podophyllin contains two mutagenic flavonoids, quercetin and kaempherol, which make up 3% and 6% of the dry weight, respectively18–20 and that potentially may enhance oncogenic HPV associated intraepithelial neoplasia.21

Regulatory Aspects and Safety Evaluation
The WHO guidelines for evaluation of herbal remedies include tests for (1) acute toxicity; (2) long term toxicity; (3) mutagenicity and carcinogenicity; (4) reproductive toxicity; and (5) local toxicity. A formal regulatory review and safety evaluation of podophyllin has never been performed, although mutagenicity, carcinogenicity, and reproductive toxicity studies indicate that podophyllin is potentially very dangerous.22–24

A high incidence of tumours has been reported in mice exposed to podophyllin containing wood bedding.22 Podophyllin may cause chromosomal changes in hamsters23 and may be co-carcinogenic with oestrogen therapy.24 Podophyllin induces increased mutation rates in Salmonella typhimurium, numerical chromosomal defects in mammalian cell cultures, and a high incidence of chromatid and chromosome deletions, chromatid exchanges, and cells with multiple aberrations in human lymphocytes. In mice, podophyllin seems teratogenic, inducing a high frequency of fetal mortality; in rats no teratogenic influence has been demonstrated.24
Podophyllotoxin

Podophyllotoxin is the active antiwart ingredient of Podophyllum; the pharmacological action is that of blocking microtubule assembly of the mitotic apparatus by binding to the tubulin.1 3

LOW CLINICAL TOXICITY

In contrast with podophyllin, topical use of 0.15%–0.5% podophyllotoxin preparations are very safe for clinical use. In patients “drenching” extremely large condylomata plaques with excessive amounts of 0.5% podophyllotoxin solution, corresponding to 0.11 mg/kg as a single dose and 0.64 mg/kg as a cumulative dose, subsequent serum levels in the range of 1–17 ng/ml of podophyllotoxin have been measured. Such quantities are far below levels of clinical significance1; cancer patients receiving daily intravenous injections of 0.5–10 mg/kg podophyllotoxin have not developed any injury beyond transient bone marrow depression.25 Von Krogh25 calculated that even if a 100% podophyllotoxin absorption in theory were excessive amounts of 0.5% podophyllotoxin preparations are more e

Table 1 Condyloma eradication following self therapy with podophyllotoxin compared with podophyllin office therapy; complete cure rates at 3–4 months’ follow up

<table>
<thead>
<tr>
<th>Podophyllotoxin</th>
<th>Podophyllin</th>
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<tbody>
<tr>
<td>Courses 0.5% solution twice daily 3 days</td>
<td>20% once weekly p Value</td>
</tr>
<tr>
<td>Von Krogh 19817</td>
<td>1–2 85% (142/173) 38% (40/105) &lt;0.001</td>
</tr>
<tr>
<td>Lauzon 198727</td>
<td>1–4 77% (37/48) 44% (23/52) &lt;0.01</td>
</tr>
<tr>
<td>Edwards et al1988</td>
<td>1–6 88% (28/32) 63% (12/19) &lt;0.05</td>
</tr>
<tr>
<td>Markiewicz et al 199028</td>
<td>1–6 79% (11/14) 38% (5/13) &lt;0.05</td>
</tr>
<tr>
<td>0.5% solution twice daily 3 days</td>
<td>25% twice weekly</td>
</tr>
<tr>
<td>Lacey et al 200129</td>
<td>1–4 63% (57/90) 37% (33/90) 0.001</td>
</tr>
<tr>
<td>0.15% cream twice daily 4 days</td>
<td>25% twice weekly</td>
</tr>
<tr>
<td>Lacey et al 200129</td>
<td>1–4 59% (40/68) 37% (33/90) 0.008</td>
</tr>
</tbody>
</table>

Carcinogenicity and genotoxicity

Rats and mice receiving up to 0.3 mg/kg/day of podophyllotoxin in the diet for 104 and 80 weeks, respectively, have not shown any evidences of an oncogenic effect. In Salmonella typhimurium podophyllin induced up to 13.6-fold increase in revertant numbers, while...
podophyllotoxin exposure merely resulted in a 1.5–1.6-fold increase attributed to chance with no dose relation. PHA stimulated human lymphocyte cultures exposed to podophyllotoxin for 25 hours did not show any clastogenic effect. No mutagenic potential has been detected in ovarian and lymphoma cell cultures, and no single strand DNA breakage has been detected in human cell cultures.

Local sensitisation potential
In the guinea pig maximisation test 0.1% and 0.5% podophyllotoxin preparations caused toxic reactions associated with the cutaneous necrosis but did not show any immunological sensitising properties.35

Reproductive toxicity
Podophyllotoxin is not teratogenic to rats or rabbits. Pregnant rats and their offspring were followed after oral administration of 0.4, 1.0, or 2.5 mg/kg/day podophyllotoxin from the 15th day of gestation to the 21st day post partum. There were no influences on fertility, gestation, mating, litter size, embryonic or fetal development, or perinatal and postnatal behaviour. A negative influence was observed in the offspring exposed to the highest dose (2.5 mg/kg) regarding survival rate, as well as delayed development and weight gain of survivors. There was no influence in exposed animals on the rate of malformations, birth weight, behaviour, or on fertility or mating in podophyllotoxin exposed mothers or in their first/second generation offspring. Although reproductive toxicity studies in animals have not shown teratogenicity and the half life appears to be short and systemic elimination occurs within a few days, we still believe that podophyllotoxin should be avoided during pregnancy since the possibility cannot be excluded that the drug might accumulate in the human fetus. As a further precaution, we also excluded that the drug might accumulate in the pregnant rat and her offspring.

Conclusions
Use of the crude herbal remedy podophyllin is associated with low production costs, but the cost benefit versus the risk ratio of the product is highly questionable. Further podophyllin use is not only redundant but should be abandoned in favour of its modern pharmaceutical replacement—that is, podophyllotoxin preparations with well defined pharmacokinetic, metabolic, and toxicity safety profiles. Podophyllotoxin solution and cream have been documented as safe and effective for self therapy of anogenital warts (table 2) and are recommended as first line therapy.

Table 2 20% Podophyllin versus 0.15–0.5% podophyllotoxin

<table>
<thead>
<tr>
<th>Podophyllin</th>
<th>Podophyllotoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-standardised, unstable</td>
<td>Standardised, stable</td>
</tr>
<tr>
<td>Local toxicity high</td>
<td>Local toxicity low</td>
</tr>
<tr>
<td>Systemic toxicity high</td>
<td>Systemic toxicity negligible</td>
</tr>
<tr>
<td>Teratogenic and fetotoxic</td>
<td>Non-teratogenic</td>
</tr>
<tr>
<td>High mutagenicity</td>
<td>No mutagenicity</td>
</tr>
<tr>
<td>Carcinogenic effect?</td>
<td>No carcinogenic effect</td>
</tr>
<tr>
<td>Low efficacy</td>
<td>High efficacy</td>
</tr>
<tr>
<td>Clinic treatment</td>
<td>Self treatment</td>
</tr>
<tr>
<td>High treatment cost</td>
<td>Moderate treatment cost</td>
</tr>
</tbody>
</table>

9 Von Krogh G. Penile condylomata acuminata: an experimental model for evaluation of topical treatment with 0.5%–1.0% ethanolic preparations of podophyllotoxin for three days. Sex Transm Dis 1981;8:179–84.
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