Self-treatment using 0·25%-0·50% podophyllotoxin-ethanol solutions against penile condylomata acuminata: a placebo-controlled comparative study.

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Abstract

***Objective*—To compare the efficacy of 0·50% and 0·25% podophyllotoxin preparations against previously untreated penile warts.**

***Design*—The study was performed as a double-blind, placebo-controlled investigation on 57 males randomly allocated to one of three groups of 19 males in each, receiving either the placebo solution (70% ethanolic vehicle) or one of the two podophyllotoxin preparations for 1–2 self-treatment courses b.i.d. for three days, separated by a one-week drug-free interval.**

***Setting*—The STD out-patient clinic of the Department of Dermatovenereology at Southern Hospital of Stockholm, Sweden.**

***Result*—The placebo solution merely exerted a marginal influence on the warts while a primary cure was documented in 72% (13/18) and 81% (13/16) of altogether 34 evaluable men who treated their warts with 0·25% and 0·50% podophyllotoxin, respectively. Follow-up investigation (range 5–23 weeks) was possible for 24 of 26 podophyllotoxin treated men who were primarily cured. Some degree of relapse occurred in nine of them (38%). Of these relapses, warts occurred on previously untreated sites only in three cases (33%), and in another four (44%) relapse was associated with regrowth on treated sites as well as on new sites. When analysing the debulking potential of podophyllotoxin, it appeared that 0·25% podophyllotoxin eradicated 184 of originally 217 warts (85%); the corresponding figure for 0·50% podophyllotoxin was as high as 130 of 135 lesions (96%). Side effects were generally mild-moderate and well tolerated.**

***Conclusion*—The results underscore the potential usefulness of low-dose podophyllotoxin preparations as first-line chemotherapy of condylomata acuminata for home-treatment. The efficacy from topical use of 0·25% podophyllotoxin detected in the study is certainly of a magnitude signifying that podophyllotoxin concentrations lower than 0·50% deserve further investigation if the drug may be incorporated into alternative vehicles such as creams or ointments.**

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Introduction

Fifty years ago it was demonstrated that topical applications of podophyllin at weekly intervals may bring about involution of condylomata acuminata lesions within three to five days.[1-3] Initially reported success rates, based on short-term evaluation, were encouraging, but subsequent studies have shown the long-term efficacy to be highly inadequate.[4-7]

Also, applications of undue podophyllin volumes may induce detrimental local and systemic toxicity.[5 8] Podophyllin preparations represent chemically complex crude plant resin extracts from the Podophyllum plant species manufactured by merely a semi-quantative method.[9] Accordingly, nonhomogeneity and nonuniformity characterise the resin composition, which is prone to vary significantly between different batches.[5 9] Severe local burns sometimes follow, and the potential for life-threatening systemic toxicity following injudicious applications have been repeatedly documented.[8] Therefore, applications must be carried out by skilled medical staff, ideally at weekly intervals, putting a heavy work load on the medical staff.

The anti-wart effect of podophyllin is exerted by *lignans*, capable of arresting mitotic cell division in the metaphase, and also inhibiting cellular nucleoside transport.[4 5 9 10] These compounds may be purified by liquid chromatography.[11] Podophyllotoxin, a lignan shared by different Podophyllum species, is one of the most potent ingredients in podophyllin.[12 13]

In previous studies we found that the eradication rate of penile condylomas could be improved by allowing the patients to self-treat their warts twice daily for three days with an ethanolic preparation of 0·5% podophyllotoxin, a concentration of drug far below that which is systematically hazardous even when treating extremely large warts.[8 14] The regimen is very well tolerated by the patients[4 14] and its use implies a significant cost-benefit gain for the health care system.[15] These aspects have subsequently been confirmed by others,[16-23] and further refinements by drug incorporation into alternative vehicles, such as cream formulations have been initiated.[24] However, few placebo-controlled evaluations have been performed and a further titration of optimal podophyllotoxin concentration for home-treatment is required.

The present study was initiated in order to compare the long-term efficacy from 1–2 repeated courses of self-treatment b.i.d. for

three days using 0·50% (Wartec® Perstorp Pharma, Science Park Ideon, S-223 70 Lund, Sweden) with 0·25% podophyllotoxin preparations against previously untreated penile warts. The study was controlled by using a 70% ethanolic vehicle as placebo treatment.

Material and methods

Study approval

The study was approved by the National Board of Health and Welfare and by the local ethical committee. Only the short-term efficacy evaluation of placebo treatment was considered ethically justifiable.

Trial preparation

Test bottles of identical appearances, containing 5 ml of the trial preparation, were provided by Conpharm AB (Uppsala, Sweden). The placebo preparation contained the following ingredients: methylrosaniline 0·05 g, spir.dil 70 g and aqua steril ad. 100 ml. The active preparations had identical composition with the exception that crystalline podophyllotoxin was added at a concentration of 5 mg/ml or 2·5 mg/ml, respectively. For the purpose of shelf-life stability all trial solutions also contained acid.acetic 1 M.

One trial bottle was given for each three-day cycle of medication, bottles being returned to the investigator subsequent to the performance of a three-day home-treatment cycle. A maximum of two treatment cycles was allowed.

Trial design

The study was performed as a double-blind, placebo-controlled investigation on 57 males randomly allocated to one of three groups of 19 males in each, receiving either the placebo solution or one of the two podophyllotoxin preparations.

All men were given detailed oral and written information regarding the purpose and design of the study and of possible side effects. Each patient was then given one bottle per period of three days of treatment and a written instruction regarding the practical procedures of therapy and of personal hygiene. Demonstration of the treatment procedure, using cotton wool swabs for applications, was given by the investigators at the initial treatment day. The men were instructed to treat their warts at home twice daily for three days, and if then not cured, to repeat the three-day home-treatment for another cycle against any residual warts (that is a minimum of six and a maximum of 12 applications). The second cycle was preferably to be initiated day 8-10 after the start of the first one, but could when required also be instituted within another week or so (mean = 9·5, SD 0·6 days, range 6-28 days).

Patients were told to clean the penis with soap and water and subsequently dry with a paper towel prior to each application, to achieve a complete painting of all warts but to avoid excess spreading to adjacent epithelium, and to allow the trial preparation to air dry for at least one minute.

Patients

The patients comprised consecutive men attending for previously untreated penile condylomas at the Department of Dermatovenereology at South Hospital of Stockholm, Sweden. Prior to enrolment in the study all men were investigated for the presence of penile inflammatory conditions and/or other genital dermatoses, as well as for the presence of any urethritis as evaluated by microscopic investigation of a methylene blue stained urethral swab sample. At the first visit concurrent syphilis was ruled out by the standard Wasserman CF test (which at the time of the study was the standard screening procedure) and HIV antibodies by an enzyme-linked immunosorbent assay ELISA technique.[28] Furthermore, urethral specimens were collected for cultures of *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Consistent use of condoms during intercourse for a period of three months was strongly advocated by the investigators.

Characterisation of lesions

A history of any previous episodes of condylomas and the duration of the current lesions were recorded. Using a standardised chart for each visit, four major categories of warts were monitored according to one or more of the following anatomical sites; the first category entailing warts in the urinary meatus (including the fossa navicularis, which was routinely inspected through meatal dilatation by a small nose speculum); the second category the preputial cavity (that is the glans penis, the coronal sulcus, the fraenulum, and/or the inner aspect of the foreskin); the third category the transitional area between the inner and outer aspect of the foreskin; and, a fourth category the penile shaft. Each of these sites were continuously monitored for the number of warts at any time during the trial.

Follow-up investigations

Patients who considered themselves as cured after the first three-day cycle of home-treatment were instructed to return for a first follow-up visit two weeks after initiation of therapy. Patients who did not consider themselves as completely cured after the first cycle were instructed to return after a week, when the first bottle of trial preparation was collected and another one was handed out. All patients were evaluated for efficacy after a maximum of 3 weeks or earlier for those having two treatment cycles. Patients considered as wart free were asked to return for long term follow-up visits at 8 weeks and preferably 24 weeks after instigation of the trial.

Patients who experienced a relapse subsequently to primary cure were classified as having a true "recurrence" if the relapse occurred on genital site(s) that were also wart-afflicted prior to therapy. Whenever a relapse afflicted anatomical subsites that had not been engaged prior to enrolment, the case was classified as "re-occurrence".

Statistical analysis

Analysis of variance and chi square tests were used in efficacy and side-effect analysis.

Results

Of the 57 enrolled patients in this trial six did not return after the first visit despite contacts over the telephone. Two were given placebo and four podophyllotoxin. These patients have not been included in this evaluation.

All of the 51 evaluable men were uncircumsised and did not exhibit any signs of inflammatory conditions or dermatoses. None exhibited signs of phimosis and the foreskin was easily retractable in all participants. Serological tests were negative for syphilis and HIV in all of the men, who were all also otherwise systemically healthy. There were no signs of urethritis; yet, while the gonorrhoea test was negative in all cases, three males (5·9%) were chlamydia culture positive and duly treated prior to receiving the trial preparation.

The mean age of the participants was 25·4 years (range, 17–48 years). The three groups of patients were fairly well matched with respect to their mean age (range, 23·2–27·2 years). Altogether 10 patients (19·6%) were below 21 years of age, 28 (55%) were in the range of 21–25 years, and another 19 men (37%) were older than 25 years.

The mean duration of condylomas before treatment was 4·1 months (range, 1–24 months), and there were no significant differences in duration between the patient groups (range, 3·7–4·6 months). In 21 patients (41%) the duration was less than 2 months, in another 13 (25%) in the range of 3-5 months, and in 10 men (20%) condylomas had been present for more than 5 months. In 13 cases an exact measure of wart duration could not be given.

The mean number of warts at first presentation was 7·8 in the placebo group, 12·1 in the group treated with 0·25% podophyllotoxin, and 8·4 in the group treated with 0·50% podophyllotoxin ($F = 1·35$, $P = 0·27$). There was a higher total number of warts in the group treated with 0·25% podophyllotoxin (206) than in the 0·50% podophyllotoxin group (134).

The placebo treatment did not induce any changes in 14 of the 17 men (82%). However, three patients had a reduction in the number of their warts. These patients were not followed for further long-term evaluations. Four of the men provided with podophyllotoxin trial preparations did not return for further evaluations. When contacted by telephone they all stated that cure had been accomplished but they were, nevertheless, not included in efficacy evaluations. All but one of the remaining 34 men were observed to have a reduction or a complete eradication of their warts as evaluated 1-3 weeks after instigated therapy. The number of patients free of any warts after one or two treatment cycles appear from table 1.

Podophyllotoxin treatment was highly significantly superior to that of placebo therapy ($p < 0·001$).Following therapy with 0·25% podophyllotoxin nine men were free of warts after the first cycle and another four following the second cycle of therapy. The corresponding figures for men treated with 0·50% podophyllotoxin were nine and four respectively. Thus, the percentage of patients primarily becoming wart-free after 1–2 cycles were 72% and 81% in the groups treated with 0·25% and 0·50% podophyllotoxin, respectively (table 1); in this respect, no differences appeared between the podophyllotoxin treated groups (Fisher's, $p = 0·69$).

Follow-up investigations were possible in altogether 24 of the 26 patients who were considered wart free after podophyllotoxin treatment. Of 20 patients followed for more than five weeks 15 still had no warts. Thirteen patients were available for follow-up for more than 20 weeks and nine of them remained free of warts (table 2). Among the nine men (38%) experiencing a relapse, three (33%) were merely afflicted with warts occurring on previously untreated sites ("re-occurrences"). In another four (44%) of these cases a relapse on previously treated sites was combined with warts developing on other anatomical subsites as well ("recurrences" and "re-occurrences" combined).

The influence on reduction of tumour burden at various locations is given in table 3. A final cure was accomplished for a total of 184 of 217 warts (85%) treated with 0·25% podophyllotoxin versus 130 of 135 lesions (96%) treated with 0·50% podophyllotoxin. The differences between the 0·25% and the 0·50% podophyllotoxin regimen were highly significant in favour of the higher drug concentration, whether analyses were based

Table 1 Number of wart free patients after 1–2 therapy cycles with 0·25%-0·50% podophyllotoxin or with placebo solutions

	Podophyllotoxin		
	0·25% (n = 18)	*0·50% (n = 16)*	*Placebo (n = 17)*
Therapy cycle			
First	9	9	0
Second	4	4	0
Cumulative	13 (72%)	13 (81%)	0

Table 2 Number of wart free patients after treatment, and at 5–7 weeks and at 20-23 weeks later.

No of wart free patients / number of evaluable patients (% wart free patients)

Treatment	*After treatment*	*5–7 weeks later*	*20–23 weeks later*
Placebo	0/17 (0)	—	—
0·25% Podophyllotoxin	13/18 (72)	5/8 (63)	2/5(40)
0·50% Podophyllotoxin	13/16 (81)	10/12 (83)	7/8 (88)

Table 3 Number of permanently eradicated warts after treatment/No. of warts prior to treatment at indicated sites (% reduction)

Treatment	*Preputial cavity*	*Transition inner/outer part of foreskin*	*Other*	*All sites*
Placebo	36/39 (8)	89/94 (5	0/0	125/133 (6)
0·25% Podophyllotoxin	10/109 (91)	22/104 (79)	1/4 (75)	33/217 (85)
0·50% Podophyllotoxin	0/74 (100)	4/58 (93)	1/3 (67)	5/135 (96)

Table 4 Patients with reported/observed side effects after 1–2 cycles of podopyllotoxin therapy or placebo treatment

	n	Side effects			
		Mild	Moderate	Pronounced	Total
Placebo	17	3	1	0	4 (24%)
0·25% Podophyllotoxin	18	9	2	3	14 (78%)
0·50% Podophyllotoxin	16	9	2	3	14 (88%)
Total	34	18 (53%)	4(12%)	6 (18%)	28 (82%)

Table 5 Classification and grading of side effects observed/reported among podophyllotoxin-treated men

Grading	Classification	
	Erythema, tenderness and/or erosions	Itching and/ or burning
Mild	13	16
Moderate	3	2
Pronounced	6	5
Total	22	23

on a complete eradication of all lesions (adj. $\chi^2 = 10{\cdot}27$, p=0.001), or on warts in the preputial cavity (Fischer's, p = 0·006), that is the site afflicting the predominant majority of patients.

Some type of side effect was reported in four of the 17 placebo treated (24%) and in 28 of the total of 34 podophyllotoxin treated (82%) patients (adj. $\chi^2 = 14{\cdot}35$, $p < 0{\cdot}001$). During placebo treatment four men experienced a slight stinging or burning during applications, and one of them also reported a moderate erythema. No differences in frequency or in severity of side effects were seen in the two groups of men treated with 0·25% and 0·50% podophyllotoxin, respectively (table 4).

Altogether 22 (65%) of the men experienced some degree of erythema, tenderness and/or superficial epithelial erosions in association with wart cure (table 5), and in 23 (68%) cases patients reported varying degrees of itching and/or burning during wart involution. Altogether six patients (18%) experienced side effects classified as more pronounced (table 4), being distributed as erythema/tenderness and/or erosions in six cases and as itching and/or burning in five cases (table 5). Yet, even the latter patients stated that these side effects were fully acceptable. In no cases were additional anti-inflammatory therapy or analgesics required. No cases of balanoposthitis were observed, and none of the men had any problems in retracting their foreskin during or after therapy.

Among the 16 patients treated with two podophyllotoxin cycles, 12 patients reported some type of side effects during the first cycle whereas only six patients reported side effects during the second cycle.

Discussion

The present study confirms previous reports on a high efficacy against penile warts from a regimen for home-treatment based on 0·5% podophyllotoxin-ethanol solutions.[15 17–24] Also, the absence of more than a marginal effect from the ethanol-placebo preparation is congruent with recent investigations. Thus, Beutner *et al*[21] found no cases of primary cure in 53 men treated with ethanol twice daily for three days for up to four cycles, and Greenberg *et al*[22] made analogous observations in females treating themselves for vulva warts. Lack of significant placebo effect has also been documented for in a double-blind study on the efficacy of a propylene glycol based podophyllotoxin cream formulation tested on vulva warts.[24]

After 1–2 cycles of podophyllotoxin therapy and as much as 72–81% of patients became free of all warts. Some degree of relapse occurred in 38% of the men. The trend towards a somewhat higher efficacy from the 0·50% compared to the 0·25% podophyllotoxin preparation reached statistical significance when reduction of the initial tumour burden, including the number of relapsing warts, was further analysed. The latter way of analysing the results, rather than considering a complete cure only, underscores the usefulness of podophyllotoxin as an agent for first-line chemotherapy of condylomata acuminata; as much as 96% of warts disappeared after the use of 0·50% podophyllotoxin, and 85% after the use of 0·25% podophyllotoxin preparations.

The efficacy of 0·25% podophyllotoxin detected in the present study is certainly of a magnitude signifying the value of further investigating the use of drug concentrations below 0.50% for condylomata therapy. This aspect is of particular importance when podophyllotoxin is incorporated into alternative vehicles such as creams or ointment formulations, when drug efficacy potentially may be enhanced because of improved penetration into the warts.

The frequency of re-occurrences in the present study (33%) apparently being the sole cause of a relapse may possibly represent an underestimation. Thus, in a previous report re-occurrences were noted in as much as 63% of the cases.[23] In order to assess accurately the type of relapse in individual cases a graphic method based on accurate drawings or photo documentation is required; such an approach was not used in the current study.

Any therapy, whether chemical or surgical, aiming at inducing wart removal through destruction/removal of the afflicted epidermis will inevitably be associated with some degree of local discomfort. Such side effects seem essential if treatment is to be effective. In the present study, accounting for an eradication of 85%–96% of the original wart number, some type(s) of side effect(s) occurred in 82% of the patients. However, as indicated also in previous studies on podophyllotoxin treatment,[23] we found that the discomfort to the patients was of short duration and was generally classified as mild to moderate. Side effects also tended to become less pronounced when therapy was repeated compared with when it was initiated. In concordance with previous experiences we found the discomfort to be considerably less severe than after treatment with podophyllin.[21-24]

Recent understanding that subclinical HPV infection frequently coexist with overt condylomas has created some ambiguity about optimal level of management, as it has been proposed that recognition of subclinical lesions forms an essential part of the management plan.[25] However, there are several objections to this point of view and we believe that today's management of condylomata patients should rely upon diagnosing and treating only those lesions that cause illness and psychosexual distress.[26 27] Accordingly, in the present investigation no effort was made to diagnose and treat subclinical lesions. Some of the relapsing warts may possibly have emanated from a biological activation of subclinical lesions coexisting with the clinical ones at initiation of the trial. The potential future use of a low-dose cream/ointment preparation of podophyllotoxin for application against subclinical lesions as well is, on the other hand, a concept that deserves further investigations.

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