

TOPICAL TREATMENT OF PENILE CONDYLOMATA ACUMINATA WITH PODOPHYLLIN, PODOPHYLLOTOXIN AND COLCHICINE

A Comparative Study

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Abstract. The effects of alcoholic solutions with 20% podophyllin from *Podophyllum peltatum* and *Podophyllum emodi*, 8% podophyllotoxin, and 8% colchicine, when applied to penile condylomata acuminata in 227 men, were statistically alike. Of the patients initially judged to be cured after 1–2 applications, 13% showed recurrence, thus bringing down the permanent cure frequency to only 43%. Local side effects were absent after only half the series of colchicine applications, whereas as much as about 3/4 of the treatment course with podophyllin and pure podophyllotoxin could be completed without provoking discomfort. Warts in the urinary meatus healed significantly less well than warts on the other genital mucous membranes. Eighty-nine per cent of patients who had previously been cured of condylomata became wart-free after 1–2 treatments, as opposed to only 40% of those who had never had this wart type previously. The use of the commercially available colchicine offers an opportunity to establish a standardized therapy; following application of an 8% solution, rinsing off should be performed after 6–8 hours.

Key words: Condylomata acuminata; Topical drug therapy; Podophyllin, podophyllotoxin and colchicine

Condylomata are virus-induced venereally transmissible genital warts having an incubation period of 2–3 months (1, 7, 20). Since 1944 podophyllin has been considered the drug of choice for the treatment of condylomata (6, 25). Concerning penile condylomata, Culp & Kaplan (5) reported 83% to be cured after one application and all cases following four applications of 25% podophyllin in mineral oil. Necrosis, followed by rejection of the warts, was noted within 2–3 days. The oil tended to spread to the adjacent mucous membranes, and balanoposthitis was not unusual. With 20% podophyllin in alcohol, the effect was more distinctly limited to the warts, and by rinsing off the substance within 12 hours, local side effects were reduced (27).

From the resin of the plants *Podophyllum peltatum* or *Podophyllum emodi*, grown in North America and the Himalayas respectively, the chemically complex powder called podophyllin is extracted. Quercetin is the pigment responsible for the colour. The biological effect is exerted by colourless so-called lignans which, as in the case of colchicine, link to the microtubule protein in G₂ phase of the cell cycle, leading to the arrest of mitosis in metaphase (16, 30, 31).

In commercially manufactured podophyllin the concentration of lignans is determined semiquantitatively (22). Precise quantitative determinations necessitate special methods (19). The lignan content varies from batch to batch. The optimum (Table 1) in podophyllin from *P. emodi* is about 40% podophyllotoxin and 2% 4'-dimethylpodophyllotoxin, whereas from *P. peltatum* the proportions are ca. 10% podophyllotoxin and 13% peltatins (11, 16). In Sweden, application of 20–25% alcoholic solutions of podophyllin from *P. peltatum* is the commonest treatment for condylomata, but with regard to rinsing instructions, one is by tradition very careful. In a retrospective study (17) we found that in only 17% of male patients the condylomata disappeared after one application, whereas 36% needed more than four applications. However, the interval between application and rinsing off of the podophyllin was only 1–2 hours in 72% of the patients. In order to discover the reason behind the discrepancy between these results and those presented on the introduction of podophyllin, a comparative investigation was conducted with alcoholic solutions of podophyllin from *P. peltatum* and *P. emodi*, and also of crystalline podophyllotoxin, as the interval between application and rinsing was simultaneously prolonged. Since lignans and col-

Table I. *Percentage content of lignans in podophyllin of varying origin*

	Podophyllo- toxin	4'-Dimethyl- podophyllotoxin	Peltatins	Total
<i>P. peltatum</i>				
Optimum	10	0	13	23
Tested batch	8		8	16
<i>P. emodi</i>				
Optimum	About 40	2	0	42
Tested batches				
1	35	Not tested		37 (max)
2	42	1		43

chicine share certain biological properties, the effect of the latter was also investigated. Application of colchicine has sporadically been mentioned as an alternative treatment for venereal warts, but reports on clinical experiences are sparse (9, 13, 15, 27, 29).

MATERIAL AND METHODS

Patients

To obtain a homogeneous and clinically easily controlled material, only men with previously untreated genital condylomata were investigated. In consecutive series, a total of 227 men were treated. Their distribution among the various treatment groups is presented in Table II. At the first visit, the duration of the affliction and possible previous episodes of venereal warts were noted. If at least 6 months had passed since the healing of an earlier infection with condylomata, the patient was considered to be a case of reinfection and was included in the investigation; cases in which a shorter interval had elapsed were excluded. At every examination of the patients, the distribution and the number of warts, as well as their range in size at each site, were recorded. This enabled a continuous follow-up study to be made on the effects of the treatment under investigation.

The condylomata were classified into three types (Table III) according to location site: the urinary meatus including fossa navicularis (Type I), the preputial cavity (Type II; glans penis, coronal sulcus, fraenum and the inner aspect of the prepuce), or the epidermis (Type III). The transitional area between the preputial cavity and the preputial epidermis was classified as epidermal.

As a routine, specimens for gonorrhoea culture were collected, and urethritis and other inflammatory conditions, e.g. balanitis, were treated as early as possible, and in most cases before commencing treatment of the condylomata. The condylomata were, as far as possible, treated once a week. After retraction of the prepuce, the solution was applied with a cotton wool swab, so that the warts were completely painted, though avoiding excess spreading to the adjacent tissues. The solution was allowed to dry, whereupon the procedure was repeated and a further drying was completed before the prepuce was

freed. Application within the urinary meatus was done immediately after micturition. The patient was then instructed to avoid micturition for the next 6–8 hours. In the case of condylomata at other locations, rinsing was recommended after successively increasing the time intervals for the different solutions (Table IV). To avoid the risk of reinfection, and to evaluate the true relapse frequency, the patients were instructed to use condoms during intercourse throughout the period of treatment, and for a further month after clinical healing. Four to six weeks after established healing, a final follow-up check was conducted, when the patients were advised to return promptly if a subsequent relapse occurred; if a patient did not attend, the case was considered as one of definite cure.

Preparations of solutions

Podophyllin from *P. peltatum* was provided by Penick & Co. (New York) and the two batches from *P. emodi* by University College Hospital, London (courtesy, J. D. Oriel, M.D.). Crystalline colchicine and podophyllotoxin were obtained from Sandoz Ltd, Basle. The latter substance is not available commercially.

The podophyllins were diluted five-fold in 70% alcohol to produce 20% solutions. To make possible a comparative study of the effect of podophyllin with optimum lignan content vis-à-vis pure podophyllotoxin, we used the latter substance in an 8% solution. However, since podophyllotoxin is completely insoluble in water (16), the substance had to be dissolved in absolute alcohol in order to prevent precipitation. Colchicine, similarly, was also used as an 8% solution, but this substance could be easily dissolved in 70% alcohol (2). The advantage of the latter type of vehicle is that one avoids very rapid evaporation from the cotton wool swab during the application. The solutions of podophyllin were tinted brown by the presence of quercetin, while 0.05% methylrosaniline was added to the colourless solutions of podophyllotoxin and colchicine to facilitate the visual control of the painted areas.

Chemical analysis of lignans

The quantitative determinations of lignan content in the podophyllin were conducted at the Central Pharmacy, Södersjukhuset, Stockholm. The podophyllin was macer-

Table II. Number of men with healing of all genital warts

Figures within parentheses denote percentages

No. of appli- cations	Applicated substance				Podophyllo- toxin <i>n</i> = 72	Colchi- cine <i>n</i> = 50	Total <i>n</i> = 227	
	<i>P. peltatum</i> <i>n</i> = 47	<i>P. emodi</i>						
		Batch 1 <i>n</i> = 31	Batch 2 <i>n</i> = 27	Total <i>n</i> = 58				
<i>Initial healing</i>								
1	13 (28)	9 (29)	7 (26)	16 (28)	32 (44)	23 (46)	84 (37)	56%
2	6 (12)	7 (23)	5 (19)	12 (20)	14 (19)	11 (22)	43 (19)	
>2	28 (60)			30 (52)	26 (36)	16 (32)	100 (44)	
<i>Permanent healing</i>								
1	9 (19)	8 (26)	6 (22)	14 (24)	23 (32)	18 (36)	64 (28)	43%
2	6 (13)	7 (23)	4 (15)	11 (19)	12 (17)	6 (12)	35 (15)	
>2	32 (68)			33 (57)	37 (51)	26 (52)	128 (57)	

ated in chloroform, evaporated after filtration, and dissolved in ethyl acetate. The solutions were applied to an Al_2O_3 column, whereby elution was performed with alcohol on UVICORD II. The fractions were evaporated to dryness and then dissolved in chloroform. The lignans were then precipitated with petroleum ether and identified by thin-layer chromatography on silica plates, using chloroform/acetic acid 70/30 as the fluid phase. Additionally, the lignans were identified by IR-spectrophotometry. Subsequent to identification, the various fractions were weighed (19).

Statistical analysis

The statistical evaluation was conducted using χ -square analysis.

RESULTS

Podophyllin from *P. peltatum* contained 16% podophyllotoxin and peltatins, and the two batches from *P. emodi* contained 35% and 42% podophyllotoxin respectively. One of the latter batches was

also analysed regarding the content of 4'-dimethyl-podophyllotoxin, which was about 1% (Table I). The sum of therapeutically active substances in the 20% solutions of podophyllin was thus 3.2% for *P. peltatum* and 7.4–8.6% for *P. emodi*.

Initially, 40–68% of the patients were cured of all genital warts after 1–2 applications (Table II), but within 4 weeks on average (range 1–8) relapse occurred in 5–20% of these cases. Thus, only 28% were cured after the first treatment and a further 15% after the second. No additional cases of relapse have been seen during a further follow-up period of 4–30 months. Neither after one nor after 1–2 treatments was there any significant difference between the four treatment groups. Nevertheless, when compared with the *P. peltatum* group, the other groups tended to have better final results.

According to the classification of condylomata into various types (Table III), the 227 men exhibited

Table III. Permanent healing after 1–2 treatments, related to type of genital wart

Type of wart	No. of pats. exhibiting warts at any one site	Permanent healing after 1–2 treatments				
		<i>P. peltatum</i>	<i>P. emodi</i>	Podophyllo-toxin	Colchi-cine	Total
Type I (urinary meatus, fossa navicularis)	40	42% (5/12)	20% (2/10)	11% (1/9)	56% (5/9)	33%
Type II (glans penis, coronal sulcus, fraenum, inner aspect of prepuce)	199	41% (16/39)	48% (25/52)	56% (36/64)	59% (26/44)	52%
Type III (epidermis)	56	27% (3/11)	56% (9/16)	39% (7/18)	27% (3/11)	39%

Table IV. Side effects (percentage) of clinically checked applications

	No. of applications clinically checked											
	<i>P. peltatum</i> 187			<i>P. emodi</i> 116			Podophyllotoxin 158			Colchicine 112		
Hours between applica- tion and rinsing ...	6-8	10-12		6-8	10-12	≈ 24	6-8	10-12	≈ 24	6-8	10-12	≈ 24
No side effects	69	7		34	34	13	6	13	57	33	19	-
Itching, burning, slight tenderness, erythema	19	3		9	3	3	1	2	18	13	17	1
Pain, swelling, minor erosions	2	-		1	1	1	1	-	1	13	2	-
Balanoposthitis	-	-		-	-	1	-	-	-	-	-	2

warts at altogether 295 sites, as some had warts of more than one type. After 1-2 treatments, condylomata in the preputial cavity healed significantly better ($p < 0.05$) than in the urinary meatus, whereas no difference was found on comparison with condylomata on the epidermis. All solutions had the same effect ($p > 0.05$) on warts in the preputial cavity, but the series are too small for analogous statistical judgements in the case of warts in the urinary meatus and on the genital epidermis. Of the 199 cases of warts in the preputial cavity, 73 healed after the first, and a further 30 after the second application which, however, was performed one week after the first one in only 66% of the cases, and in the remainder at intervals varying from 2 to 9 weeks. The second application gave identical results, irrespective of whether it was conducted 1 week after the first application, or whether a longer interval had elapsed ($p > 0.05$).

No statistical difference was apparent to denote whether the results were related to the number of warts or their duration.

Sixteen of 18 (89%) of the patients who had also previously been cured of condylomata were free of all warts after 1-2 treatments, as opposed to 84 of 209 (40%) of those who had never previously had that type of wart. The difference here is highly significant ($p < 0.001$).

Side effects appeared after half the colchicine applications, whereas 76-81% of the applications with podophyllin and podophyllotoxin could be completed without provoking discomfort (Table IV). More pronounced symptoms occurred most often in cases of multiple or large condylomata in the preputial cavity, and in the colchicine group

after 15% of the applications as opposed to 2-3% with the other substances. Pain, when felt, was experienced after 1-3 days and was most intense after treatment with colchicine, with a maximum of discomfort after 3-5 days. Spontaneous relief usually developed within a couple of days, and local applications of corticosteroid had a beneficial effect. Superficial erosions corresponding to the wart sites were not unusual one week after the colchicine treatment. Balanoposthitis occurred in one man with unsatisfactory genital hygiene, and in two further patients with numerous confluent warts in the preputial cavity, where rinsing had been performed after 24 hours. In a few cases, rubrosquamous irritation of the scrotum occurred when the substance applied had spread beyond the areas painted.

DISCUSSION

Although the lignan content in the second batch of podophyllin from *P. emodi* was optimal and 2.5 times greater than in *P. peltatum*, the clinical effect was roughly identical, as shown by cure rates after 1-2 applications of 32 and 37% respectively. Thus, the lignan content in the peltatum podophyllin was still within therapeutic limits. However, treatment with emodi podophyllin or pure podophyllotoxin gives an overall slight trend towards improved results. This may be attributed partly to the tendency to prolong the interval before rinsing off of these substances (Table IV). Due to a relatively higher frequency of local irritation (13, 29), this was not the case with colchicine, though an analogous trend towards improved results was still found, suggesting that this substance has a greater clinical potency

than lignans. This may be due to the fact that linkage of colchicine to the cellular microtubuli is irreversible, while in the case of lignans it is reversible (30). Comparatively speaking, podophyllotoxin causes insignificant local side effects, and since podophyllin is a chemically complex mixture, the severe local reactions sometimes observed after podophyllin applications (12) could emanate from substances other than the lignans, and could therefore possibly vary from batch to batch.

Our treatment results with lignans differ markedly from the original reports: in 96% vs. 75% of cases, penile condylomata disappeared after 1–2 applications with 25% peltatum podophyllin in mineral oil (5) or 5–10% podophyllotoxin in alcohol (28). As these studies were carried out on soldiers, the movements of military organizations would appear to have interrupted complete follow-up investigations (5). Cohen (4) found that only 33% of cases of penile condylomata healed after one application of podophyllin. Gersh (8) observed that more than one application was usually necessary for condylomata of the preputial cavity, and that 35% of his patients returned with recurrence within 3 months. Only 41–56% of our patients with this type of condylomata were cured after 1–2 treatments with lignans, despite the fact that the penetration properties on mucous membranes can be presumed to be most favourable, especially because of an extra occlusive effect as none of our patients had been circumcised.

The smallness of the materials may partly explain the great differences between the results from different treatment groups regarding condylomata in the urinary meatus and on the genital epidermis. Furthermore, condylomata classified as epidermal behave differently, clinically. At the root of the penis they are often ridged and the treatment effect is better than for the usually flattened warts on the shaft of the penis. On the transitional area between the inner and outer aspect of the prepuce the mucous membrane gradually changes to epidermis, and the warts can be either ridged or more flattened.

Poorer healing of warts in the urinary meatus may result from the rinsing off of the treatment substance during micturition (5).

The prognosis for common warts is affected by virus-induced, humoral or cellular, immune responses and is poorest in old tumours, when the viral content tends to decrease and the number of

tumours to increase (10, 14, 23, 24, 26). The possible prognostic significance of immunological mechanisms in venereal warts has not been studied. There is a likelihood that an immunological 'memory' can also arise with this wart type, since we found the prognosis to be significantly better in patients who had previously been cured of condylomata, than in those who had never suffered from venereal warts.

By inhibition of mitosis, lignans and colchicine cause cellular necrosis in the basal cell layer and in adjacent parts of the stratum spinosum (21, 27, 28), so that cells essential for the replication of the virus are destroyed and liberation of the viral antigen is achieved. Damage to the epitheliadermal barrier does not always occur (cf. Table IV), and in the dermis only a sparse scattering of lymphocytes appears (27). Substances causing a greater degree of dermal inflammation as well as epidermal ulceration may pose a greater risk for liberated antigen to stimulate the immune mechanism. The irritation effect of colchicine can thus be of possible advantage. Perhaps epidermal cell destruction could be made more effective if the applications were performed more often than once a week, or if substances having alternative modes of action on the cellular cycle were used, for example 5-fluoro-uracil (3, 12, 18).

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