Podophyllotoxin 0.5% v podophyllin 20% to treat penile warts

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SUMMARY The increasing incidence of genital warts has led to more public awareness of this infection and its possible sequelae. Currently available treatment remains unsatisfactory, and there is pressure to develop effective and convenient alternatives. Podophyllotoxin is standardised and stable, whereas podophyllin has a variable composition. In an open comparison of self applied podophyllotoxin 0.5% versus podophyllin 20% applied by a doctor to treat external penile warts, podophyllotoxin was more effective and gave quicker resolution than podophyllin. Side effects were similar for both preparations, and few patients experienced complications severe enough to stop treatment. Podophyllotoxin can therefore be used safely and effectively for home treatment monitored at an outpatient clinic and provides a useful alternative to treatment with podophyllin at overburdened genitourinary medicine clinics.

Genital warts are a common and increasing problem.¹ Treatment is often tedious and unreliable and requires regular clinic attendance for an unpredictable period. Most specialists prefer to supervise topical treatment in view of the consequences of overenthusiastic or injudicious self administration and reports of systemic toxicity associated with podophyllin.^{2,3}

Podophyllin is a non-standardised unstable plant extract that contains several active constituents, the most active being podophyllotoxin; podophyllin 20% can contain 4% to 8% podophyllotoxin.⁴ Podophyllotoxin 0.5%, in contrast, is a pure and stable solution. This low concentration provides treatment that appears to be safe yet effective for use at home.⁴

The study reported here was designed to compare the clinical efficacy and side effects of podophyllotoxin solution 0.5% with those of podophyllin 20% in alcohol for treating penile warts. The podophyllotoxin was used at home, and the podophyllin was applied by a doctor.

Patients, materials, and methods

We recruited men with diagnoses, based on clinical appearance, of external penile warts. They were excluded if they had had treatment for warts in the

preceding 28 days or if the area to be treated exceeded 10 cm².

At their first visit we screened all patients for other sexually transmitted diseases, including syphilis, gonorrhoea, non-gonococcal urethritis and chlamydial infection, and trichomoniasis, using methods based on those described previously.⁵ Using wire loops, we collected urethral secretions for Gram stain, gonococcal culture, and wet film examination for *Trichomonas vaginalis*. Material for chlamydial culture was collected with wire mounted cotton swabs inserted 5 cm into the urethra. Criteria for diagnosing non-gonococcal urethritis were based on those of Swartz *et al.*⁶ We advised patients to use condoms during treatment and for the subsequent three months, and we urged them to persuade regular sexual partners to attend for examination and, if indicated, treatment.

Patients were allocated treatment by means of a computer generated randomisation code. Those allocated to treatment with podophyllotoxin had it applied at the first visit by the doctor and were instructed to continue application morning and evening to complete three consecutive days' treatment. They were asked to return a week later for further assessment. If the warts were still present, patients continued treatment each week for up to six weeks. Patients experiencing side effects were advised to stop treatment until they were reviewed, when the doctor decided whether to continue treatment. Those allocated treatment with podophyllin were treated by the doctor once a week for up to six weeks.

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Accepted for publication 20 February 1988

Before treatment started we took blood samples to investigate full blood counts, liver function, and concentrations of urea and electrolytes. These investigations were repeated at weeks 3 and 6 or at the time of resolution if this was sooner.

Resolution was assessed by the doctor, and defined as the disappearance of the tumour. Patients whose warts had not resolved after six weeks were withdrawn from the trial and regarded as treatment failures. Relapse was defined as resolution followed by reappearance of the tumour during the three months of follow up. All patients were asked to return three months after resolution; those who defaulted were reminded and sent a further appointment.

Results

Of 65 patients recruited, 14 subsequently defaulted. The remaining 51 had been randomly allocated treatment on a 2:1 basis; 32 received podophyllotoxin and 19 received podophyllin. Table 1 shows the demographic data of all 65 patients.

Table 2 compares the outcome of the two treatment regimens. Podophyllotoxin gave better results, as 28/32 treated with podophyllotoxin but only 12/19 treated with podophyllin showed resolution within six weeks of treatment ($\chi^2 = 4.17$; $p < 0.05$). The response with podophyllotoxin was also quicker, with 24/32 showing resolution at week four compared with 8 of 19 in the podophyllin group ($\chi^2 = 5.48$; $p < 0.02$).

Reattendance after three months was unsatisfactory; 8/13 treated with podophyllotoxin and 4/8 treated with podophyllin remained in remission. The default rate was too high to allow comparison.

No biochemical abnormalities were observed.

SIDE EFFECTS

Two patients treated with podophyllotoxin experienced side effects that interrupted treatment; one had erythema that persisted for three weeks, and one had penile swelling. One patient treated with podophyllin also developed erythema with preputial tightening. All three patients' problems resolved without active

Table 1 Demographic data of 65 men with penile warts (figures are numbers of patients except where stated)

	Podophyllotoxin (n = 41)	Podophyllin (n = 24)
Age (years):		
Mean	27	29
Range	20-42	19-45
Racial origin:		
Black	3	1
White	36	23
Asian	2	0
Sexual orientation:		
Homosexual	1	0
Heterosexual	40	24

Table 2 Results of two treatment regimens in 65 men with penile warts (figures are numbers of patients)

	Podophyllotoxin	Podophyllin
Patients entered	42	23
Defaulters	10	4
Evaluable patients	32	19
Failure at six weeks	4	7
Resolution at six weeks	28	12
Resolution at three months	8	4
Relapse by three months	5	4

intervention when the treatment for warts was stopped.

Patients in both groups (21/32 treated with podophyllotoxin, 15/19 treated with podophyllin) experienced transient side effects in the form of trivial irritation and mild erythema, but treatment was continued.

Discussion

We compared a new formulation, podophyllotoxin, with an established treatment, podophyllin. The results show that podophyllotoxin 0.5% is an effective treatment for genital warts, with more patients showing resolution after four and six weeks of treatment. Side effects were all minor and resolved without active intervention.

Podophyllin has long been a popular initial treatment for genital warts, but in practice problems arise—local reactions, occasional systemic toxicity,^{2,3} and unpredictable effects. Different studies report different outcomes, possibly reflecting variation in composition and stability of currently available preparations of podophyllin. Maiti and Haye reported results resembling ours in a non-comparative study of similar numbers of patients using weak concentrations of commercially available podophyllin.⁷ Several of their patients had superficial chemical burns that required active treatment, but the outcome was not mentioned. We remain unconvinced about the safety of self application of apparently weak solutions of podophyllin when concentration and stability cannot be ensured. Furthermore, we have not found any other reports of podophyllin used in this manner.

Many doctors and patients have become disillusioned with the use of currently available, simple, non-invasive methods. They may try other techniques, such as electrocautery, laser, infra-red coagulation, cryotherapy, and surgery. (Thin RNT and Whatley J, unpublished observation)⁸⁻¹⁰ These methods are time consuming for doctors and patients; though they may have more immediate responses, new warts still form and there may be relapse later.¹¹ Accurate information about long term outcome is lacking, as most studies only assess the outcome at three to four months.⁸⁻¹⁰

Many clinics report an increase in the number of

patients with wart virus infection,¹ and many patients are aware of the possible sequelae. There are thus problems in meeting the demands for adequate and effective treatment. We still need safe, simple, first line treatment. Podophyllotoxin 0.5% can now be added to the list of treatments. It is effective, standardised, and stable, so can be used safely at home in contrast to podophyllin.

We thank Dr O Hammershoj of Pharma-medica AS, for the supply of podophyllotoxin, and Julie Whatley, for statistical help.

References

- 1 Communicable Disease Surveillance Centre. Sexually transmitted disease surveillance in Britain: 1985. *Communicable Disease Report* 1987 November 13.
- 2 Stoehr GP, Peterson AL, Taylor WJ. Systemic complications of local podophyllin therapy. *Ann Intern Med* 1978;**89**:362-3.
- 3 Cassidy ED, Drewry J, Fanning JP. Podophyllin toxicity: a report of a fatal case and a review of the literature. *J Toxicol Clin Toxicol* 1982;**19**:35-44.
- 4 Von Krogh. Condylomata acuminata: an updated review. *Seminars in Dermatology* 1983;**2**:109-29.
- 5 Bradbeer CS, Thin RN. Comparison of econazole and isoconazole as single dose treatment for vaginal candidosis. *Gentourin Med* 1985;**61**:396-8.
- 6 Swartz SL, Kraus SJ, Harrman KL, Stargel MD, Brown WJ, Allen S. Diagnosis and etiology of non-gonococcal urethritis. *J Infect Dis* 1978;**138**:445-54.
- 7 Maiti H, Haye KR. Self treatment of condyloma acuminata with podophyllin solution. *The Practitioner* 1985;**229**:38-9.
- 8 Bekassy Z, Westrom L. Infra-red coagulation in the treatment of condyloma acuminata in the female genital tract. *Sex Transm Dis* 1987;**14**:209-12.
- 9 McMillan A, Scott GR. Outpatient treatment of perianal warts by scissor excision. *Gentourin Med* 1987;**63**:114-5.
- 10 Gollock JM, Stafford K, Hunter JM. Scissor excision of anogenital warts. *British Journal of Venereal Diseases* 1982;**58**:400-1.
- 11 Frenczy A, Mitao M, Nagai N, Silverstein SJ, Crum CP. Latent papillomavirus and recurring genital warts. *N Engl J Med* 1985;**313**:784-8.