Original article

Podophyllin 0·5% or 2·0% *v* podophyllotoxin 0·5% for the self treatment of penile warts: a double blind randomised study

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Objective: To compare the effectiveness and cost of self treatment of penile warts with a commercial preparation of podophyllotoxin 0·5% (PDX 0·5%) with podophyllin 0·5% and podophyllin 2·0% sourced from *Podophyllum emodii*.
Design: A prospective double blind randomised study.
Subjects: 315 patients with penile warts attending two departments of genitourinary medicine.
Main outcome measures: Absence of warts, cessation of treatment due to severe side effects at 5 weeks.
Results: Of the 315 patients, 244 conformed to the protocol. Analysis was on an intention to treat basis. At 5 weeks no significant differences were found in the extent of healing of warts or in side effects for the three treatment groups. The costs of drug treatment (excluding staff time) are at least £10·00 less for podophyllin than podophyllotoxin. A fourfold variation in the active constituents of the podophyllin preparations did not produce appreciably different clinical responses. In a subanalysis no evidence of deterioration in effectiveness of podophyllin over time was demonstrated.
Conclusions: Penile warts in selected cases can be safely treated with 0·5–2·0% podophyllin self applied by the patient at a fraction of the cost of commercially available podophyllotoxin. The shelf life of the podophyllin extracts is at least 3 months. These findings may be especially relevant in countries where resources for health care are limited.
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Keywords: penis, warts; podophyllin; podophyllotoxin

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Introduction

Anogenital warts are a common problem among genitourinary medicine (GUM) clinic attenders. In the year 1994 alone there were 25 467 male patients who attended GUM departments in England with first presentation genital warts.[1] An established first line treatment for anogenital warts is physician/nurse applied podophyllin, a non-standardised plant extract, up to three times per week. This is extremely intensive of clinical staff and patient time.

Commercial preparations of podophyllotoxin 0·5% (PDX 0·5%) (a purified derivative of podophyllin) (Condyline, Nycomed Ltd, Warticon, Perstopp Pharma) are available for the self treatment of anogenital warts and comparative studies have shown self treatment with PDX 0·5% to compare favourably with weekly clinic applied podophyllin 20%–40%.[2–4] PDX 0·5% also has theoretical advantages when compared with podophyllin in that it is chemically defined, pure, and is stable with a defined shelf life but is considerably more expensive. Podophyllin 0·5–2·0% (PODO 0·5–2·0%) self applied in the same manner as PDX 0·5% has also been shown to be an effective treatment for penile warts.[5] PODO 0·5–2·0% contains podophyllotoxin in the approximate range of 0·06%–0·25% but also contains other biologically active substances.[6] One small study has previously compared PODO 0·5% with PDX 0·5% and found no difference in outcome or side effects.[7] Potentially, PODO 0·5–2·0% offers an alternative to PDX 0·5% at a significant cost saving.

The primary aim of this study was to compare the efficacy and side effects of PDX 0·5%, PODO 0·5%, and PODO 2·0% for the self treatment of penile warts. It was designed as a three way randomised, double blind study. The secondary aim was to assess whether the time between manufacture and dispensing of PODO 0·5–2·0% affected clinical efficacy and side effects.

Patients

Patients attending the departments of genitourinary medicine at Birmingham General Hospital and the Coventry and Warwickshire hospital who presented with first episode, untreated penile warts were eligible for the study. Patients were excluded if they had non-penile warts requiring separate treatment, any substantial risk for HIV infection, another painful penile condition, intrameatal warts, had received any treatment for their warts in the previous 12 months, or were under 16 years old. All patients were routinely screened for other sexually transmitted diseases (STDs). Written informed consent was obtained and the study was approved by the relevant hospital ethics committees.

Materials and methods

The study recruitment took place within the routine clinics of both centres but, as far as possible, review was performed by two main observers in each centre at dedicated times. Wherever possible one of these observers recruited patients.

At recruitment the following characteristics were noted: the length of time warts had been present; the number of warts were counted and the size noted diagrammatically on a map of the genitals; the type of warts was categorised as to whether they were sessile, acuminate, or both. Circumcision status was not recorded.

Patients were allocated their treatment by means of a computer generated random allocation list. A total of 106, 103, and 106 patients, respectively, were allocated to: (1) 3 ml of podophyllotoxin 0·5% (PDX 0·5%). (Warticon, Perstopp Pharma); (2) 5 ml of podophyllin 0·5% (PODO 0·5%); (3) 5 ml of podophyllin 2·0% (PODO 2·0%).

The podophyllin was prepared in the Birmingham General Hospital pharmacy, from *Podophyllum hexandrum (emodii)* derived podophyllin resin powder in 90% industrial methylated spirits. Treatment packs were kept at ambient temperature on a shelf in the hospital pharmacy. Each treatment was dispensed by the hospital pharmacy in sealed boxes with obscured contents labels. A record was kept of the dates of manufacture and dispensing for each patient. Treatment bottles were not brought along to review appointments. Patients were instructed to apply the preparation twice daily for 3 consecutive days per week using 1·0 µl soft plastic microbiological loops (Technical Service Consultants Ltd). Patients were instructed that if soreness occurred they should stop applying the medication but could recommence the following week. If soreness/side effects proved unacceptable they were to contact the clinic and would exit the study. Identical patient information leaflets were placed in each box which gave instructions on how to apply the medication and warning about side effects. Patients were given a diary card to record when they applied their medication. They were asked to attend for review for any other clinical condition (except their warts) and for their STD screen results 2 weeks later. They were asked to attend for the purposes of the trial at 5 weeks and 3 months after commencing treatment.

At the time of review diary cards were collected and the severity of side effects and whether these had caused the patient to stop treatment were noted. Records were made of patient satisfaction with treatment, the number of remaining warts, a diagrammatic estimation was made of the wart size, and treatment diary cards were collected. Patients with warts were subsequently categorised by comparison of surface area/number in comparison with their entry records as: healed—that is, no warts found; improved—that is, warts reduced in surface area/number but still present; no change; or worse.

If patients did not attend for review at week 5 they were sent a questionnaire and a stamped addressed envelope through the post asking for details of their response (side effects and whether warts healed completely) at the missed appointment time and for the return of their diary cards.

STATISTICS

The trial size was based on an expected 50% default/non-evaluable rate and a primary endpoint of whether warts were healed completely/not healed. Using the methods of Cohen[8] it was estimated that 300 patients entered—that is, 150 evaluable patients, would give a 90% power to detect medium differences at the 5% level. A medium difference is defined as a difference between proportions ranging around 20%.

The results were entered onto a computer database and the analyses were carried out using SAS at the West Midlands Health Authority information department. Analysis was on an intention to treat basis. Before data analysis the report forms were reviewed for: patients with major violations of the treatment protocol—for example, those who never collected their treatment, used it for 1 day, or used it continuously; inappropriate recruitment—that is, the exclusion/inclusion criteria had not been properly applied. These had all entries at follow up set to "unknown results".

χ^2 tests (or Fisher's exact test where appropriate) were used throughout except for the analysis by time since manufacture, which used Kruskal-Wallis tests comparing the manufacturing/dispensing time (M/D time) across the categories of each variable.

Results

In all, 315 patients were recruited from September 1991 to October 1992. The patients' characteristics at entry are shown in table 1.

We had aimed to recruit a largely unselected population. Because of the number of patients required and the limited resources available, most of the entry documentation was performed in busy routine clinics. A proportion of this was by members of staff who did not have a specific interest in this study. Consequently some entries were either not completed properly or were illegible. These are shown as "unknown" on table 1 and included in the statistical analysis. The time warts had been pre-

Table 1 Entry characteristics for all patients

	PDX 0·5%	*PODO 0·5%*	*PODO 2·0%*
All patients	106	103	106
Time warts present:			
Unknown	22	11	19
< 1 month	24	27	31
1–3 months	36	45	33
> 3 months	24	20	23
Number of warts present:			
Unknown	22	17	20
1–5	45	54	55
5–10	28	20	24
> 10	11	12	7
Type of warts:			
Unknown	28	19	25
Acuminate	40	38	29
Sessile	30	41	47
Mixed	8	5	5

Table 2 Week 5 outcome on clinical examination only

	PDX 0·5%	PODO 0·5%	PODO 2·0%
No entered	106	103	106
Protocol eligible	77	86	81
State of warts:			
Unevaluable	3	4	5
Improved	3	5	5
No change	4	6	5
Worse	1	1	1
Healed completely	18	28	28
Total not healed	8	12	11
Side effects:			
Unevaluable	5	7	3
Mild/none	22	33	32
Moderate	2	2	5
Severe	0	2	0
Severe/withdrawn	0	0	4

sent was unknown for 52 (16·5%), the number of warts present was unknown for 59 (19%), and the type of warts was unknown for 72 (29%) patients.

Of those patients for whom there was complete documentation 196 of 263 (75%) had had their warts for less than 3 months ($p = 0·32$). A total of 154 of 256 (60%) had less than five warts and 226 of 256 (88%) had less than 10 warts ($p = 0·61$). Roughly equal numbers of patients (107 *v* 118) were classified as acuminate *v* sessile on their clinical appearance and 18 (7·4%) were mixed ($p = 0·21$). There were no clinically or statistically significant differences between the drug groups at the 5% level. The groups were therefore comparable in terms of their entry criteria.

A total of 19 patients who did not conform to the entry criteria and a further 52 classified as "protocol violators" had all follow up entries set to "unknown results". Only 105 of 277 protocol eligible patients attended for clinical examination at week 5. The results are given in table 2. Eight of 26 (69%) who had received PDX 0·5% were healed completely compared with 28 of 40 (70%) and 28 of 39 (72%) who had received PODO 0·5/2·0%. No significant differences were shown at the 5% level ($p = 0·97$).

In all, 126 (117 protocol eligible) patients who failed to attend for review at week 5 and for whom a postal address/permission to write had been given were sent postal questionnaires; 59 (55 protocol eligible) questionnaires were returned. None of the returned questionnaires said that treatment had been stopped because of side effects. These numbers were added to the week 5 examination figures to give an overall outcome as shown in table 3.

Only four patients reported stopping treatment due to side effects and all of these had received PODO 2·0%. These settled with simple conservative measures including saline bathing. Fisher's exact test was used for pairwise comparisons between the groups for side effects that were "severe/severe treatment stopped". This showed no significant differences between the PDX 0·5% (0/106) *v* PODO 2·0% (4/106) groups ($p = 0·36$ with Bonferroni's correction).

Table 3 Week 5 results for overall outcome (combined examination and postal data)

	PDX 0·5%	PODO 0·5%	PODO 2·0%
No entered	106	103	106
Protocol eligible	77	86	81
Warts healed?			
Unknown	56	48	53
Yes	38	41	42
No	12	14	11
Stopped due to side effects?			
Unknown	58	54	52
No	48	49	50
Yes	0	0	4

A subanalysis was carried out on the effects of the manufacture/dispensing time (M/D time) on safety and efficacy of self applied PODO. Of 209 patients entered 42 were not eligible or were protocol violators. The M/D time for all patients varied between 1 and 179 days (one patient who did not take his treatment was recorded as having an M/D time of 0). It was slightly skewed with an interquartile range of 45 to 88 and a median of 67. There was no significant effect at the 5% level of M/D time on entry characteristics or outcome (with combined week 5 clinical examination/postal data $p = 0·25$ for healing, $p = 0·69$ for side effects). Only 76 patients attended at 3 months for review. In view of the low numbers no analysis was made.

Discussion

In common with other studies of genital wart treatment, we could not obtain any meaningful follow up data beyond 5 weeks. At 5 weeks this study was also affected by a larger default rate than expected. This is presumably because patients were largely unselected including for probable compliance. Only 105 (41%) of protocol eligible patients (33% of all entrants) had evaluable data as to whether they were cleared of warts on clinical examination at 5 weeks. The postal questionnaire, however, raised the number of patients to 158 (65% of protocol eligible, 50% of all entrants) on whom there was 5 weeks of cure rate data. In previous penile wart treatment studies comparing clinic applied podophyllin with PDX 0·5%, 5 week attendance rates have been in the order of 60%.[2-4] These studies have, however, been open and included only selected protocol eligible, compliant patients in analyses which were not on an intention to treat basis. Caution must therefore be exercised when generalising findings of these studies to routine clinic attenders who may be less compliant not only with reattendance but also with their self application technique. These previous studies have also only had sufficient statistical power to detect large differences in outcome. An example of this is the study by Kinghorn *et al.*[4] This had 133 evaluable male patients at 5 weeks from six different centres and, by our calculation, had only a 72% power to exclude medium sized differences in cure rates at the 5% level. In comparison, our study had a double blind, randomised, intention to treat design, with a largely unselected patient group. If the patient questionnaire data are included then numbers are sufficient for the study to achieve its intended power. Whether side effects are sufficient for a treatment to stop is in any event a subjective decision by the patient. Whether warts have healed completely is also a subjective judgment and patients may be

no more or less reliable witnesses than a nurse/doctor. We, therefore, consider the data from the questionnaire to be valid and useful. Also since the data from the questionnaire were evenly spread across the treatment groups any potential bias should be accounted for by the randomised, double blind design of the study. Although we would have wished for a lower default rate and better initial documentation we therefore consider that this study withstands comparison with previous studies.

We conclude therefore that for the self treatment of penile warts there are at worst only minor differences in efficacy between two formulations of podophyllin (PODO 0·5/2·0%) and 0·5% podophyllotoxin (PDX 0·5%). PODO 0·5 and 2·0% are also stable in their clinical effects for at least 3 months between manufacture and dispensing. We found that side effects were generally minor with all treatments and when they occurred resolved with simple conservative measures. Although four patients using PODO 2·0% had to stop treatment because of severe side effects no long term problems ensued. Statistically, this rate of serious side effects was not different from the other groups. Even if this represents a real difference concealed by a type 2 statistical error similar side effects were not seen with PODO 0·5%. We would therefore choose to use this concentration of PODO in the future.

On the basis of AMES test reactivity doubts have been raised over the mutagenicity of quercetin and kaempherol which are constituents of unrefined podophyllin.[6] Despite this, penile and vulval carcinoma remain rare and no convincing association has been demonstrated with prior use of podophyllin. Self application of PODO 0·5% would at least give less total exposure to quercetin and kaempherol than the widely used two to three times weekly clinic application of podophyllin 20–40%.

PDX 0·5% may be more effective than clinic applied 20% podophyllin.[2–4] This study shows, however, that PDX 0·5% is no better than weaker strengths of podophyllin (PODO 0·5–2·0%) when these are self applied in the same way as PDX 0·5% to penile warts. PODO 0·5%–2% is stable for at least 3 months and its concentration is not particularly critical. The theoretical benefits of PDX 0·5% therefore seem to be of little practical importance. The choice between PDX 0·5% and PODO 0·5% should be on the basis of cost and licensing/supply considerations.

The cost of PDX 0·5% (September 1993 *British National Formulary*) at the time of the study was £16·00. The cost of 5 ml of PODO 0·5% was £1·50 (for a lot of 50 bottles) from the Burton on Trent manufacturing pharmacy. Even when taking into consideration the cost of the additional applicators needed for PODO 0·5% and any discount that could be negotiated for PDX 0·5% a marked price differential remains of about £10·00 per patient. A recent cost analysis of self treatment with PDX 0·5% compared with clinic applied podophyllin[9] showed only a marginal, statistically insignificant difference in favour of PDX 0·5% (£25·73 *v* £27·15 per patient cured). Substitution of PDX 0·5% by PODO 0·5% would clearly swing the cost in favour of self treatment.

PODO 0·5% is not licensed in the UK for the self treatment of penile warts but this is not necessarily a bar to its use. Many other commonly used treatments do not follow strict licensing criteria. In the UK under the Medicines Act it is the responsibility of an individual doctor to prescribe safe effective treatment whether or not this is licensed. This study provides reassurance that PODO 0·5% is an effective alternative to PDX 0·5% for use within UK departments of genitourinary medicine. If PODO 0·5% is used in the UK it will need to be purchased by pharmacists from a central pharmacy with a manufacturing licence.

In the financial year ending April 1995, 136 general practitioner prescriptions were dispensed for PDX 0·5% in Birmingham at a cost of £2024 (Dr S Chapman, personal communication). This is equivalent to £10 000 for the whole West Midlands Region and £100 000 per year nationally. As a small volume, unlicensed medication PODO 0·5% supplies are therefore unlikely to be available through community pharmacies. Ideally, all patients with genital warts should be encouraged to attend for full "STD screening" at their local genitourinary medicine department where, if PODO 0·5% is used for self treatment, they will receive a cheaper as well as more comprehensive treatment. In countries where the regulations on pharmacy manufacturing differ and where healthcare resources are limited PODO 0·5% may be an affordable treatment the use of which will free medical and nursing staff and improve patient compliance.

In this study, as in the previous studies of self applied PODO 0·5–2·0%, *P hexandrum (emodii)* derived podophyllin was used. No comment can therefore be made as to the safety and efficacy of self application of low strength podophyllin derived from *P peltatum*.

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