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E. C. Benton, M. W. Nolan, D. Kemmett & H. A. Cubie

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Trial of inosine pranobex in the management of cutaneous viral warts

EC Benton[1], MW Nolan[1], D Kemmett[1] & HA Cubie[2]

[1]*University Department of Dermatology, Royal Infirmary, Edinburgh and* [2]*Regional Virus Laboratory, City Hospital, Edinburgh, UK.*

Fifty patients with cutaneous mosaic warts resistant to standard therapy took part in a double-blind, placebo-controlled study to assess the efficacy of inosine pranobex used as an adjunct to standard topical treatments. No statistically significant difference was found in cure rates between the active (37.5%) and placebo treatments (34.6%) at 6 months, nor was there any relationship between clinical response and either antibody production or in vitro assay of lymphocyte proliferative activity against human papilloma virus (HPV) type 2 in either group. (*J Dermatol Treat* (1991) **1**: 295–297)

Introduction

Cutaneous viral warts may be extensive and persistent not only in patients with depressed cell-mediated immunity, eg organ transplant recipients,[1] but also in apparently healthy patients. There is evidence that such patients may have altered T-cell subpopulations and altered cell-mediated immunity.[2,3] This suggests that the use of an immunostimulant such as inosine pranobex might be of benefit. This preparation is a molecular complex of inosine and the *p*-acetamidobenzoic acid salt of *N,N*-dimethylamino isopropanol.[4] In vivo in humans it may reduce the frequency of recrudescences of herpes simplex infection,[5] although it has now been superseded by acyclovir.[6] It has been found to reduce the rate of progression of HIV-infection to full blown AIDS.[7] Open trials of inosine pranobex in the treatment of molluscum contagiosum[8] and laryngeal papillomata[9] have suggested a beneficial effect.

In the treatment of genital warts, inosine pranobex, used in conjunction with laser therapy,[10] podophyllin or cryotherapy,[11,12] appears to enhance remission rates, although less encouraging results were obtained by Davidson-Parker et al.[13]

We therefore decided to evaluate the efficacy of inosine pranobex, as an adjunct to standard topical therapy, in the treatment of cutaneous mosaic viral warts caused by human papillomavirus type 2 (HPV-2), as these tend to respond poorly to standard therapy.[14]

Patients and methods

Healthy subjects aged 12 years or more with mosaic warts of the feet or hands of at least one year's duration, and unresponsive to at least 3 months of treatment at the clinic, including cryotherapy, were included in the study. They were randomly assigned either to active or to placebo groups on a double-blind basis. In designing the study we assumed that the placebo group would have a 30% response rate, since viral warts undergo spontaneous remission, and that a significant clinical benefit of inosine pranobex would be a doubling of this, ie 60% response. This meant that, if 50 patients completed the study, the power to detect this difference in response between placebo and active compounds would be 52% whereas if 90 were enrolled the power would be 80%.

Patients took either inosine pranobex tablets 1 g three times daily or matching lactose tablets for the first month of the trial period, and were monitored at four-weekly intervals. Topical therapy of salicylic acid paint or plasters, and monthly liquid nitrogen cryotherapy were continued. Diagrams were completed to show the extent of warts at each visit. Adverse effects of systemic or topical treatment were noted. Compliance was assessed by counting remaining tablets after the first month of treatment. Results were analysed using the Chi-squared test with Yate's correction.

In a group of randomly selected subjects, 20 ml blood was withdrawn on three separate visits. Lymphocyte proliferation assays were carried out as described by Cubie and Norval[15] using concanavalin A (Con A) and phytohaemagglutinin (PHA) as non-specific T-cell mitogens, pokeweed mitogen (PWM) as a B-cell stimulator and antigens prepared from glycine-extracted and caesium-chloride-purified HPV-2.[15] Humoral antibodies to HPV-2 antigens were assessed using the ELISA system previously described by Cubie and Norval.[15]

Results

A total of 52 patients were enrolled into the study. One defaulted from follow-up, and another withdrew early because of a suspected adverse reaction to the tablets (a throat infection). This was the only adverse reaction reported and was thought to be unrelated to the patient's treatment with the placebo.

Results were therefore available for analysis from 50 patients, 26 in the placebo group and 24 in the active group. Both groups were well matched for sex, age, duration of warts, previous treatment and site of warts (Table I). Compliance was good in both groups with a mean of 92% of medication taken in each group. No patient took less than two-thirds of prescribed treatment.

On assessment at 3 months after the start of the trial three patients were clear of warts in both the active (12.5%) and placebo (11.5%) groups. The clinical response to treatment at 6 months is shown in Table II. Nine patients in each group were cured of their warts at 6 months, 37.5% on inosine pranobex, 34.6% on placebo.

Correspondence: Dr EC Benton, University Department of Dermatology, The Royal Infirmary, Edinburgh EH3 9YW, UK

The difference of 2.9% (95% confidence intervals of − 23.8 to + 29.5) was not statistically significant.

The results of immunological assessment showed that lymphocytes from all ten patients responded positively to Con A, PHA and PWM at entry and at all subsequent times of testing. Positive stimulation indices (SI) to glycine-extracted or purified HPV-2 antigens were detected in four patients (Table III) at the time of entry to the study, and one further patient developed positive responses. However, there appeared to be no correlation between the presence of positive SI and the clinical course.

No significant change in antibody titres was detected in patients from either the active or placebo groups (Table IV), although three of four patients in whom antibodies were detected at some stage did show resolution of warts. However, as antibodies were present in two of these three patients prior to treatment, this result cannot be attributed to inosine pranobex.

Table I Clinical data for the participants in the study

	Active	*Placebo*
Total number of patients	24	26
Age (years)	15–59 (mean 33)	21–61 (mean 31)
Sex (M:F)	12:12	12:14
Duration of warts (years)	1–30 (mean 4.7)	1–15 (mean 3.7)
Site:		
Feet only	11	11
Hands only	5	6
Hands & feet	8	9
Compliance (medication taken) (%)	66–100 (mean 92)	70–100 (mean 92)

Table II Clinical response in active and placebo treated patients

Response	*Inosine pranobex*	*Placebo*	*Significance of difference*
Cure	37.5% (9)	34.6% (9)	NS
>90% clear	12.5% (3)	7.7% (2)	NS
>50% clear	4.0% (1)	7.7% (2)	NS
No change	46.0% (11)	50.0% (13)	NS

NS, not significant.

Discussion

Experiments by Morison[3] suggest that clinically immunocompetent patients with long-standing viral warts have depressed cell-mediated immunity (CMI) as measured by lymphocyte migration inhibition to non-specific mitogens. We found that, although only 20% of the patients in this study were tested, all responded normally to the non-specific mitogens, suggesting the absence of any underlying systemic defect in their lymphoproliferative response. However, other factors may contribute to the poor clinical response to treatment: first, the small amounts of virus present in long-standing mosaic warts and, second, the reduction in, and mor-

Table III Lymphoproliferative responses to HPV-2 antigens in ten patients treated with inosine pranobex or placebo

		Stimulation indices						
		Baseline		*Baseline + 1 month*		*Baseline + 2 months*		
Treatment	*Patient no.*	*$glyH_2$*	*CsH_2*	*$glyH_2$*	*CsH_2*	*$glyH_2$*	*CsH_2*	*Clinical response*
A	1	1.2	–	1.5	1.9	–	–	Cure 6 months
A	2	0.9	–	1.4	1.2	2.1	2.1	Cure 3 months
A	3	13.5	–	1.6	2.3	1.3	0.9	Nil
A	4	1.1	1.0	0.9	0.6	1.5	1.1	Cure 6 months
A	5	0.8	1.1	–	–	1.6	1.0	Cure 3 months
P	6	2.5	–	1.1	0.9	0.7	–	Cure 3 months
P	7	10.8	–	1.4	–	1.5	–	Cure 6 months
P	8	0.6	0.6	1.1	1.1	1.2	1.4	Cure 6 months
P	9	1.0	0.8	0.8	1.2	–	–	Nil
P	10	1.8	3.5	0.5	1.6	2.8	0.6	Nil

A, active; P, placebo; $glyH_2$, glycine-extracted HPV-2 antigen; CsH_2, caesium-extracted HPV-2 antigen. Stimulation index >2 is positive.

Table IV Antibodies to HPV-2 detected by ELISA in ten patients treated with inosine pranobex or placebo

Treatment	*Patient no*	*Baseline*	*Baseline + 1 month*	*Baseline + 2 months*	*Clinical response*
A	1	<50	<50	–	Cure 6 months
A	2	200	200	400	Cure 3 months
A	3	<50	<50	<50	Nil
A	4	<50	50	<50	Cure 6 months
A	5	50	–	<50	Cure 3 months
P	6	<50	<50	<50	Cure 3 months
P	7	<50	<50	<50	Cure 6 months
P	8	<50	<50	<50	Cure 6 months
P	9	200	100	–	Nil
P	10	<50	<50	<50	Nil

A, active; P, placebo. Positive result >50.

phological alteration of, antigen-presenting Langerhans' cells in the region of HPV infection.[16] These factors may contribute to a localized immunosuppressive effect. It is disappointing, therefore, that administration of inosine pranobex, which in vitro appears to be a useful immunopotentiator, had no apparent effect in vivo. If this treatment had produced a significant immune response to HPV-2 infection, one would have expected complete resolution of warts rather than partial clearing.

We therefore based the power calculations for this study on being able to detect at least a doubling of the estimated spontaneous resolution rate, ie from 30% to 60%. Our estimated spontaneous resolution rate of 30% was confirmed by a placebo response rate at 6 months of 34.6%, but there was virtually no difference between this and the response rate of 37.5% in the active group. It seems unlikely, even by increasing patient numbers from 50 to 90, thereby increasing the power of the study from 52% to 80%, that we could have detected a clinically meaningful response. We conclude that, for patients with long-standing cutaneous mosaic warts, the administration of inosine pranobex as an adjunct to standard topical therapy has no major clinical benefit.

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