

PHOTODYNAMIC INACTIVATION OF VERRUCAE VULGARES. II

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Abstract. Photodynamic inactivation therapy, consisting of a double-blind, paired comparison treatment schedule, was used in treating 56 patients for recalcitrant, symmetrical verrucae vulgares. 0.1% proflavine in 100% dimethylsulphoxide (DMSO) and 0.1% neutral red in 100% DMSO were used as active dyes, and 1% picric acid in 100% DMSO and 1% color ruber in 100% DMSO served as corresponding placebos. A Westinghouse sunlamp and black light were used to irradiate the warts dyed with proflavine and its placebo, and the warts dyed with neutral red and its placebo were irradiated with an ordinary light bulb (Osram 588597). 50 patients completed the treatment. 10 of the 27 patients treated with proflavine and 10 of the 23 patients treated with neutral red were cured by the end of an 8 week period, with the warts disappearing simultaneously from the actively as well as the placebo-treated side. Complement fixing antibodies against wart virus were detected in one of the cured patients and 2 who were treatment failures.

Key words: Photodynamic inactivation; Verrucae vulgares; Neutral red; Proflavine

Verrucae vulgares (v.v.) are becoming an epidemiological problem (4, 13). This virus-induced, benign tumour is often embarrassing and can be quite painful when located on the sole of the foot.

Photodynamically active dyes dissolved in dimethylsulphoxide (DMSO) as well as specific wavelengths of light can penetrate v.v. both in vivo and in vitro (17). In this investigation we have evaluated a treatment schedule attempting photodynamic inactivation of the wart virus.

PATIENTS AND METHODS

56 patients (37 male and 19 female) with symmetrical, multiple v.v. on either both hands or both feet participated in this study. 7 were under 10 years of age; 29 were 10 to 20 years old and 20 were over 20 years of age. 6 had been afflicted with v.v. for less than 6 months; 11 of the patients had been afflicted for from 6 to 12 months, and 39 had had the disease for over 12 months. Traditional treat-

ment had proved unsuccessful for many of these patients or had been followed by recurrences. No treatment had been given for 4 weeks prior to the initiation of photodynamic inactivation therapy.

The following dyes and placebos were used: (a) 0.1% proflavine (3.6-Diaminoacridinum monohydrogen sulphate, May & Baker) in 100% DMSO; 1% picric acid (Merck no. 601) in 100% DMSO (placebo for a); (b) 0.1% neutral red (Merck no. 1369) in 100% DMSO; 1% color ruber (C.I. 16255) in 100% DMSO (placebo for b).

The dyes were freshly prepared for each patient, and the bottles were wrapped in aluminium foil to keep light out. All the bottles were identical in appearance, and the active dyes were indistinguishable from the corresponding placebos.

A double-blind, paired comparison treatment schedule was initiated. Following randomization, the active dye was applied to all warts on either the right or left side, and the placebo to those on the opposite side. The dye was applied with a glass dropper, and a light-impenetrable occlusive dressing was placed over the treatment area. 24 hours later the warts were pared.

Those areas dyed with proflavine and its placebo were irradiated with a light bank of Westinghouse sunlamps and black lights filtered through pyrex glass with emission evenly distributed in the UV-A. The distance from the light source to the skin was 10 cm, and the duration of the irradiation, 20 min. The energy of UV-A reaching the warts was 2 mW/cm². The v.v. dyed with neutral red and the corresponding placebo were irradiated with an ordinary light bulb (Osram 588597, peak emission 550-650 nm, corresponding to the maximum absorption of the dye) for 20 min at a distance of 10 cm. The energy of visible light reaching the warts was 24 mW/cm².

These treatments were given once a week for 7 weeks (8 treatments), and the results were evaluated one week after the last treatment.

Those patients who had no clinical evidence of v.v. at the final examination were considered cured, the other patients as treatment failures.

Determination of complement-fixing antibodies to wart virus was made for 45 of the adult patients at the initial examination (3). This test was repeated for 36 of these patients after 3 weeks.

The rate of recurrence was determined on the basis of a questionnaire sent to the patients 3 months after the completion of treatment.

Table I. Results of treatment of *verrucae vulgares* in 56 patients by photodynamic inactivation

	Proflavine	Neutral red	Total
Cured	11	10	21
Treatment failures	19	14	33
Total	30	24	54

RESULTS

50 of 56 patients received eight treatments. 27 of these were treated with proflavine and the corresponding placebo and 23 with neutral red and its placebo. 4 patients failed to return after the third treatment, and 2 patients received only one treatment. Our results are calculated on the basis of those patients who received all 8 treatments.

10 of the 27 patients treated with proflavine and the placebo dye and 10 of the 23 patients treated with neutral red and its placebo were cured by the end of the treatment period (Table I).

The warts disappeared simultaneously from both the right and the left side of all the patients who were cured.

The largest number of cures occurred among patients under 10 years of age. We were unable to demonstrate a correlation between the length of time the warts had been present and the cure rate.

Nearly all the v.v. became dry and keratotic and appeared to involute during the treatment period. Among those patients who eventually became treatment failures, however, the v.v. regained their original appearance 3 to 4 weeks after conclusion of the treatment.

No side effects, such as dye intolerance or light hypersensitivity, were observed.

The initial examination of the serum of 3 of 45 adult patients revealed the presence of complement-fixing wart antibodies. These antibodies were not present upon re-examination 3 weeks later. 2 of 3 patients who had complement-fixing antibodies were treatment failures; the third was cured.

DISCUSSION

The treatment of warts is often time-consuming, troublesome and painful. The spontaneous course of the disease is generally favourable. When selecting treatment, therefore, one should be certain that

this will neither be followed by scar formation nor have any other permanent side effect (4).

One of the most effective treatment modalities is curettage. This treatment is impractical, however, for large numbers of warts or when these are located on plantar pressure areas or periungually. The recurrence rate of v.v. following curettage is approximately 20% (6). A new, and apparently effective, treatment consists of sensitizing the patient to dinitrochlorobenzene and then applying this chemical to the v.v. in a concentration high enough to cause an intense inflammatory response (5). This treatment could, however, lead to cross sensitization, and severe local reactions sometimes occur.

Since 1973, when Felber published his results of photodynamic inactivation of herpes simplex infections on skin or mucous membranes (2) a number of publications on this subject have appeared. Varying results have been obtained after employing Felber's method (9, 10, 15, 16). Unfortunately, unlike herpes simplex virus, human wart virus cannot be studied *in vitro*. One author reports the cure of warts in 3 of 5 patients by using 0.1% proflavine and "white light" (11).

The results presented here show a cure rate of 37% of those patients treated with proflavine and 43% of those treated with neutral red over a 7 week period. Comparable observations of the spontaneous course indicate a cure rate of less than 10% (7, 8). Although our results are not encouraging, it should be pointed out that many of the patients had been treated unsuccessfully prior to our treatment and that all of the patients had multiple warts, many of which had been present for over a year. For such patients, photodynamic inactivation can be a useful alternative treatment modality. It is simple, painless and non-scarring, although somewhat time consuming.

The fact that most cures were seen among children is in agreement with the results of other treatments as well as the spontaneous course of the disease (1, 14).

Photodynamic action is probably not solely responsible for the cures obtained with this treatment, as the warts disappeared from the side treated with active dye and the placebo-treated side simultaneously. If a local destruction of virus based on photodynamic action had taken place, one would expect the warts to disappear only on the side treated with photodynamically active dye. We did

not as expected find complement-fixing antibodies in spite of the fact that the warts disappeared on both sides simultaneously (12). It is possible, however, that the antibodies could not be detected by the technique employed and that cell-mediated immunity also played a role in the destruction of the warts.

One or more of the following possibilities could also account for the disappearance of the warts on both sides: 1) an effect of the light itself, 2) virucidal action of both active and placebo dyes, 3) virucidal action of DMSO, or 4) paring of the warts, which could increase the spontaneous cure rate. We do not find our results sufficiently encouraging to continue with this type of treatment in its present form, and these possibilities have not yet been explored.

REFERENCES

1. Auken, G., Gade, M. & Pilgaard, C. E.: Behandling af hånd- og fodvorter med Verucid®. *Ugeskr Læger* 137: 3036, 1975.
2. Felber, T. D., Smith, E. B., Knox, J. M., Wallis, C. & Melnick, J. L.: Photodynamic inactivation of herpes simplex. *JAMA* 223: 289, 1973.
3. Genner, J.: Verrucae vulgares. II. Demonstration of a complement fixation reaction. *Acta Dermatovener (Stockholm)* 51: 365, 1971.
4. Genner, J.: Vorter. *Ugeskr Læger* 136: 1170, 1974.
5. Greenberg, J. H., Smith, T. L. & Katz, R. M.: Verrucae vulgares rejection. *Arch Dermatol* 107: 580, 1973.
6. Hancke, C.: Curettage af vorter. *Ugeskr Læger* 136: 1127, 1974.
7. Massing, A. M. & Epstein, W. L.: Natural history of warts. A two-year study. *Arch Dermatol* 87: 74, 1963.
8. Memmesheimer, A. M. & Eisenlohr, E.: Untersuchungen über die Suggestivbehandlung der Warten. *Dermatol Zeitschr* 62: 63, 1931.
9. Meyers, M. G., Oxman, M. N., Clark, J. E. & Arndt, K. A.: Failure of neutral-red photodynamic inactivation in recurrent herpes simplex virus infections. *N Engl J Med* 293: 945, 1975.
10. Moore, C., Wallis, C., Melnick, J. L. & Kuns, M. D.: Photodynamic treatment of herpes keratitis. *Infect Immun* 5: 169, 1972.
11. Morison, W. L.: Anti-viral treatment of warts. *Br J Dermatol* 92: 97, 1975.
12. Pyrhönen, S. & Johansson, E.: Regression of warts. An immunological study. *Lancet* 1: 592, 1975.
13. Rasmussen, K. A.: Verrucae plantares symptomatology and epidemiology. *Acta Dermatovener (Stockholm)* 38: Suppl. 39, 1958.
14. Rook, A., Wilkinson, D. S. & Ebling F. J. G.: *Textbook of Dermatology*. Blackwell Scientific Publications, London 1972.
15. Roome, A. P. C. H., Tinkler, A. E., Holton, A. L., Montefiore, D. G. & Waller, D.: Neutral red with photoinactivation in the treatment of herpes genitalis. *Br J Vener Dis* 51: 130, 1975.
16. Taylor, P. K. & Doherty, N. R.: Comparison of the treatment of herpes genitalis in men with proflavine photoinactivation, idoxuridine ointment, and normal saline. *Br J Vener Dis* 51: 125, 1975.
17. Veien, N. K., Wettermark, G., Genner, J. & Brodt-hagen, H.: Photodynamic inactivation of verrucae vulgares. I. *Acta Dermatovener (Stockholm)* 57: 441, 1977.

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