

Photodynamic Therapy of Recalcitrant Warts with 5-Aminolevulinic Acid: A Retrospective Analysis

Sir,
Photodynamic therapy (PDT) with topical application of 5-aminolevulinic acid (ALA) has been successful in the treatment of superficial non-melanoma skin tumours (1). When applied topically to the skin, ALA is absorbed into the epidermal cells and biosynthesized to the light-sensitive metabolite photoporphyrin IX (PpIX). When cells with accumulated PpIX are exposed to light of certain wavelengths, free radicals are released as singlet oxygen, leading to cell death (2). Recently it has been reported that ALA-PDT also has antiviral properties (3). Selective production of PpIX has been demonstrated by fluorescence measurements after ALA application to genital warts, indicating a specific affinity for ALA in human papilloma virus infected tissue (4). A preliminary study showed that repetitive treatment with ALA and white light has a curative effect on recalcitrant verrucae (5). Encouraged by these results, we treated patients who were referred to our department with warts resistant to other treatments, with ALA-PDT.

PATIENTS AND METHODS

A total of 62 patients (20 males, 42 females, age range 16–79 years) who were referred to the department of dermatology with recalcitrant warts were treated with ALA-PDT.

Diagnoses of the warts were made clinically. Photographs were taken before treatment and after the warts were cleared. All kind of warts, from solitary, multiple, hyperkeratotic, deep plantar and mosaic warts, were treated. The warts were primarily located on the hands and feet, except in 1 patient with warts on an arm and plane warts in the face. The hyperkeratoses overlying the warts were pared down with a scalpel to visualization of the blood vessels. Care was taken not to cause bleeding, as any surface blood may have absorbed some of the light energy, thus preventing the light from penetrating the wart tissue.

After paring, a visible layer of 20% ALA (Sigma, Bie and Berntsen, Denmark) was applied to the warts. The warts were then covered with a hydrocolloid occlusion (Tegaderm®) to enhance the absorption of ALA. After 4–5 h the dressing and the remaining cream were removed and the ALA-treated area was irradiated with white light from a slide projector at a distance of 15 cm for 30 min (Kindermann, Osram 250 W) with 25 mW/cm² and a total dose of 45 J/cm². The treatment was repeated 3 times at 1-week intervals. The warts were covered with a bandage for up to 48 h after light exposure to avoid additional light exposure. Follow-up visits were performed 2 months after treatment. The patients were told to pare down and apply Verucid® (salicylic acid 10%, lactic acid 11%) once to twice a week in the follow-up period. If all ALA-PDT warts were cleared, the patient was registered as "cleared". If all ALA-PDT-treated warts were not cleared the patient was registered as "not cleared". The cleared patients were followed to observe recurrences from 5 to 17 months. Patients without clearance after 2 months of follow-up were offered alternative treatments.

RESULTS

All 62 patients had been treated with a variety of other treatment modalities prior to referral to the department of dermatology, ranging from simple local application of various verucids to lasers and surgery.

During light exposure about 50% of the patients felt burning and stinging pain in the ALA-PDT treated warts. In some cases severe pain or itching were reported. Seven patients did not complete the first irradiation and, because of severe pain, they did not want to continue treatment. Three patients were lost to follow-up. Of the remaining 52 patients who completed the ALA-PDT treatment, 30 (58%) were cleared of all warts. The age of the patients and their number of warts was not different from the non-cleared group. We performed ALA-PDT in 5 immunocompromised patients. Three of these patients had a transplant and were being treated with immunosuppressive agents. Two were HIV-positive. Warts failed to resolve in 1 of the HIV-infected patient and 2 of the transplanted patients. One transplant patient terminated the treatment because of severe pain during the first irradiation. In the other HIV-infected patient the warts were cleared.

A few days after an ALA-PDT treatment, some warts developed a brown to black discoloration, probably due to embolization and rupture of the small vessels. The brown discoloration due to coagulated blood could be pared off with a scalpel. This was done before the next ALA-PDT treatment was given.

Following ALA-PDT treatment no wound or inflammation was observed and no lesion care was required. The average follow-up time of the 30 patients cleared of their warts ranged from 3 to 17 months and during this period no scarring was observed. Nail dystrophy was not observed in the patients treated for periungual warts. No recurrences were observed and no long-term side-effects were reported by any of the patients.

DISCUSSION

In a preliminary study, repetitive ALA-PDT treatments with white light cleared 70% of ALA-PDT-treated warts (5). In the retrospective analysis described here we found a cure rate of 58% of wart patients treated with ALA-PDT. The 2 studies cannot be compared, since in the preliminary study the number of warts in a randomized area is used as an effect parameter, whereas in this study the cure rate of patients is used. However, from these 2 not blinded and not placebo-controlled studies we believe that ALA-PDT may also be effective in the treatment of wart infections when used, as in this study, as a routine treatment in a dermatological outpatient clinic.

REFERENCES

1. Wolf P, Rieger E, Kerl H. Topical photodynamic therapy with endogenous porphyrins after application of 5-aminolevulinic acid. *J Am Acad Dermatol* 1993; 28: 17–21.
2. Henderson BW, Dougherty TJ. How does photodynamic therapy work? *Photochem Photobiol* 1992; 55: 145–57.
3. Smetana Z, Malik Z, Orenstein A, Mendelson E, Ben-hur E. Treatment of viral infections with 5-aminolevulinic acid and light. *Lasers Surg Med* 1997; 21: 351–358.

4. Ross EV, Romero R, Kollias N, Crum C, Anderson R. Selectivity of protoporphyrin IX fluorescence for condylomata after topical application of 5-aminolevulinic acid: implications for photodynamic therapy. *Br J Dermatol* 1997; 137: 736–742.
5. Stender IM, Lock-Andersen J, Wulf HC. Successful treatment of recalcitrant warts with topical application of 5-aminolevulinic acid. A pilot study. *Clin Exp Dermatol* 1999; (In press).

Accepted March 10, 1999.

Ida-Marie Stender and Hans Christian Wulf
Department of Dermatology, Bispebjerg Hospital D92, University of Copenhagen, Bispebjerg Bakke, DK-2400 Copenhagen, Denmark.
E-mail: ims01@bbh.hosp.dk.

Stevens-Johnson Syndrome after Sertraline

Sir,

Sertraline (Zoloft®) is a new selective inhibitor of serotonin re-uptake. This family of antidepressant drugs is considered to be safe, and cutaneous adverse reactions have rarely been reported (1). We report here a patient who developed Stevens-Johnson syndrome (SJS) after starting treatment with sertraline (Zoloft®).

A 96-year-old woman was admitted with a cutaneous and mucosal eruption. Sertraline and arginine chlorhydrate (Arginine Veyron®) treatment had been initiated 3 weeks before the eruption. Sertraline had replaced paroxetine (Deroxat®), initiated 7 weeks before the eruption for depression. Her general condition was good, and her temperature was 37°C. The cutaneous lesions were found on the face, trunk and proximal parts of the limbs, and were erythematous or purpuric, with an atypical flat target appearance, without significant epidermal detachment. Nikolsky's sign was negative. She had painful oral erosions and conjunctivitis. Histological examination of a skin biopsy showed total necrosis of the epidermis, direct immunofluorescence was negative, and the blood cell count was normal. Serology for herpes virus I and II showed previous immunization and serology for *Mycoplasma pneumoniae* was negative. Sertraline and arginine chlorhydrate treatment were withdrawn and the cutaneous eruption disappeared in 7 days. Control of serology for *Mycoplasma pneumoniae* was negative.

The diagnosis of SJS was retained because of the association of macular and purpuric lesions with an atypical flat target appearance involving the trunk and proximal limbs, 2 different mucosal sites and total necrosis of the epidermis (2). This syndrome is usually related to drug intake (3), and serology for herpes and *Mycoplasma pneumoniae* were negative. According to the standards of the French drug surveillance system, sertraline and arginine chlorhydrate were the only culprit drugs (4). Imputability of arginine chlorhydrate is nil, because it is an amino acid, and no side effect has been reported with this drug. One case of erythema multiforme with involvement of the trunk and face has been reported with sertraline (5) but, to our knowledge, this is the first case of SJS observed with sertraline treatment. Nevertheless, SJS and toxic epidermal necrolysis (TEN) have been

reported with 2 other members of the family of selective inhibitors of serotonin re-uptake (fluvoxamine and fluoxetine) (6, 7). Cross-reactivity between several members of this family has been observed in 2 cases (8). In the case reported here, paroxetine was not imputable because it had been initiated 7 weeks before the eruption. If a severe cutaneous side effect (SJS or TEN) occurs, it would be better to change the drug family (8).

REFERENCES

1. Wagner W, Plekkenpol B, Gray TE, Vlaskamp H, Essers H. Review of fluvoxamine safety database. *Drugs* 1992; 43 (Suppl 2): 48–54.
2. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme. *Arch Dermatol* 1993; 129: 92–96.
3. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; 333: 1600–1607.
4. Begaud B, Evreux JC, Jouglard J, Lagier G. Unexpected or toxic drug reaction assessment (imputation): actualization of the method used in France. *Thérapie* 1985; 40: 111–118.
5. Gales BJ, Gales MA. Erythema multiforme and angioedema with indapamide and sertraline. *Am J Hosp Pharm* 1994; 51: 118–119.
6. Wolkenstein P, Revuz J, Diehl JL, Langeron O, Roupie E, Machet L. Toxic epidermal necrolysis after fluvoxamine (letter). *Lancet* 1993; 342: 304–305.
7. Bodokh I, Lacour JP, Rosenthal E, Chichmanian RM, Perrin C, Vitetta A, et al. Syndrome de Lyell ou nécrolyse épidermique toxique et syndrome de Stevens-Johnson après traitement par fluoxétine. *Thérapie* 1992; 47: 441.
8. Beauquier B, Fahs H. Effets secondaires dermatologiques des antidépresseurs inhibiteurs de la recapture de la sérotonine : hypothèse d'une allergie croisée. A propos de deux cas. *Encéphale* 1998; 24: 62–4.

Accepted January 21, 1999

V. Jan¹, C. Toledano¹, L. Machet¹, M.C. Machet², L. Vaillant¹ and G. Lorette¹
Departments of ¹Dermatology and ²Pathology, CHU Trousseau, F-37044 Tours Cedex, France.