

## 5-FLUORO-URACIL CREAM IN THE SUCCESSFUL TREATMENT OF THERAPEUTICALLY REFRACTORY CONDYLOMATA ACUMINATA OF THE URINARY MEATUS

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**Abstract.** A therapeutic trial of 5% 5-Fluoro-uracil in cream form was conducted in 40 men with condylomata acuminata unresponsive to other therapeutic measures. Sixty per cent of the condylomata on the genital and/or anal mucosa showed complete regression. The most promising results were recorded in the cases of condylomata affecting the urinary meatus. These lesions disappeared in 13 of 14 cases after an average of 3 weeks' treatment with subjectively few side effects. With regard to this type of condylomata it may be said that a great therapeutical advance has been achieved. The treatment of other condylomata involving the genital or anal mucosa often causes intolerable discomfort to the patients. The method should in these cases therefore be attempted only when the lesions prove to be refractory to other methods of treatment. In its present form the application of 5-FU cream is difficult to confine solely to the condylomata itself. The cream appears to have little or no effect on condylomata at sites other than the mucosa.

**Key words.** Condylomata acuminata; Drug therapy; Fluoro-uracil

In 1944 a topical application of podophyllin was introduced for the treatment of condylomata acuminata (4). The results were reported to be excellent; in 80% of the cases a single treatment resulted in complete regression of the lesions. Subsequently, a 20-25% solution of the drug in alcohol (21) was considered to be the drug of choice for the treatment of this disease (15, 19). When the lesions involved the urethra (4, 8, 9) or the inner aspect of the anus (17, 22) the method was nevertheless found to be ineffective. The drug exerts its effect in the G<sub>2</sub> phase of the cellular cycle by linkage of podophyllotoxin and related derivatives to the microtubule protein of the cells, resulting in the arrest of mitosis in the metaphase (14, 24).

In Sweden this therapy has been used for many

years but the results have been disappointing during the past few years where a single application of the drug resulting in complete regression of the condylomata was observed only in 17% of 166 men and 26% of 50 men respectively (12, 13). One reason for this may be that the concentration of the antimetabolic components of the podophyllin in use fell below the critical limit required for the drug to be fully effective. This prompted us to search for methods of treatment which could be used as alternatives to the one described. 5-Fluoro-uracil (5-FU) is a pyrimidine antagonist within the group of antimetabolites. It is incorporated into RNA, forming abnormal nucleotides, and also inhibits the enzyme thymidylate synthetase which is of major importance in the synthesis of DNA. The drug becomes effective in the S phase of the cellular cycle and causes disturbances in the growth and division of cells (1, 3, 11). A 5% concentration of 5-FU in the form of cream has been widely accepted for topical therapy in superficial basal cell carcinoma and actinic keratosis (5, 6, 18). As encouraging results of topical application of the cream have been reported in cases of condylomata acuminata (7, 10, 16, 22) the therapeutic value of this method was assessed in 40 patients with condylomata which were unresponsive to other methods of treatment.

### MATERIAL AND METHOD

The series included 37 men with genital and/or anal condylomata which had been present from between one and 48 months, the average duration being about one year. These had persisted despite the application of a 20% solution of podophyllin in alcohol between 2 and 30 times, the mean number of treatments being 10-11 times. In

Table I. Results and side effects of topical application of 5-FU in 40 men with a total of 50 location sites of genital and/or anal condylomata acuminata

Type I=Penile mucous membranes (glans penis, coronal sulcus, fraenum, inner aspect of prepuce), Type II=Penile skin, Type III=Urinary meatus, Type IV=Anal skin, Type V=Anal mucous membranes (inner aspect of anus, mucocutaneous junction of anus)

|                                                        | Site     |         |          |         |         | Total no. of location sites |
|--------------------------------------------------------|----------|---------|----------|---------|---------|-----------------------------|
|                                                        | Type I   | Type II | Type III | Type IV | Type V  |                             |
| No. of patients exhibiting condylomata at any one site | 24       | 2       | 14       | 3       | 7       | 50                          |
| Results <sup>a</sup>                                   |          |         |          |         |         |                             |
| 0                                                      | 9        | 1       | 0        | 2       | 1       | 13                          |
| +                                                      | 4        | 1       | 1        | 0       | 3       | 9                           |
| ++                                                     | 11 (46%) | 0       | 13 (93%) | 1 (33%) | 3 (43%) | 28 (56%)                    |
| Side effects <sup>b</sup>                              |          |         |          |         |         |                             |
| 0                                                      | 5        | 1       | 5        | 2       | 2       | 15                          |
| (+)                                                    | 1        | 0       | 1        | 0       | 0       | 2                           |
| +                                                      | 7        | 0       | 3        | 1       | 2       | 13                          |
| ++                                                     | 11       | 1       | 5        | 0       | 3       | 20                          |

<sup>a</sup> +=partial regression, supplementary therapy necessary, ++=total regression.

<sup>b</sup> (+)=itching, burning etc. with or without erythema, +=ulceration causing no or moderate subjective discomfort, ++=ulceration causing subjective discomfort necessitating interruption of treatment.

addition, the series included 3 men with anal condylomata present for 12 months but as yet untreated.

At every examination of the patients, the distribution and the number of warts and the range of their sizes at each site were recorded. This enabled a continuous follow-up study to be made on the effect of the treatment to be conducted.

The condylomata were classified according to their sites into five types of warts (Table I) with special reference to the warts known to be unresponsive to treatment (Types III and V), and to their location on the mucosa or epidermis respectively. In all cases of anal condylomata proctoscopy was carried out before treatment was initiated.

The patients were told to apply the 5-FU cream at first twice daily, i.e. in the morning and in the evening, but to apply it only in the evening if they experienced any local side effects. If side effects were experienced, they were also instructed to bathe the lesions in the morning with a 3% solution of boric acid, followed by the local application of either antimicrobial cream or liniment to which corticosteroid was usually added. The patients were advised to use plastic gloves when applying the cream and were informed that accidental application of the latter to the mucosa of the eye was associated with the risk of complications.

In the cases in which the condylomata were located on the inner aspect of the anus, the patients were told to apply the cream close to the anorectal sphincter and to remove all excess cream from around the anus.

Cotton swabs were used for the treatment of condylomata involving the urinary meatus.

## RESULTS

Forty patients with a total of 50 condylomata sites (Table I) were treated with 5-FU. In 7 of the 8 patients with anal condylomata the lesions involved the inner aspect of the anus. Table I shows the result of the treatment and the side effects observed. Twenty-eight of the 50 condylomata sites regressed completely, 2 condylomata sites classified as type I recurred 2 and 3 weeks respectively subsequent to the first treatment. After retreatment, however, they were found to have completely regressed at the end of a follow-up period of 6 and 7 months respectively. In the remaining cases no recurrence was observed during a follow-up of 6 to 13 months' duration.

At the site of the condylomata and/or on the adjacent mucosa or skin, irritation differing in degree of severity was observed during the treatment of 35 of the 50 condylomata sites. Usually this side effect appeared between 5 and 7 days after the beginning of the treatment and expressed itself in the form of erythema, itching and a sensation of burning. In the majority of cases superficial ulcerations, which occasionally were rather painful, developed within a further few days. For this reason

Table 11. Average time (weeks) of topical treatment with 5-FU in 40 men with a total of 50 location sites of genital and/or anal condylomata acuminata

Type I=Penile mucous membranes (glans penis, coronal sulcus, fraenum, inner aspect of prepuce), Type II=Penile skin, Type III=Urinary meatus, Type IV=Anal skin, Type V=Anal mucous membranes (inner aspect of anus, mucocutaneous junction of anus)

|                          | Site   |         |          |         |        | Total |
|--------------------------|--------|---------|----------|---------|--------|-------|
|                          | Type I | Type II | Type III | Type IV | Type V |       |
| Total regression         | 2.5    | —       | 3.2      | 6.0     | 9.3    | 3.4   |
| No or partial regression | 3.6    | 5.3     | 12.0     | 10.5    | 5.0    | 4.5   |

the treatment of 20 of the 50 condylomata sites was discontinued after an average 2 weeks' treatment despite the simultaneous administration of local anti-inflammatory therapy.

The mean treatment time was 4 weeks on average, the range being between 1 and 12 weeks. Only 14 groups of condylomata were treated for a period of 2 weeks or less. Table 11 shows the average duration of the treatment of the different types of condylomata.

## DISCUSSION

The effect of topical treatment of condylomata acuminata with 5-FU up to the present time has been studied only in small series of patients, and little information is available regarding the practical details of the treatment. Témime (22) observed complete regression of the lesions in 3 cases of genital and 2 cases of intra-anal condylomata. Local application of 5-FU resulted in disappearance of the lesions in 8 of 9, 8 of 11 and 5 of 10 cases of condylomata but the sites of the lesions are not stated (7, 10, 16). Nel & Fourie (16) treated their patients for 8 weeks on average, whereas Haye (10) did so for a maximum of 4 weeks. Témime (22) reported that all his patients developed varying degrees of inflammation at the lesion sites. Nevertheless he was able to continue the treatment by the alternate application of anti-inflammatory preparations and 5-FU. In our material these measures were given a trial in 27 of the 35 condylomata sites in which treatment was associated with side effects. However, the treatment of 20 of these 27 condylomata sites had to be terminated since the patients were unwilling to continue the therapy on account of the persistence of painful sores. Apart from individual sensitivity, extended ulcerations observed

could have been due to a too generous application of the cream, which is not particularly viscous and therefore tends to spread from the condylomata to the adjacent mucosa or skin. It may be assumed that the side effects can be reduced by modification of the vehicle. The side effects may have been aggravated—and the regression of the warts accelerated—by the occlusion effect in the cases of condylomata classified Types III–V, and also in Type I, as none of these patients were circumcised.

The side effects observed in this investigation correspond to those previously described in studies on experimental animals (2). These have shown that the daily application of 5-FU for about a week invariably resulted in epithelial-connective tissue separation of the mucosa, but not of the skin. The difference may be due to the relatively higher turnover rate in the mucosa. Although 5-FU seems to possess a certain affinity for tumour cells, it does not selectively destroy these, but inhibits their growth and the proliferation of other tissues having a high mitotic rate (1).

Treatment time was particularly short in the cases of condylomata on the glans penis, coronal sulcus, fraenum and inner surface of the prepuce because of the relatively severe subjective side effects (Table 1). Some patients reported that the sores and a sensation of tightness only hindered erection, but many complained of a continuous sensation of burning or pain. One patient developed a clear-cut balanoposthitis. However, some patients did not complain of any discomfort at all.

In the cases of condylomata on the anal mucous membrane the treatment caused great discomfort to the patients, particularly in connection with defecation on account of fissures and sores involving the mucocutaneous junction of the anus. As this type of

condylomata has been reported to be particularly refractory to treatment, we tried to persuade these patients to continue the treatment despite the side effects. However, in some cases, it was necessary to interrupt the treatment for short periods. This explains the relatively long treatment time in those cases in which the lesions disappeared completely (Table II). It would appear to be difficult to confine the application of the cream to the mucosa in these cases, as occasional irritation of the perianal skin was observed.

Although 5 of 14 patients with condylomata involving the urinary meatus experienced dysuria during the treatment, this side effect was nevertheless tolerable, and did not necessitate discontinuation of the treatment in any case. In 13 of the 14 patients in which the condylomata affected the urinary meatus, the lesions regressed completely after an average 3-week treatment period. These excellent results may be ascribed to the fact that these condylomata involved a relatively limited area to which the application of the cream is more easily confined. Of the condylomata on the mucosa (Types I, III and V) the lesions regressed completely in 60% of the cases. Since the patients with these venereal warts represent selected cases, in which the lesions proved to be refractory to other treatment methods, this result is encouraging. The high frequency of regression (93%) in the cases of condylomata involving the urinary meatus reflects a marked advance in the treatment of this type of genital wart. Condylomata Types I and V showed complete regression in 46 and 43% of the cases, but the results of the treatment cannot be regarded as satisfactory on account of the high frequency of side effects reported in these cases. As regards Type V, however, reliable alternative methods of treatment are as yet not available, and we therefore consider it justified to give a trial of 5-FU in selected and cooperative patients under careful medical supervision. Keratin is assumed to hinder penetration of 5-FU and this may account for the poor result observed with the use of this preparation in cases of condylomata located on the epidermis (Type II and IV) and in cases of common warts (20, 23).

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