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INSTILLATION OF THIO-TEPA (TIFOSYL) IN VESICAL PAPILLOMATOSIS

by

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The treatment of vesical papillomatosis is a serious problem in urology. Transurethral excision or coagulation are the conventional methods but the frequency of recurrence is high and repeated treatments are often necessary. Papillomata may sometimes be so widespread inside the bladder that electrocoagulation at one or several sessions may be inadequate as a method of treatment. Attempts have been made to instil radioactive solutions through a rubber bag or directly into the bladder to destroy the papillomata, and ^{60}Co, ^{82}Br, ^{198}Au and ^{76}As have been employed to this end (EINHORN et coll. 1964). The results have not been satisfactory. Recurrence and complications such as contracted bladder, haematuria and vesico-ureteral reflux are not uncommon. High radiation doses are necessary to destroy the papillomata but these may in turn result in damage to surrounding healthy tissue.

The use of chemotherapeutic agents topically in the bladder has long been employed in cases of widespread vesical papillomatosis. The various chemotherapeutic agents injected have included silver nitrate (HERRING 1903), podyphyllin (SEMPLE 1948, KELLY & HARTWELL 1954) and over the last ten years tifosyl (Thio-tepa) (JONES & SWINNEY 1961, ESQUIVEL et coll. 1965, VEENEMA

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Table

Summary of the results of tifosyl treatments reported in the literature

Authors and year of publication	Number of patients	Results	Papilloma	Carcinoma stages			
				A	B	C	D
Jones & Swinney 1961	16	No effect	2	—	—	2	—
		Partial destruction	7	—	—	1	—
		Complete destruction	4	—	—	—	—
Veenema et coll. 1962	57	No effect	11	—	3*	—	7
		Partial destruction	14	—	7*	—	2
		Complete destruction	13	—	—	—	—
Esquivel, Mackenzie & Whitemore 1964	20	No effect	3	—	6	1	2
		Partial destruction	2	2	2	1	—
		Complete destruction	3	—	—	—	—

* includes those who received prior radiotherapy

et coll. 1962). The results of tifosyl treatment reported in the literature are summarized in the accompanying Table.

We have used tifosyl instillation since 1963 but since 1967 in accordance with special principles and unitary doses. Twenty-nine patients with widespread papillomatosis have had installations of tifosyl (Thio-tepa) into the bladder. Eight of these were women and twenty-one were men, between 46 and 80 years of age. The average period of time for the papillomatosis before tifosyl treatment was 5.3 (1 to 17) years and repeated coagulations had been performed for recurrence.

Method. A complete series of treatments consisted of six installations of tifosyl in doses of 50 mg per instillation. Treatment was given on alternate days, usually in the out-patient department. The patients assumed several positions during the treatment in order to ensure complete contact between the bladder wall and the active agent. The patients were asked to keep the solution (50 ml) in the bladder for two hours. To avoid dilution of the solution in the bladder, the fluid intake was restricted 12 hours before treatment.

Results

A clinical grading of the effect of treatment on the papillomata was carried out during the cystoscopies, which were performed 4 to 6 weeks after the tifosyl treatment. A further series of treatments was usually given if no effect was observed after the first one. No further treatment was given if regression of the papillomata had occurred. No coagulation of the remaining papillomata was performed until it was felt that no further regression could be expected.

The clinical cystoscopic results were codified 0 to 3, where zero indicates no effect or progress, 1 indicates reduction of necrosis of the papillomata, 2 stands fore one or more papillomata gone, and 3 for all papillomata gone. The following results were obtained:

Codes:	0	1	2	3	Total
One series	4	—	4	6	14
Two series	1	1	3	4	9
Three series	—	—	4	2	6

Complete regression occurred in twelve out of twenty-nine cases (41 %), seven of these occurring directly and five others after coagulation of some small residual papillomata. Complete regression or almost complete regression (codes 2 and 3) occurred in twenty-three out of the twenty-nine cases (80 %). No effect could be observed in five (17 %) of the cases.

The number of treatment series in the different groups are given below:

	Number of patients	Series given
Code 0	4	1
	2	2
Code 1	1	2
Code 2	4	1
	3	2
	4	3
Code 3	6	1
	4	2
	2	3

The observation period, starting with the first treatment with tifosyl, averaged one year (between 2 months and 5 years). The period is too short to allow evaluation of the long-term frequency of recurrence. It seems, however, as if a complete series of tifosyl treatments makes it easier to control the remaining papillomata by coagulation.

Results related to the primary papilloma size. In principle, only those patients were chosen for tifosyl therapy who at cystoscopy had thin, slender papillomata spread over the mucous membrane of the bladder at the sites of multiple previous electrocoagulations. There had been much difficulty in effectively destroying new recurrent papillomata by electrocoagulation, and instillation therapy with tifosyl had therefore been adopted. The results are tabulated below according to the size of the lesion:

Codes	0	1	2	3	Total
'Carpet' (widespread papillomatosis)	4	—	8	9	21
< Pea size	—	1	2	3	6
= Pea size	—	—	1	—	1
> Pea size	1	—	—	—	1

Results related to the histologic grade of malignancy. Biopsies were performed in all cases (except one) before treatment, where the histologic malignancy was grade I or II, as shown below:

Codes	0	1	2	3	Total
Grade MI	2	1	7	6	16
Grade MII	3	—	4	5	12
Grade 0	—	—	—	1	1

There was no difference in the results of treatment between the two grades of malignancy.

Results related to bladder infection. An adequate bacteriologic investigation was not made in connection with the treatment in twenty-one cases in which the results could only be judged by the clinical condition of the patient. Only one of the other eight cases developed infection of the bladder after instillation of tifosyl and this patient experienced no discomfort. The others either had no trouble with constriction or infection, or it was slight. Prophylactic antibiotic therapy was used in connection with the treatment, as related below:

Codes	0	1	2	3	Total
Infection before and after treatment	1	—	2	1	4
Infection before treatment only	—	1	—	—	1
Infection after treatment only	—	—	—	1	1
No infection	1	—	—	1	2
Not investigated	3	1	8	9	21

Complications. Four of the twenty-nine patients treated with tifosyl had complications that might be considered as side effects. In one man, the tifosyl treatment was interrupted after five instillations because of pain and discomfort in the bladder. One woman became tired and had small haemorrhages in the skin of the lower parts of the legs and experienced giddiness three weeks after a tifosyl instillation series; the lowest thrombocyte value was 85 000; all the symptoms disappeared later. The third patient was a man who had a decrease in the thrombocyte values, from 186 000 to 47 000, without symptoms or signs in connection with the treatment series; the values returned to normal later. The fourth patient was a woman, aged 71, who had had suprapubic cystotomy seven years earlier with resection of a walnut-sized papilloma. Five years later, the bladder was covered with papillomata. Eight coagulations were performed, one of them in connection with the sectio alta. One year before the instillation of tifosyl, perforation of the bladder occurred in connection with coagulation and biopsy of the papillomata. Dilatation of the left ureter was present and nephroureterectomy revealed a papilloma in the ureter; postoperative ileus required laparotomy. Multiple papillomata of the bladder occurred 6 months later. Coagulation of as many papillomata as possible was carried out and tifosyl was instilled ten times in doses of 50 mg per instillation every second day. The day after the last instillation the white blood cell count was 9 000 and the thrombocyte count normal. Four days later, the white blood cells decreased from 2 500 to 50 for a few days and the thrombocytes from 10 000 to 3 000. The patient died of sepsis probably caused by pancytopenia. Autopsy revealed no tumour or papillomatous tissue in the bladder but marked cystitis with ulceration. The period between the coagulation and the instillation of tifosyl was probably too short and the drug was carried into the blood stream via the ulcerated vesical mucous membrane.

SUMMARY

Twenty-nine cases of widespread vesical papillomatosis were treated by the instillation of tifosyl. The method is described. Complete or almost complete regression was achieved in twenty-three of the cases.

ZUSAMMENFASSUNG

Spülungen mit Tifosyl zur Behandlung ausgebreiteter Papillomatose der Harnblase wurden an neunundzwanzig Fällen verwandt. Die Methode wird beschrieben. In dreiundzwanzig Fällen erfolgte komplette Heilung oder wenigstens ein beinahe vollständiger Rückgang der Erkrankung.

RÉSUMÉ

Trente-neuf cas de papillomatose vésicale étendue ont été traités par instillation de tifosyl. Description de la méthode. On a observé une regression complète ou presque complète dans vingt-trois de ces cas.

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