

SELACHYL ALCOHOL AS AN ADJUNCT TO RADIATION TREATMENT OF CARCINOMA OF THE CERVIX

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The alpha-glyceryl ethers, or alpha-alkoxyglycerols, are widely distributed in nature, occurring in human bone marrow, liver, red blood cells and milk. They are most abundant in the liver oil of certain species of shark.

Alkoxyglycerols have the formula $\text{CH}_2\text{OH} \cdot \text{CHOH} \cdot \text{CH}_2\text{O} \cdot \text{R}$ with R being a long-chain aliphatic radicle. Batyl, chimyl and selachyl alcohols are the most common members of the group. The first two have 18 and 16 carbons respectively, in the sidechain and are saturated whereas selachyl, with 18 carbons, is unsaturated.

The alkoxyglycerols are absorbed readily from the gut and are of very low toxicity. They have anti-inflammatory properties (BURFORD & GOWDEY 1968) and are weak inhibitors of tumour growth in experimental animals (ABATUROVA & SHUBINA 1964). They have become best known however for their effect of stimulating red cell, white cell and platelet formation in experimental animals (LINMAN 1960, SANDLER 1949, SUKI & GROLLMAN 1960) and for giving some protection from the effects of irradiation in experimental animals and in humans treated for malignant disease (BROHULT & HOLMBERG 1954, EDLUND 1954, GHYS 1960).

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Table 1
Distribution of patients by clinic

	Group 1	Group 2
Hamilton	73	69
Kingston	5	4
London	60	66
Ottawa	39	48
Thunder Bay	27	14
Total	204	201

BROHULT (1963) published a report of great practical interest. A large group of patients with carcinoma of the cervix was given a mixture of alkoxyglycerol esters during the course of irradiation. Compared with a control group, the white cells and platelets were significantly protected from the effects of radiation and the patient survival rates were significantly higher. The survival rates, in turn, seemed directly related to the total amount of esters taken.

Material and Methods

Because of the clinical importance of BROHULT's observations an investigation was designed to determine whether selachyl alcohol, in conjunction with radiation therapy, might have protective effects on the blood and result in higher survival rates. In this respect our investigation differs from that of BROHULT who, for most of her patients, used an ester mixture from Greenland shark liver oil containing alkoxyglycerols with 14—22 C-atoms in the side-chain, selachyl alcohol accounting for 60 per cent of the alkoxyglycerol content.

Selachyl alcohol was chosen for several reasons. It is the predominant alkoxyglycerol in the source material of shark liver oil (BROHULT 1963) and has been reported as more effective than ester mixtures or batyl alcohol in protecting marrow from the effects of radiation (BROHULT 1958). It has also been reported as more effective than batyl alcohol in inhibiting the growth of animal tumours (ABATUROVA & SHUBINA). Moreover, it was readily available in a form easily taken by our patients.

Between September 1964 and February 1967, five of the clinics of the Ontario Cancer Treatment and Research Foundation cooperated in the investigation of 439 patients diagnosed as having carcinoma of the cervix. Treatment consisted, usually, of two radium insertions followed by external irradiation, the whole being given, where practical, over a four to five week period.

Table 2
Stage of disease

	Group 1		Group 2	
	No.	Per cent	No.	Per cent
Stage 1	85	42	77	38
Stage 2	86	42	93	47
Stage 3	25	12	29	14
Stage 4	8	4	2	1
Total	204		201	

The investigation was of the double blind type. The patients were divided randomly. A telephone call was made to a secretary at the London clinic who opened the presenting envelope of a series in which each member had previously been labelled either Group 1 or Group 2.

Thus, patients were divided into two, hopefully homogeneous groups. Each patient was to receive radiation treatment and each patient would, during the course of treatment, take six capsules per day labelled according to the group to which she had been assigned. The capsules, indistinguishable in appearance, each contained cottonseed oil as a carrying or blending agent. One group however, shown to be Group 1 after breaking the code upon completion of this written report, took capsules which contained, in addition, 100 mg of selachyl alcohol as a natural concentrate, (600 mg per day). Group 2 received capsules which contained only cottonseed oil. A dose of 600 mg per day was chosen because this amount corresponded to the highest intake of esters in BROHULT's material.

Haemoglobin, white blood cell and platelet values were estimated before treatment and at weekly intervals until radiation treatment was completed.

Of the 439 patients, 34 were subsequently excluded, leaving 204 patients in Group 1 and 201 patients in Group 2. The reasons for exclusion are listed below.

	<i>Group 1</i>	<i>Group 2</i>
Admitted in error	8	7
Insufficient medication	4	5
Errors in medication	2	5
Intent of treatment altered	—	3

Table 3
Radiation treatment

	Group 1	Group 2
Radium only	2	5
External irradiation only	4	7
Radium and external irradiation	198	189
Total	204	201

Patients admitted to the material in error had already been operated upon as part of treatment or were found subsequently to have been incorrectly diagnosed, the correct diagnosis being carcinoma in situ or carcinoma of the endometrium. If patients did not take medication for four-fifths of the period of radiation treatment they were excluded as were several who in error received both types of capsule. Also excluded were two patients for whom the intent of treatment was altered from radium and external radiation to radium and surgery. In another case no treatment was given.

The mean age for patients in Groups 1 and 2 was 50 and 52 years, respectively. The distribution of patients from the five cooperating clinics is shown in Table 1. Table 2 shows the distribution of stages of the disease within the two groups and Table 3 the type of irradiation.

Table 4
Complications

	Group 1	Group 2
Nausea, vomiting, diarrhoea	10	12
Skin rash	5	1
Infection	2	4
Jau ndice	1	3
Thrombosis	2	—
Phlebitis	1	—
Haemorrhage	1	—
Pulmonary emboli (lipiodol)	—	1
Pleural effusion	1	—
Ruptured ovarian cyst	—	1
Dehydration	—	1
Total	23	23

Table 5*Differences in blood values before treatment and on completion of treatment*

	Category	No.	Mean differ- ence (before — after)	Standard deviation	t-test	Mean difference (Group 1 — Group 2)	t-test
Haemoglobin (g %)	Group 1	115	0.58	1.1739	5.2983	-0.1968	-1.1731
	Group 2	108	0.7768	1.3296	6.0716		
White cells	Group 1	120	2 645	2 728.85	10.6178	-114.10	-0.3120
	Group 2	115	2 759	2 874.16	10.2944		
Platelets	Group 1	105	30 380	91 240	3.4119	9 410	0.7563
	Group 2	97	39 790	84 300	4.6489		

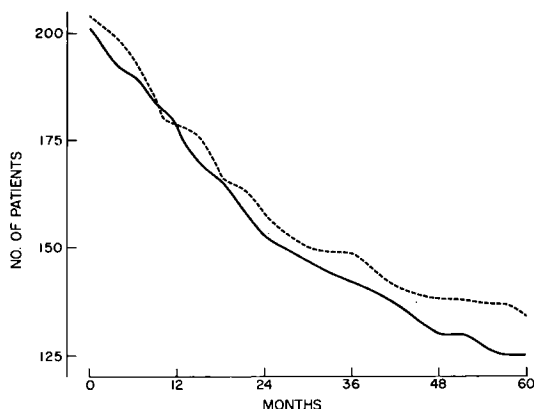
In each group only ten patients failed to complete the planned course of irradiation. In Group 1 the period of treatment was longer than 5 weeks in 52 cases and in Group 2, in 50 cases.

Observations

Of the complications (Table 4) it is difficult to say whether any one may have been related to selachyl alcohol. The higher incidence of skin rash in Group 1 may be significant. The three cases of jaundice in Group 2 occurred at one clinic early in the investigation and nearly resulted in its termination. In retrospect, all cases of jaundice were possibly related to methoxyfluothane anaesthesia. Two patients died of coronary and cerebral thrombosis and another of fluid and electrolyte imbalance associated with severe diabetes.

One purpose was to determine whether selachyl alcohol had a protective effect on the hemopoietic system. This group of patients consisted of those who completed their treatment in five weeks or less and whose haematologic examination had been carried out as planned. Table 5 summarizes a comparison of the blood values of the two groups before, and upon the completion of treatment. Statistical analysis of the data indicates that during the period of treatment each group had a significant fall in the haemoglobin, white cell and platelet values but that there was no significant difference between the fall noted for each group. Thus, no protective effect of selachyl alcohol upon the blood was demonstrated.

The five year follow-up of the 405 patients was satisfactory as no patients



Decline in number of survivors, by month, for five years. Broken line: Group 1. Solid line: Group 2.

were lost. The figure shows, by month, for a five year period, the decline in the number of survivors and reveals no marked difference between the two groups. Within Group 1, 70 died and within Group 2, 76.

A χ^2 -test was carried out of the observed difference in the proportions surviving at the end of five years. The results of the test were as follows:

$$\chi^2 = 0.537, 1 \text{ df } 0.50, p > 0.30$$

Thus, the observed difference fell far short of statistical significance at the 5 per cent level.

No significant improvement of survival rates for patients receiving selachyl alcohol during the course of radiation treatment was therefore demonstrated.

Discussion

As stated, our investigation began in 1964 with the objective of extending the observations of BROHULT (1963). In 1970, BROHULT et coll. reported further experiences on alkoxyglycerols and their use in cancer treatment. Over a two year period from 1964 to 1966, a large group of patients irradiated for carcinoma of the cervix also received alkoxyglycerols. The form in which the medication was given is not stated. About half the patients received medication over an eight day period prior to the irradiation. The remainder, as previously, received medication only during the period of radiation therapy and these patients, over the three year period of follow-up, showed no significant difference in mortality from a control group receiving irradiation only. Expressed differently, it would seem that BROHULT was unable to confirm the higher survival rates, reported in 1963, for patients receiving alkoxyglycerols during the course of radiation treatment.

BROHULT's other patients who received medication prophylactically showed a significantly higher survival rate. Although not so stated, the reason, presumably, for giving alkoxyglycerols prophylactically was that serum ornithine carbamoyl transferase (S-OCT) rises during irradiation (BROHULT 1969) and that the elevation is less when alkoxyglycerols are given prophylactically (BROHULT et coll. 1972).

The present report is comparable to BROHULT's of 1963 where alkoxyglycerols were not given prophylactically. Confirmation of her more recent work will be awaited with interest by all concerned with the treatment of carcinoma of the cervix.

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SUMMARY

Over 400 patients with carcinoma of the cervix were divided randomly into two groups, one of which received selachyl alcohol 600 mg daily during the course of radiation treatment. Analysis of haemoglobin, white cell and platelet values upon completion of treatment, and of survival rates over a five year period revealed no significant differences between the two groups.

ZUSAMMENFASSUNG

Über 400 Patienten mit einem Cervixkarzinom wurden zufällig in zwei Gruppen aufgeteilt; die eine von diesen erhielt täglich im Verlauf der Strahlenbehandlung 600 mg Selachyl Alkohol. Die Analyse des Hämoglobins, der weissen Blutzellen und der Thrombocyten bis zur Vollendung der Behandlung sowie die Überlebensrate während einer Fünfjahres-Periode ergaben keine signifikanten Unterschiede zwischen diesen beiden Gruppen.

RÉSUMÉ

Plus de 400 malades atteintes de carcinome du col de l'utérus ont été réparties au hasard en deux groupes dont l'un a eu un traitement quotidien par 600 mg de selachyl alcool au cours du traitement par les radiations. L'analyse du taux de l'hémoglobine et la numération des globules blancs et des plaquettes à la fin du traitement et l'étude des taux de survie sur une période de 5 ans n'a pas montré de différences significatives entre ces deux groupes.

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