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EFFECT OF ALKOXYGLYCEROLS ON THE FREQUENCY OF INJURIES FOLLOWING RADIATION THERAPY FOR CARCINOMA OF THE UTERINE CERVIX

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Abstract. The incidence of injuries following intracavitary and external radiation therapy is markedly decreased in all stages of the disease by the administration of alkoxyglycerols. Complex injuries (due to radiation injury and tumour growth in combination) were reduced to about 1/3 in a group receiving alkoxyglycerols prophylactically, i.e. before, during and after radiation treatment, when compared with a control group. Using non-prophylactic administration of alkoxyglycerols, i.e. during and after radiation treatment, no effect was observed on complex injuries, while—as for the prophylactic group—the injuries due to radiation only, were significantly decreased. The use of so called "increased amount" of radium in the intracavitary irradiator was followed by an unexpectedly high incidence of radiation injuries, which was considerably reduced, however, by alkoxyglycerols, especially when administered prophylactically.

Alkoxyglycerols are found in small quantities in several natural products. They are relatively abundant in the haemopoietic organs of mammals, particularly the bone marrow. These substances also occur in relatively high concentrations in the human mother's milk. They occur most abundantly, however, in the liver oil of certain species of shark. These oils contain up to 50% of alkoxyglycerol esters (1, 7, 8). The general formula for alkoxyglycerols is $CH_2OH \cdot CHOH \cdot CH_2O \cdot R$, where R is a long-chain aliphatic radical.

The alkoxyglycerols have earlier proved to be of medical interest. The first studies commenced with the oral administration of different fractions of cattle bone marrow to cases of leukemia in children. Alkoxyglycerols promote the growth of Lactobacillus lactis (1) and the formation of antibodies (2, 4) and, to some extent, they prevent leucopenia and thrombocytopenia as a result of radiation. The administration of alkoxyglycerols before, during and after radiotherapy for carcinoma of the uterine cervix also brings about higher survival rates than if radiation treatment alone is given (1, 2).

The aim with the present study has been to investigate whether or not alkoxyglycerols administered in a prophylactic or non-prophylactic manner, influence the incidence of radiation injuries and the growth of residual or recurrent tumour following radiotherapy for carcinoma of the uterine cervix. Problems connected with the development of radiation tissue damage following radiotherapy have earlier been elucidated in several publications from the Radiumhemmet in Stockholm, where all patients included in the present study received their treatment (6, 9, 10, 11, 12, 13, 14).

MATERIALS AND METHODS

The clinical experiments in this study have been conducted using alkoxyglycerol preparations from the liver oil of the Greenland shark. The preparation, produced by AB Astra with the working name AT 18, is a concentrate containing 85% free alkoxyglycerols. The content of different alkoxyglycerols from various sources is given in Table I.

The alkoxyglycerols were administered orally in capsules, 2 capsules 3 times a day, each capsule containing 0.1 g of alkoxyglycerols. The total daily dosage thus was 0.6 g.

The series of cases with invasive carcinoma of the uterine cervix, treated at the Department of Gynecology, Radiumhemmet, Stockholm, were reviewed during various periods. The patients comprised all stages, see Table II, and were allotted to one of the following groups:

Table I. *The percentage composition (weight) of alkoxyglycerols from various sources*

Analyses according to Hallgren and Larsson (2, 3). The number of carbon atoms in the first column refers to the long-chain component of the molecule. The number after the colon denotes the number of double bonds

Alkoxy-glycerols	Human bone marrow	Human milk	Liver oil: Greenland shark
14:0			2.0
15[a]			0.7
16:0	29.4	23.9	9.1
16:1		trace	10.8
17[a]	7.6	3.6	3.6
18:0	24.6	22.8	2.8
18:1	16.7	33.8	59.4
18:2		1.4	1.6
18:3			?
19[a]	6.1	2.4	1.5
20:0	2.9	1.6	
20:1	3.2	2.3	6.2
22:0	0.7	0.7	
22:1	5.1	3.4	2.2
24		2.1	

[a] Both branched and normal chains C_{15}, C_{17} and C_{19} are present.

I. Patients given alkoxyglycerols "prophylactically": i.e. during 7 days before, during the treatment period, and for 1–3 months after the completement of therapy.

II. Patients given alkoxyglycerols only during the period of radiotherapy and for 1–3 months thereafter, "non-prophylactic" administration.

III. Patients given radiotherapy only.

Groups I and II cases were treated during the period January 1, 1964–February 15, 1966. During this period 99% of the patients with carcinoma of the uterine cervix received alkoxyglycerols. Group III patients were treated during 1963 (348 patients) and February 16–December 31, 1966 (309 patients).

In addition to the patients followed up for more than five years and characterized above, a double blind study comprising 279 patients was conducted 1970–1972. These patients have been followed up for 3.5 years from the initiation of therapy.

The treatment was, in almost all cases, initiated with intracavitary radium application. This consisted typically of two radium insertions, separated by an interval of about three weeks. 53–200 mg of radium was homogeneously distributed in an interauterine applicator, 19–70 mm in active length. The enclosure was 0.30 mm Au + 0.35 mm Pt and a stainless steel container with a wall thickness of 2.00–2.75 mm. In cases in which both intrauterine and intravaginal radium was applied, no radium was introduced in the distal 15 mm of the cervix, whereas in cases of endocervical tumour growth, as well as in cases, in which the growth had extended paracervically, the amount of radium in the intrauterine irradiator was increased ("increased amount" of radium) and radium sources were applied also in the low endocervix. No radium was inserted in the vagina. The vaginal radium when employed was enclosed in a flat or curved applicator, or in a few cases in two cylinders, so as to cover a maximum surface area, and it was placed as close to the tumour as possible. The applicators were held in place by a tampon, which also increased the distance to the rectum. 58–250 mg of radium were used in the vagina.

The computation of doses delivered to the posterior wall of the bladder and to the anterior wall of the rectum was made on the bases of routinely performed dose rate measurements. Consecutive dose rate values were noted at centimeter intervals progressing from the bladder base caudally, through the urethra, and along the rectal wall. Measurements were in all instantaneously performed with a slightly modified Siemens Gammameter with the patient in lithotomy position immediately after the application of the intrauterine sources (9, 10, 15). The external radiotherapy was given either with conventional roentgen rays or with cobalt irradiation according to one of the following techniques:

Four fields, two abdominal and two gluteal, were utilized when conventional roentgen rays were used. An exposure of 6×400 R was given over 4–6 weeks. The external irradiation using Cobalt-60, two opposed beams, was administered through 250–400 cm^2 anterior and posterior fields. An exposure of 2000–5000 R was given in fractions of 300–400 R, six days a week. Lead shields were sometimes placed over the site of the uterine cervix in the anterior or the posterior beam or both, in an attempt to

Table II. *Definitions of clinical stages*[a]

Stage I	Carcinoma strictly confined to the cervix.
Stage I A	Cases of early stromal invasion (pre-clinical carcinoma).
Stage I B	All other cases of stage I.
Stage II A	The carcinoma extends beyond the cervix but has not extended on to the pelvic wall. The carcinoma involves the vagina, but not the lower third. No parametrial involvement.
Stage II B	The carcinoma extends beyond the cervix but has not extended on to the pelvic wall. The carcinoma involves the vagina, but not the lower third. Parametrial involvement.
Stage III	The carcinoma has extended on to the pelvic wall. On rectal examination there is no cancerfree space between the tumour and the pelvic wall. The tumour involves the lower third of the vagina.
Stage IV	The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum.

[a] Definitions according to FIGO (International Federation of Gynecology and Obstetrics).

Table III. *Injuries following radiation therapy. All stages included*

I=total injuries, R=injuries due to radiation treatment, C=complex injuries, due to tumour growth or to a combination of tumour growth and radiation treatment, N_I=number of patients with injuries, N_C=number of patients with complex injuries, M=more than one injury per patient, multiple injuries

Group	No. of pats.	I		R		C		N_I		N_C		M	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
A. 1963–1966													
I[a]	458	83	18.1	59	12.9	24	5.2	78	17.0	22	4.8	5	1.1
II[b]	381	93	24.4	34	8.9	59	15.5	69	18.1	41	10.8	23	6.0
III[c]	657	244	37.1	150	22.8	94	14.3	189	28.8	76	11.6	43	6.5
B. 1970–1972													
[a]	137	36	26.3	28	20.4	8	5.8	32	23.4	8	5.8	4	2.9
[c]	142	74	52.1	40	28.2	34	23.9	52	36.6	24	16.9	16	11.3

[a] Administration of alkoxyglycerols *prophylactically* and during radiation treatment.
[b] Administration of alkoxyglycerols *only* during radiation treatment.
[c] Radiation treatment only.

protect those portions of the pelvis, already having received a high dose of radiation from the intracavitary sources. With a three beam technique, Cobalt irradiation was delivered through one 250 cm² anterior field and two 120 cm² lateral fields. Weekly tumour doses were 700–800 rad, with the total tumour dose being 4 000–5 000 rad. A shielding block was sometimes used in the anterior beam in all or in part of the fractions. For data regarding the calculation of the dose from the external irradiation the reader is referred to previously published reports.

In the calculation of the incidence of radiation injuries (bladder, rectum, ureters, and intestine) the principles given by Kottmeier (14), Kottmeier & Gray (13), and Gray & Kottmeier (6) have been used in this investigation.

In earlier follow-up studies, regard has been paid to injuries due to radiation treatment only (R). In this kind of study, however, it has been necessary to include the injuries due to tumour growth and to the combination of radiation tissue damage and residual or recurrent tumour growth. This is because the alkoxyglycerols may have a multifaceted target of action. These injuries, due to either tumour growth or to tumour growth and radiation damage in combination are called complex injuries (C). The sum of them (R+C) is defined as the total number of injuries (I). Furthermore, in this study of the effects of alkoxyglycerols in connection with radiotherapy it has been considered necessary to give figures for the incidence of occurrence of more than one injury per patient, i.e. multiple injuries (M).

The injuries have been classified according to the following schedule given by Kottmeier:

Grade I: Injuries producing mild subjective symptoms accompanied by minimal objective changes in the mucosa. These injuries are considered as radiation reactions and have consequently been omitted.

Grade II: Injuries which are composed of moderately severe objective changes, such as areas of necrosis, ulcers or moderate stenosis.

Grade III: Bladder and ureter injuries comprising radiation fistulas, and rectal and intestinal injuries comprising stenoses that require colostomy.

Grade IV: Rectal and intestinal injuries which are all fistulas.

Injuries which appear within three months of surgery plus radiotherapy have been excluded, and those injuries which are not clearly related to the radiation treatment or to tumour growth have also been omitted. Only the injuries which appear within 5 years after the onset of radiation treatment have been taken into consideration in this investigation. Patients with complex injuries (C) have clinically detectable cancer, residual cancer or recurrent tumour growth, confirmed by biopsy or autopsy.

RESULTS

Reduction of injuries after administration of alkoxyglycerols

The effect of alkoxyglycerols on the incidence of injuries following radiation treatment has been studied, comparing groups I and II with each other, and with the control group III, the total number of injuries, injuries due to radiation treatment and complex injuries in the different groups are given in Table III A.

It is observed that:

1. The incidence of injuries is considerably lower in the alkoxyglycerol groups than in the control group—especially for group I where alkoxyglycerols have been administered prophylactically. The incidence of total injuries is reduced to about 50%.

2. Complex injuries are reduced to about 1/3 in the prophylactic group compared with the control group.

Table IV. *Different types of injuries*

Group	No. of pats.	Injuries	I No.	I %	R No.	R %	C No.	C %
I	458	Bladder	20	4.4	13	2.9	7	1.5
		Rectum	45	9.8	33	7.2	12	2.6
		Intestine	7	1.5	7	1.5	–	–
		Ureter	11	2.4	6	1.3	5	1.1
Total			83	18.1	59	12.9	24	5.2
II	381	Bladder	33	8.7	13	3.4	20	5.3
		Rectum	39	10.2	17	4.5	22	5.8
		Intestine	4	1.0	2	0.5	2	0.5
		Ureter	17	4.5	2	0.5	15	3.9
Total			93	24.4	34	8.9	59	15.5
III	657	Bladder	58	8.8	33	5.0	25	3.8
		Rectum	124	18.8	96	14.6	28	4.2
		Intestine	15	2.3	10	1.5	5	0.8
		Ureter	47	7.2	11	1.7	36	5.5
Total			244	37.1	150	22.8	94	14.3

3. Multiple injuries are less frequent in the prophylactic group compared with the control group (1.1% compared with 6.5%).

4. When alkoxyglycerols are administered only during and after radiation treatment (group II) no effect is observed on the incidence of complex injuries, while a significant decrease is found for the injuries due to radiation only (22.8% to 8.9%).

5. The preliminary results from the double blind study, where the patients have been followed up for 3.5 years after the commencement of treatment, indicate that the prophylactic administration of alkoxyglycerols reduced the total incidence of injuries to about 50%, Table III B.

Effect of alkoxyglycerols on the different types of injuries

Injuries or damage following radiotherapy for carcinoma of the uterine cervix affect the bladder, the rectum, the small intestine, and the ureters. The incidence of each of these organ-related injuries in the groups I–III is given in Table IV. It is observed that injuries affecting the urinary bladder and the rectum dominate. The total incidence of injuries associated with these organs is reduced with about 50% in the group of patients given alkoxyglycerols prophylactically as compared with the control group. The incidence of the ureter injuries is considerably lower in the prophylactic group than in the control group.

The incidence of injuries according to the different clinical stages of the disease

The incidence of injuries following radiation therapy, distributed according to the different stages of the disease in groups I–III, is given in Table V. The same characteristics are observed for all stages, i.e. a decrease of the total incidence of injuries following administration of alkoxyglycerols, especially a marked decrease in the incidence of complex injuries after prophylactic administration. No change in the incidence of complex injuries is seen to occur in cases where alkoxyglycerols are given only during and after radiotherapy.

The incidence figures given in Table III A for the groups I, II and III should be corrected with regard to differences in the distribution according to clinical stages in order to allow a valid comparison. The data in the Tables V and VI provides the information to make this correction.

Table V. *Injuries following radiation therapy (1963–1966). Distribution according to clinical stages*

Stage	Group I No. of pats.	I No.	I %	R No.	R %	C No.	C %	Group II No. of pats.	I No.	I %	R No.	R %	C No.	C %
I A	45	–	–	–	–	–	–	44	1	2.3	1	2.3	–	–
I B	159	23	14.5	18	11.3	5	3.1	107	17	15.9	10	9.3	7	6.5
II A	129	24	18.6	13	10.1	11	8.5	76	18	23.7	6	7.9	12	15.8
II B	71	20	28.2	18	25.4	2	2.8	73	26	35.6	5	6.8	21	28.8
III	39	14	35.9	10	25.6	4	10.3	60	18	30.0	9	15.0	9	15.0
IV	15	2	13.3	–	–	2	13.3	21	13	61.9	3	14.3	10	47.6
I–IV	458	83	18.1	59	12.9	24	5.2	381	93	24.4	34	8.9	59	15.5

If the figures for groups I and II are normalized to the same distribution of clinical stages as group III (controls), the following corrected figures for incidence of total injuries (I) are obtained: 18.7% for group I, and 25.6% for group II (cf. not corrected figures of 18.1% and 24.4%, respectively).

The change in distribution according to clinical stages observed to occur after the prophylactic administration of alkoxyglycerols (as evident in Table VI) involves a shift in distribution towards earlier stages. Regression of tumour growth induced by the prophylactic administration of alkoxyglycerols is the probable explanation which will be discussed in detail in a separate paper (5).

Table VI. *Distribution according to clinical stages for the groups I, II, and III (1963–1966)*

	Group I		Group II		Group III	
Stage	No.	%	No.	%	No.	%
I A	45	9.8	44	11.5	84	12.8
I B	159	34.7	107	28.1	160	24.4
II A	129	28.2	76	19.9	171	26.0
II B	71	15.5	73	19.2	132	20.1
III	39	8.5	60	15.8	77	11.7
IV	15	3.3	21	5.5	33	5.0
I–IV	458		381		657	

Effect of alkoxyglycerols on the incidence of injuries associated with two different modalities of intracavitary radium treatment

The effect of the administration of alkoxyglycerols has been considered for two different modalities, namely:

1. Treatment with conventional amounts of radium, i.e. an intrauterine irradiator with <100 mg of radium and a vaginal irradiator with <90 mg of radium. This treatment modality is characterized by the letter L.

2. Treatment with increased amounts of radium, i.e. an intrauterine irradiator with >100 mg of radium and a vaginal irradiator with >90 mg of radium. This treatment modality is characterized by the letter H.

The percentage figures for the distribution of different injuries with regard to the characteristic of the intracavitary treatment are given in Table VII A and VII B for the groups I–III and the double blind study, respectively. The same characteristics are found for the two treatment modalities, that is a decrease in the total incidence of injuries after alkoxyglycerol administration, a remarkable reduction in the incidence of complex injuries after prophylactic administration of alkoxyglycerols, and no change at all in the incidence of complex injuries when alkoxyglycerols were given only during and after radiation therapy.

Striking differences were observed when the two intracavitary treatment modalities were compared:

1. For the controls (group III) the total incidence of injuries, both R and C, is remarkably higher in treatment modality H than in treatment modality L. It is reduced with more than 60% in the group given alkoxyglycerols in prophylactic administration.

2. The incidence of radiation injuries is nearly the same in the two treatment modalities, H and L, for the patients given alkoxyglycerols in prophylactic administration.

The same tendency is observed in the double blind study (Table VII B).

Group III

No. of pats.	I		R		C	
	No.	%	No.	%	No.	%
84	4	4.8	4	4.8	–	–
160	38	23.8	25	15.6	13	8.1
171	56	32.7	34	19.9	22	12.9
132	79	59.8	48	36.4	31	23.5
77	51	66.2	34	44.2	17	22.1
33	16	48.5	5	15.2	11	33.3
657	244	37.1	150	22.8	94	14.3

DISCUSSION

The analysis of injuries of the bladder (and ureters) and rectum (and intestine) following intracavitary and external radiation therapy for carcinoma of the uterine cervix has shown a marked decrease in the incidence of injuries in cases where alkoxyglycerols are administered. There are noticable differences in effect, however, related to the schedule of the administration of alkoxyglycerols, and related to whether the injury represents a pure radiation damage of the tissue or represents a combination of

Table VII. *Incidence of injuries associated with two different modalities of intracavitary treatment*

Group	No. of pats.	I No.	%	R No.	%	C No.	%	N_I No.	%	N_C No.	%	M No.	%	3-year survivals No.	%	5-year survivals No.	%
A. 1963–1966																	
Intrauterine irradiator <100 mg Ra-ekv, vaginal irradiator <90 mg Ra-ekv at both treatment courses (L.)																	
I	224	38	17.0	29	13.0	9	4.0	36	16.1	7	3.1	2	0.9	190	84.8	176	78.6
II	178	32	18.0	14	7.9	18	10.1	23	12.9	12	6.7	8	4.5	138	77.5	130	73.0
III	349	92	26.4	58	16.6	34	9.7	70	20.1	28	8.0	17	4.9	289	82.8	274	78.5
Intrauterine irradiator >100 mg Ra-ekv and/or vaginal irradiator >90 mg Ra-ekv at one or both treatment courses (H.)																	
I	230	45	19.5	30	13.0	15	6.5	42	18.3	15	6.5	3	1.3	164	71.3	139	60.4
II	202	61	30.2	20	9.9	41	20.3	46	22.8	29	14.4	15	7.4	106	52.5	93	46.0
III	299	152	50.8	92	30.8	60	20.1	119	39.8	48	16.1	26	8.7	172	57.5	149	49.8
B. 1970–1972																	
Intrauterine irradiator <100 mg Ra-ekv, vaginal irradiator <90 mg Ra-ekv at both treatment courses (L.)																	
I	106	24	22.6	18	17.0	6	5.7	22	20.8	6	5.7	2	1.9	86	81.3		
II	115	50	43.5	30	26.1	20	17.4	35	30.4	15	13.0	12	10.4	86	74.8		
Intrauterine irradiator >100 mg Ra-ekv and/or vaginal irradiator >90 mg Ra-ekv at one or both treatment courses (H.																	
I[a]	27	12	44.4	10	37.0	2	7.4	10	37.0	2	7.4	2	7.4	18	66.7		
II[b]	25	21	84.0	10	40.0	11	44.0	15	60.0	7	28.0	3	12.0	13	52.0		

[a] Group I: Prophylactic treatment. [b] Group II: Controls.

radiation injury and residual or recurrent tumour growth. The prophylactic treatment with alkoxyglycerols in combination with radiotherapy apparently prevents the development of radiation damage and the growth of the tumour, separately or combined. Non-prophylactic administration of alkoxyglycerols does not seem to influence the tumour growth—but still protects against radiation damage.

It has been worth-while to include the complex injuries in this study since the incidence of these injuries is characteristic for the different groups: a great reduction was seen in case of prophylactic administration with alkoxyglycerols (group I), while no reduction was observed when these compounds were given only during the radiation treatment (group II).

The complex injuries, (C), are in all the studied situations reduced to about 1/3 when alkoxyglycerols are administered before, during and after radiation treatment. The difference between the incidences of complex injuries in group I (prophylactic group) and group III (control group) is statistically significant, $p<0.001$. Prophylactic administration is therefore of paramount importance for the reduction of the incidence of total injuries, and especially for the reduction of complex injuries. The administration of alkoxyglycerols merely during and after radiation therapy does not reduce the incidence of these injuries.

In this connection it is of interest to mention that the capacity for forming antibodies after vaccination can be influenced by the administration of alkoxyglycerols. This fact was observed in a study in which patients were vaccinated against typhus–paratyphus one day before, and one day after the implantation of radium. In the group given alkoxyglycerols, certain antibodies were formed to a greater extent than in the group receiving merely radiation treatment (4). It is therefore probable, that the general immunological response can be enhanced by treatment with alkoxyglycerols, and thereby the defence mechanism of the body against malignant cells intensified.

The introduction of the concept of complex injuries facilitates a probable explanation why the incidence of radiation injuries is higher in the prophylactic group than in the non-prophylactic group.

As mentioned before, no decrease of incidence of complex injuries is observed when alkoxyglycerols are administered only during radiation treatment. However, there is a remarkable effect on the radiation injuries, which are reduced from 22.8% to

8.9%, if all patients are taken into consideration. The decrease of radiation injuries is even slightly higher than for the prophylactic group, Tables III A, V, and VII A. The suggested explanation would be that complex injuries, (C), are representative of two components: one, C_{R+T}, is due to radiation damage and tumour growth in combination and the other, C_T, is due to tumour growth alone. If, for a proportion of the injuries, $C_{R+T}+C_T$, the C_T components are reduced or eliminated, the residue of the complex injury would be interpreted as a radiation injury, (R). It is thereby inferred that a transformation om a complex to a radiation injury can occur if alkoxyglycerols are given in prophylactic administration, but not if they are given only during and after therapy.

The incidence of complex injuries has an addi- onal facet of interest. It has namely been found hat about 99% of the patients with complex injuries will be dead within five years after the initiation of radiotherapy. Thus a decrease of complex injuries would likely correspond to a considerable increase in the five year survival rate. Data are available that support this contention.

By a comparison of the two intracavitary treatment modalities, L and H respectively, it is found that the incidence of injuries is considerably higher following the employment of "increased" rather than conventional amounts of radium. This despite the fact that the majority of the patients in the H group (about 85% of them) have received a calculated dose on the bladder wall <5 000 rad and on the rectal wall <4 000 rad. This underlines the statement made above that the increased amount of in- acavitary radium was used in advanced, bulky tumours. It is therefore not surprising that the incidence of injuries is more dependent on the amount of radium (times application time) than on the calculated dose contribution to the bladder or rectal alls.

One of the most striking effects of prophylactic administration of alkoxyglycerols described in this investigation is that it produced a decrease with more than 60% of the incidence of total injuries, (I), in the group treated with increased amount of radium in the intracavitary irradiator.

The data described in the study strongly suggest that alkoxyglycerols have two distinct effects: inhibition of tumour growth and protection against tissue damage following radiation. The study of the so called complex injuries and the comparison between prophylactic and non-prophylactic administration of alkoxyglycerols have made it possible to separate these two effects.

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