

ASTRID BROHULT, JOHAN BROHULT, SVEN BROHULT
and INGEMAR JOELSSON

Effect of Alkoxyglycerols on the Frequency of Fistulas Following Radiation Therapy for Carcinoma of the Uterine Cervix

Reprinted from

Acta Obstetricia et Gynecologica Scandinavica, Vol. 58, No. 2, 1979

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

Astrid Brohult, Johan Brohult, Sven Brohult and Ingemar Joelsson

From the Clinical Laboratory and the Department of Gynecology, Radiumhemmet, the Department of Internal Medicine IV, Södersjukhuset, the Royal Academy of Engineering Sciences, Stockholm, and the Department of Obstetrics and Gynecology, University of Umeå, Umeå, Sweden

Abstract. The incidence of injuries following radiation therapy for carcinoma of the uterine cervix is markedly decreased by the administration of alkoxyglycerols. This is the case for less harmful injuries as well as for the more severe ones, i.e. the fistulas. Recto-vaginal and vesico-vaginal fistulas are reduced with 47 per cent when alkoxyglycerols are administered prior to radiation treatment.

Alkoxyglycerols occur in small quantities in several natural products. They are relatively abundant in the hemopoietic 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 per cent of alkoxyglycerol esters (1, 9, 10). The general formula for alkoxyglycerols is:



where R is a long-chain aliphatic radical. The most common natural sources are the saturated batyl and chimyl alcohols (with 18 and 16 carbon atoms, respectively, in the side chain) and the unsaturated squalyl alcohol with 18 carbon atoms in the side chain.

The alkoxyglycerols have proved to be of medical interest (1-8). The administration of alkoxyglycerols before, during and after radiation treatment reduces to a large extent (ca. 50 per cent) the frequency of injuries following radiation therapy (5, 7).

The aim with the present study has been to investigate the incidence of severe injuries, (i.e. vesico-vaginal and recto-vaginal fistulas) 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 (11, 12, 14, 15, 16, 17).

MATERIAL 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 per cent free alkoxyglycerols.

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 were allotted to one of the following groups:

- I. Patients given alkoxyglycerols "prophylactically": i.e. during 7 days before, during the treatment period, and for 1-3 months after the completion of radiotherapy.
- II. Patients given alkoxyglycerols only during the period of radiotherapy and for 1-3 months thereafter, "non-prophylactic" administration.
- III. Patients given solely radiotherapy.

Groups I, II and III cases were studied during the time period 1963 - 1966, category A. Group I and III cases were studied also 1970 - 1972, category B. 99 per cent of the patients, treated for carcinoma of the uterine cervix during the period January 1, 1964 - February 15, 1966 received alkoxyglycerols either prophylactically or as non-prophylactic administration. These patients are enclosed in groups I and II of category A. Patients within group III of category A were treated during 1963 (348 patients) and February 16-December 31, 1966 (309 patients). A double blind study comprising 279 patients was conducted 1970 - 1972. These patients form Group I and III of category B. While category A patients have been followed for more than 5 years, the category B 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 followed by external radiotherapy. For data regarding radiation treatment the reader is referred to previously published reports (12, 13).

In the calculation of the incidence of radiation injuries in the bladder, rectum, ureters, and small intestine the principles given by Kottmeier and Gray have been used in this investigation (17, 16, 11).

In earlier follow-up studies, regard has only been paid to injuries due to radiation (R). In this study, however, the in-

Table I. *Injuries following radiation therapy according to type of injury and grade of severity.*

I = total injuries. R = injuries due to radiation treatment. C = complex injuries, due to tumor growth or to a combination of tumor growth and radiation treatment.

Group	No. of pats.	I						R						C					
		Grade II		Grade III		Grade IV		Grade II		Grade III		Grade IV		Grade II		Grade III		GradeIV	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
A. 1963-1966																			
I ^a	454	41	9.0	26	5.7	16	3.5	32	7.1	17	3.7	10	2.2	9	2.0	9	2.0	6	1.3
II ^b	380	48	12.6	29	7.6	16	4.2	24	6.3	7	1.8	3	0.8	24	6.3	22	5.8	13	3.4
III ^c	648	156	24.1	46	7.1	42	6.5	112	17.3	18	2.8	20	3.1	44	6.8	28	4.3	22	3.4
B. 1970 - 1972																			
I ^a	137	26	19.0	5	3.7	5	3.7	21	15.3	2	1.5	5	3.7	5	3.7	3	2.2	—	—
III ^c	142	49	34.5	16	11.3	9	6.3	26	18.3	10	7.0	4	2.8	23	16.2	6	4.2	5	3.5

^a Administration of alkoxyglycerols *prophylactically* and *during* radiation treatment

^b Administration of alkoxyglycerols *only during* radiation treatment

^c Radiation treatment only

injuries due to tumor growth and to the combination of radiation tissue damage and residual or recurrent tumor growth have been considered in addition to the pure radiation injuries. These injuries are called complex injuries (C). The sum of the injuries (R + C) is defined as the total number of injuries (I). Furthermore, figures for the incidence of occurrence of more than one injury per patient, i.e. multiple injuries (M), are given.

The injuries have been classified according to the following schedule given by Kottmeier (17):

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 fistulas, and rectal and intestinal injuries comprising stenoses that require colostomy.

Grade IV Rectal and intestinal 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 tumor 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 tumor growth, confirmed by biopsy or autopsy.

RESULTS

Effect of alkoxyglycerols on the different grades of injuries. As a supplement to the earlier presentation of the effect of alkoxyglycerols, the effect of these a-

gents on the different grades of injuries has now been analysed (Table I). In category A, a sufficient number of patients for a valid statistical analysis is being found. The results within category B, with only a few patients in the various subgroups, are similar to the results in category A. It is observed that:

1. The incidence of total grade II injuries (I, grade II) is 9 per cent in the prophylactic group and 24 per cent in the control group, i.e. a reduction with 60 per cent.
2. The incidence of grade II radiation injuries (R, grade II) is considerably reduced while virtually no effect is observed on radiation injuries of grade III and IV.
3. The complex injuries of all grades are markedly reduced.
4. In the "non-prophylactic" group the radiation injuries are reduced while the incidence of the complex injuries remain the same.

Incidence of fistulas following radiation therapy. It is of special interest to study the effect of alkoxyglycerols on the incidence of fistulas following radiation therapy. The fistulas have been separately collected and the figures are given in Table II. Bladder injuries of grade III and rectal injuries of grade IV are fistulas. It is observed that:

1. The total number of fistulas [I, grade (III + IV)] is considerably lower in the prophylactic group I than in the control group III (6.2 per cent compared with 11.6 per cent).
2. The fistulas belonging to the complex injury group [C, grade (III + IV)] have decreased to 2.9 per cent

Table II. Incidence of fistulas following radiation therapy.

I = total fistulas. R = fistulas due to radiation treatment. C = complex fistulas, due to tumor growth or to a combination of tumor growth and radiation treatment.

Group	No. of pats.	I (fistulas)						R (fistulas)						C (fistulas)					
		Bladder		Rectal		Total		Bladder		Rectal		Total		Bladder		Rectal		Total	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
A. 1963-1966																			
I ^a	454	12	2.6	16	3.5	28	6.2	5	1.1	10	2.2	15	3.3	7	1.5	6	1.3	13	2.9
II ^b	380	20	5.3	16	4.2	36	9.5	2	0.5	3	0.8	5	1.3	18	4.7	13	3.4	31	8.2
III ^c	648	33	5.1	42	6.5	75	11.6	8	1.2	20	3.1	28	4.3	25	3.9	22	3.4	47	7.3
B. 1970 - 1972																			
I ^a	137	3	2.2	5	3.7	8	5.8	—	—	5	3.7	5	3.7	3	2.2	—	—	3	2.2
III ^c	142	7	4.9	9	6.3	16	11.3	1	0.7	4	2.8	5	3.5	6	4.2	5	3.5	11	7.8

^a Administration of alkoxyglycerols *prophylactically* and *during* radiation treatment

^b Administration of alkoxyglycerols *only during* radiation treatment

^c Radiation treatment only

compared with 7.3 per cent.

3. The pure radiation fistulas but not the fistulas of complex origin are decreased in number in the non-prophylactic group.

The same results are obtained for the patients included in category B, but the number of fistulas is too small for a valid comparison.

DISCUSSION

For the sake of comparison we have included the results from an earlier publication (7) in which the injuries following radiation therapy have been characterized as injuries due to radiation treatment (R) and injuries on the basis of tumor growth or a combination of tumor growth and radiation treatment (C). The main result can be briefly summarized as follows: the incidence of injuries in the prophylactic group, (I, group I), was reduced with about 50 per cent and the complex injuries in the same group, (C, group I), with about 65 per cent when compared with the control group (group III). In the non-prophylactic group (group II), no effect was observed on the incidence of complex injuries, while a significant decrease was found for the injuries judged to be due to radiation solely, Table III. These over-all results are mirrored very closely by the analysis of specific subgroups, presented now.

As there is always a certain degree of subjectivity in the interpretation of injuries following radiation treatment it has been considered of interest to analyse

the effect of alkoxyglycerol treatment on the injuries divided by grade of severity. Especial interest has been focused on the bladder injuries grade III and the rectal injuries grade IV, i.e. the fistulas because an injury of this degree can not be misinterpreted. The result of the analysis shows that the effect of alkoxyglycerols on fistula formation is similar to the effect on injuries in general; a marked effect on the total incidence of fistulas with a greater effect on fistulas on the basis of radiation injury and suspect tumor growth in combination (C) than on pure radiation fistulas (R).

These results are mainly based on retrospective analysis of patient-materials. The results in the small randomized series of patients point, however, in the same direction.

It should be recalled that taking only radiation injuries (R) into consideration, these injuries are in most cases healed after a period of 6-12 months. Even if the radiation injuries are painful for the patient, they have only a marginal effect on the survival rate. Considering, on the other hand, patients with complex injuries, one faces a different situation: almost all of these patients are dead (98-100 %) within five years. These complex injuries are reduced to one third when alkoxyglycerols are given prophylactically in comparison with the patients who received radiation therapy only.

Grade III bladder and grade IV rectal injuries are the fistulas. They are reduced from 11.6 per cent to 6.2 per cent by the prophylactic alkoxyglycerol ad-

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

I = total injuries. R = injuries due to radiation treatment. C = complex injuries, due to tumor growth or to a combination of tumor 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													
I ^a	137	36	26.3	28	20.4	8	5.8	32	23.4	8	5.8	4	2.9
III ^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

ministration, a decrease of 47 per cent. It is of importance to mention that the beneficial effect of alkoxyglycerols is observed not only for the less harmful radiation injuries (especially grade II) but also for the more severe injuries like fistulas.

It has been demonstrated in earlier publications that alkoxyglycerols have several important effects in cancer therapy. Alkoxyglycerols prevent for example to some extent the leucopenia and trombocytopenia resulting of radiation (1). Furthermore, an inhibition of tumor growth and a decrease of the number of both radiation and complex injuries are observed when alkoxyglycerols have been administered prior to radiation treatment of patients with cancer of the uterine cervix (7, 8). In this paper it has been pointed out that the fistulas have been markedly reduced. A prophylactic administration of alkoxyglycerols could certainly be of value as a complement to radiation in cancer therapy.

ACKNOWLEDGEMENTS

This work was supported by grants from the Knut and Alice Wallenberg Foundation and from the Sven and Dagmar Salén Foundation.

We wish to thank Prof. Hans Ludvig Kottmeier and Doc Bengt Tjernberg, former and present head of the Department of Gynecology of Radiumhemmet, Stockholm, for helpful discussions.

REFERENCES

1. Brohult, A.: Alkoxyglycerols and their use in radiation treatment. *Acta Radiol*, Suppl 223, 1963.
2. Brohult, A., Brohult, J. & Brohult, S.: Biochemical effects of alkoxyglycerols and their use in cancer therapy. *Acta Chem Scand* 24:730, 1970.
3. Brohult, A., Brohult, J. & Brohult, S.: Effect of alkoxyglycerols on the serum ornithine carbamoyltransferase in connection with radiation treatment. *Experientia* 28:146, 1972.
4. Brohult, A., Brohult, J. & Brohult, S.: Effect of irradiation and alkoxyglycerol treatment on the formation of antibodies after Salmonella vaccination. *Experientia* 28:954, 1972.
5. Brohult, A., Brohult, J. & Brohult, S.: Effect of alkoxyglycerols of the frequency of injuries following radiation therapy. *Experientia* 29:81, 1973.
6. Brohult, A., Brohult, J. & Brohult, S.: Alkoxyglycerols in cancer therapy. To be published.
7. Brohult, A., Brohult, J., Brohult, S. & Joelsson, I.: Effect of alkoxyglycerols on the frequency of injuries following radiation therapy for carcinoma of the uterine cervix. *Acta Obstet Gynecol Scand* 4:441, 1977.
8. Brohult, A., Brohult, J. & Brohult, S.: Regression of tumour growth after administration of alkoxyglycerols. *Acta Obstet Gynecol Scand* 1:57, 1978.
9. Hallgren, B. & Larsson, S.: The glyceryl ethers in the liver oils of elasmobranch fish. *J Lipid Res* 3:31, 1962.
10. Hallgren, B. & Larsson, S.: The glyceryl ethers in man and cow. *J Lipid Res* 3:39, 1962.
11. Gray, M.J. & Kottmeier, H.L.: Rectal and bladder injuries following radiumtherapy for carcinoma of the cervix at Radiumhemmet. *Amer J Obstet Gynecol* 74:1294, 1957.
12. Joelsson, I.: Radiotherapy of carcinoma of the uterine cervix with special regard to external irradiation. *Acta Radiol*, Suppl 302, 1970.

13. Joelsson, I. & Bäckström, A.: Dose rate measurements in bladder and rectum. *Acta Radiol Ther Phys Biol* 8:343, 1969.
14. Joelsson, I., Räf, L. & Söderberg, G.: Stenosis of the small bowel as a complication in radiation therapy of carcinoma of the uterine cervix. *Acta Radiol Ther Phys Biol* 10:593, 1971
15. Kottmeier, H.L.: Carcinoma of the Female Genitalia. The Abraham Flexner Lectures, Series No. 11. The Williams & Wilkins Co., Baltimore, 1953.
16. Kottmeier, H.L. & Gray, M.J.: Rectal and bladder injuries in relation to radiation dosage in carcinoma of the cervix. A five year follow up. *Am J Obstet Gynecol* 82:74, 1961.
17. Kottmeier, H.L.: Complications following radiation therapy in carcinoma of the cervix and their treatment. *Am J Obstet Gynecol* 88:854, 1964.

Submitted for publication Nov. 22, 1977

Astrid Brohult
Clinical laboratory
Radiumhemmet
S-104 01 Stockholm
Sweden

ANNOUNCEMENT

A European Congress of Obstetric Anaesthesia and Analgesia will take place at the Birmingham Metropole Hotel, adjacent to the National Exhibition Centre, from the 17th to the 20th September, 1979.

Further details may be obtained from:

Dr. J. Selwyn Crawford, Consultant Anaesthetist,
Birmingham Maternity Hospital,
Edgbaston,
Birmingham B15 2TG,
England.

An International Congress on *Interdisciplinary Aspects in Diseases of the Female Breast* will take place in Hamburg May 27 - 31, 1980, organized by the Senologic International Society.

Themes of Congress:

Benign and malignant diseases of the female breast - psychology, etiology, endocrinology, histopathology, diagnosis, prognosis, therapy.

Direct inquires to:

Professor Dr. H.-J. Frischbier,
Universitäts-Frauenklinik,
Martinistrasse 52,
200 Hamburg 20,
Germany.