Biochemical Effects of Alkoxyglycerols and Their Use in Cancer Therapy

ASTRID BROHULT,[a] JOHAN BROHULT[b] and SVEN BROHULT[c]

[a] *Radiumhemmet, Karolinska Sjukhuset, Fack, S-104 01 Stockholm 60*
[b] *4th Medical Department, Södersjukhuset, Fack, S-100 64 Stockholm 38,*
[c] *Royal Academy of Engineering Sciences, P.O. Box 5073, S-102 42 Stockholm 5, Sweden*

Alkoxyglycerols occur in small quantities in many natural products. In the haemopoietic organs of mammals, particularly the bone marrow, they are relatively abundant. They also occur in relatively high concentrations in human mother's milk.[1] They occur most abundantly in nature in the liver oil of certain species of shark.[2,3] The general formula for alkoxyglycerols is $CH_2OH{\cdot}CHOH{\cdot}CH_2O{\cdot}R$, where R is a longchain aliphatic radical. The most common natural alcohols are the saturated batyl and chimyl alcohols (with 18 and 16 carbon atoms, respectively, in the side chain) as well as the unsaturated selachyl alcohol with 18 carbon atoms in the side chain. The alkoxyglycerols occur most frequently as fatty acid esters.

The alkoxyglycerols have proved to be of medical interest. To some extent they prevent leucopenia and thrombocytopenia. The administration of alkoxyglycerols to patients with cancer of the uterine cervix results in higher survival rates than if radiation treatment alone is given.[4]

The alkoxyglycerols act as growth factors: they promote the growth of *Lactobacillus lactis*. The effects is different for different alkoxyglycerols; the saturated chimyl alcohol with 16 carbon atoms in the side chain gave a relatively small growth in relation to the saturated batyl alcohol with 18 carbon atoms in the side chain.[4]

The ornithine carbamoyl transferase (OCT) in serum (S-OCT) rises in connection with radiation.[5] It has now been proved that the S-OCT values are lower when alkoxyglycerols have been given prophylactically.[6]

In the clinical experiments, preparations from the liver oil of Greenland shark have been used. These oils contain up to 50 % of alkoxyglycerol esters. The content of different alkoxyglycerols from various sources is given in Table 1.

Table 1. The percentage composition (weight) of alkoxyglycerols from various sources.

Alkoxyglycerols	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	

Analyses according to Hallgren and Larsson.[1] 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.

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

Between January 1, 1964 and February 15, 1966, 849 patients with cancer of the uterine cervix (98.7 % of all such cases) were given alkoxyglycerols in connection with radiation treatment at Radiumhemmet. About half of the patients (Group P) received the alkoxyglycerols prophylactically 8 days before the radiation treatment, whereas the rest (Group T) only received it during the treatment. The dose was always 0.6 g/day; the duration of the treatment varied, however, for the different patients, the range being 2–11 weeks. Thus, there was a considerable variation in the total amount of alkoxyglycerols given. In order to study the effect of varying doses, the prophylactic Group P was ranked according to this total and divided in two equal-sized groups: the H-group received on an average 95 g alkoxyglycerols and the L-group 65 g.

The mortality rates of the differently treated groups were compared with the mortality rates of 1968 patients (Group C) treated during four years before, and with 938 patients during three years after the alkoxyglycerol period at the Radiumhemmet. The mortality rates of the two groups before and after the alkoxyglycerol period were the same as far as known today. The Group C serves as a reference in this study. In comparing the results, the observed mortality has been reduced by the normal mortality as obtained from the Swedish Bureau of Statistics for the period 1962—1966. Thus, the true mortality in the cancer of the cervix was obtained.

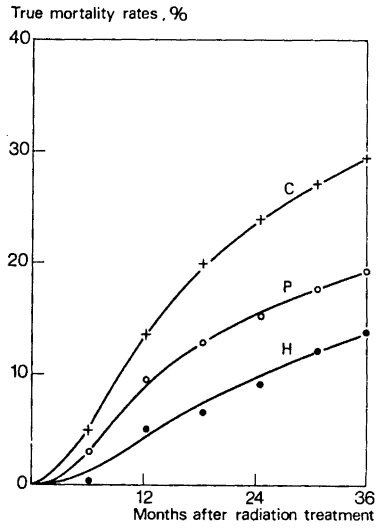

Fig. 1. Mortality rates (cancer colli uteri). ×: C, control group; ○: P, treated prophylactically with alkoxyglycerols; ●: H, treated as P but with higher doses.

As is seen in Fig. 1 the administration of alkoxyglycerols prophylactically before the radiation treatment markedly affects the mortality rates. The control group, C, having received radiation treatment only, has a mortality of 29.6 % after three years, whereas the whole Group P treated prophylactically with alkoxyglycerols has a mortality of 19.6 %. If comparison is made with half of the Group P, that is Group H, that obtained the highest dose of alkoxyglycerols, the difference is still more pronounced, the mortality being 13.7 %. The Group L, not shown in the figure, has a correspondently higher mortality rate. No significant difference is found between the controls C and the Group T that obtained the alkoxyglycerols only during the radiation treatment. Thus, for any effect to be obtained, the alkoxyglycerols must be given before the onset of the radiation treatment.

To elucidate the mechanism of action, the material has been analyzed further as will be discussed in detail elsewhere.[6] Suffice it to point out here two observations regarding the mode of action of the alkoxyglycerols: an influence upon the stage distribution of the cancer of the uterine cervix and an effect on the capacity to form antibodies in general.

The alkoxyglycerols seem to effect the tumour before, as well as after the radiation treatment. This is apparent from an observed shift in the distribution of the stages for the cancer of the cervix at Radiumhemmet for the period during which the prophylactic treatment was pursued, as compared to the periods before and after it. During the period of prophylactic treatment a larger number of patients had tumours in less advanced stages. This shift towards lower stages is statistically significant. The mechanism of the effect is not yet clearly understood, and it should be studied further. Possibly, the effect might be the result of an immunological reaction as indicated below.

The general immunological response seems to be enhanced by treatment with alkoxyglycerols. Thus, the capacity for forming antibodies after vaccination can be influenced as was observed from a study in which 54 patients, not included in any of the groups above, were vaccinated against typhus-paratyphus one day before and the day after the implantation of radium. Every second patient was given 0.3 g alkoxyglycerols per day for three weeks immediately after the first vaccination. In the group given alkoxyglycerols certain antibodies were formed to a greater extent than in the group receiving radiation treatment only. Furthermore, the formation of certain antibodies after vaccination occurred to a greater extent in the patients that later were found to have a lower mortality rate.

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A General Set of Computer Programs for the Determination of Crystal Structures by Means of Symbolic Addition Methods

OVE LINDGREN, OLIVER LINDQVIST and JENS NYBORG

Department of Inorganic Chemistry, Chalmers University of Technology and the University of Göteborg, P.O. Box, S-402 20 Göteborg 5, Sweden

A set of computer programs (GAASA I—VI) for solving crystal structures by "Direct Methods", mainly according to the procedure of symbolic addition, using the Σ_2 relation, developed by Hauptmann and Karle,[1,2] has been written. All space groups, centrosymmetric as well as non-centrosymmetric, are included.

The programs have been written in FORTRAN IV for the IBM-360 system. Each of the six parts is compiled separately, and all data are stored between the different programs on disc or magnetic tape. The core memory requirement is at present 143 000 bytes, which, technically, permits the treatment of structures with 15 000—20 000 reflections in the limiting sphere. For more moderate structures, the core memory requirement could easily be lowered to about 80 000 bytes, but below this limit, considerable rewriting of the programs would be necessary.

The required input is a list of independent, observed structure factors ($h,k,l,|F_o|$, $\sin\theta/\lambda$), preferably stored on disc or magnetic tape. Each of the six subprograms requires, moreover, a number of control cards which define the structural problem.

The course of the phase determination is as follows:

GAASA I — Absolute scale and overall temperature factor according to Wilson[3] are evaluated.

GAASA II — $|E|$ values are calculated from $|F_o|_{abs}$, and $|E|$ statistics are performed. The reflections are sorted in decreasing order of $|E|$.

GAASA III — All symmetry dependent reflections are generated. A list of pairs according to the Σ_2 relation is prepared for each $|E|$ value. Only $|E|$ values greater than a limit, chosen by the user, are taken into account.

GAASA IV — Symbols are assigned for phases or signs of a number of reflections (*e.g.* 10) with large $|E|$ values. Symbolic addition is applied in a cyclic procedure, giving symbols for the phases of new reflections and equations between the symbols, which are subsequently solved. When a sufficient number of symbols have been evaluated, origin determining signs or phases are inserted for the remaining symbols.

GAASA V — Centrosymmetric case. The set of E values are expanded using the Σ_2 summation.

GAASA VI — Non-centrosymmetric case. The phase assignment of the largest $|E|$ values is first performed according to formula *2.9* given by Karle and Karle[2] and the phases are refined using the tangent formula.[4] $|E|_{calc}$ values are then evaluated.

From *GAASA V* or *VI* a list of h, k, l, A, and B ($A=|E|\cos\alpha$, $B=|E|\sin\alpha$) are stored on disc for Fourier summation.

The first tests of this set of programs were performed on two small, already known structures:

(1) Catechol, $C_6H_4(OH)_2$, with one molecule in the asymmetric unit of $P2_1/a$.[5] Signs were evaluated for 109 of 111 reflections with $|E|>1.5$, and all determinations were correct. All heavy atoms were very well resolved in E maps summed with these 109 reflections (11 % of all observed and non-observed reflections), and no additional significant maxima appeared. The execution time for *GAASA I—IV* for this structure is less than 15 min for an IBM 360/50 computer.