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ORAL ALKYL GLYCEROL ETHER IMPROVEMENT
IN RADIATION, RADIOMIMETIC, OR CYTO-
STATIC TUMOR THERAPIESAstrid Helena Brohult and Sven Fritiof Abraham Brohult,
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7 Claims

ABSTRACT OF THE DISCLOSURE

An improvement in the use of alkyl glycerol ethers in conjunction with radiation therapy in the treatment of tumors is disclosed characterized by the premedication of patients prior to radiation therapy. The use of alkyl glycerol ethers concurrently with radiation therapy is also discussed.

This is a continuation of our copending application Ser. No. 530,357 filed Feb. 28, 1966, which application is a continuation-in-part of our prior application Ser. No. 392,637 filed Aug. 27, 1964; both prior applications now abandoned.

This invention is concerned with certain novel pharmaceutical preparations and with novel processes for their prophylactic and curative use. In particular it is concerned with the use of certain higher alkyl ethers of glycerol and particularly the glycerol ethers known as batyl, chimyl and selachyl alcohols as well as the glycerol monoalkyl ether where the alkyl group contains 16 carbon atoms and one double bond. The invention also comprises the fatty acid esters of these glycerol ethers, including mono- and di-esters of naturally occurring saturated or unsaturated acids. These compounds occur in various fish liver oils, particularly in those from the Elasmobranch group. For instance the liver oil of the Greenland shark contains ethers with 14-22 carbon atoms in the ether side-chain. Both saturated and unsaturated alcohols are present, selachyl alcohol making up about 60 percent of the ether content.

The present invention is based upon the discovery that certain glycerol ethers, when adequately administered, have a beneficial influence upon the body of human and, generally, animal, at least mammal animal beings, in its efforts in protecting itself against and combating various kinds of attacks.

The glycerol ethers contemplated should be α -ethers and preferably have the general formula



wherein R represents an aliphatic, including alicyclic, hydrocarbon radical containing not more than 26 carbon atoms, or their physiologically innocuous esters. The radical R should, of course, be physiologically innocuous or sufficiently nontoxic in the administration forms and quantities contemplated. Of particular interest are the glycerol ethers wherein the hydrocarbon radical contains 14-24 and especially 16 and 18 carbon atoms. The compound or a mixture of any two or more thereof may, as a principle, be administered in a conventional way such as by injection, orally or possibly as an ointment. Dosage quantities of active substances will be referred to hereinbelow by mg. per kg. body weight calculated as glycerol ether, the ether chain (R) having a molecular weight corresponding to that of batyl alcohol.

These glycerol ethers cause an activation and stimula-

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tion of the defence mechanism of a person or animal treated. Pharmaceutical preparations of such compounds act prophylactically and curatively against exposure to harmful radiation. It has been shown that the survival time after radiation treatment of cancer is increased.

In cases of leucopenia and thrombocytopenia caused by (radiation treatment, continuous administration of radiomimetics or cytostatics.) A significant increase in leucocyte and thrombocyte counts has been obtained after treatment with glycerol ethers. In some cases normal values for leucocytes and thrombocytes have been found after treatment for only one week. Thus the present preparations are useful in protecting the body, especially the blood-forming tissues, against harmful side effects and they are consequently of great importance for restoring or maintaining a normal blood picture.

The survival times for a group of 350 patients suffering from cancer of the uterine cervix increase with the total amount of glycerol ethers administered during the radiation treatment. The increase is observed for 1-year, 5-year and 7-year survivals.

The defence mechanism of the body is effectively stimulated by the administration of the compounds according to the present invention. The theoretical explanation for the observed results is not known with certainty. It has been shown, however, that the glycerol ethers do not inhibit the growth of microorganisms but on the contrary stimulate the growth of for instance *Lactobacillus lactis*. Consequently the antiinfection action of the glycerol ethers is different from that of, for example, antibiotics. Furthermore the effectiveness of the glycerol ethers against the effect of harmful radiation suggests a mechanism quite different from that of conventional chemotherapeutic agents, and that the effects are of a systemic nature. At present one can only hazard the guess that defence mechanisms in the organism, notably the reticuloendothelial system, are activated.

For the oral administration the optimum dose varies somewhat and the attending physician in each case will determine the optimum dose for the individual patient being treated. The optimum dosage as well as the effective range of dosage will depend on such variables as the size, age and sex of the patient or animal, the particular pathological condition involved, and the nature of other prior or concurrent treatment.

In general the effective dose contains from about 0.5 mg. to about 25 mg. glycerol ether per kg. body weight per day and especially from 2.5-12.5 mg. per kg. body weight per day. The dose administered may either consist exclusively of one of said glycerol ethers, or may be a mixture of any two or more of them. It has been shown that the valuable therapeutic results mentioned above, especially in the treatment of leukopenia and thrombocytopenia, caused for example by exposure to harmful radiation, are obtained at a dosage of about 5 mg. per kg. body weight per day calculated as glycerol ether which corresponds to about 12 mg. of the natural fatty acid esters. This dose causes no side effects and is not accompanied by any toxic manifestations. According to the invention it is possible to use, separately or in mixture, synthetically prepared glycerol ethers, but it is preferable to use a mixture of glycerol ethers derived from the liver oils of Elasmobranch fish.

The glycerol ethers or their esters may be used in association with any suitable well tolerated and physiologically innocuous pharmaceutical additives. For instance pharmaceutical compositions may be prepared which contain one, two, several or all of the active compounds together with suitable diluents, dispersing and emulsifying agents as well as flavouring agents.

The invention includes within its scope pharmaceutical compositions in the form of dosage units comprising one

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or more of the active compounds and suitable for convenient administration in the dosage quantities which cause the therapeutic effects described above.

Preferably the glycerol ethers and their esters are administered in the form of capsules or tablets containing the active compounds.

EXAMPLE I

A concentrate of fatty acid esters of glycerol ethers was prepared from Greenland shark liver oil. The oil was subjected to molecular distillation. The residue, containing 28.5% of fatty acid esters of glycerol ethers, was hydrolysed by lipase of Ricinus seeds. The hydrolysis step was followed by further molecular distillation. The content of fatty acid esters of glycerol ethers in the concentrate was 59% corresponding to 23.5% of free glycerol ethers.

EXAMPLE II

The concentrate of fatty acid esters of glycerol ethers from Greenland shark liver oil prepared as described in Example I was subjected to saponification with potassium hydroxide. The unsaponifiable fraction was extracted with ether. After removing the ether, the residue was deodorized by vacuum steam stripping. The finished product had a content of 85% (w./w. of free glycerol ethers).

EXAMPLE III

To produce a suitable pharmaceutical preparation to be administered drop-wise containing the following ingredients:

A mixture of free glycerol ethers derived from Greenland shark liver oil as described in Example II containing 85% by weight of free glycerol ethers	65
Polyoxyethylene sorbitan monooleate (Tween 80®)	2.5
Sorbitan monooleate (Span 80®)	2.5
Peppermint oil	1.8
Anethol	1.4
Ethanol, ad. 100 g.	

The dispersing agents and flavouring agents were dissolved in the ethanol and this solution was added to the mixture of free glycerol ethers.

EXAMPLE IV

Batyl alcohol, synthetically prepared	65
Tween 80®	2.8
Peppermint oil	2.2
Ethanol, ad. 100 g.	

The ingredients were mixed as described in Example III.

EXAMPLE V

Batyl alcohol, synthetically prepared	30.0
Chimyl alcohol, synthetically prepared	30.0
Tween 80®	3.0
Span 80®	3.0
Peppermint oil	1.5
Anethol	1.5
Ethanol, ad. 100 g.	

The solution was prepared as described in Example III.

EXAMPLE VI

Selachyl alcohol, synthetically prepared	1,000
Tween 80®	30

The dispersing agent was added to the selachyl alcohol. The resulting mixture was capsulated. Each capsule containing 103 mg. of the mixture.

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EXAMPLE VII

A concentrate of fatty acid esters of glycerol ethers from Greenland shark liver oil as described in Example I with an ester content corresponding to 23.5% of free glycerol ethers	500
Tween 80®	10
Span 80®	10

The dispersing agents were added to the concentrate and the resulting mixture was capsulated. Each capsule containing 450 mg. of the mixture.

EXAMPLE VIII

A mixture of free glycerol ethers derived from Greenland shark liver oil as described in Example II containing 85% by weight of free glycerol ethers	2,400
Tween 80®	75
Span 80®	75
Ethanol	80
Anethol	50

The dispersing agents were added to the concentrate. The anethol was dissolved in the ethanol and the solution was added to the concentrate. Each capsule containing 270 mg. of the mixture.

EXAMPLE IX

A mixture of free glycerol ethers derived from Greenland shark liver oil as described in Example II containing 85% by weight of free glycerol ethers	118
Tween 80®	3
Span 80®	3
Aerosil®	100
Lactose	100
Starch	100
Gelatin	2
Stearic acid	5
Talcum	7

The oily components were mixed with Aerosil, registered trade mark for colloidal silica. From lactose and starch was made a granulate with gelatin. The components were mixed and tablets were prepared.

The tablets may be coated as with a solution of 30% by weight of polyethylen glycol (av. M.V. 6,000) and 15% by weight of polyphenyl pyrrolidon in 99.5% ethanol. The solution is added in portions and the tablets are powdered with sugar between each addition. When the tablets have obtained a weight of 0.55 g. they are coated with an aqueous solution of 66% by weight of sugar and 3% by weight of gelatin up to a weight of about 0.8 g.

The most interesting aspect of applicants' discovery is the fact that the remarkable effect on the bodily defence mechanism seems to depend, generally, on the seemingly slight difference between the molecule of an ordinary tri-glyceride and the molecule of a compound identical with that tri-glyceride but for the carbonyl oxygen of one of the carboxylic acid groups in the tri-glyceride being replaced by hydrogen. One is thus led to believe that in the general formula for the present glycerol ethers the composition of the radical R is of little general importance and may instead be of importance for modifying the effect of the substance according to specific indications of bodily irregularities.

It has furthermore been discovered that the survival times of patients suffering from uterine cervix cancer can be improved significantly by administering the alkoxy-glycerols prophylactically before irradiating the patient. Tests have been made on 400 patients treated in one year according to the normal routine with regard to irradiation, i.e. normal doses of radiation from intracavitary radium application and/or external X-ray. All patients were

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treated with alkoxyglycerols in normal doses. These treatments are described in Astrid Brohult, "Alkoxyglycerols and their use in radiation treatment," Acta Radiologica, 1963. However, in 100 of the patients the administration of alkoxyglycerols started 7 days before the irradiation. One year after the treatment 15% of the patients treated normally had died, while only 9% of the patients treated prophylactically had died.

What is claimed is:

1. In the process for treating tumors characterized by radiation, radiomimetic or cytostatic treatment, the improvement comprising orally administering prior to said treatment an amount of an alkyl glycerol ether which is effective to increase the probability of survival and to reduce harmful leucopenia and thrombocytopenia caused by said treatment, said alkyl glycerol ether being at least one member of the group consisting of ethers of the formula



and physiologically innocuous esters of said ethers where R is selected from the group consisting of hydrocarbon radicals with 14 to 24 carbon atoms, said radical being so selected that said ethers and esters have the chemical composition of alkyl glycerol ethers which occur in the liver oils of Elasmobranch fish.

2. A process according to claim 1 for the treatment of uterine cervix cancer wherein the cancer is treated by radiation, wherein the administration of said alkyl glycerol ether is commenced approximately seven days before radiation.

3. A process according to claim 2 wherein said ethers and esters are derived from the liver oil of Greenland shark.

4. A process according to claim 2 wherein said alkyl glycerol ether is at least one member of the group consisting of chimyl alcohol, batyl alcohol and selachyl alcohol, and physiologically innocuous esters thereof.

5. In the process of treating tumors in humans characterized by a regimen of successive radiation treatments, the improvement comprising orally administering prior to the first of said successive treatments an amount of an alkyl glycerol ether between about 2.5 and 12.5 mg./kg. body weight daily which is effective to increase the probability of survival and to reduce harmful leucopenia and thrombocytopenia caused by said treatment, and continuing said administration until said regimen of successive treatments is completed, said alkyl glycerol ether

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being at least one member of the group consisting of ethers of the formula



and physiologically innocuous esters of said ethers, where R is selected from the group consisting of hydrocarbon radicals with 14 to 24 carbon atoms, said radical being so selected that said ethers and esters have the chemical composition of alkyl glycerol ethers which occur in the liver oils of Elasmobranch fish.

6. A process according to claim 5 wherein the administration of said alkyl glycerol ether is commenced approximately seven days before the first of said successive radiation treatments and administration is continued daily until said successive radiation treatments are completed.

7. A process according to claim 6 wherein said alkyl glycerol ether is at least one member of the group consisting of chimyl alcohol, batyl alcohol, and selachyl alcohol, and physiologically innocuous esters thereof.

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