Description

This invention relates to the treatment of certain diseases and disorders primarily, but not exclusively, in the field of human medicine and to compositions for use therein.

The essential fatty acids (EFAs) are of two types, the n-3 (or omega-3) series derived from alpha-linolenic acid and the n-6 (or omega-6) series derived from linoleic acid. Linoleic acid and alpha-linolenic acid are like vitamins in that they cannot be manufactured in the body and therefore must be provided in the diet. The body can metabolise them along the pathways below and such metabolism is believed to be essential if they are to fulfil their functions. The pathways are:

n-6	n-3	Structure
18:2		delta-9,12 octadecadienoic acid
18:3	18:3	delta-6,9,12 and delta-9,12,15 octadecatrienoic acids
	18:4	delta-6,9,12,15 octadecatetraenoic acid
20:3		delta-8,11,14 eicosatrienoic acid
20:4	20:4	delta-5,8,11,14 and delta-8,11,14,17 eicosatetraenoic acids
	20:5	delta-5,8,11,14,17 eicosapentaenoic acid
22:4		delta-7,10,13,16 docosatetraenoic acid
22:5	22:5	delta-4,7,10,13,16 and delta-7,10,13,16,19 docosapentaenoic acid
	22:6	delta-4,7,10,13,16,19 docosahexaenoic acid

The acids are in the natural all-cis configurations. In the n-6 series commonly used names for the 18:2, 18:3, 20:3, 20:4 and 22:4 acids are linoleic acid, gamma-linolenic acid (GLA), dihomo-gamma-linolenic acid (DGLA), arachidonic acid (AA) and adrenic acid. In the n-3 series only alpha-linolenic acid (18:3) is commonly referred to by a non-systematic name.

The elongation stages in the natural metabolic pathway are much more rapid than the desaturations. The sequence believed to be mediated by common enzymes in the two pathways, are:

n-6		n-3
18:2		18:3
	delta-6 desaturase	
18:3		18:4
	elongation	
20:3		20:4
	delta-5 desaturase	
20:4		20:5
	elongation	
22:4		22:5
	delta-4 desaturase	
22:5		22:6

The n-3 acids are metabolised preferentially and as a result plasma levels of 18:3 are low and 18:4 and 20:4 are in trace amounts only. In contrast the n-6 acids are all normally detectable, though 18:3 is at low levels, being apparently converted to 20:3 more rapidly than its relatively slow production from 18:2.

METABOLIC DEFECTS

Atopy is an inherited tendency to develop one or more of a group of diseases of which eczema, asthma and allergic rhinitis are the major ones. Some people have only eczema, some have only asthma or rhinitis, some have two or more of the conditions, some have none but may have children who have one of the problems. Atopy is associated with abnormal immune responses and it is generally believed that in order to develop a clinical disease one must have the inherited abnormality in immune responsiveness, coupled with exposure to some environ-mental factor which brings out that abnormality. People with atopic inheritance who are lucky enough not to be exposed to the environmental factor will not develop any obvious illness but may pass on the abnormality to their children. The precise mode of inheritance is not clear. A number of allergens and environmental factors which can trigger clinical atopic disease are known but it is likely that many more are not. Epidermiological surveys have shown that migraine, Crohn's disease, ulcerative colitis, otitis media and nephrotic syndrome are all considerably commoner in people with than in those without atopy. The presence of atopy greatly increases the risk of developing one of these conditions.

We have found that humans with atopic eczema have a defect in conversion of linoleic acid to GLA. While linoleic acid levels are normal or elevated, levels of DGLA and AA are low, indicating a block in the first step of the n-6 metabolic pathway. Administration of GLA in the form of evening primrose oil partially corrects the deficits in DGLA and AA.

We have also found that patients with painful lumpy breasts, not caused by breast cancer, (benign breast disease) have normal or elevated levels of linoleic acid and low levels of DGLA, AA, 22:4 n-6 and 22:5 n-6. Administration of GLA in the form of evening primrose oil partly corrects the biochemical deficits and produces clinical improvement, especially in those patients whose breast condition worsened before each menstrual period. Patients who had breast problems unrelated to menstruation showed a lesser response.

We have, further, analysed blood samples from patients with atopic eczema and benign breast disease and have found that while alpha-linolenic acid levels are normal, levels of the long chain n-3 acids, 20:5 n-3, 22:5 n-3 and 22:6 n-3 are low, especially in patients with breast disease not related to menstruation. Figures for eczema and asthma for example are (plasma phospholipids):

Fatty acid	Normal	Asthma	Eczema
18:2 n-6	21.45 ± 2.81	21.99 ± 3.31	24.50 ± 3.42 **
18:3 n-6	0.16 ± 0.12	0.22 ± 0.31	nd ***
20:3 n-6	3.06 ± 0.60	2.96 ± 0.55	2.63 ± 0.52 *
20:4 n-6	11.36 ± 1.67	9.18 ± 1.39***	6.75 ± 1.12***
22:4 n-6	0.73 ± 0.26	0.14 ± 0.22***	0.38 ± 0.24 **
22:5 n-6	1.12 ± 0.67	nd ***	0.13 ± 0.09 **
18:3 n-3	0.27 ± 0.53	0.38 ± 0.15	0.36 ± 0.17
20:5 n-3	1.01 ± 0.36	1.19 ± 0.44	0.75 ± 0.57 **
22:5 n-3	0.93 ± 0.27	1.22 ± 0.23***	0.74 ± 0.19***
22:6 n-3	3.54 ± 0.89	3.88 ± 0.99*	2.43 ± 0.62***

nd means not detected

Difference probabilities (Student's t test)

x p < 0.01

xx p < 0.001

xxx p < 0.0001

Figures for benign breast disease are for example:

Fatty acid	Control	Non-cyclical breast disease
18:2 n-6	21.45 ± 0.84	22.33 ± 0.89
20:3 n-6	3.06 ± 0.09	2.54 ± 0.14
20:4 n-6	11.36 ± 0.24	7.69 ± 0.36
22:4 n-6	0.73 ± 0.04	0.33 ± 0.05
22:5 n-6	1.12 ± 0.09	0.73 ± 0.09
18:3 n-3	0.27 ± 0.11	0.26 ± 0.03
20:5 n-3	1.01 ± 0.05	0.96 ± 0.08
22:5 n-3	0.93 ± 0.04	0.68 ± 0.09
22:6 n-3	3.54 ± 0.13	2.28 ± 0.15

The method of determination was:

Plasma samples (1 ml) were extracted with chloroform:methanol (2:1). The extract was filtered through sodium sulphate, evaporated to dryness, and taken up in 0.5 ml chloroform:methanol. The lipid fractions were separated by thin layer chromatography on silica gel plates. The phospholipid fraction, taken to reflect essential fatty acid changes most sensitively, was methylated using boron trifluoride-methanol. The resulting methyl esters of the fatty acids were separated and measured using a Hewlett Packard 5880 gas chromatograph with a six foot column packed with 10% silar on chromosorb WAW 106/230. The carrier gas was helium (30 ml/min). Oven temperature was programmed to rise from 165°C to 190°C at 2°C/min. Detector temperature 220°C and injector temperature 200°C. Retention times and peak areas were

automatically computed by a Hewlett Packard Level 4 integrator. Peaks were identified by comparison with standard fatty acid methyl esters. Thus patients with these disorders are deficient not only in the long chain EFAs of the n-6 series but also in the long chain EFAs of the n-3 series, and full correction of symptoms requires correction of both deficiencies. We believe that such combined deficiencies are a general feature of patients with atopic disorders and disorders associated with atopy, of patients with benign breast disease, of patients with breast cancer (which is commoner where there is pre-existing non-cancerous breast disease) and cancers generally, and of patients with other disorders associated with defects in metabolism of n-6 fatty acids. Such disorders include, alcoholism, and diabetes which interfere with the conversion of linoleic acid to GLA. There is for example strong evidence that the conversion of linoleic acid to GLA is restricted or absent in cancer cells. Further, in normal tissues the same enzyme converts linoleic acid to GLA as desaturates alpha-linolenic acid to form 18:4 n-3. In both cases the activity is a delta-6-desaturase activity and the presence of either one of the acids inhibits the desaturation of the other. Thus, cancer cells, and any other cells where the delta-6 desaturase activity is low and particularly those of alcoholic and diabetic patients are going to be dificient in the metabolites of alpha-linoleic acid.

THEORY

Without limitation to any theory it follows from the discussion above that there are two basic rationales.

A. Correction of deficiency. If levels of normal body constituents are below normal in a disease situation then it is a reasonable proposition that those low levels are contributing to and perhaps causing the disease and therefore that they should be corrected. We have demonstrated that abnormal levels of high fatty acids are indeed present in the conditions discussed herein.

B. Correction of a 1-series/2-series PG balance. As appears from many earlier patent applications and other publications of work by the inventor, the actions of the 1-series PG's and other metabolic products derived from DGLA are almost all either desirable or neutral, but the actions of the 2-series PG's and other metabolic products derived from arachidonic acid are very mixed, some being desirable and some being highly undesirable. Studies of the interactions between the metabolism of the n-6 acids and that of the n-3 acids have shown that elongation reactions (e.g. GLA to DGLA) are highly efficient and there is very little competition either way. In contrast, the two series of fatty acids compete with one another effectively for the desaturation processes. This means that the n-3 fatty acids will interfere with both delta-6 and delta-5 desaturation in the n-6 series. This competition seems to occur even when the n-3 fatty acid is not actually a substrate for the enzyme concerned. For example, 20:5 n-3 competitively inhibits delta-6 desaturation. A consequence of this is that the presence of n-3 fatty acids in a combination will lead to some inhibition of the conversion of DGLA to arachidonic acid by the delta-5-desaturase. As a result of the presence of the n-3 EFAs, the efficiency of either GLA or DGLA in increasing the ratio of DGLA products to arachidonic acid products will therefore be increased. The present invention thus complements earlier patents of the inventor's in which emphasis is laid on 1-series/2-series PG balance, in view of which GLA and DGLA are the preferred n-6 acids for use in the present invention.

In the light of the discussion above the present invention may be summarised as: a pharmaceutical or dietary composition for use in the treatment of diabetes, comprising effective amounts of one or more of the metabolites of linoleic acid (GLA, DGLA, AA, 22:4 n-6 or 22:5 n-6) and one or more of the metabolites of alpha-linolenic acid (18:4 n-3, 20:4 n-3, 20:5 n-3, 22:5 n-3 or 22:6 n-3), as such or in the form of an ester, salt, amide or other derivative convertible in the body thereto alone or in an acceptable pharmaceutical carrier or diluent.

The acids may be administered in the form of the acid itself or as an ester, amide, salt or any other functional derivative capable of being converted to a biologically active form of the acid within the body and may be from natural or synthetic sources.

Most studies have shown that the metabolism of the n-3 EFAs is more efficient than that of the n-6 EFAs. Judging by their presence in various body tissues, the important n-3 EFAs are thus 20:5 n-3 and 22:6 n-3. One therefore wants most preferably to use combinations of either 18:4 n-3 or 20:4 n-3 which can give rise to 20:5 n-3 and 22:6 n-3, or of those acids themselves, with either GLA or DGLA.

Doses for each acid are from 1 mg to 50 g per day, preferably 50 mg to 5 g per day, conveniently in conventional gelatine capsules.

FORMS AND SOURCES OF GAMMA-LINOLENIC AND OTHER ACIDS

Conventional sources of the acids include Evening Primrose (Oenothera) oil containing about 9% of GLA and oils from marine or migratory fish which contain substantial amounts of 20:5 n-3 and 22:6 n-3.

Suitable physiologically functional derivatives, convertible in the body to the acids to enter the matabolic pathways given earlier herein, are physiologically acceptable salts, esters (particularly glycerides and simple C_1 to C_4 alkyl esters), amides and phospholipids. Indirect identification of useful derivatives is by their having the valuable effect in the body of the acid itself, but conversion can be shown directly by gas chromatographic analysis of concentrations in blood, body fat, or other tissue by standard techniques for example those of Pelick et al. p. 23, "Analysis of Lipids and Lipoproteins" Ed. Perkins, American Oil Chemists Society, Champaign, Illinois, U.S.A.

DIETARY COMPOSITIONS

The invention is chiefly described in terms of use of pharmaceutical compositions, but it will be understood that the gamma-linolenic and other acids being in the nature of dietary supplements could be incorporated in a dietary margarine or other foodstuffs: use of such foodstuffs, possibly containing other active materials and generally referred to in this description as dietary or pharmaceutical compositions, are within the purview of the invention and thus of the term pharmaceutical compositions or the like used in the claims.

VETERINARY APPLICATIONS

It will be understood that where a disorder of a kind calling for treatment in animals arises, the invention while described primarily in terms of human medicine and treatment is equally applicable in the veterinary field.

PHARMACEUTICAL PRESENTATION

The compositions used according to the invention are conveniently in a form suitable for oral, rectal, parenteral or topical administration in a suitable pharmaceutical vehicle, as discussed in detail for example in U.K. Patent Specification No. 1,082,624 and in any case very well known generally for any particular kind of preparation. Thus for example tablets, capsules, ingestible liquid or powder preparations, creams and lotions for topical application, or suppositories, can be prepared as required. Injectable solutions of hydrolysed Oenothera oil may be prepared using albumin to solubilise the free acid.

Advantageously a preservative is incorporated into the preparations. Alpha-tocopherol in a concentration of about 0.1% by weight has been found suitable for the purpose.

It will be understood that the absolute quantity of active ingredients present in any dosage unit should not exceed that appropriate to the rate and manner of administration to be employed but on the other hand should also desirably be adequate to allow the desired rate of administration to be achieved by a small number of doses. The rate of administration will moreover depend on the precise pharmacological action desired.

The following are specific examples of the invention:

EXAMPLE 1

A capsule containing 60% Evening Primrose oil and 40% mackerel oil administered in 0.5 g capsules six times per day for the conditions listed herein.

EXAMPLE 2

A capsule containing 70% Evening Primrose oil and 30% salmon oil administered in 0.5 g capsules eight times per day for the conditions listed herein.

EXAMPLE 3

A 0.25 g capsule containing 150 mg of GLA and 100 mg of 20:5 n-3 administered three times per day for the conditions listed herein.

EXAMPLE 4

A capsule containing 50 mg of DGLA, 50 mg of AA, 20 mg of 22:4 n-6, 20 mg of 22:5 n-6, 50 mg of 20:5 n-3, 20 mg of 22:5 n-3 and 20 mg of 22:6 n-3 taken four times a day for the conditions listed herein.

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. The use of one or more of the metabolites of linoleic acid (GLA, DGLA, AA, 22:4 n-6 or 22:5 n-6) together with one or more of the metabolites of alpha-linolenic acid (18:4 n-3, 20:4 n-3, 20:5 n-3, 22:5 n-3 or 22:6 n-3), as such or in the form of an ester, salt, amide or other derivative convertible in the body thereto, and alone or in an acceptable pharmaceutical carrier or diluent, for the preparation of a medicament constituted by a pharmaceutical or dietary composition for use in the treatment of diabetes.

2. The use according to claim 1 wherein the metabolites of linoleic acid used are one or both of GLA or DGLA.

3. The use according to claim 1 or claim 2 wherein the composition is in dosage unit form suited to administration of 1 mg to 50 g/day, preferably 50 mg to 5 g/day of each said acid.

Claims for the following Contracting State : AT

1. A method for the preparation of a pharmaceutical or dietary composition for use in the treatment of diabetes wherein one or more of the metabolites of linoleic acid (GLA, DGLA, AA, 22:4 n-6 or 22:5 n-6) is combined with one or more of the metabolites of alpha-linolenic acid (18:4 n-3, 20:4 n-3, 20:5 n-3, 22:5 n-3 or 22:6 n-3), as such or in the form of an ester, salt, amide or other derivative convertible in the body thereto, and optionally further combining with an acceptable pharmaceutical carrier or diluent.

2. A method according to claim 1 wherein the metabolites of linoleic acid are one or both of GLA or DGLA.

3. A method according to claims 1 or 2, wherein a composition is prepared in dosage unit form suited to administration of from 1 mg to 50 g/day, preferably 50 mg to 5 g/day.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verwendung eines oder mehrerer der Metaboliten der Linolsäure (GLA, DGLA, AA, 22:4 n-6 oder 22:5 n-6) zusammen mit einem oder mehreren der Metaboliten der Alpha-Linolensäure (18:4 n-3, 20:4 n-3, 20:5 n-3, 22:5 n-3 oder 22:6 n-3) als solche oder in der Form eines Esters, Salzes, Amides oder anderen Derivates, das dazu in dem Körper umwandelbar ist, alleine oder in einem akzeptablen pharmazeutischen Träger oder Verdünnungsmittel, für die Zubereitung eines Medikamentes, das durch eine pharmazeutische oder diätetische Zusammensetzung gebildet wird zur Verwendung bei der Behandlung von Diabetes.

2. Verwendung gemäß Anspruch 1, wobei die Metaboliten der verwendeten Linolsäure GLA und/oder DGLA sind.

3. Verwendung gemäß Anspruch 1 oder Anspruch 2, wobei die Zusammensetzung eine Dosierungseinheitsform ist, die geeignet zur Verabreichung von 1 mg bis 50 g/Tag, bevorzugt 50 mg bis 5 g/Tag jeder besagten Säure ist.

Patentansprüche für folgenden Vertragsstaat : AT

1. Verfahren zur Zubereitung einer pharmazeutischen oder diätetischen Zusammensetzung zur Verwendung bei der Behandlung von Diabetes, wobei ein oder mehrere der Metaboliten der Linolsäure (GLA, DGLA, AA, 22:4 n-6 oder 22:5 n-6) verbunden wird mit einem oder mehreren der Metaboliten der

EXAMPLE 4

A capsule containing 50 mg of DGLA, 50 mg of AA, 20 mg of 22:4 n-6, 20 mg of 22:5 n-6, 50 mg of 20:5 n-3, 20 mg of 22:5 n-3 and 20 mg of 22:6 n-3 taken four times a day for the conditions listed herein.

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. The use of one or more of the metabolites of linoleic acid (GLA, DGLA, AA, 22:4 n-6 or 22:5 n-6) together with one or more of the metabolites of alpha-linolenic acid (18:4 n-3, 20:4 n-3, 20:5 n-3, 22:5 n-3 or 22:6 n-3), as such or in the form of an ester, salt, amide or other derivative convertible in the body thereto, and alone or in an acceptable pharmaceutical carrier or diluent, for the preparation of a medicament constituted by a pharmaceutical or dietary composition for use in the treatment of diabetes.

2. The use according to claim 1 wherein the metabolites of linoleic acid used are one or both of GLA or DGLA.

3. The use according to claim 1 or claim 2 wherein the composition is in dosage unit form suited to administration of 1 mg to 50 g/day, preferably 50 mg to 5 g/day of each said acid.

Claims for the following Contracting State : AT

1. A method for the preparation of a pharmaceutical or dietary composition for use in the treatment of diabetes wherein one or more of the metabolites of linoleic acid (GLA, DGLA, AA, 22:4 n-6 or 22:5 n-6) is combined with one or more of the metabolites of alpha-linolenic acid (18:4 n-3, 20:4 n-3, 20:5 n-3, 22:5 n-3 or 22:6 n-3), as such or in the form of an ester, salt, amide or other derivative convertible in the body thereto, and optionally further combining with an acceptable pharmaceutical carrier or diluent.

2. A method according to claim 1 wherein the metabolites of linoleic acid are one or both of GLA or DGLA.

3. A method according to claims 1 or 2, wherein a composition is prepared in dosage unit form suited to administration of from 1 mg to 50 g/day, preferably 50 mg to 5 g/day.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verwendung eines oder mehrerer der Metaboliten der Linolsäure (GLA, DGLA, AA, 22:4 n-6 oder 22:5 n-6) zusammen mit einem oder mehreren der Metaboliten der Alpha-Linolensäure (18:4 n-3, 20:4 n-3, 20:5 n-3, 22:5 n-3 oder 22:6 n-3) als solche oder in der Form eines Esters, Salzes, Amides oder anderen Derivates, das dazu in dem Körper umwandelbar ist, alleine oder in einem akzeptablen pharmazeutischen Träger oder Verdünnungsmittel, für die Zubereitung eines Medikamentes, das durch eine pharmazeutische oder diätetische Zusammensetzung gebildet wird zur Verwendung bei der Behandlung von Diabetes.

2. Verwendung gemäß Anspruch 1, wobei die Metaboliten der verwendeten Linolsäure GLA und/oder DGLA sind.

3. Verwendung gemäß Anspruch 1 oder Anspruch 2, wobei die Zusammensetzung eine Dosierungseinheitsform ist, die geeignet zur Verabreichung von 1 mg bis 50 g/Tag, bevorzugt 50 mg bis 5 g/Tag jeder besagten Säure ist.

Patentansprüche für folgenden Vertragsstaat : AT

1. Verfahren zur Zubereitung einer pharmazeutischen oder diätetischen Zusammensetzung zur Verwendung bei der Behandlung von Diabetes, wobei ein oder mehrere der Metaboliten der Linolsäure (GLA, DGLA, AA, 22:4 n-6 oder 22:5 n-6) verbunden wird mit einem oder mehreren der Metaboliten der

* C L M S *

Alpha-Linolensäure (18:4 n-3, 20:4 n-3, 20:5 n-3, 22:5 n-3 oder 22:6 n-3) als solche oder in der Form eines Esters, Salzes, Amides oder anderen Derivates, das sich dazu in dem Körper umwandelt, und optional einem weiteren Kombinieren mit einem akzeptablen pharmazeutischen Träger oder Verdünnungsmittel.

2. Verfahren gemäß Anspruch 1, wobei die Metaboliten der Linolsäure GLA und/oder DGLA sind.

3. Verfahren gemäß den Ansprüchen 1 oder 2, worin eine Zusammensetzung zubereitet wird in einer Dosierungseinheitsform, die zur Verabreichung von 1 mg bis 50 g/Tag, bevorzugt 50 mg bis 5g/Tag geeignet ist.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Utilisation d'un ou plusieurs des métabolites de l'acide linoléique (GLA, DGLA, AA, 22:4 n-6 ou 22:5 n-6), en même temps qu'un ou plusieurs des métabolites de l'acide alpha-linolénique (18:4 n-3, 20:4 n-3, 20:5 n-3, 22:5 n-3 ou 22:6 n-3), en l'état ou sous forme d'un ester, d'un sel, d'un amide ou d'un autre dérivé convertible dans l'organisme en ces métabolites, et seul ou dans un support ou un diluant pharmaceutiquement acceptable, pour préparer un médicament constitué d'une composition pharmaceutique ou diététique destinée à être utilisée dans le traitement du diabète.

2. Utilisation selon la revendication 1, dans laquelle les métabolites utilisés de l'acide linoléique sont représentés par un ou deux des acides GLA ou DGLA.

3. Utilisation selon la revendication 1 ou 2, dans laquelle la composition se présente sous une forme posologique unitaire convenant à l'administration de 1 mg à 50 g/jour, de préférence de 50 mg à 5 g/jour de chacun de ces acides.

Revendications pour l'Etat contractant suivant : AT

1. Procédé pour préparer une composition pharmaceutique ou diététique destinée à être utilisée dans le traitement du diabète, dans lequel on combine un ou plusieurs des métabolites de l'acide linoléique (GLA, DGLA, AA, 22:4 n-6 ou 22:5 n-6) avec un ou plusieurs des métabolites de l'acide alpha-linolénique (18:4 n-3, 20:4 n-3, 20:5 n-3, 22:5 n-3 ou 22:6 n-3), en l'état ou sous forme d'un ester, d'un sel, d'un amide ou d'un autre dérivé convertible dans l'organisme en ces métabolites, et dans lequel on procède en outre à une combinaison avec un excipient ou diluant pharmaceutiquement acceptable.

2. Procédé selon la revendication 1, dans lequel les métabolites de l'acide linoléique sont constitués de l'un des acides GLA ou DGLA, ou des deux.

3. Procédé selon la revendication 1 ou 2, dans lequel on prépare une composition selon une forme posologique unitaire convenant à l'administration de 1 mg à 50 g/jour et de préférence de 50 mg à 5 g/jour.