Description

FIELD OF THE INVENTION

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.

GENERAL BACKGROUND

The essential fatty acids (EFAs) are of two types, the n-3 (or ω-3) series derived from α-linolenic acid and the n-6 (or ω-6) series derived from linoleic acid. Linoleic acid and α-linolenic acid are like vitamins in that they cannot be manufacturered 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, γ-linolenic acid (GLA), dihomo-γ-linolenic acid (DGLA), arachidonic acid (AA) and adrenic acid. In the n-3 series only α-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
	Δ^6 desaturase	
18:3		18:4
	elongation	
20:3		20:4
	Δ^5 desaturase	
20:4		20:5
	elongation	
22:4		22:5
	Δ^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 environmental 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. Epidemiological 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, 22:4n-6 and 22:5n-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 α-linolenic acid levels are normal, levels of the long chain n-3 acids, 20:5n-3, 22:5n-3 and 22:6n-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
18:2n-6	21.45±2.81	21.99±3.31	24.50 ± 3.42 ^{xx}
18:3n-6	0.16 ±0.12	0.22±0.31	nd ^{xxx}
20:3n-6	3.06 ±0.60	2.96±0.55	2.63 ± 0.52 ^{x}
20:4n-6	11.36 ±1.67	9.18 ±1.39^{xxx}	6.75 ± 1.12 ^{xxx}
22:4n-6	0.73 ±0.26	0.14 ±0.22^{xxx}	0.38 ± 0.24^{xx}
22:5n-6	1.12 ±0.67	nd ^{xxx}	0.13 ± 0.09 ^{xx}
18:3n-3	0.27 ±0.53	0.38 ±0.15	0.36 ± 0.17
20:5n-3	1.01 ±0.36	1.19 ±0.44	0.75 ± 0.57^{xx}
22:5n-3	0.93 ±0.27	1.22 ±0.23^{xxx}	0.74 ± 0.19 ^{xxx}
22:6n-3	3.54 ±0.89	3.88 ±0.99^{x}	2.43 ± 0.62 ^{xxx}

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
18:2n-6	21.45 ± 0.84	22.33 ± 0.89
20:3n-6	3.06 ± 0.09	2.54 ± 0.14
20:4n-6	11.36 ± 0.24	7.69 ± 0.36
22:4n-6	0.73 ± 0.04	0.33 ± 0.05
22:5n-6	1.12 ± 0.09	0.73 ± 0.09
18:3n-3	0.27 ± 0.11	0.26 ± 0.03
20:5n-3	1.01 ± 0.05	0.96 ± 0.08
22:5n-3	0.93 ± 0.04	0.68 ± 0.09
22:6n-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 1.83 m (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 was 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, and of patients with benign breast disease.

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 such as EP-B-0,003,407 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.

PRIOR PATENTS

Among publications on the use of essential fatty acids in therapy are GB-A-2,033,745 which concerns thrombo-embolic disorders, FR-A-2,231,379 which concerns combatting "syndromes of excitation and anxiety" and EP-A-0,106,571 which concerns prophylaxis against multiplication of cancer cells.

DETAILED STATEMENT OF THE INVENTION

In the light of the discussion above, the present invention may be summarised as: 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 atopic disorders, including eczema, asthma, allergies (especially allergic rhinitis), migraine; disorders associated with atopy including Crohn's disease, ulcerative colitis, otitis media, nephrotic syndrome; and benign breast disease.

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 20:5n-3 and 22:6n-3. One therefore wants most preferably to use combinations of either 18:4n-3 or 20:4n-3 which can give rise to 20:5n-3 and 22:6n-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 SOURCE OF γ-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 20:5n-3 and 22:6n-3.

Suitable physiologically functional derivatives, convertible in the body to the acids to enter the metabolic pathways given earlier herein, are physiologically acceptable salts, esters (particularly glycerides and simple C_1 - 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 γ-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 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. α-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 20:5n-3 administered 3 times per day for the conditions listed herein.

EXAMPLE 4

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

Claims

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

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

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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

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medicament constituted by a pharmaceutical or dietary composition for use in the treatment of atopic disorders, including eczema, asthma, allergies (especially allergic rhinitis), migraine; disorders associated with atopy including Crohn's disease, ulcerative colitis, otitis media, nephrotic syndrome; and benign breast disease.

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. The method for the praparation of a medicament constituted by a pharmaceuticl or dietary composition for use in the treatment of atopic disorders, including eczema, asthma, allergies (especially allergic rhinitis), migraine; disorders associated with atopy including Crohn s disease, ulcerative colitis, otitis media, nephrotic syndrome; and benign breast disease, characterised in that 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 alone or in an acceptable pharmaceutical carrier or diluent.

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

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

Revendications

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

1. Usage d'un ou plusieurs des métabolites de l'acide linoléique (GLA, DGLA, AA, 22:4n-6 ou 22:5n-6) avec un ou plusieurs des métabolites de l'acide α-linolénique (18:4n-3, 20:4n-3, 20:5n-3, 22:5n-3 ou 22:6n-3), en tant que tels ou sous la forme d'un ester, sel, amide ou autre dérivé convertible dans l'organisme en ces métabolites, seuls ou dans un diluant ou véhicule pharmaceutique acceptable, pour la préparation d'un médicament constitué par une composition pharmaceutique ou alimentaire à utiliser dans le traitement de troubles atopiques comprenant eczéma, asthme, allergies (notamment rhinites allergiques), migraine ; de troubles liés à l'atopie comprenant la maladie de Crohn, la rectocolite hémorragique, l'otite moyenne, le syndrome néphrotique ; et de la mammopathie bénigne.

2. Usage selon la revendication 1, dans lequel les métabolites de l'acide linoléique utilisés sont soit GLA, soit DGLA, soit l'un et l'autre.

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

Revendications pour l'Etat contractant suivant : AT

1. Procédé de préparation d'un médicament consistant en une composition pharmaceutique ou alimentaire à utiliser dans le traitement de troubles atopiques, comprenant eczéma, asthme, allergies (notamment rhinites allergiques), migraine ; de troubles liés à l'atopie comprenant la maladie de Crohn, la rectocolite hémorragique, l'otite moyenne, le syndrome néphrotique ; et de la mammopathie bénigne, caractérisé en ce qu'un ou plusieurs des métabolites de l'acide linoléique (GLA, DGLA, AA, 22:4n-6 ou 22:5n-6) sont associés à un ou plusieurs des métabolites de l'acide α-linolénique (18:4n-3, 20:4n-3, 20:5n-3, 22:5n-3 ou 22:6n-3), en tant que tels ou sous la forme d'un ester, sel, amide ou autre dérivé convertible dans l'organisme en ces métabolites, seuls ou dans un diluant ou véhicule pharmaceutique acceptable.

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2. Procédé selon la revendication 1, dans lequel les métabolites de l'acide linoléique utilisés sont soit GLA, soit DGLA, soit l'un et l'autre.

3. Procédé selon la revendication 1 ou la revendication 2, dans lequel la composition est préparée sous une forme posologique unitaire convenant à l'administration de 1 mg à 50 g/j, de préférence de 50 mg à 5 g/j, de chacun desdits acides.

Patentansprüche

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

1. Die Verwendung eines oder mehrerer Metaboliten der Linolen-Säure (GLA, DGLA, AA, 22:4 n-6 oder 22:5 n-6), zusammen mit einem oder mehreren Metaboliten der Alpha-Linolen-Säure (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 Form eines Esters, Salzes, Amides oder anderen Derivates, das im Körper dazu konvertibel ist, alleine oder in einem akzeptablen pharmazeutischen Carrier oder Verdünnungsmittel, zur Zubereitung eines Medikamentes, das durch eine pharmazeutische oder diätetische Zusammenstellung konstituiert wird, um für die Behandlung von atopischen Krankheiten, unter anderem Ekzemen, Asthma, Allergien (besonders allergischer Rhinitis), Migräne: Krankheiten, die mit Atopie verbunden sind, unter anderem die Crohn-Krankheit, Colitis ulcerosa, Otitis media, nephrotisches Syndrom: und gutartigen Brusterkrankungen benutzt zu werden.

2. Die Verwendung gemäß Anspruch 1, wobei die Metabolite der verwendeten Linolensäure eine oder beide der GLA oder DGLA sind.

3. Die Verwendung gemäß Anspruch 1 oder 2, wobei die Zusammenstellung in einer Dosierungseinheitsform besteht, die zur Verabreichung von 1 mg bis 50 g/täglich geeignet ist, vorteilhafterweise von 50 mg bis 5 g/täglich von jeder besagten Säure.

Patentansprüche für folgenden Vertragsstaat : AT

1. Verfahren zur Zubereitung eines Medikamentes, das durch eine pharmazeutische oder diätetische Zusammensetzung konstituiert wird, zur Verwendung bei der Behandlung von atopischen Krankheiten, unter anderem Ekzemen, Asthma, Allergien (besonders allergische Rhinitis), Migräne; Krankheiten, die mit Atopie verbunden sind, unter anderem die Crohn-Krankheit, Colitis ulcerosa, Otitis media, nephrotisches Syndrom; und gutartige Brusterkrankungen, wobei ein oder mehrere Metabolite der Linolensäure (GLA, DGLA, AA 22:4 n-6 oder 22:5 n-6) mit einem oder mehreren Metaboliten der Alpha-Linolen-Säure (18:4 n-3, 20:4 n-3, 20:5 n-3, 22:5 n-3 oder 22:6 n-3) verbunden werden, als solche oder in Form eines Esters, Salzes, Amides oder anderen Derivates, das im Körper dazu konvertibel ist, alleine oder in einem akzeptablen pharmazeutischen Carrier oder Verdünnungsmittel.

2. Verfahren gemäß Anspruch 1, wobei die Metabolite der verwendeten Linolensäure eine oder beide der GLA oder DGLA sind.

3. Verfahren gemäß Anspruch 1 oder 2, wobei die Zusammenstellung in einer Dosierungseinheitsform besteht, die zur Verabreichung von 1 mg bis 50 g/täglich geeignet ist, vorteilhafterweise von 50 mg bis 5 g/täglich von jeder besagten Säure.