ELSEVIER

Schizophrenia Research 49 (2001) 243–251

SCHIZOPHRENIA RESEARCH

www.elsevier.com/locate/schres

Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia

Malcolm Peet[a,*], Jan Brind[a], C.N. Ramchand[a], Sandeep Shah[b], G.K. Vankar[b]

[a]*Academic Department of Psychiatry, Northern General Hospital, The Longley Centre, Norwood Grange Drive, Sheffield S5 7JT, UK*
[b]*Department of Psychiatry, S.S.G. Hospital and Medical College, M.S. University, Baroda, India*

Received 28 March 2000; accepted 9 May 2000

Abstract

Evidence that the metabolism of phospholipids and polyunsaturated fatty acids (PUFA) is abnormal in schizophrenia provided the rationale for intervention studies using PUFA supplementation. An initial open label study indicating efficacy for n-3 PUFA in schizophrenia led to two small double-blind pilot studies. The first study was designed to distinguish between the possible effects of two different n-3 PUFA: eicosapentaenoic acid (EPA) and docohexaenoic acid (DHA). Forty-five schizophrenic patients on stable antipsychotic medication who were still symptomatic were treated with either EPA, DHA or placebo for 3 months. Improvement on EPA measured by the Positive and Negative Syndrome Scale (PANSS) was statistically superior to both DHA and placebo using changes in percentage scores on the total PANSS. EPA was significantly superior to DHA for positive symptoms using ANOVA for repeated measures. In the second placebo-controlled study, EPA was used as a sole treatment, though the use of antipsychotic drugs was still permitted if this was clinically imperative. By the end of the study, all 12 patients on placebo, but only eight out of 14 patients on EPA, were taking antipsychotic drugs. Despite this, patients taking EPA had significantly lower scores on the PANSS rating scale by the end of the study. It is concluded that EPA may represent a new treatment approach to schizophrenia, and this requires investigation by large-scale placebo-controlled trials.

Keywords: Docosahexaenoic acid; Eicosapentaenoic acid; Schizophrenia; Treatment

1. Introduction

The search for new treatments for schizophrenia has focused mainly on modulating neurotransmitters and their receptors, despite the relative lack of evidence of a primary abnormality in these systems. Novel treatment approaches to schizophrenia are likely to come only on the basis of new hypotheses relating to aetiology. The phospholipid hypothesis of schizophrenia, recently reviewed by Horrobin (1998), has proved to be of considerable heuristic value.

There is substantial evidence of phospholipid and polyunsaturated fatty acid (PUFA) metabolic abnormalities in schizophrenia (Peet et al., 1999). Studies of peripheral tissues, including erythrocytes and skin fibroblasts, have shown reduced levels of phospholipid subtypes (phosphatidylcholine and phosphatidylethanolamine) in schizophrenic patients (Hitzemann et al., 1985; Keshaven et al., 1993; Mahadik et al., 1994). Recent studies using ^{31}P magnetic resonance spectroscopy have shown increased levels of phosphodiesters and decreased levels of phosphomonoesters in

* Corresponding author. Tel.: +44-114-2261509; fax: +44-114-2261522.
E-mail address: m.peet@sheffield.ac.uk (M. Peet).

0920-9964/01/$ - see front matter
PII: S0920-9964(00)00083-9

prefrontal and temporal brain of drug-naïve schizophrenic patients (Pettegrew et al., 1991; Stanley et al., 1994; Fukuzako et al., 1999). Since phosphomonoesters are utilized in phospholipid synthesis, and phosphodiesters are phospholipid breakdown products, these data have been taken to imply increased phospholipid turnover in the brains of schizophrenic patients. Increased levels of the phospholipid breakdown product lysophosphatidylcholine have also been reported in platelets from schizophrenic patients (Pangerl et al., 1991).

There have been several investigations of the PUFA content of membrane phospholipids in schizophrenia. Although earlier studies produced inconsistent results, more recent investigations have produced a more consistent picture of depleted n-6 and n-3 PUFA in red blood cells (Vaddadi et al., 1989; Glen et al., 1994; Yao et al., 1994a; Peet et al., 1995) and brain (Horrobin et al., 1991; Yao, 1999) of schizophrenic patients.

An associated biochemical abnormality in schizophrenia is elevated activity of phospholipase A2 (PLA2) in plasma (Gattaz et al., 1987) serum (Gattaz et al., 1990; Noponen et al., 1993) and platelets (Gattaz et al., 1995) from drug-free schizophrenic patients, although there was a negative report from Albers et al. (1993). This enzyme releases fatty acids from phospholipids. Ross et al. (1997) pointed out that there are several different species of phospholipase A2, and they found that the calcium-independent phospholipase A2 was elevated in schizophrenic patients whereas calcium-stimulated PLA2 levels were normal. They subsequently showed that this enzyme activity is also increased in pre-temporal cortex (Ross, 1999).

Overall, the evidence suggests that schizophrenia is associated with abnormal phospholipid metabolism, including an increased rate of breakdown possibly due to excess PLA2 activity.

Fatty acids in the diet, both essential and non-essential, have significant effects upon neuronal membrane phospholipid composition (Marteinsdottir et al., 1998; Abedin et al., 1999). Therefore, it would be expected that any dietary changes could mitigate or aggravate an underlying abnormality of phospholipid metabolism. There is evidence of a correlation between dietary fat consumption and schizophrenic symptomology.

Christensen and Christensen (1998) reported that the ratio of saturated fatty acids (SFA) to PUFA in the national diet correlated with outcome figures for schizophrenia published by the World Health Organization. Those countries that obtained relatively more of their dietary fat from land animals and birds (mostly SFA) and relatively less of their fat from vegetable, fish and seafood sources (mostly PUFA) had a worse outcome of schizophrenia. This accounted for 97% of the variance in outcome between countries. Similar relationships have been shown within groups of schizophrenic patients. Yao et al. (1994b) showed that the SFA-to-PUFA ratio in red blood cell membranes showed a significant positive relationship with severity of positive schizophrenic symptoms. Mellor et al. (1996) reported that a greater intake of n-3 PUFA and particularly eicosapentaenoic acid (EPA) in the normal daily diet was associated with less severe positive schizophrenic symptoms.

These associations between dietary fat and schizophrenic symptoms do not prove cause and effect, but taken together with the biochemical evidence, they provided us with a strong rationale for intervention studies using PUFA. Previous studies using n-6 PUFA in the treatment of schizophrenia gave mixed results (Vaddadi et al., 1986, 1989; Wolkin et al., 1986). In one previous study using n-3 PUFA, linseed oil (50% alpha-linolenic acid) was given to five schizophrenic patients, with apparent benefit (Rudin, 1981). We chose to investigate n-3 PUFA because that was the strongest dietary correlation found by our group (Mellor et al., 1996).

In an initial supplementation study, 20 schizophrenic patients who were still symptomatic despite best efforts to treat them with antipsychotic drugs, were given 10 g per day of concentrated fish oil (MaxEPA) in addition to their existing antipsychotic medication, which remained unchanged during the 6 week study period. Patients showed a significant improvement in scores on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and on the Abnormal Involuntary Movement Scale (Kane et al., 1992). There is no known pharmacokinetic interaction between PUFA and antipsychotic drugs, so this appeared to be a true pharmacological effect. Multiple regression analysis showed that improvement in schizophrenic symptoms was importantly related to

Table 1
Scores on the total and positive subscale of the PANSS before and after treatment for patients taking EPA, DHA or placebo

	Total PANSS score (mean ± S.D.)			Positive PANSS score[a] (mean ± S.D.)		
	Pre	Post[b]	Percentage change	Pre	Post	Percentage change[c]
EPA ($n = 15$)	69.9 (12.9)	55.5 (12.2)	20.1 (13.6)	18.9 (5.4)	14.6 (5.9)	23.8 (15.0)
DHA ($n = 16$)	73.4 (17.9)	65.3 (19.0)	9.5 (20.4)	17.8 (5.4)	16.7 (5.3)	3.3 (27.2)
Placebo ($N = 14$)	76.2 (20.6)	65.9 (14.9)	10.7 (18.2)	18.7 (5.7)	15.8 (5.1)	13.7 (22.1)

[a] EPA vs. DHA ANOVA for repeated measures: $F = 5.24$; $P = 0.03$.
[b] EPA vs. placebo: $t = 2.1$; $P = 0.05$.
[c] ANOVA: $F = 3.3$; $P = 0.045$.

the increased level of n-3 PUFA measured in red blood cell membranes. Ten grams of MaxEPA per day contains 1.7 g of EPA and 1.1 g of docosahexaenoic acid (DHA). Whilst these are both n-3 PUFA, they have differing metabolic functions. Thus, DHA is primarily a membrane structural component, whereas EPA takes part in eicosanoid synthesis. The two fatty acids can have differing physiological effects (Bates et al., 1993; De Caterina et al., 1994; Willumsen et al., 1996; Gilbert et al., 1999). Therefore, we considered it important to differentiate between the possible effects of EPA and DHA in schizophrenia. A pilot double-blind trial was therefore conducted to compare and EPA enriched oil with a DHA enriched oil and a corn oil placebo.

2. Double-blind placebo controlled trial comparing EPA and DHA

2.1. Subjects and methods

Subjects of the study were outpatients in Sheffield, UK with a DSM IV (American Psychiatric Association, 1994) diagnosis of schizophrenia. All were receiving a stable dosage of antipsychotic medication, and no change in dosage was anticipated during the study. They were required to be still symptomatic, with a PANSS score of at least 40, despite medical treatment that was considered appropriate by the responsible consultant psychiatrist. No patient suffered from significant physical illness or other psychiatric disorders including mood disorders or learning disability. Patients were taking a variety of antipsychotic drugs in both oral and depot preparations, and some were also taking anti-cholinergic medication to treat side-effects. All patients gave informed consent to the study, which had been approved by the appropriate Ethics Committee.

Patients continued on their normal medication, which the responsible consultant psychiatrist was asked to keep stable during the 3 months of treatment. Patients were randomly allocated to treatment with either an EPA enriched oil containing 2 g of EPA (Kirunal, Laxdale Limited, Stirling, UK), a DHA enriched oil, or a corn oil placebo. The dose of EPA was set at 2 g daily because the concentrated fish oil used in the open-label pilot study contained 1.7 g of EPA; the same dose of DHA was used. The oils, which were indistinguishable by colour, texture and taste, were provided in bottles, consecutively numbered, based on a randomization code that was not available to the investigators. Patients were rated on the PANSS scale at the beginning and end of treatment. In addition, blood was taken for the measurement of red blood cell (RBC) PUFA levels using the method described by Manku et al. (1983).

2.2. Results

Fifty-five patients were randomized to treatment. Of these, 10 discontinued treatment and therefore had only the baseline rating completed. Of these, three never started the treatment, one stopped because he felt better, one felt ill and forgetful, three complained of gastro-intestinal symptoms (nausea, irritable bowel, indigestion), and two were lost to follow-up. Of the 45 patients entered into the analysis, 15 were given EPA (10m, 5f, age 44.2 ± 11.3), 16

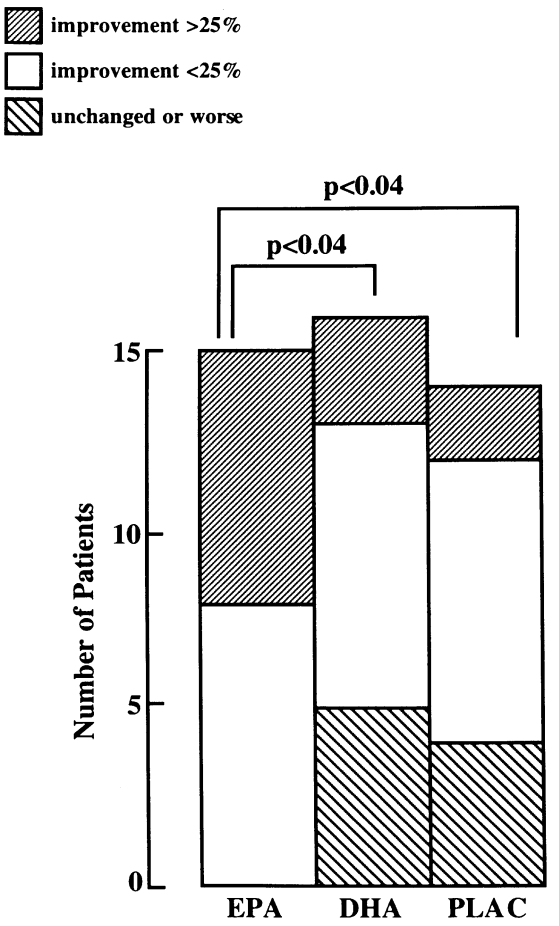

Fig. 1. Numbers of patients showing greater or less than 25% improvement, or showing clinical worsening, during treatment with EPA, DHA or placebo.

were given DHA (12m, 4f, age 42.0 ± 10.6), and 14 were given placebo (8m, 6f, age 43.8 ± 10.8).

The raw scores before and after treatment are shown in Table 1. No significant differences between the treatment groups existed prior to treatment, though the total PANSS score in the EPA group tended to be lower than those in the other two groups. After treatment, the total PANSS score in the EPA group was significantly lower than that in the placebo group. Using ANOVA for repeated measures (thus taking baseline differences into account), there was a significant treatment effect favouring EPA over DHA on the positive PANSS score. Considering percentage improvement, there was an advantage to EPA, particularly on the positive symptoms score. Within this, the difference between EPA and DHA was significant ($t = 2.58$; $P < 0.05$). There was no significant treatment effect on negative symptoms (mean improvement 9.7% for EPA, 9.4% for DHA and 8.0% for placebo). Data were further analysed using an improvement cut-off of 25%, which has been a criterion in previous studies of antipsychotic treatment. Patients were categorized as showing more than 25% improvement, less than 25% improvement, or being unchanged or worse on the total PANSS score. This is shown in Fig. 1. There is a significant group effect (Kruskal–Wallis one-way ANOVA, Chi-square = 7.6, $P = 0.02$). Pairwise comparison using Chi-square tests showed a significant difference between EPA and DHA (Chi-square = 6.57, $P = 0.04$) and between EPA and placebo (Chi-square = 6.75, $P = 0.04$).

RBC levels of PUFA were available for 12 patients in each group. The results are shown in Table 2. As expected, the largest rises in EPA and DHA levels

Table 2
RBC membrane levels of EPA, DHA and AA before and after treatment with EPA, DHA or placebo[a]

Treatment group	RBC PUFA levels					
	EPA		DHA		AA	
	Pre	Post	Pre	Post	Pre	Post
EPA	0.8 (0.3)	3.4 (1.6)**	4.6 (1.0)	5.9 (1.6)*	11.5 (4.8)	10.8 (3.3)
DHA	0.7 (0.2)	2.2 (1.4)*	3.8 (1.1)	8.3 (2.0)**	11.6 (3.8)	11.9 (1.9)
Placebo	0.6 (0.2)	0.8 (0.3)	3.7 (1.1)	4.3 (1.7)	10.4 (4.8)	12.9 (5.2)
EPA vs. DHA	n.s.	$P = 0.009$	n.s.	$P = 0.004$	n.s.	n.s.

[a] * $P < 0.05$; ** $P < 0.001$; pre- vs. post-treatment.

Table 3
Days on antipsychotic drugs and PANSS rating scale scores (total and positive symptoms) for patients taking EPA or placebo

	Days on antipsychotic drug	PANSS total		PANSS positive	
		Pre	Post	Pre	Post
EPA ($n = 14$)	35.1 (34.7)	70.4 (10.1)	44.6 (8.7)	23.1 (8.7)	12.5 (2.8)
Placebo ($n = 12$)	65.3 (18.9)	79.3 (18.6)	57.1 (15.5)	24.7 (8.2)	17.7 (8.6)
Student's *t*-test	$P < 0.02$	n.s.	$P < 0.02$	n.s.	$P < 0.05$

were in the EPA and DHA treatment groups, respectively. There were also small rises of EPA in the DHA treated group, and vice versa.

Within the EPA group, significant correlations (Pearson) were found between the change in positive PANSS ratings and baseline PUFA levels. Patients with the most improvement in the PANSS scores were those with the highest initial levels of EPA ($r = 0.71$, $P = 0.02$) and AA ($r = 0.58$, $P = 0.04$). Since the PUFA levels were intercorrelated, these relationships were further investigated using forward stepwise multiple regression analysis. Only baseline EPA emerged as a significant predictor of improvement in clinical scores ($t = 2.84$, $P = 0.02$, adjusted R^2 0.44). No such correlations were found within the DHA- and placebo-treated groups, or for the sample as a whole.

3. Placebo-controlled trial of EPA as a sole treatment for schizophrenia

3.1. Subjects and methods

Subjects for the study were 30 DSM IV (American Psychiatric Association, 1994) diagnosed schizophrenic patients on no medication who presented as new or relapsed cases to the psychiatric clinic in Baroda, India. The study, which was part of an ongoing research collaboration, was approved by the local Ethical Committee, which included senior academics and clinicians, and all patients gave informed consent. Prior to starting the double-blind study, a small open-label study had shown marked beneficial effects of EPA in Indian patients on modest doses of antipsychotic medication (Shah et al., 1998). Patients were allocated at random to be treated double blind with capsules containing either 2 g/day of EPA in the form of EPA-enriched oil (Kirunal) or an identical appearing matching corn oil placebo for 3 months. These were provided in pre-randomized numbered containers. The aim was to use the trial medication as a sole treatment when possible, but for ethical reasons, the introduction of conventional anti-psychotic medication was permitted when this was considered clinically imperative. Outcome measures included the need for, and duration of, conventional treatment and the PANSS, which was completed at the beginning and end of the study.

3.2. Results

There were no significant group differences in age, gender or duration of illness (EPA 11m/4f, age 33.4 ± 8.5 years; duration 5.7 ± 3.9 years; placebo 7m/8f, age 36.7 ± 8.1 years, duration 7.1 ± 4.1 years). Nine patients were drug-naïve on entering the study, and the remainder had received no antipsychotic drugs for at least 2 weeks. Four patients had no final PANSS rating completed (three on placebo, one on EPA); of these, three patients were lost to follow-up, and one died of accidental burns unrelated to the illness. In the placebo group, every patient required conventional antipsychotic medication by the end of the trial period. In contrast, six patients on EPA were not taking antipsychotic medication at the end of the study (Fisher's Exact test $P < 0.02$ vs. placebo). Of these six, four had gone through the entire treatment period without any antipsychotic medication, one had received antipsychotic drugs for the first week only, and one had received a single dose of depot antipsychotic medication (flupenthixol deconoate 25 mg) at the start of the trial (regarded statistically as 14 days' treatment). The antipsychotic drugs used were usually typical, mainly haloperidol, but three patients in the placebo group were given clozapine. On average,

EPA treated patients spent little more than a month on conventional treatment in contrast to more than 2 months for the placebo group (Table 3). Despite this substantial difference in the level of antipsychotic treatment, patients on EPA had significantly lower PANSS scores by the end of the study relative to the placebo treated group; this applied particularly to the positive symptom sub-scale (Table 3). There was no obvious difference in outcomes between patients who had been medicated previously and those who were drug-naïve, but numbers were too small for statistical comparison. A responder analysis was also carried out, using 50% improvement in rating scale scores as the criterion. On the positive PANSS rating, only two out of 12 patients on placebo showed more than 50% improvement, compared with eight out of 14 patients on EPA (Fisher's Exact test, two-tail, $P = 0.05$). No side-effects attributable to EPA were observed during the study, though these were assessed only by spontaneous patient report.

4. Discussion

It is in the nature of pilot studies to be indicative rather than definitive. They are intended to provide pointers to the design of more definitive studies. Indeed, it is unlikely that a placebo controlled trial of, say, chlorpromazine or olanzapine would produce statistically significant results in this patient population and with such small numbers. We were therefore surprised to find the level of statistical significance that emerged from these two studies.

The first pilot study was designed to investigate the possible differential effects of EPA and DHA as an adjunct to antipsychotic medication. The effect of EPA on positive symptoms was statistically superior to DHA, whether analysed either by ANOVA for repeated measures or by percentage improvement. On these measures, the difference between EPA and placebo did not reach statistical significance, but the numerical trend was in the expected direction. The final scores on the total PANSS were significantly lower in the EPA-treated patients than in those given placebo, but this is confounded by a non-significant difference between the two treatments at baseline. In a subsequent analysis, using a cut-off point of 25% improvement, EPA showed statistical superiority to both DHA and placebo on the total PANSS score. Following the initial abstracted report of our first pilot study (Peet et al., 1997), Puri and Richardson (1998) reported a single case treated with EPA as a sole agent, with apparently dramatic benefit. Our second pilot study was an attempt to investigate the possible efficacy of EPA as a sole treatment for schizophrenia under double-blind, placebo-controlled conditions. Ethical considerations prohibited us from doing the 'pure' study comparing EPA and placebo with no provision for the use of antipsychotic medication. The need to use antipsychotic drugs was based on clinical judgement rather than predetermined criteria, but the double-blind nature of the trial renders this a valid outcome measure. Significant differences emerged between EPA and placebo for both the need to use antipsychotic medication and the end-point score on the PANSS. Positive symptoms again showed the most improvement, with a higher proportion of patients showing more than 50% improvement on EPA.

The superiority of EPA over DHA was unexpected. Our initial hypothesis focused on abnormalities of cell-membrane composition. DHA is a major constituent of neuronal membrane phospholipids. Changes in membrane phospholipid fatty acid composiiton will alter the configuration and function of neurotransmitter receptors, including those for dopamine (Loh and Law, 1980; Delion et al., 1996; Litman and Mitchell, 1996). However, EPA is present in only very small quantities in neuronal membranes (Horrobin et al., 1991). It is therefore unlikely that any effect of EPA would be mediated through direct incorporation into neuronal membrane phospholipid. Also, we found that patients with the lowest RBC membrane EPA levels showed the least response to treatment with EPA. This would not be predicted if EPA treatment was simply correcting a membrane deficiency. Previous studies have shown that there is a bimodal distribution of PUFA levels in RBC membranes of schizophrenic patients, with one group having extremely low PUFA levels and another group having only a moderate reduction of PUFA relative to healthy controls (Glen et al., 1994; Peet et al., 1995). It may be that the group with particularly low levels, which responded less well to EPA treatment, have a more serious metabolic abnormality that cannot be corrected simply by the administration of EPA.

EPA has other important biological functions. It is the precursor of a number of eicosanoids and other metabolic products that have important functions as second messengers and neuromodulators (Sumĭda et al., 1993). It also has other biological effects such as inhibition of PLA2 (Finnen and Lovell, 1991) inhibition of cyclo-oxygenase (Obata et al., 1999), increase of intracellular calcium levels (Okuda et al., 1994), reversal of cancer cachexia (Tisdale, 1993), and effects on gene expression (Willumsen et al., 1996; Yokota et al., 1998). Some of these effects can be linked hypothetically to a therapeutic benefit of EPA in schizophrenia. Thus, if the reported increase of PLA2 activity in schizophrenia is of aetiological importance (Ross et al., 1997), inhibition of this enzyme might be therapeutically beneficial. A number of current antipsychotic drugs are known to inhibit PLA2 (Gattaz et al., 1987; Trzeciak et al., 1995). Exploration of the possible mode of action of EPA has followed behind the original clinical observation of efficacy in our first pilot study. If the therapeutic effect of EPA is confirmed, further biochemical investigation will be necessary to unravel the mode of action.

The positive outcome of these pilot treatment studies, together with direct evidence of abnormal PUFA and phospholipid metabolism in schizophrenia (Peet et al., 1999), gives strong support to the phospholipid hypothesis of schizophrenia (Horrobin, 1998). Several physiological abnormalities in schizophrenia also provide indirect evidence of abnormal PUFA metabolism. It is now well established that schizophrenic patients show a markedly reduced skin flush reaction to niacin compared to healthy controls. This can be investigated by a simple skin patch test (Ward et al., 1998) and is abnormal in both medicated and unmedicated schizophrenic patients (Shah et al., 1999). Integrity of the niacin skin flush depends on conversion of AA to phospholipase D2 via the cyclo-oxygenase enzyme system (Morrow et al., 1992). Rheumatoid arthritis, which is rare in schizophrenic patients (Eaton et al., 1992), is partly mediated through the same biochemical pathway. In a different paradigm, the electro-retinogram has been shown to be abnormal in schizophrenic patients, in a manner that is consistent with depletion of retinal DHA (Warner et al., 1999).

If the efficacy of EPA is established by larger studies, then this could represent a new class of treatment for schizophrenia. EPA in these doses is free of harmful side-effects and indeed is beneficial to cardiovascular health because of antithrombotic, triglyceride-lowering and antiarrhythmic effects (Connor and Connor, 1997; Howe et al., 1999). It therefore has a very high patient acceptability, in contrast to most of the currently available treatments for which poor compliance due to unpleasant side-effects is a common problem (Collaborative Working Group on Clinical Trial Evaluation, 1998). In addition, there is increasing interest in the possibility of early intervention, at the stage when only prodromal symptoms are present (Yung and McGorry, 1997). Prediction of schizophrenia on the basis of prodromal symptoms produces many false positives (Yung et al., 1998), and the use of normal antipsychotic medication as a preventative would expose large numbers of patients to antipsychotic side-effects without any benefits. It has been suggested that the new atypical antipsychotics would be advantageous for pre-psychotic intervention because of their reduced level of side-effects (Waddington et al., 1997), and risperidone has been tried for this purpose (Tsuang et al., 1999). A treatment such as EPA would have a clear advantage in this regard.

Acknowledgements

We are grateful to Dr David Horrobin and Laxdale Limited for supplying the materials and some financial support for this work.

References

Abedin, L., Lien, E.L., Vingrys, A.J., Sinclair, A.J., 1999. The effects of dietary alpha-linolic acid compared with docosahexaenoic acid on brain, retina, liver and heart in the guinea pig. Lipids 34, 475–482.

Albers, M.A., Meurer, H., Märki, F., Klotz, J., 1993. Phosopholipase A2 activity in serum of neuroleptic-naïve psychiatric in patients. Pharmacopsychiatry 26, 94–98.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). fourth ed., American Psychiatric Association, Washington, DC.

Bates, E.J., Ferrante, A., Harvey, D.P., Nandoskar, M., Poulos, A., 1993. Docosahexaenoic acid (22:6, n-3) but not eicosapentaenoic acid (20:5, n-3) can induce neutrophil-mediated injury of

cultured endothelial cells: involvement of neutrophil elastase. J. Leukoc. Biol. 54, 590–598.

Christensen, O., Christensen, E., 1998. Fat consumption and schizophrenia. Acta Psychiatr. Scand. 78, 587–591.

Collaborative Working Group on Clinical Trial Evaluation, 1998. Adverse effects of the atypical antipsychotics. J. Clin. Psychiatry 59 (12), 17–22.

Connor, S.L., Connor, W.E., 1997. Are fish oils beneficial in the prevention and treatment of coronary artery disease?. Am. J. Clin. Nutr. 66 (4), 1020S–1031S.

De Caterina, R., Cybulsky, M.I., Clinton, S.K., Gimbrone Jr., M.A., Libby, P., 1994. The omega-3 fatty acid docosahexaenoate reduces cytokine-induced expression of proatherogenic and proinflammatory proteins in human endothelial cells. Arterioscler. Thromb. 14, 1829–1836.

Delion, S., Chalon, S., Guilloteau, D., Besnard, J.C., Durand, G., 1996. Alpha-linolenic acid dietary deficiency alters age-related changes of dopaminergic and serotoninergic neurotransmission in the rat frontal cortex. J. Neurochem. 66, 1582–1591.

Eaton, W.W., Hayward, C., Ram, R., 1992. Schizophrenia and rheumatoid arthritis: a review. Schizophr. Res. 6, 181–192.

Finnen, M.J., Lovell, C.R., 1991. Purification and characterisation of phospholipase A2 from human epidermis. Biochem. Soc. Trans. 19, 91.

Fukuzako, H., Fukuzako, T., Hashiguchi, T., Kodama, S., Takigawa, M., Fujimoto, T., 1999. Changes in levels of phosphorus metabolites in temporal lobes of drug-naïve schizophrenic patients. Am. J. Psychiatry 156, 1205–1208.

Gattaz, W.F., Kollisch, M., Thuren, T., Virtanen, J.A., Kinnunen, P.K.J., 1987. Increased plasma phospholipase-A2 activity in schizophrenic patients: reduction after neuroleptic therapy. Biol. Psychiatry 22, 421–426.

Gattaz, W.F., Hubner, C.K., Nevalainen, T.J., Thuren, T., Kinnimen, P.K.J., 1990. Increased serum phospholipase-A2 activity in schizophrenia: a replication study. Biol. Psychiatry 28, 495–501.

Gattaz, W.F., Schmitt, A., Maras, A.M., 1995. Increased platelet phospholipase A2 activity in schizophrenia. Schizophr. Res. 16, 1–6.

Gilbert, M., Achard, F., Dalloz, S., Maclouf, J., Benistant, C., Legarde, M., 1999. Opposite regulation of prostaglandin H synthase isoforms by eicosapentaenoic and docosahexaenoic acids. Lipids 34, 219.

Glen, A., Glen, E.M., Horrobin, D.F., Vaddadi, K.S., Spellman, M., Morse-Fisher, N., Ellis, K., Skinner, F.S., 1994. A red cell membrane abnormality in a subgroup of schizophrenic patients: evidence for two diseases. Schizophr. Res. 12, 53–61.

Hitzemann, R.J., Mark, C., Hirschowitz, J., Garver, D.L., 1985. Characteristics of phospholipid methylation in human erythrocyte ghosts: relationship to the psychoses and affective disorders. Biol. Psychiatry 20, 297–307.

Horrobin, D.F., Manku, M.S., Hillman, S., Glen, A.I., 1991. Fatty acid levels in the brains of schizophrenics and normal controls. Biol. Psychiatry 30, 795–805.

Horrobin, D.F., 1998. The membrane phospholipid hypothesis as a biochemical basis for the neurodevelopmental hypothesis of schizophrenia. Schizophr. Res. 30, 193–208.

Howe, P.R., Clifton, P.M., James, M.J., 1999. Equal antithrombotic and triglyceride-lowering effectiveness of eicosapentaenoic acid-rich and docosahexaenoic acid-rich fish oil supplements. Lipids 34, S307–S308.

Kane, J.M., Jeste, D.V., Barnes, T.E., Casey, D.E., Cole, J.O., Davis, J.M., Gualtieri, C.T., Schooler, N.R., Spragne, R.L., Wettstein, R.M., 1992. Tardive Dyskinesia: A Task Force Report of the American Psychiatric Association. APA, Washington, DC.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Keshaven, M.S., Mallinger, A.G., Pettegrew, J.W., Dippold, C., 1993. Erythrocyte membrane phospholipids in psychotic patients. Psychiatry Res. 49, 89–95.

Litman, B.J., Mitchell, D.C., 1996. A role for phospholipid polyunsaturation in modulating membrane protein function. Lipids 31, S193–S197.

Loh, H.H., Law, P.Y., 1980. Role of membrane lipids in receptor mechanisms. Ann. Rev. Pharmacol. Toxicol. 20, 201–234.

Mahadik, S.P., Mukherjee, S., Correnti, E.E., Kelkar, H.S., Wakade, C.G., Costa, R.M., Scheffer, R., 1994. Plasma membrane phospholipid and cholesterol distribution of skin fibroblasts from drug-naïve patients at the onset of psychosis. Schizophr. Res. 13, 239–247.

Manku, M.S., Horrobin, D.F., Huang, S., Morse, N., 1983. Fatty acids in plasma and red cell membranes. Lipids 18, 906–908.

Marteinsdottir, I., Horrobin, D.F., Stenfors, C., Theodorsson, E., Mathe, A.A., 1998. Changes in dietary fatty acids alter phospholipid fatty acid composition in selected regions of rat brain. Prog. Neuropsychopharmacol. Biol. Psychiatry 22, 1007–1021.

Mellor, J., Laugharne, J.D.E., Peet, M., 1996. Omega-3 fatty acid supplementation in schizophrenic patients. Human Psychopharmacol. 11, 39–46.

Morrow, J.D., Awad, J.A., Oates, J.A., Roberts, L.J., 1992. Identification of skin as a major site of prostaglandin D2 release following oral administration of niacin in humans. J. Invest. Dermatol. 98, 812–815.

Noponen, M., Sanfilipo, M., Samanich, K., Ryer, H., Ko, G., Angrist, B., Watkin, A., Duncan, E., Retrosen, J., 1993. Elevated PLA2 activity in schizophrenics and other psychiatric disorders. Biol. Psychiatry 34, 641–649.

Obata, T., Nagakura, T., Masaki, T., Masaki, T., Maekawa, K., Yamashita, K., 1999. Eicosapentaenoic acid inhibits prostaglandin D2 generation by inhibiting cyclo-oxygenase-2 in cultured human mast cells. Clin. Exp. Allergy 29, 1129–1135.

Okuda, Y., Ezure, M., Tsukahara, K., Sawada, T., Mizutani, M., Katori, T., Bannai, C., Yamashita, K., 1994. Eicosapentaenoic acid enhances intracellular free calcium in cultured human endothelial cells. Biochem. Med. Metab. Biol. 51, 166–168.

Pangerl, A.M., Steudle, A., Jaroni, H.W., Rufer, R., Gattaz, W.F., 1991. Increased platelet membrane lysophosphatidylcholine in schizophrenia. Biol. Psychiatry 30, 837–840.

Peet, M., Laugharne, J.D.E., Rangarajan, N., Horrobin, D.F., Reynolds, G., 1995. Depleted red cell membrane essential fatty acids in drug-treated schizophrenic patients. J. Psychiatr. Res. 29, 227–232.

Peet, M., Laugharne, J.D.E., Mellor, J., 1997. Double-blind trial of fatty acid supplementation in the treatment of schizophrenia. International Congress on Schizophrenia Research, Colorado Springs, CO, April. .

Peet, M., Glen, I., Horrobin, D.F. (Eds.), 1999. Phospholipid Spectrum Disorder in Schizophrenia Marius Press, Carnforth, UK.

Pettegrew, J.W., Keshevan, M.S., Panchalingam, K., Strychor, S., Kaplan, T.B., Tretta, M.G., Allen, M., 1991. Alterations in brain high-energy phosphate and membrane phospholipid metabolism in first-episode, drug-naïve schizophrenics. A pilot study of the dorsal prefrontal cortex by in vivo phosphorus 31 nuclear magnetic resonance spectroscopy. Arch. Gen. Psychiatry 48, 563–568.

Puri, B.K., Richardson, A.J., 1998. Sustained remission of positive and negative symptoms of schizophrenia following treatment with eicosapentaenoic acid. Arch. Gen. Psychiatry 55, 188–189.

Ross, B.M., Hudson, C., Erlich, J., Warsh, J.J., Kish, S.J., 1997. Increased phospholipid breakdown in schizophrenia: evidence for the involvement of a calcium-independent phospholipase A2. Arch. Gen. Psychiatry 54, 487–494.

Ross, B.M., 1999. Brain and blood phospholipase activity in psychiatric disorders. In: Peet, M., Glen, I., Horrobin, D.F. (Eds.). Phospholipid Spectrum Disorder in Psychiatry. Marius Press, Carnforth, UK, pp. 23–29.

Rudin, D.O., 1981. The major psychoses and neuroses as omega-3 essential fatty acid deficiency syndrome: substrate pellagra. Biol. Psychiatry 16, 837–848.

Shah, S., Vankar, G.K., Telang, S.D., Ramchand, C.N., Peet, M., 1998. Eicosapentaenoic acid (EPA) as an adjunct in the treatment of schizophrenia. 9th Biennial Winter Workshop on Schizophrenia, Davos, Switzerland, February.

Shah, S., Vankar, K., Ramchand, C.N., Peet, M., 2000. Lack of niacin skin flush response in unmedicated schizophrenic patients. Schizophr. Res in press.

Stanley, J.A., Williamson, P.C., Drost, D.J., Carr, T.J., Rylett, R.J., Morrison-Stewart, S., Thompson, R.T., 1994. Membrane phospholipid metabolism and schizophrenia: in vivo ^{31}P-MR spectroscopy study. Schizophr. Res. 13, 209–215.

Sumida, C., Graber, R., Nunez, E., 1993. Role of fatty acids in signal transduction: modulators and messengers. Prostaglandins Leukot. Essent. Fatty Acids 48, 117–122.

Tisdale, M.J., 1993. Mechanism of lipid mobilisation associated with cancer cachexia: interaction between the polyunsaturated fatty acid, eicosapentaenoic acid and inhibitory guanine nucleotide-regulatory protein. Prostaglandins Leukot. Essent. Fatty Acids 48, 105–109.

Trzeciak, H.I., Kalacinski, W., Malecki, A., Kokot, D., 1995. Effect of neuroleptics on phospholipase A2 activity in the brain of rats. Eur. Arch. Psychiatry. Clin. Neurosci. 245, 179–182.

Tsuang, M.T., Stone, W.S., Serdman, L.J., Faraone, S.V., Zimmet, S., Wojcik, J., Kelleher, J.P., Green, A.I., 1999. Treatment of non-psychotic relatives of patients with schizophrenia: four case studies. Biol. Psychiatry 45, 1412–1418.

Vaddadi, K.S., Gilleard, C.J., Mindham, R.H.S., Butler, R.A., 1986. A controlled trial of a prostaglandin E_1 precursor in chronic neuroleptic-resistant schizophrenic patients. Psychopharmacology 88, 362–367.

Vaddadi, K.S., Courtney, P., Gilleard, C.J., Manku, M.S., Horrobin, D.F., 1989. A double blind trial of essential fatty acid supplementation in patients with tardive dyskinesia. Psychiatry Res. 27, 313–323.

Waddington, J.L., Scully, P.J., O'Callaghan, E., 1997. The new antipsychotics and their potential for early intervention in schizophrenia. Schizophr. Res. 28, 207–222.

Ward, P.E., Sutherland, J., Glen, E.M.T., Glen, A.I.M., 1998. Niacin skin flush in schizophrenia a preliminary report. Schizophr. Res. 29, 269–274.

Warner, R., Laugharne, J., Peet, M., Brown, L., Rogers, N., 1999. Retinal function as a marker for cell membrane omega-3 fatty acid depletion in schizophrenia: a pilot study. Biol. Psychiatry 45, 1138–1142.

Willumsen, N., Vaagenes, H., Lie, O., Rustan, A.C., Berge, R.K., 1996. Eicosapentaenoic acid, but not docosahexaenoic acid, increases mitochondrial fatty acid oxidation and upregulates 2,4-dienoyl-CoA reductase gene expression in rats. Lipids 31, 579–592.

Wolkin, A., Jordan, B., Peselow, E., Rubinstein, M., Retrosen, J., 1986. Essential fatty acid supplementation in tardive dyskinesia. Am. J. Psychiatry 143, 912–914.

Yao, J.K., van Kammen, D.P., Welker, J.A., 1994a. Red blood cell membrane dynamics in schizophrenia II: fatty acid composition. Schizophr. Res. 13, 217–226.

Yao, J.K., van Kammen, D.P., Welker, J.A., Gurklis, J., 1994b. Red blood cell membrane dynamics in schizophrenia III. Correlation of fatty acid abnormalities with clinical measures. Schizophr. Res. 13, 227–232.

Yao, J.K., 1999. Red blood cell and platelet fatty acid metabolism in schizophrenia. In: Peet, M., Glen, I., Horrobin, D.F. (Eds.). Phospholipid Spectrum Disorder in Schizophrenia. Marius Press, Carnforth, UK, pp. 57–74.

Yokota, K., Tsuruhamim, K., Nishimura, K., Nagayam, T., Jisaka, M., Takinami, K., 1998. Modification of membrane phospholipids with n-6 and n-3 essential fatty acids regulates the gene expression of prostaglandin endoperoxide synthase isoforms upon agonist stimulation. In: Riemersma, R.A., Armstrong, R., Kelly, R.W., Wilson, R. (Eds.), Essential Fatty Acids and Eicosanoids. Invited Papers from the Fourth International Congress. AOCS Press, Champaign, IL, pp. 68–73.

Yung, A.R., McGorry, P.D., 1997. Is pre-psychotic intervention realistic in schizophrenia and related disorders?. Aust. NZ J. Psychiatry 31, 799–805.

Yung, A.R., Phillips, L.J., McGarry, P.D., McFarlane, C.A., Francey, S., Harrigan, S., Patton, G.C., Jackson, H.J., 1998. Prediction of psychosis. A step towards indicated prevention of schizophrenia. Br. J. Psychiatry 172, 14–20.